The unnatural history of congenital heart disease

outcome up to 40 years after surgical repair

Judith A.A.E. Cuypers

THE UNNATURAL HISTORY OF CONGENITAL HEART DISEASE:

OUTCOME UP TO 40 YEARS AFTER SURGICAL REPAIR IN CHILDHOOD.

Judith Anne Adriane Ellen Cuypers

ISBN: 978-94-6169-761-5

Layout: Optima Grafische Communicatie (www.ogc.nl)
Printed by:Optima Grafische Communicatie (www.ogc.nl)

The Unnatural History of Congenital Heart Disease: outcome up to 40 years after surgical repair in childhood.

Het onnatuurlijke beloop van congenitale hartafwijkingen:
uitkomsten 40 jaar na chirurgische correctie op kinderleeftijd.

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus
Prof.dr. H.A.P. Pols
en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
dinsdag 15 december 2015 om 15.30 uur

door

Judith Anne Adriane Ellen Cuypers
geboren te Heeze

Erasmus University Rotterdam

Promotiecommissie:

Promotoren:	Prof.dr. J.W. Roos-Hesselink
	Prof.dr. A.J.J.C. Bogers
Overige leden:	Prof.dr. F. Zijlstra
	Prof.dr. W.A. Helbing
	Prof.dr. W. Budts

De in dit proefschrift beschreven studie werd mede mogelijk gemaakt door een grant van de Nederlandse Hartstichting (grant number 2009-B-073).

Het verschijnen van dit proefschrift werd mede mogelijk gemaakt door de steun van de Nederlandse Hartstichting

gesubsidieerd door Hartstichting

"Schrijven is blijven zitten tot het er staat."
Koot en Bie

Voor mijn familie

TABLE OF CONTENTS

PART 1

Introduction

1

General introduction and outline of the thesis

INTRODUCTION

Preface

Congenital cardiac defects are the most common congenital defects, comprising one third of all major congenital anomalies. Since the introduction of congenital cardiac surgery, the outlook for children born with a congenital heart defect has improved spectacularly. This thesis describes the outcome up to 40 years after surgical repair of congenital heart disease, which we call the "unnatural history" of congenital heart disease.

Epidemiology of congenital heart disease

The incidence of congenital heart disease shows a tendency to increase worldwide and is currently estimated to be around 8 per 1000 live births.[1] There are intercontinental differences, with the highest birth prevalence in Asia (> 9 per 1000). The worldwide increase in incidence is best explained by better recognition of congenital heart defects due to better diagnostic tools, such as echocardiography, rather than a real increase. Also, the better survival of congenital heart disease patients may have an impact, because patients with congenital heart disease now reach adulthood and most start a family. Their offspring have a higher risk of recurrent congenital heart disease. Furthermore, the fact that women become mothers at older age nowadays may play a role, for mothers over the age of 35 have an overall higher risk of congenital defects in their offspring. On the other hand, better preconception investigations have resulted in early recognition of abnormalities during development, with subsequently early termination in severe cases.

The eight most frequent cardiac abnormalities, who represent about 85% of all congenital heart defects, are ventricular septal defect (VSD) (34%), atrial septal defect (ASD) (13%), persistent ductus arteriosus (10%), pulmonary stenosis (8%), tetralogy of Fallot (5%), coarctation of the aorta (5%), transposition of the great arteries (TGA)(5%) and aortic stenosis (4%).[1]

Around 50% of the children born with a congenital heart defect have a mild defect that has little or no hemodynamic consequences. These children don't need immediate treatment and some septal defects even close spontaneously during childhood. The other 50% do need treatment at young age. In the pre-surgical era, about half of those that needed treatment died in the first year of life, and only 15% reached adulthood. Especially children born with more complex, cyanotic heart disease, had little chance to survive their first year. Everything changed with the introduction of cardiac surgery: in 1944, a shunt was developed by doctors Blalock (in close cooperation with Vivien Thomas) and Taussig, to improve pulmonary blood flow in duct dependent cyanotic heart defects by way of connecting the subclavian artery to the ipsilateral pulmonary artery branch. This procedure is called the "Blalock-Taussig shunt" ever since.[2-4] Particular

progress came in 1953, when the first cardiac surgery (on a patient with an atrial septal defect) was performed with the use of cardiopulmonary bypass, developed by Gibbon.[5,6] By these developments the perspective of children born with a congenital heart defect has improved spectacularly. Nowadays, of all children born with a heart defect, 95% will reach adulthood.[7]

Due to the tremendous improvements in diagnosis, surgical treatment and perioperative care, the prevalence of adult congenital heart disease has increased tremendously.[8] More and more patients reach adulthood and adults with congenital heart disease have indeed outnumbered the children with congenital heart disease.[9] The median age of adult patients with congenital heart disease is gradually increasing too.[9] More and more patients reach middle age and even patients above 60 are not a rarity any more. Their prevalence has been reported to have increased sixfold since 2000.[10] This tendency is also seen in the Netherlands (Figure 1).

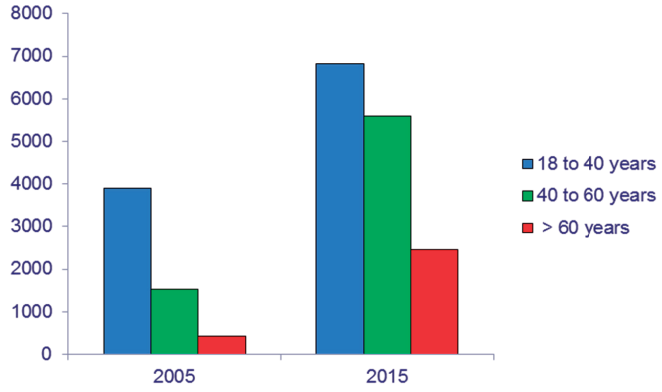


Figure 1. Age distribution of patients included in the Dutch ConCor database

Long-term outcome after surgical repair of congenital heart disease

In the early years of cardiopulmonary-bypass surgery, as congenital cardiac surgery proved to be a very successful treatment strategy with low perioperative mortality and low complication rates, both cardiothoracic surgeons and (pediatric) cardiologists were very optimistic and often even thought that their patients could be considered completely "cured". However, one or two decades later, they had to adjust their opinions, as it became apparent that patients did suffer from residual problems and late complications. A substantial amount of patients needed a reoperation or catheter-based intervention, some of them developed arrhythmias or heart failure and some even died suddenly, unexpectedly, at young adult age.[7]

Reoperations may be necessary for residual defects, that were deemed unimportant at the time of the initial surgery, or impossible to take care of in one operation. Further-

more, due to residual abnormalities that could not be repaired at all, or even as a result of the surgical techniques used, problems that need reintervention could arise years after the initial operation. For example, in the earliest years of surgical repair of tetralogy of Fallot, large pericardial patches were used to provide unobstructed flow through the right ventricular outflow tract and pulmonary valve into the pulmonary circulation. The resulting pulmonary regurgitation was at the time thought to be harmless. Afterwards, this regurgitation proved not to be benign at all.[11] Reoperation for severe pulmonary regurgitation is now the most frequent reintervention in adults after Fallot repair.

Arrhythmias may be atrial or ventricular and can be related to surgical scars, anatomical abnormalities, chamber dilatation with abnormal wall stress or hemodynamic overload. Atrial arrhythmias are usually benign, but can be ill tolerated or even lethal in patients with complex lesions such as single ventricle anatomy (Fontan circulation) or a systemic right ventricle, as is the case in TGA patients after an atrial switch operation.[12] Ventricular arrhythmias are less often encountered but can be life-threatening. For all arrhythmias it is important to first treat all underlying hemodynamic problems where possible. Other treatment strategies may include medication, ablation and pacemaker or ICD implantation. The decision for treatment and the choice for a specific treatment are less well established in congenital patients.

Heart failure is infrequently seen in childhood, but may develop in adult life. Ventricular function may be damaged due to perioperative factors, or by longstanding hypoxemia in cyanotic defects before repair took place. Also valvular lesions, residual obstructions, arrhythmias and ischemia may play a role. Right ventricular function is often compromised by longstanding volume overload due to pulmonary regurgitation in Fallot patients, as mentioned above. Eventually, this right ventricular dysfunction will have impact on left ventricular function too.[13] In TGA patients after Mustard repair, systemic right ventricular function is known to deteriorate over time.[14] Because of the inevitable development of heart failure in these Mustard patients, the atrial switch operations for TGA have been largely abandoned since the 1980s, when a new technique became available: the arterial switch operation. However, many patients who underwent an atrial switch operation are still alive today.

Sudden cardiac death (*SCD*) occurs more often in congenital heart disease patients than in the general population. Its estimated overall annual incidence is 0.09%.[15] Patients with repaired cyanotic heart disease appear to be at the greatest risk, but SCD also happens in simple congenital heart disease. Risk stratification for this traumatic complication in these often still young patients remains difficult. Risk factors appear to be systemic ventricular dysfunction, left ventricular outflow tract obstruction and prolonged QRS-duration (> 180 ms), but they have been investigated almost exclusively in Fallot and TGA patients.[12, 16]

The impact of sports participation is not well studied. Competitive sports may be dangerous for these patients and may lead to sudden death, although on the other hand a healthy life-style is advisable. Many doctors are afraid for sudden death and may be too restrictive, but good data on the safety of sports is lacking.

As a consequence of all these problems that may be encountered, congenital heart disease is nowadays considered to be more like a chronic disease.

The major evolutions described above have led to a substantial increase in outpatient visits to our adult congenital heart disease clinic (Figure 2). These adult and elderly patients require specialized care, for which more and more cardiologists will have to be trained in this subspecialty.[17] Gradually, the focus of care has evolved from keeping our patients alive to treatment of residual problems and improving quality of life. Together with our patients, we are now experiencing the long-term outcome after surgery at young age: the "unnatural history" of congenital heart disease.

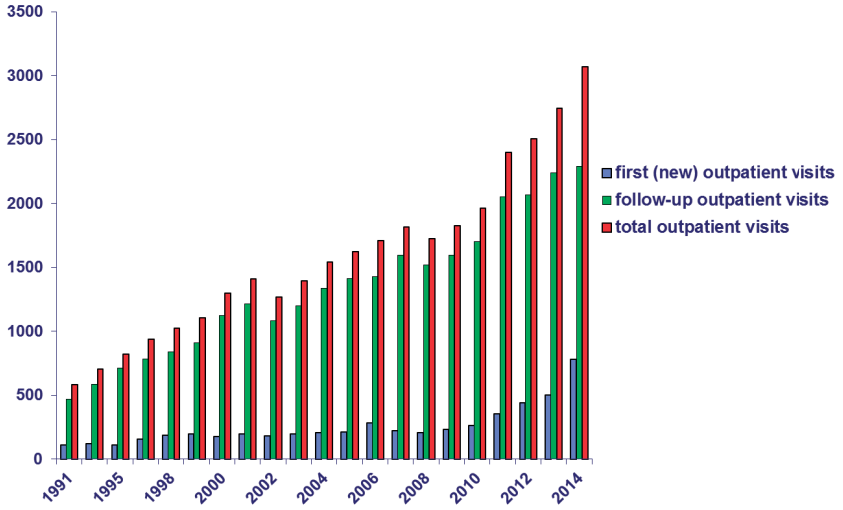


Figure 2. Numbers of outpatient clinic visits over the last decades

Dealing with patients with congenital heart disease as a profession, cardiac surgeons, pediatric cardiologists, anesthetists and congenital heart disease cardiologist have "grown up" alongside their patients. Their knowledge and experiences have made major improvements possible, but it remains very difficult to predict what exactly we should expect for the future. For both patients and their treating physicians it is of major importance to know what can be expected in whom and of which late complications to be aware.

With great foresight, in 1990 the Rotterdam Quality of Life Study was initiated. In this study, all consecutive patients operated between 1968 and 1980 in the Erasmus MC (formerly known as Dijkzigt Hospital) at young age (<15 years) are followed longitudinally. The patients with 1 of the 5 most common congenital heart defects: 1. Atrial septal defect (ASD), 2. Ventricular septal defect (VSD), 3. isolated pulmonary stenosis (PS), 4. Tetralogy of Fallot and 5. Transposition of the great arteries (TGA) were included and all successfully operated patients were invited for an extensive medical and psychological investigation in-hospital every ten years.

Specific lesions

In **atrial septal defec**t (figure 3), the cross-over ("shunt") of blood from the higher pressure left heart to the lower pressure right heart at the atrial level (figure 3B) will cause volume overload of the right heart. This will eventually cause dilatation of both right atrium and ventricle. If volume overload persists, eventually right ventricular function may be compromised with the risk of developing heart failure. Also, the increased blood flow through the pulmonary vascular bed may lead to elevated pulmonary pressures and eventually pulmonary hypertension. Stretch of the atrial wall due to atrial dilatation may give rise to atrial arrhythmia. Closure of an hemodynamically significant ASD in childhood has been proven to be beneficial. Long term outcome concerns are persistence of ventricular dilatation, late development of pulmonary hypertension and atrial arrhythmias.[18-21]

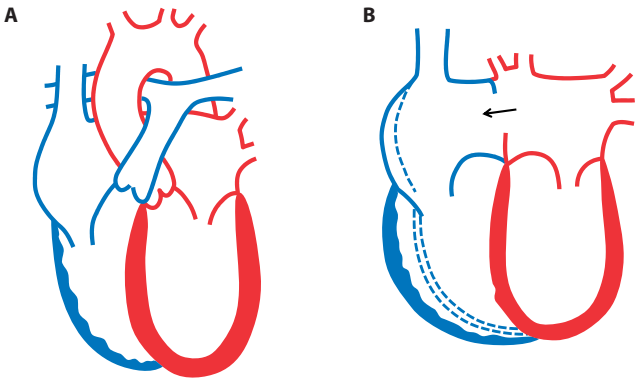


Figure 3A. Normal heart
Figure 3B. Atrial Septal Defect

In **ventricular septal defect** (Figure 4), shunting of blood from the left ventricle to the right will cause volume load on the left ventricle, which will dilate in case of a substantial shunt size. Longstanding (a few years) increased blood flow through the pulmonary

vasculature will cause pulmonary hypertension. Again, eventually ventricular functional deterioration may ensue. In case of a very close proximity of the VSD to the aortic valve, a high velocity shunt jet may cause prolapse of the aortic cusps, causing aortic regurgitation.[22] Mid- to long-term outcome after surgical correction of a VSD in childhood is good, but there is concern about late arrhythmia, sinus node disease, the development of aortic regurgitation and late sudden death.[23, 24]

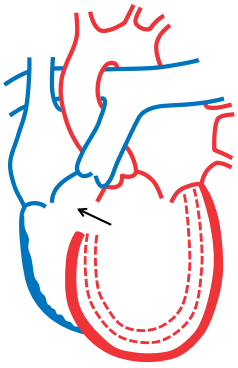


Figure 4. Ventricular Septal Defect

In isolated **pulmonary stenosis** (Figure 5), the right ventricle has to produce high pressures to pump blood into the pulmonary arteries. This will cause right ventricular hypertrophy, and at a late stage dilatation and eventually failure. Survival after surgical repair in childhood is good up to mid- to long-term follow-up, but postoperative pulmonary regurgitation is common, especially when a transannular patch was used to repair the stenosis. This pulmonary regurgitation is known to be tolerated well for a long time, up to decades, but may cause right ventricular damage in the long run.[25]

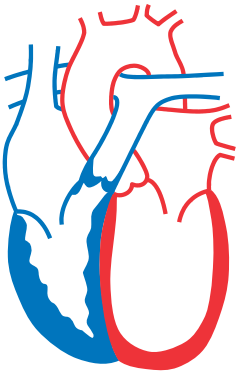


Figure 5. Pulmonary stenosis

Tetralogy of Fallot (Figure 6) is a cyanotic congenital heart defect caused by malalignment of the ventricular septum: the outflow part of the septum is displaced anteriorly, cranially and rightward and does not connect to the muscular part of the septum. Besides a ventricular septal defect, this causes the aorta to override the septum and the right ventricular outflow tract to be very narrow. This infundibular pulmonary stenosis gives rise to right ventricular hypertrophy. If uncorrected, patients will be cyanotic due to hypoperfusion of the pulmonary vascular bed and right-to-left shunt over the VSD. Without repair, mortality in the first year of life is very high. With the introduction of the Blalock-Taussig shunt in the 1940s survival of Fallot patients has improved, but the introduction of complete repair has really changed their prospects. In complete repair, the VSD is closed with a patch, the infundibular pulmonary stenosis is relieved by resection of the hypertrophied muscular tissue and often a patch plasty of the pulmonary valve (transannular patch) is performed. Long-term concerns after repair in childhood are pulmonary regurgitation, right ventricular dysfunction, arrhythmia, aortic regurgitation and late sudden death.[26-28]

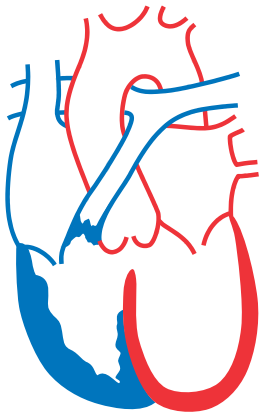


Figure 6. Tetralogy of Fallot

In **transposition of the great arteries** (Figure 7) the systemic and pulmonary circulation are completely separated because the systemic venous blood is pumped back into the systemic circulation immediately by the right ventricle that is connected to the aorta instead of the pulmonary artery. Likewise, the pulmonary venous blood is redirected to the pulmonary circulation again by the pulmonary artery that is connected to the left ventricle. Without any possibility to mix desaturated and saturated blood (i.e. and ASD or VSD), this condition is not compatible with life. Therefore, immediate treatment making mixing of blood possible is life-saving and surgical repair is in the neonatal period is eminent. From the 1960s, surgical repair was performed by the Senning or Mustard op-

eration, both atrial switch procedures: the systemic venous return is redirected by baffles to the left, subpulmonary ventricle, while the pulmonary venous return is redirected to the subaortic right ventricle. This will cause the circulation of blood to be functionally normal, but not anatomically: the anatomic left ventricle sustains the pulmonary circulation and the anatomic right ventricle has to sustain the systemic circulation. After two to three decades, the systemic right ventricle will show marked deterioration of function. Patients who had an atrial switch operation have a limited life-expectancy and many will develop heart failure or arrhythmias. Also there is an increased risk of sudden death.[14, 29, 30]

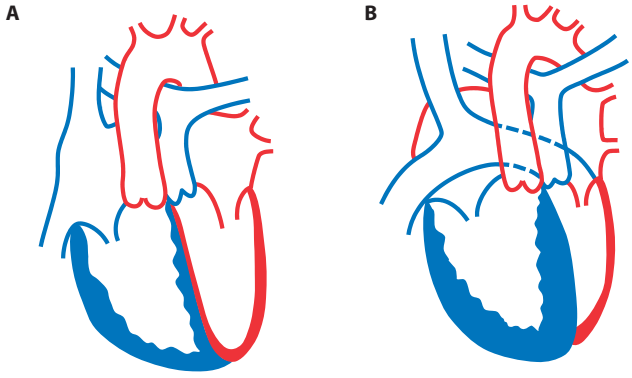


Figure 7A. Transposition of the great arteries
Figure 7B. Mustard repair

Psychosocial outcome

Repair for congenital heart disease does not only affect the medical outcome, but also has important implications for quality of life. It may affect the subjective health status, but also educational levels, sports participation and, for instance, sexual functioning may be hampered.

Historically, patients with congenital heart disease are known to have lower educational levels and are often living more dependently than the normal population.[31-33]. They are more likely to suffer from psychopathology at young adult age and they do experience problems with getting a job and getting health or life insurance.[34-36] Nevertheless, their overall satisfaction with life is very good and at least as good, or even better than in the normal population.

In previous studies on the psychosocial well-being of adults with congenital heart disease, focus was on psychopathology and educational and occupational levels. Hardly any literature exists, however, on sexual functioning and sports participation in adult pa-

tients with congenital heart disease. Regarding subjective quality of life, these aspects of daily life may be of great significance.

In the sparse studies that have addressed sexual functioning, sexual problems are reported in up to 20% of the patients [37, 38] and misplaced anxieties regarding pregnancy and delivery do exist.[38]

Sports participation was often discouraged in children with congenital heart disease in the past, out of safety concerns and fear of sudden death. This may have led to decreased sports participation in adults with congenital heart disease, while exercising may have beneficial effects also in this group. There are several reports on the positive effects of exercise training in patients with acquired heart disease.[39] In contrast, other patients, even with complex congenital heart disease, do engage in sports that would have been discouraged for valid reasons if they had asked their doctor. This may lead to unsafe situations.

Purpose of the study

The goal of this study is to prospectively investigate survival and late morbidity in a large unselected cohort of patients operated for congenital heart disease in childhood and to assess changes in cardiac function over time. In addition to this medical investigation, an extensive psychological investigation is performed to investigate the impact of having congenital heart disease on psychosocial outcome and quality of life. The patients are examined every ten years. They are invited to the outpatient clinic for an extensive medical examination, including ECG, Holter monitoring, echocardiography and exercise testing. The patients were examined for the first time in 1990 by Folkert Meijboom (medical part) and Lisbeth Utens (psychological part), the second time in 2001 by Jolien Roos-Hesselink (medical part) and Susan van Rijen (psychological part). The current thesis is based on the third medical examination in 2011-12. The psychological outcome has been described by Petra Opić. [40]

In the current study, several improved diagnostic techniques were introduced, which were not available in the past studies. For example, cardiac magnetic resonance imaging was added in the ASD, Fallot and Mustard groups. For the evaluation of psychosocial outcomes, the patients were interviewed and fulfilled an extensive questionnaire to evaluate their psychological well-being and quality of life. In addition, sexual functioning and engagement in sports was investigated.

Newly used diagnostic tools

Over the last decade, there have been many improvements in diagnostic techniques to assess cardiac function in detail. Nowadays, *cardiac magnetic resonance imaging* (CMR) is the gold standard to assess ventricular function. This technique was used now for the first time in the Quality of Life Study. In echocardiography, which is still the most used

imaging technique in cardiology, image quality can be hampered by lack of good echo windows and aberrant position of the heart in the thorax. Also, especially in congenital heart disease, the heart can be too large to be captured by the echo beam. The advantage of CMR over echocardiography in congenital heart disease is that it can visualize the whole heart as well as its surrounding vasculature with high resolution images, regardless of a patients posture and the position of the heart, making it much easier to assess cardiac and vascular anatomy.[41] Also, determination of endocardial borders is easier, and subsequently calculation of ventricular volumes. By scanning the heart in multiple slices through the whole cardiac cycle, end-diastolic and end-systolic volumes can be calculated. The difference between these volumes is the ventricular stroke volume. The ratio of stroke volume and end-diastolic volume is the ejection fraction of the ventricle, which gives a good indication of ventricular systolic function. Although systolic ventricular function may be abnormal at rest, for example in patients with repaired tetralogy of Fallot, there is evidence that contractile reserve may be preserved, at least during childhood. Whether this is also the case in adult patients is not known. Decreased contractile reserve may be a prognosticator of decrease in systolic function at rest. Ventricular contractile reserve can be assessed with dobutamine stress CMR.[42] Infusion of dobutamine will simulate exercise, during which ventricular contraction should increase. In this study, this was performed in patients with tetralogy of Fallot. A low dose of dobutamine intravenously is enough to evoke the increase in contractility. Infusion of high dose dobutamine is used in acquired heart disease, mainly coronary artery disease, to detect myocardial ischemia. Whether ischemia plays a role in the deterioration of ventricular function in Fallot patients, is unknown. There are reports on increased fibrosis in the hypertrophied right ventricles of Fallot patients.[43] Whether this is the result of ischemia or of other factors in unknown. This is why we decided to perform high dose dobutamine stress CMR as well, to detect potential ischemia.

Over time, also the methods to study exercise capacity have changed. It still is performed by bicycle ergometry, but cardiac exercise testing has evolved to *cardiopulmonary exercise testing*,[44] which was included now in the study protocol for the first time. In cardiopulmonary exercise testing, in addition to determination of exercise capacity, maximal oxygen consumption (VO_2max) is assessed. This allows differentiation between the different causes of decreased exercise capacity, which may be cardiac, pulmonary or the effect of decreased physical fitness. Analyzing exhaled gas compositions can verify whether a patient has exercised maximally, that is whether anaerobic metabolism was addressed.

Also for the first time, we added determination of levels of *NT-proBNP* to the study protocol. NT-proBNP is a well-established biomarker which has proved to be of clinical relevance in heart failure in acquired heart disease, but whose role in clinical practice in congenital heart disease still has to be elucidated. Other studies in our department have

shown that in congenital heart disease, NT-proBNP levels are often elevated, even in the absence of any clinical sign of heart failure.[45] In the current study, we tried to relate levels of NT-proBNP to clinical and cardiac functional parameters.

CURRENT (THIRD) QUALITY OF LIFE STUDY

From the earlier reports on our cohort and from other literature, we know that up to 25 years postoperatively, late mortality and morbidity are low for patients with a mild lesion, but substantial in patients with a more complex lesion such as after repair of Fallot or TGA. In these two latter groups, there is concern about ventricular function, especially in the TGA patients, who experience the problems of having a systemic right ventricle mentioned above. From other literature, exercise capacity is known to be related to mortality and hospitalization.[46] Literature on outcome beyond 25 years is virtually nonexistent. This is why we performed a third follow-up study in the Rotterdam Quality of Life cohort in 2011 (2010-2012). The aims of this study were as follows:

1. To describe the very long term (30-40 years) outcome i.e. survival and morbidity in this unselected cohort of consecutively operated patients.
2. To determine cardiac function and functional capacity beyond 25 years of follow-up, with the up-to-date echocardiographic, exercise and magnetic resonance imaging techniques.
3. To detect changes in cardiac function over time, using the diagnostic imaging techniques that were used historically.
4. To try to identify predictors for late outcome.
5. To determine psychosocial outcome, including participation in work and sports, sexual functioning and psychopathology.

OUTLINE OF THIS THESIS:

In chapter 2,3 and 5 to 7, the medical results of the Quality of Life 2011-2012 study in the five different diagnosis groups are described: atrial septal defect, ventricular septal defect, pulmonary stenosis, tetralogy of Fallot and transposition of the great arteries corrected with Mustard surgery. In detail mortality, morbidity and current clinical condition are described 35 years after cardiac surgery.

In chapter 4, the consequences and current treatment of pulmonary stenosis is reviewed, including the historical results of the different treatment modalities.

In the subsequent chapters, we describe the psychosocial outcomes in more detail, with specific papers on sexual functioning and sports activation.

Because of the many changes that have taken place in the treatment of congenital heart disease since the beginning of the cardiopulmonary bypass surgery, results described in this study, on our earliest cohort of patients, cannot be extrapolated unadjusted to patients who have been operated during a later era. As mentioned above, the atrial switch operation (Mustard and Senning operation) for TGA has been abandoned. Patients born with TGA nowadays are treated with an arterial switch operation, preferably. In the last chapter of this thesis, results of our first and second cohort of subsequently operated TGA patients are compared, the first cohort treated with atrial and the second by arterial switch.

REFERENCES

1. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, Roos-Hesselink JW. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol.* 2011;58:2241-2247.
2. Salmon GW, Barkley HT. The Blalock-Taussig operation. *J Pediatr.* 1947;31:54-59.
3. Beaty CA, George TJ, Conte JV. Historical perspectives of The American Association for Thoracic Surgery: Alfred Blalock (1899-1964). *J Thorac Cardiovasc Surg.* 2012;143:260-263.
4. Blalock A, Taussig HB. Landmark article May 19, 1945: The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia. By Alfred Blalock and Helen B. Taussig. *JAMA.* 1984;251:2123-2138.
5. Theruvath TP, Ikonomidis JS. Historical perspectives of The American Association for Thoracic Surgery: John H. Gibbon, Jr (1903-1973). *J Thorac Cardiovasc Surg.* 2014;147:833-836.
6. Kirklin JW, Dushane JW, Patrick RT, Donald DE, Hetzel PS, Harshbarger HG, Wood EH. Intracardiac surgery with the aid of a mechanical pump-oxygenator system (gibbon type): report of eight cases. *Proc Staff Meet Mayo Clin.* 1955;30:201-206.
7. Warnes CA. The adult with congenital heart disease: born to be bad? *J Am Coll Cardiol.* 2005;46:1-8.
8. van der Bom T, Zomer AC, Zwinderman AH, Meijboom FJ, Bouma BJ, Mulder BJ. The changing epidemiology of congenital heart disease. *Nat Rev Cardiol.* 2011;8:50-60.
9. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation.* 2007;115:163-172.
10. Tutarel O, Kempny A, Alonso-Gonzalez R, Jabbour R, Li W, Uebing A, Dimopoulos K, Swan L, Gatzoulis MA, Diller GP. Congenital heart disease beyond the age of 60: emergence of a new population with high resource utilization, high morbidity, and high mortality. *Eur Heart J.* 2014;35:725-732.
11. Bouzas B, Kilner PJ, Gatzoulis MA. Pulmonary regurgitation: not a benign lesion. *Eur Heart J.* 2005;26:433-439.
12. Khairy P, Dore A, Talajic M, Dubuc M, Poirier N, Roy D, Mercier LA. Arrhythmias in adult congenital heart disease. *Expert Rev Cardiovasc Ther.* 2006;4:83-95.
13. Wald RM, Marie Valente A, Marelli A. Heart failure in adult congenital heart disease: Emerging concepts with a focus on tetralogy of Fallot. *Trends Cardiovasc Med.* 2015;25:422-432.
14. Warnes CA. Transposition of the great arteries. *Circulation.* 2006;114:2699-2709.
15. Yap SC, Harris L. Sudden cardiac death in adults with congenital heart disease. *Expert Rev Cardiovasc Ther.* 2009;7:1605-1620.
16. Koyak Z, Harris L, de Groot JR, Silversides CK, Oechslin EN, Bouma BJ, Budts W, Zwinderman AH, Van Gelder IC, Mulder BJ. Sudden cardiac death in adult congenital heart disease. *Circulation.* 2012;126:1944-1954.
17. Webb G, Mulder BJ, Aboulhosn J, Daniels CJ, Elizari MA, Hong G, Horlick E, Landzberg MJ, Marelli AJ, O'Donnell CP, Oechslin EN, Pearson DD, Pieper EP, Saxena A, Schwerzmann M, Stout

KK, Warnes CA, Khairy P. The care of adults with congenital heart disease across the globe: Current assessment and future perspective: A position statement from the International Society for Adult Congenital Heart Disease (ISACHD). *Int J Cardiol.* 2015;195:326-333.

18. Gabriels C, De Meester P, Pasquet A, De Backer J, Paelinck BP, Morissens M, Van De Bruaene A, Delcroix M, Budts W. A different view on predictors of pulmonary hypertension in secundum atrial septal defect. *Int J Cardiol.* 2014;176:833-840.
19. Geva T, Martins JD, Wald RM. Atrial septal defects. *Lancet.* 2014;383:1921-1932.
20. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, van Domburg R, van Rijen EH, Utens EM, Bogers AJ, Simoons ML. Excellent survival and low incidence of arrhythmias, stroke and heart failure long-term after surgical ASD closure at young age. A prospective follow-up study of 21-33 years. *Eur Heart J.* 2003;24:190-197.
21. Meijboom F, Hess J, Szatmari A, Utens EM, McGhie J, Deckers JW, Roelandt JR, Bos E. Long-term follow-up (9 to 20 years) after surgical closure of atrial septal defect at a young age. *Am J Cardiol.* 1993;72:1431-1434.
22. Penny DJ, Vick GW, 3rd. Ventricular septal defect. *Lancet.* 2011;377:1103-1112.
23. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, Van Domburg R, Van Rijen EH, Utens EM, Bogers AJ, Simoons ML. Outcome of patients after surgical closure of ventricular septal defect at young age: longitudinal follow-up of 22-34 years. *Eur Heart J.* 2004;25:1057-1062.
24. Meijboom F, Szatmari A, Utens E, Deckers JW, Roelandt JR, Bos E, Hess J. Long-term follow-up after surgical closure of ventricular septal defect in infancy and childhood. *J Am Coll Cardiol.* 1994;24:1358-1364.
25. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, vanDomburg RT, vanRijen EH, Utens EM, Bogers AJ, Simoons ML. Long-term outcome after surgery for pulmonary stenosis (a longitudinal study of 22-33 years). *Eur Heart J.* 2006;27:482-488.
26. Apitz C, Webb GD, Redington AN. Tetralogy of Fallot. *Lancet.* 2009;374:1462-1471.
27. Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic findings. *Circulation.* 1995;91:2214-2219.
28. Meijboom F, Szatmari A, Deckers JW, Utens EM, Roelandt JR, Bos E, Hess J. Cardiac status and health-related quality of life in the long term after surgical repair of tetralogy of Fallot in infancy and childhood. *J Thorac Cardiovasc Surg.* 1995;110:883-891.
29. Meijboom F, Szatmari A, Deckers JW, Utens EM, Roelandt JR, Bos E, Hess J. Long-term follow-up (10 to 17 years) after Mustard repair for transposition of the great arteries. *J Thorac Cardiovasc Surg.* 1996;111:1158-1168.
30. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, van Domburg R, van Rijen EH, Utens EM, McGhie J, Bos E, Bogers AJ, Simoons ML. Decline in ventricular function and clinical condition after Mustard repair for transposition of the great arteries (a prospective study of 22-29 years). *Eur Heart J.* 2004;25:1264-1270.
31. Utens EM, Verhulst FC, Erdman RA, Meijboom FJ, Duivenvoorden HJ, Bos E, Roelandt JR, Hess J. Psychosocial functioning of young adults after surgical correction for congenital heart disease in childhood: a follow-up study. *J Psychosom Res.* 1994;38:745-758.

32. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. *Eur Heart J.* 2003;24:673-683.

33. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Current subjective state of health, and longitudinal psychological well-being over a period of 10 years, in a cohort of adults with congenital cardiac disease. *Cardiol Young.* 2005;15:168-175.

34. Utens EM, Verhulst FC, Meijboom FJ, Duivenvoorden HJ, Erdman RA, Bos E, Roelandt JT, Hess J. Behavioural and emotional problems in children and adolescents with congenital heart disease. *Psychol Med.* 1993;23:415-424.

35. Utens EM, Verhulst FC, Duivenvoorden HJ, Meijboom FJ, Erdman RA, Hess J. Prediction of behavioural and emotional problems in children and adolescents with operated congenital heart disease. *Eur Heart J.* 1998;19:801-807.

36. Utens EM, Bieman HJ, Verhulst FC, Meijboom FJ, Erdman RA, Hess J. Psychopathology in young adults with congenital heart disease. Follow-up results. *Eur Heart J.* 1998;19:647-651.

37. Moons P, Van Deyk K, Marquet K, De Bleser L, Budts W, De Geest S. Sexual functioning and congenital heart disease: Something to worry about? *Int J Cardiol.* 2007;121:30-35.

38. Kaemmerer M, Vigl M, Seifert-Klauss V, Nagdyman N, Bauer U, Schneider KT, Kaemmerer H. Counseling reproductive health issues in women with congenital heart disease. *Clin Res Cardiol.* 2012;101:901-907.

39. Gielen S, Laughlin MH, O'Conner C, Duncker DJ. Exercise training in patients with heart disease: review of beneficial effects and clinical recommendations. *Prog Cardiovasc Dis.* 2015;57:347-355.

40. Opic P. *Impact of Congenital Heart Disease at Adulthood*. Rotterdam, the Netherlands: department of Cardiology Erasmus MC, Erasmus University Rotterdam; 2013.

41. Bonello B, Kilner PJ. Review of the role of cardiovascular magnetic resonance in congenital heart disease, with a focus on right ventricle assessment. *Arch Cardiovasc Dis.* 2012;105:605-613.

42. Helbing WA, Luijnenburg SE, Moelker A, Robbers-Visser D. Cardiac stress testing after surgery for congenital heart disease. *Curr Opin Pediatr.* 2010;22:579-586.

43. Babu-Narayan SV, Kilner PJ, Li W, Moon JC, Goktekin O, Davlouros PA, Khan M, Ho SY, Pennell DJ, Gatzoulis MA. Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of fallot and its relationship to adverse markers of clinical outcome. *Circulation.* 2006;113:405-413.

44. Myers J. Applications of cardiopulmonary exercise testing in the management of cardiovascular and pulmonary disease. *Int J Sports Med.* 2005;26 Suppl 1:S49-55.

45. Eindhoven JA, van den Bosch AE, Jansen PR, Boersma E, Roos-Hesselink JW. The usefulness of brain natriuretic peptide in complex congenital heart disease: a systematic review. *J Am Coll Cardiol.* 2012;60:2140-2149.

46. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation.* 2005;112:828-835.

PART 2

Long-term outcome after surgical repair of congenital heart disease

2

The unnatural history of an atrial septal defect (ASD): longitudinal follow-up of 35 years after surgical ASD closure at young age.

Judith A. A. E. Cuypers, Petra Opić, Myrthe E. Menting, Elisabeth M. W. J. Utens, Maarten Witsenburg, Wim A. Helbing, Annemien E. van den Bosch, Mohamed Ouhlous, Ron T. van Domburg, Folkert J. Meijboom, Ad J. J. C. Bogers, Jolien W. Roos-Hesselink

Heart. 2013 Sep;99(18):1346-52

ABSTRACT

Objective

To describe the very long-term outcome after surgical closure of an atrial septal defect (ASD).

Design

Longitudinal cohort study of 135 consecutive patients who underwent surgical ASD repair at age <15 years between 1968 and 1980. The study protocol included ECG, echocardiography, exercise testing, N-terminal prohormone of brain natriuretic hormone, Holter monitoring and cardiac MRI.

Main outcome measures

Survival, major events (cardiac reinterventions, stroke, symptomatic arrhythmia or heart failure) and ventricular function.

Results

After 35 years (range 30–41), survival status was obtained in 131 of 135 patients (97%): five died (4%), including two sudden deaths in the last decade. Fourteen patients (16%) had symptomatic supraventricular tachyarrhythmias and six (6%) had a pacemaker implanted which was predicted by early postoperative arrhythmias. Two reoperations were performed. One ischaemic stroke occurred. Left ventricular (LV) and right ventricular (RV) ejection fractions (EF) were 58±7% and 51±6%, respectively. RVEF was diminished in 17 patients (31%) and in 11 (20%) the RV was dilated. Exercise capacity and quality of life were comparable to the normal population. No clear differences were found between ASD-II or sinus venosus type ASD.

Conclusions

Very long-term outcome after surgical ASD closure in childhood shows good survival and low morbidity. Early surgical closure prevents pulmonary hypertension and reduces the occurrence of supraventricular arrhythmias. Early postoperative arrhythmias are predictive for the need for pacemaker implantation during early follow-up, but the rate of late pacemaker implantation remains low. Although RVEF was unexpectedly found to be decreased in one-third of patients, the functional status remains excellent.

INTRODUCTION

While transcatheter closure with a device is the current method of choice for correction in patients with a suitable atrial septal defect (ASD), surgical closure was first choice treatment until the 1990s and is still the only treatment for large and non-centrally located defects. After successful operation at a young age, the natural history of patients with ASD improved dramatically, with life expectancy similar to that of the general population.[1–3]

The retrospective study of Murphy et al[1] was the first to demonstrate the benefits of early surgical closure. The incidence of postoperative atrial arrhythmias appeared to be related to the age of the patient at the time of repair. Benefits of closure in childhood have been confirmed by others,[3–7] although persistent ventricular dilation has been reported in some but not all studies.

Early and mid-term follow-up of transcatheter ASD closure shows excellent results.[8] For a comparison of both closure techniques, information on outcome beyond 30 years is crucial.

The aim of the present study was to provide data on mortality, morbidity and ventricular function up to 40 years after surgery. The investigation is based on a unique longitudinal cohort of consecutively operated patients who we examine in hospital every 10 years using the same protocol.

METHODS

Study population

All patients who underwent surgical closure of secundum (ASD-II) or sinus venosus type ASD in our institution between 1968 and 1980 at an age <15 years were included in this study. The first follow-up study was performed in 1990, the second in 2000–2001 and the current third study in 2010–2011. Detailed information on the surgical procedure and earlier results have been published previously.[3 5] Current patient survival status was obtained from the Dutch National Population Registry. All living patients who participated in one or both of the earlier studies were approached for participation in the current study. The in-hospital cardiac examination included medical history, physical examination, standard 12-lead ECG, 24-h ambulatory ECG (Holter), echocardiography, bicycle ergometry with oxygen consumption measurement, N-terminal prohormone of brain natriuretic hormone (NT-pro-BNP), cardiac MRI (CMR) and the 36-item Short Form Health Survey (SF-36) questionnaire. If the patient was unwilling or unable to visit the clinic, a written questionnaire was sent to obtain information on morbidity and permission to use available information from their medical records.

Major events

Survival was compared with that of the normal age-matched Dutch population. Major events were defined as cardiac reinterventions, stroke, symptomatic arrhythmia, heart failure or endocarditis. Arrhythmias were defined as symptomatic if antiarrhythmic medication was prescribed, cardioversion or catheter based or surgical ablation had been applied, or pacemaker implantation was performed.

ECG and Holter monitoring

Standard 12-lead surface ECGs and Holter recordings were analysed as described previously.[3] ECGs with pacemaker rhythm were excluded for comparison of conduction times. Heart rate variability (HRV) was compared with that of 10 years earlier using the SD of all normal RR intervals (SDNN).

Echocardiography

Complete two-dimensional (2D) and colour flow Doppler imaging as well as pulsed-wave and continuous-wave Doppler echocardiography was performed using an iE33 xMATRIX X5-1 echocardiograph (Philips Medical Systems, Best, The Netherlands). All up-to-date techniques and definitions were used following the current guidelines.[9–15] For right ventricular (RV) function the following parameters were used: fractional area change (FAC) (normal if ≥35%), S' of the tricuspid annulus (normal if ≥10 cm/s) and tricuspid annular plane systolic excursion (TAPSE) (normal if ≥16 mm). For left ventricular (LV) function, 2D ejection fraction (EF) according to the Simpson rule was obtained. For comparison with the two previous studies, ventricular function was also assessed visually. Dilation was defined as left atrial (LA) dimension >45 mm and LV enddiastolic dimension >58 mm.[3 5]

Bicycle ergometry

Maximal exercise capacity and maximal oxygen consumption (VO_2max) were assessed by bicycle ergometry with gradual increments of workload of 20 Watts/min. Exercise capacity and peak VO_2 were compared with that of normal individuals corrected for age, gender, body height and weight. Exercise capacity and peak VO_2 <85% of the predicted value were considered to be decreased. Performance was considered maximal when a respiratory quotient (RER) of ≥1.1 was reached.

NT-pro-BNP

After a 30 min rest, venous blood samples were collected for determination of NT-pro-BNP. Standard kits to determine NT-pro-BNP levels were used (Roche Diagnostics, Basel, Switzerland) with a cut-off value for elevation of 14 pmol/L.[16]

CMR imaging

CMR imaging was performed using a Signa 1.5 Tesla whole body scanner (General Electric Medical Systems, Milwaukee, Wisconsin, USA) using dedicated phased-array cardiac surface coils. Details of the MR sequence used have been reported previously.[17] For CMR analysis, a commercially available Advanced Windows workstation (GE Medical Systems) was used, equipped with Q-mass (V.5.2, Medis Medical Imaging Systems, Leiden, The Netherlands). The ventricular volumetric data set was quantitatively analysed using manual outlining of endocardial borders in end-systole and end-diastole. Biventricular end-diastolic volume (EDV), end-systolic volume (ESV), SV, EF and the regurgitation fractions of the valves were calculated. The results were compared with reported normal values: RVEF ≤49% and LVEF ≤54% were considered decreased and RV EDV >107.5 mL/m^2, RV ESV >47.2 mL/m^2, LV EDV >102.5 mL/m^2 and LV ESV >38.7 mL/m^2 were considered enlarged.[18]

Health status assessment and family history

The results of the SF-36 questionnaire were compared with those in the normal Dutch population.[19] Patients were also asked for the presence of a congenital heart defect in one of their first- or second-degree relatives.

Statistical analysis

Continuous data are presented as mean±SD unless indicated otherwise. Categorical variables are represented by frequencies and percentages. Comparison of continuous variables between independent groups was made by Student t tests. In the case of a skewed distribution in paired groups, the Wilcoxon signed rank test was performed. When comparing frequencies, the χ^2 test or Fisher exact test was used where applicable, and for paired categorical data the McNemar test. For quantifying associations between two variables the Pearson correlation test was applied. Univariate and multivariate analysis of predictors of survival and major events was performed with the Cox proportional hazards model. A priori the following variables were selected: age at operation, ASD subtype, preoperative shunt size, cardiopulmonary bypass time and postoperative arrhythmia. HRV in 2001 was tested as a predictor for arrhythmias thereafter. The probability of survival and event-free survival over time was displayed as a Kaplan–Meier plot. The level of significance was chosen at $p<0.05$ (two-sided).

RESULTS

Survival

Information on survival status was obtained in 131 of the 135 patients. Four patients were lost to follow-up before 2001. During the total follow-up period, five patients died (4%). Two patients (both ASD-II) were found dead in bed 28 and 36 years after surgery. In neither of the patients was an autopsy performed. One of them had complained of palpitations 2 weeks before he died but he had not consulted a physician. The other was known to have diminished LV function attributed to longstanding RV pacing. Both patients had no risk factors for coronary disease. The other three patients died from non-cardiac causes (cancer in two, suicide in one). Cumulative survival after ASD surgery was 100% after 10 and 20 years, 98% after 30 years and 91% after 40 years (figure 1). This is comparable to the normal Dutch population.[20] Survival in the ASD-II and sinus venosus subgroups was not significantly different.

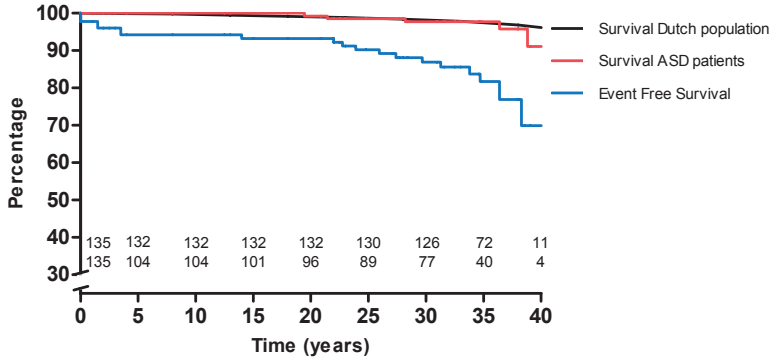


Figure 1. Survival and survival free of major events (defined as reoperation, arrhythmia, heart failure, endocarditis, pacemaker implantation, hospitalisation and death). All-cause mortality, n=5; cardiac surgery, n=2; stroke, n=1; symptomatic arrhythmia, n=16.
Survival of the normal population is shown from the age of 7.5 years, the mean age at operation of the cohort. ASD, atrial septal defect.

Study population

The original study cohort consisted of 135 patients (105 ASD-II and 30 sinus venosus type). Table 1 demonstrates their characteristics. Age at operation was 7.5±3.5 years (range 0–14). There was no in-hospital or early mortality. Of the 105 eligible patients (alive and participating in the earlier studies), 85 (81%) agreed to participate in the third follow-up study after a mean follow-up of 35 years (range 30–41). Of the 21 patients with sinus venosus defect, 19 had an anomalous pulmonary venous drainage; one patient had a persistent left superior caval vein.

Table 1. Patient characteristics

	Total	1990	2001	2011
Number of patients	135	104	94	85
Male	59 (44%)	44 (42%)	39 (41%)	33 (39%)
Cardiac catheterization at diagnosis				
QP-QS ratio	2.3:1	2.3:1	2.3:1	2.3 ± 0.7
Peak systolic PA pressure	26	26	26	26 ± 7
Surgical data				
Age at operation	7.5±3.5	7.3	7.5	7.4 ± 3.5
Mode of closure				
Direct closure	76%	75%	75%	72%
Closure with patch	24%	25%	25%	28%
Sinus venosus type ASD	22%	22%	23%	25%
Follow-up since surgery		15 (10-22)	26 (21-33)	35 ± 2.7 (30-41)
Age at the time of study		22	33	43 ± 4.8 (32-54)

Major events

Event-free survival is plotted in figure 1.

Reinterventions

Before 2001 one additional operation was performed for closure of a patent arterial duct. Between 2001 and 2011, one cardiac reoperation was necessary for symptomatic mitral valve regurgitation. Both operations were in patients with ASD-II.

Arrhythmia

Until 2001, 10 patients had symptomatic arrhythmias and, in the last 10 years, six additional patients developed symptomatic arrhythmias. One showed frequent symptomatic sinus arrests necessitating permanent pacemaker implantation. Three were treated medically for atrial flutter (n=1) or atrial fibrillation (n=2), one needed electrical cardioversion for atrial flutter and afterwards underwent catheter ablation and one patient was treated medically for supraventricular tachycardia (SVT). During the total follow-up period 16% of the patients developed symptomatic arrhythmias.

Heart failure

None of the patients developed heart failure.

Stroke

An ischaemic stroke occurred in one patient with sinus venosus type ASD. No evidence of residual shunt or arrhythmia was found.

ECG and Holter monitoring

Twelve-lead ECG data are presented in table 2. Atrial flutter was found in two patients, of whom one was new. The QRS duration increased significantly during the last 10 years, but only one new case of right bundle branch block was found. On the 24-h Holter no sustained ventricular tachycardia (VT) was found in 1990, 2001 or 2011 (table 2). There was a trend towards more supraventricular arrhythmias over time. Atrioventricular (AV) conduction disturbances were observed in nine patients.

Table 2. Standard 12-lead electrocardiogram, 24-h Holter, bicycle ergometry and echocardiographic parameters comparing 1990, 2001 and 2011.

				P-value*	
	1990	**2001**	**2011**	**2011 vs 1990**	**2011 vs 2001**
ECG					
Rhythm					
Sinus	93 (89%)	82 (89%)	63 (89%)	0.6	1.0
Atrial	6 (6%)	5 (5%)	3 (4%)	-	1.0
Nodal	1 (1%)	1 (1%)	0	-	-
Atrial flutter	0	1 (1%)	2 (3%)	-	1.0
Pacemaker	4 (4%)	3 (3%)	3 (4%)	0.5	1.0
PR interval	153.7	153.2	161.0	**0.002**	**<0.0001**
PR > 200 ms	3%	5%	9%	-	0.06
QRS duration	88.3	96.1	100.4	**<0.0001**	**0.001**
QTc segment	388	388	400	**<0.0001**	**<0.0001**
LVH or RVH	4.1%	4.6%	1.4%	1.0	1.0
24-hour Holter					
Supraventricular arrhythmias	44 (45%)	36 (41%)	39 (57%)	0.2	0.6
Sinus node disease	38 (39%)	27 (31%)	16 (24%)	0.3	0.5
SVT	6 (6%)	18 (21%)	30 (44%)	**<0.0001**	0.06
Paroxysmal A fibrillation	0	0	0	-	-
Paroxysmal A flutter	0	1 (1%)	0	-	-
Continuous A flutter	0	1 (1%)	1 (2%)	-	1.0
VT 3-10 complex	3 (3%)	4 (5%)	4 (6%)	1.0	1.0
VT > 10 complex	0	0	0	-	-
Conduction disturbances	17 (17%)	8 (9%)	10 (15%)	1.0	0.2
First degree AV block	14 (14%)	8 (9%)	7 (10%)	0.8	0.7
Second AV block	2 (2%)	0	2 (3%)	1.0	-
Third AV block	0	0	0	-	-
Bicycle ergometry					
Maximum heart rate (% of expected)	92%	92%	90%	0.6	0.5
Maximum exercise capacity (% of expected)	104%	95%	96%		-
Significant arrhythmia	0	0	0		-
VO2 max (% of expected)	-	-	96%		-
RER max	-	-	1.3		-

Table 2. (continued)

				P-value*	
	1990	**2001**	**2011**	**2011 vs 1990**	**2011 vs 2001**
Echocardiography					
RA dilatation	5.8%	18.7%	23.5%	0.007	0.8
RV dilatation	26.0%	23.5%	34.3%	0.2	0.5
LA dilatation	1.0%	12.2%	15.7%	0.008	0.7
LV dilatation	4.0%	8.8%	2.9%	1.0	0.1
LV systolic function normal	97.1%	95.5%	95.5%	0.6	1.0
RV systolic function normal	100%	100%	67.2%	-	**<0.0001**
Valve insufficiency (>trace)					
AoI	0%	1.1%	2.9%	-	-
MI	11.5%	13.5%	20.0%	0.8	0.1
PI	44.2%	45.0%	55.7%	**<0.02**	**<0.02**
TI	42.3%	48.3%	57.1%	1.0	0.7
Vmax PI	1.6 m/s	1.5 m/s	1.7 m/s	0.7	0.8
Vmax TI	2.1 m/s	2.2 m/s	2.3 m/s	**0.03**	**0.03**

LVH = left ventricular hypertrophy; RVH = right ventricular hypertrophy; SVT = supraventricular tachycardia; VT = ventricular tachycardia; AV = atrioventricular; RA = right atrium; RV = right ventricle; LA = left atrium; LV = left ventricle; AoI = aortic insufficiency; MI = mitral insufficiency; PI = pulmonary insufficiency; TI = tricuspid insufficiency; Vmax = maximal velocity found with Doppler echocardiography; RER = respiratory exchange ratio; VO2 max was not performed in 1990/2001

*Because of incomplete follow-up (paired) data, not all *P*-values are displayed.

Heart rate variability

The mean SD of all normal RR intervals (SDNN) was 166.7±57.9 ms in 2001 and 143.4±42.0 ms in 2011 (p=0.2). There was no difference in HRV between patients with ASD-II and sinus venosus types.

Echocardiography

Echocardiographic findings are summarised in tables 2 and 3. No residual shunts were found. A normal diastolic LV function was observed in 88% of patients, mild abnormal relaxation in 9% and pseudonormal diastolic filling in 3%. TAPSE was decreased in 22% of the patients, FAC was reduced in 10% and S' was diminished in 43%. Comparing patients with ASD-II and sinus venosus defects, there were no significant differences except that S' and TAPSE were significantly lower in patients with sinus venosus type whereas RV FAC was higher.

Bicycle ergometry

The results of exercise testing in 1990, 2001 and 2011 are listed in table 2. Eighteen patients (27%) had a diminished exercise capacity at last follow-up. Mean peak VO_2 was 96±25% (range 60–194%). One-third had a mean peak VO_2 of <85%, one-third 85–100%

Table 3. Echocardiographic parameters 2011

	ASD-II	Sinus venosus defect	P-value
Left ventricle			
E/A-ratio	1.3 ± 0.4	1.3 ± 0.4	0.99
E/E'-ratio	8.4 ± 5.0	8.5 ± 3.4	0.95
DET (ms)	226 ± 46	224 ± 49	0.94
LVEF Simpson (%)	56 ± 5	57 ± 9	0.56
Right ventricle			
TAPSE (mm)	19 ± 4	16 ± 2	**< 0.01**
RV pressure (mmHg)	27 ± 5	26 ± 4	0.60.
FAC (%)	43 ± 9	53 ± 7	**< 0.01**
S' (mm)	11 ± 2	9 ± 2	**< 0.01**

E/A ratio = ratio early filling velocity on transmitral Doppler-late filling; E/E' ratio = ratio early filling velocity on transmitral Doppler-early relaxation velocity on tissue Doppler; DET = deceleration time; LVEF Simpson = left ventricular ejection fraction according to modified Simpson rule; TAPSE = tricuspid annular plane systolic excursion; FAC = fractional area change of right ventricle; S' = tricuspid annulus maximal systolic tissue Doppler velocity.

and one-third performed >100%. The threshold RER of 1.1 was reached in 97%. Patients with reduced exercise capacity or peak VO_2 did not differ significantly from those with a normal test result with regard to preoperative shunt size, age at the time of operation or findings by echocardiography or CMR (dimensions and ventricular function). There were no significant differences between patients with ASD-II and sinus venosus defects but there was a trend towards a better workload in the patients with sinus venosus type ASD (p=0.07).

NT-pro-BNP

An increased NT-pro-BNP level (>14.0 pmol/L) was present in 53% of the patients. Values varied from 1.5 to 116 pmol/L with a mean of 15.0 pmol/L. No correlation between NT-pro-BNP and age, age at surgery, ASD type or LV and RV dimensions or function was found.

CMR imaging

CMR was performed in 57 patients. Reasons for not having a CMR investigation were patients' refusal, prematurely ended because of claustrophobia and two patients had a pacemaker. One study could not be analysed due to technical problems. The results of CMR are summarised in table 4. There were no differences in mean ventricular volumes or EFs between patients with ASD-II and sinus venosus type defects. However, there was a trend towards more dilated RV volumes in the sinus venosus group (dilated ESV in 57% vs 27%, p=0.054).

Table 4. Cardiac Magnetic Resonance Imaging

	ASD II	Sinus venosus defect	P-value
LV EDV/BSA, mean (mL/m2) ± SD (range)	80 ± 15	83 ± 16	0.6
LV EDV dilatation	5%	14%	0.3
LV ESV/BSA	33 ± 10	36 ± 11	0.4
LV ESV dilatation	24%	43%	0.2
LV EF (%)	59 ± 7	57 ± 8	0.4
LV EF decreased	17%	29%	0.4
RV EDV/BSA	92 ± 15	96 ± 16	0.4
RV EDV dilatation	17 %	29%	0.4
RV ESV/BSA	44 ± 10	48 ± 11	0.2
RV ESV dilatation	27%	57%	**0.05**
RV EF (%)	52 ± 6	50 ± 7	0.2
RV EF decreased	24%	50%	0.1

A RV EF ≤ 49% and LV EF ≤ 54% were considered decreased and a RV EDV >107.5 mL/m^2, a RV ESV > 47.2 mL/m^2, a LV EDV >102.5 mL/m^2 and a LV ESV > 38.7 mL/m^2 were considered enlarged.
BSA = body surface area; EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; LV = left ventricle; RV = right ventricle.

Health status assessment and family history

The mean scores on the SF-36 survey for the patients and the normal population are shown in figure 2. Having had an event did not adversely affect SF-36 scores. A self-reported family history of congenital heart disease was found in 23% of patients (n=16); of these, 56% were in first degree relatives. The majority of family members also had an ASD (n=8). Other defects were a ventricular septal defect (n=3), patent ductus arteriosus (n=2), univentricular heart (n=1) and valvular heart disease (n=2). Some had more than one defect. Information on genetic testing was not recorded.

Predictors for late events

Univariate analysis identified only the occurrence of arrhythmias in the early postoperative period as a predictor for the need for permanent pacing during follow-up (HR=16 (95% CI 3 to 70); p<0.0001). Multivariate analysis was not performed because the number of events was too low.

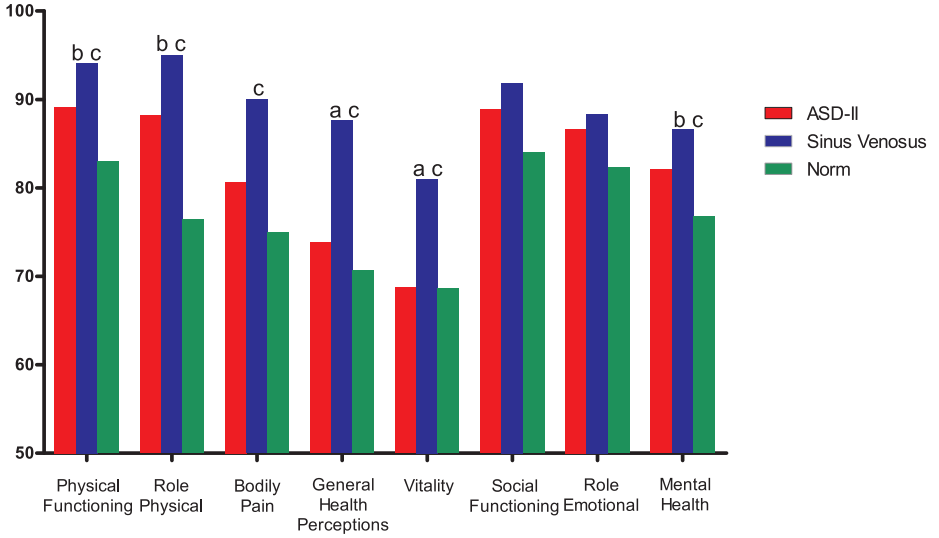


Figure 2. Results of the Short Form Health Survey questionnaire for patients with both types of atrial septal defect (ASD) and the normal Dutch population. a=significant
difference between patients with ASD-II and sinus venosus type ASD; b=significant difference between patients with ASD-II and the normal Dutch population; c=significant
difference between patients with sinus venosus type ASD and the normal Dutch population. Higher scores reflect higher levels of functioning or well-being.

DISCUSSION

In this cohort of patients who underwent surgical closure of a haemodynamically significant ASD 30–41 years ago we found very good survival, no pulmonary hypertension, good exercise performance and a low incidence of supraventricular arrhythmias. Total survival was comparable to the normal Dutch population. However, two patients in the ASD-II group suffered from sudden death in the last decade, at the age of 36 and 40 years. In these patients arrhythmia as the cause of death cannot be excluded and is even very likely in one. Signs of pulmonary hypertension, a major problem that may occur in patients without closure of the ASD,[1 21] were not found. In addition, the clinical condition of the patients appeared excellent with normal exercise capacity in most patients. Neither heart failure nor residual shunts were observed. One patient developed an ischaemic stroke but a clear relation to the heart defect could not be found. However, 6% of patients required pacemaker implantation during total follow-up.

Arrhythmias

Of the 41% (n=36) of patients with some form of asymptomatic atrial arrhythmia on Holter recording 10 years ago,[3] 8% had developed new symptomatic arrhythmias in the

past 10 years. This was comparable to the incidence in patients with a negative Holter recording in 2001. Thus, the predictive value of the asymptomatic arrhythmias seen on Holter monitoring seems limited. The prevalence of atrial fibrillation in our patients (12%) is higher than in the general population (<0.5%)[22] but substantially lower than that reported in natural history studies of patients with ASD (up to 50%) and after surgical closure at adult age.[1 4 6 7 21 23] This indicates that early closure is beneficial in the very long term. Surgical scars do not seem to induce atrial flutters on a large scale. The lower incidence of atrial fibrillation appears to be related to earlier termination of the left-to-right shunt, thereby preventing right-sided pressure overload and further right atrium dilation which would have increased the vulnerability to atrial arrhythmias.[7 24] Whether device ASD closure will also prevent the occurrence of SVTs in the long term or will make patients prone to arrhythmias by direct stretching of the atrial septum or circular scar formation around the device remains to be established.

Ventricular dimensions, function and pressure

On echocardiography we found a mildly impaired RV function in one-third of our patients. This is somewhat unexpected as RV function was normal in all patients 10 years ago. This finding may be due to advances in the assessment of RV function as nowadays we use more sophisticated parameters than the mere visual assessment which was the only available method used in our earlier studies. We found no association between RV function and changes in QRS duration. The findings of FAC and S' wave as well as the CMR results confirm abnormal RV function in a quarter of our patients. CMR was not performed in our earlier studies but RV dilation has also been described by others after shorter follow-up. De Koning et al[25] described this in younger patients who had their surgical correction in a more recent era. In contrast to others and our results, no RV dilation on CMR was reported by Bolz et al even though the same normal values were applied and the mean age at operation is comparable (6.5 vs 7.6 years).[26–28] However, their follow-up period was shorter. Mild LV function impairment was found in one-fifth of our patients on CMR. This might be a result of the preoperative volume overload due to ventricular interaction. Literature on LV function after surgical ASD repair is lacking, but there are some reports of improvements of LV systolic function after transcatheter ASD closure.[29 30]

ASD-II versus sinus venosus type ASD

We did not find any significant difference in survival, occurrence of events, incidence of arrhythmias, ECG (QRS duration) and Holter-ECG or exercise capacity between patients undergoing surgery for ASD-II and sinus venosus defects. However, TAPSE and S' were slightly reduced on echocardiography in patients with sinus venosus defects. On the other hand, RV FAC was higher in this group. Integrating all these results, patients with

a sinus venosus defect may have a worse longitudinal RV function with probably a compensatory preserved circumferential function. New studies with larger patient groups are needed to confirm these findings.

Predictors for late events

The occurrence of arrhythmias in the early postoperative period showed a strong relation with the need for permanent pacing during early follow-up. Most pacemakers had been implanted in the early years after surgery, most are probably related to surgical damage to the conduction system for two of the three patients (66%) requiring pacemaker implantation within 4 years after surgery had a bradycardia as their postoperative arrhythmia. However, two patients needed a pacemaker for AV block very late after surgery. This is an unexpected finding for which we do not have a clear explanation. We were not able to identify any other predictors for mortality, late events or ventricular dysfunction.

Study limitations

As in most studies in this field, the numbers are relatively low and therefore all results should be interpreted with caution. The number of patients lost to follow-up was limited with regard to information on survival status, but is larger considering study participation: only 65% of the survivors of the total cohort participated in the last follow-up. The patients considered ineligible for participation were either lost to follow-up, had moved far abroad or did not participate in the previous studies. We believe, however, that after a follow-up of almost 40 years, participation of 80% of eligible patients is very acceptable and can be regarded as a representative sample.

CONCLUSIONS

Very long-term (30–41 years) outcome after surgical ASD closure in childhood shows excellent survival and low morbidity, although two sudden unexplained deaths occurred at 28 and 36 years after surgery. No pulmonary hypertension and a low incidence of supraventricular arrhythmias were found. The general health and exercise capacity of the patients are excellent and comparable with the normal Dutch population. Persistent RV dilation, which was observed in our earlier follow-up studies in this cohort of patients, was confirmed by CMR. Although EFs of both RV and LV are unexpectedly decreased and RV volumes remain enlarged in some of the patients, their clinical condition remains sound.

REFERENCES

1 Murphy JG, Gersh BJ, McGoon MD, et al. Long-term outcome after surgical repair of isolated atrial septal defect. Follow-up at 27 to 32 years. *N Engl J Med* 1990;323:1645–50.

2 Nieminen HP, Jokinen EV, Sairanen HI. Late results of pediatric cardiac surgery in Finland: a population-based study with 96% follow-up. *Circulation* 2001;104:570–5.

3 Roos-Hesselink JW, Meijboom FJ, Spitaels SE, et al. Excellent survival and low incidence of arrhythmias, stroke and heart failure long-term after surgical ASD closure at young age. A prospective follow-up study of 21–33 years. *Eur Heart J* 2003;24:190–7.

4 Shah D, Azhar M, Oakley CM, et al. Natural history of secundum atrial septal defect in adults after medical or surgical treatment: a historical prospective study. *Br Heart J* 1994;71:224–7; discussion 8.

5 Meijboom F, Hess J, Szatmari A, et al. Long-term follow-up (9 to 20 years) after surgical closure of atrial septal defect at a young age. *Am J Cardiol* 1993;72:1431–4.

6 Konstantinides S, Geibel A, Olschewski M, et al. A comparison of surgical and medical therapy for atrial septal defect in adults. *N Engl J Med* 1995;333:469–73.

7 Gatzoulis MA, Freeman MA, Siu SC, et al. Atrial arrhythmia after surgical closure of atrial septal defects in adults. *N Engl J Med* 1999;340:839–46.

8 Ueda H, Yanagi S, Nakamura H, et al. Device closure of atrial septal defect: immediate and mid-term results. *Circ J* 2012;76:1229–34.

9 Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr* 2009;22:1–23; quiz 101–2.

10 Lancellotti P, Tribouilloy C, Hagendorff A, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 1: aortic and pulmonary regurgitation (native valve disease). *Eur J Echocardiogr* 2010;11:223–44.

11 Lancellotti P, Moura L, Pierard LA, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr* 2010;11:307–32.

12 Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006;7:79–108.

13 Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 2009;10:165–93.

14 Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;23:685–713; quiz 86–8.

15 Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009;30:2493–537.

16 Hildebrandt P, Collinson PO. Amino-terminal pro-B-type natriuretic peptide testing to assist the diagnostic evaluation of heart failure in symptomatic primary care patients. *Am J Cardiol* 2008;101:25–8.

17 van den Berg J, Hop WC, Strengers JL, et al. Clinical condition at mid-to-late follow-up after transatrial-transpulmonary repair of tetralogy of Fallot. *J Thorac Cardiovasc Surg* 2007;133:470–7.

18 Rominger MB, Bachmann GF, Pabst W, et al. Right ventricular volumes and ejection fraction with fast cine MR imaging in breath-hold technique: applicability, normal values from 52 volunteers, and evaluation of 325 adult cardiac patients. *J Magn Reson Imaging* 1999;10:908–18.

19 Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51:1055–68.

20 (CBS) NCBoS. Continuous quality of life survey of the Dutch population. The Hague/ Heerlen: Sdu Publisher, 2010.

21 Craig RJ, Selzer A. Natural history and prognosis of atrial septal defect. *Circulation* 1968;37:805–15.

22 Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;285:2370–5.

23 Berger F, Vogel M, Kramer A, et al. Incidence of atrial flutter/fibrillation in adults with atrial septal defect before and after surgery. *Ann Thorac Surg* 1999; 68:75–8.

24 Warnes CA. The adult with congenital heart disease: born to be bad?. *J Am Coll Cardiol* 2005;46:1–8.

25 de Koning WB, van Osch-Gevers LM, Robbers-Visser D, et al. Enlarged right ventricular size at 11 years' follow-up after closure of secundum-type atrial septal defect in children. *Cardiol Young* 2013;23:7–13.

26 Bolz D, Lacina T, Buser P, et al. Long-term outcome after surgical closure of atrial septal defect in childhood with extensive assessment including MRI measurement of the ventricles. *Pediatr Cardiol* 2005;26:614–21.

27 Kort HW, Balzer DT, Johnson MC. Resolution of right heart enlargement after closure of secundum atrial septal defect with transcatheter technique. *J Am Coll Cardiol* 2001;38:1528–32.

28 Meyer RA, Korfhagen JC, Covitz W, et al. Long-term follow-up study after closure of secundum atrial septal defect in children: an echocardiographic study. *Am J Cardiol* 1982;50:143–8.

29 Dong L, Zhang F, Shu X, et al. Left ventricular torsion in patients with secundum atrial septal defect. *Circ J* 2009;73:1308–14.

30 Lim DS, Gutgesell HP, Rocchini AP. Left ventricular function by pressure-volume loop analysis before and after percutaneous repair of large atrial septal defects. *J Interv Cardiol* 2008.

3

The unnatural history of the ventricular septal defect: outcome up to 40 years after surgical closure

Myrthe E. Menting, MD, Judith A.A.E. Cuypers, MD, Petra Opić, MSC, Elisabeth M.W.J. Utens, PHD, Maarten Witsenburg, MD, PHD, Annemien E. van den Bosch, MD, PHD, Ron T. van Domburg, PHD, Folkert J. Meijboom, MD, PHD, Eric Boersma, PHD, Ad J.J.C. Bogers, MD, PHD, Jolien W. Roos-Hesselink, M, PHD

Journal of the American College of Cardiology 2015;65:1941–51

ABSTRACT

Background

Few prospective data are available regarding long-term outcomes after surgical closure of a ventricular septal defect (VSD).

Objectives

The objective of this study was to investigate clinical outcomes >30 years after surgical VSD closure.

Methods

Patients who underwent surgical VSD closure during childhood between 1968 and 1980 were reexamined every 10 years. In 2012, we invited eligible patients to undergo another examination, which included electrocardiography, Holter monitoring, echocardiography, bicycle ergometry, measurement of N-terminal pro–B-type natriuretic peptide, and subjective health assessment.

Results

Cumulative survival was 86% at 40 years. Causes of mortality were arrhythmia, heart failure, endocarditis, during valvular surgery, pulmonary hypertension, noncardiac causes, and unknown causes. Cumulative event-free survival after surgery was 72% at 40 years. Symptomatic arrhythmias occurred in 13% of patients and surgical or catheter-based reinterventions in 12%. Prevalence of impaired right ventricular systolic function increased from 1% in 2001 to 17% in 2012 ($p = 0.001$). Left ventricular systolic function was impaired but stable in 21% of patients. Aortic regurgitation occurred more often in the last 20 years ($p = 0.039$), and mean exercise capacity decreased ($p = 0.003$). N-terminal pro–B-type natriuretic peptide (median: 11.6 pmol/l [interquartile range: 7.0 to 19.8 pmol/l]) was elevated (>14 pmol/l) in 38% of patients. A concomitant cardiac lesion, for example patent ductus arteriosus, and aortic cross-clamp time were determinants of late events (hazard ratio: 2.84 [95% confidence interval: 1.23 to 6.53] and hazard ratio: 1.47 per 10 min [95% confidence interval: 1.22 to 1.99], respectively). Patients rated their subjective health status significantly better than a reference population.

Conclusions

Survival up to 40 years after successful surgical VSD closure is slightly lower than in the general Dutch population. Morbidity is not negligible, especially in patients with a concomitant cardiac lesion.

INTRODUCTION

Ventricular septal defect (VSD) is by far the most common congenital heart defect, with a birth prevalence of 2.62 per 1,000 live births.[1,2] Small defects may not have hemodynamic consequences, but the presence of a significant left-to-right shunt can cause left ventricular (LV) overload, pulmonary arterial hypertension, ventricular dysfunction, arrhythmias, and aortic regurgitation.[3,4] Surgical closure at a young age is still the treatment of choice, and mid- to long-term results are good with regard to survival, morbidity, and quality of life.[5-7] Therefore, most such patients have been discharged from routine cardiological follow-up. For both patients and their treating physicians, it is essential to know whether the pre-operative left-to-right shunt and the VSD patch affect biventricular function or the conduction system in the long term. However, information on mortality and morbidity beyond 30 years after surgical VSD closure is scarce, and almost all such data were collected retrospectively, which introduces the possible bias of including only patients with residual morbidity who are still seen at outpatient clinics. Our study is part of a unique, ongoing longitudinal follow-up of patients with congenital heart defects who underwent surgery at a young age at our institution between 1968 and 1980. The current study had 3 objectives: first, to evaluate survival 30 to 40 years after surgical VSD closure in an unselected cohort; second, to investigate the current clinical condition of survivors by extensive in-hospital examination and to detect determinants of outcome; and third, to evaluate the present subjective health status of survivors.

METHODS

Study patients

All consecutive patients who underwent surgical VSD closure at our institution between 1968 and 1980 at <15 years of age formed the original study cohort. This cohort was first studied in 1990, with a second follow-up performed in 200.[5,6] In 2010 to 2012, survival status was obtained from the Dutch National Population Registry, and all surviving patients who had participated in 1 or both of the previous studies were actively invited to participate in a third study for clinical examination at the outpatient clinic of Erasmus Medical Center. The study protocol was approved by the institutional Medical Ethics Committee. Written informed consent was obtained from all participants.

Adverse events

Survival rates were compared with the expected survival rates of an age-matched Dutch population. Adverse events included all-cause mortality, surgical or catheter-based cardiac reinterventions, symptomatic arrhythmias (requiring medication, cardioversion,

ablation, or insertion of a pacemaker/implantable cardioverter-defibrillator [ICD]), endocarditis, and heart failure (requiring medication or hospital admission). Mortality and events were defined as "early" when they occurred within 30 days post-operatively and "late" when they occurred beyond 30 days. All events were assessed by 2 independent investigators (M.E.M., J.A.A.E.C.).

Clinical assessment

Examinations included history, physical examination, standard 12-lead electrocardiography (ECG), 24-h Holter monitoring, echocardiography, cardiopulmonary exercise testing, and N-terminal pro–B-type natriuretic peptide (NTproBNP) measurement. If a patient was unwilling or unable to visit the outpatient clinic, questionnaires were sent to obtain information on morbidity and subjective health status and to receive permission to use the patient's medical records.

Electrocardiography and 24-h Holter monitoring

Standard 12-lead surface ECGs were analyzed for rhythm, PR interval, and QRS duration. A 24-h Holter monitoring was performed with a CardioPerfect Holter DR180þ 3-channel recorder (Welch Allyn Cardio Control, NorthEast Monitoring, Maynard, Massachusetts). Sinus node disease (SND) was defined according to the Kugler criteria: nodal escape rhythm, sinus arrest >3 s, or severe sinus bradycardia (<30 beats/min at night or <40 beats/min during daytime).[8]

Cardiopulmonary exercise testing

Maximal workload, heart rate, and peak oxygen consumption (peak VO_2) were assessed by bicycle ergometry with a gradual workload increment of 20 W/min (ramp protocol) and compared with normative values corrected for age, sex, height, and weight. Performance was considered maximal when a respiratory exchange ratio >1 was reached.

Echocardiography

A complete 2-dimensional transthoracic echocardiogram was performed with the commercially available IE33 system (Philips Medical Systems, Best, the Netherlands). Cardiac dimensions, ventricular function, and valvular function were measured according to published guidelines.[9-12] LV and right ventricular (RV) systolic function were assessed visually to enable comparison with the 2 previous studies. Systolic function was graded as normal or mildly, moderately, or severely impaired. Additionally, more objective measurements, including LV ejection fraction (Simpson's method), RV fractional area change, and tricuspid annulus plane systolic excursion, were used to quantify systolic ventricular function. Measurements were obtained by 2 independent observers (M.E.M., J.A.A.E.C.).

NT-proBNP measurement

Peripheral venous blood samples were collected after 30 minutes of rest. Plasma NT-proBNP levels were determined with use of the commercially available electrochemiluminescence immunoassay Elecsys (Roche Diagnostics, Basel, Switzerland). The normal value in our hospital is <14 pmol/l.

Subjective health assessment

The 36-item short-form health survey (SF-36) was completed to assess subjective health status. Results for the patients were compared with their results from 10 years earlier and with normative data from the general Dutch population.[13]

Statistical analysis

Continuous data are presented as mean SD or median with interquartile range (IQR) depending on the data distribution. Categorical data are presented as frequencies and percentages. Changes in patient characteristics since the follow-up study in 1990 and 2001 were evaluated by estimating a trend by use of mixed models, which take missing values into account. Changes in characteristics between 2001 and 2012 were analyzed by paired Student t tests. Differences between independent subgroups were evaluated by unpaired Student t tests or Mann-Whitney U tests (continuous data) and by chi-square test or Fisher exact test (categorical data). To quantify correlations between 2 variables, the Spearman correlation test was used. Cumulative survival and event-free survival for all patients and for patients with successful VSD surgery (i.e., excluding early post-operative mortality) were determined by the Kaplan-Meier method. We compared the cumulative survival of isolated and nonisolated VSD patients by the log-rank test. Cumulative event incidences were computed with the use of a nonparametric estimator of cumulative incidence functions, with death as a competing risk. Univariable and multivariable Cox regression analyses were used to identify determinants of pre-defined adverse events: all-cause mortality, arrhythmias, reinterventions, heart failure, and endocarditis. The mixed models were estimated by use of SAS software (version 9.3, SAS Institute, Inc., Cary, North Carolina). The cumulative incidence functions were estimated with R (version 3.1.1, R Foundation for Statistical Computing, Wien, Austria). All other statistical analyses were performed with the Statistical Package for Social Sciences (version 21, SPSS Inc., Chicago, Illinois). The statistical tests were 2-sided, and $p < 0.05$ was considered statistically significant. Further information on statistical analysis can be found in the Online Appendix.

RESULTS

Study patients

The original study cohort consisted of 174 consecutive patients who underwent surgical VSD closure between 1968 and 1980. Figure 1 presents an overview of patient participation for the current study. Baseline characteristics, including surgical details and follow-up duration, are presented in Table 1. Further baseline and surgical details have been reported previously.[5,6] Median follow-up duration of the actively included patients was 35.8 years (IQR: 34.0 to 37.3 years; range 30.4 to 40.3 years). Of 91 patients, 70 participated in-hospital, and 21 completed the questionnaires and gave permission to use their hospital records. Twenty-seven of the 91 patients (30%) had 1 or more concomitant cardiac lesions (nonisolated VSD), including patent foramen ovale (n = 11), pulmonary stenosis (n = 10), patent arterial duct (n = 6), aortic coarctation (n = 5), atrial septal defect (n = 4, of whom 2 had partial abnormal pulmonary venous return), mitral stenosis (n = 2), and aortic stenosis (n = 1). A patent foramen ovale was included as a concomitant lesion when an intervention was performed to close it. There were no discrepancies between assessments of the 2 evaluators regarding post-surgical events.

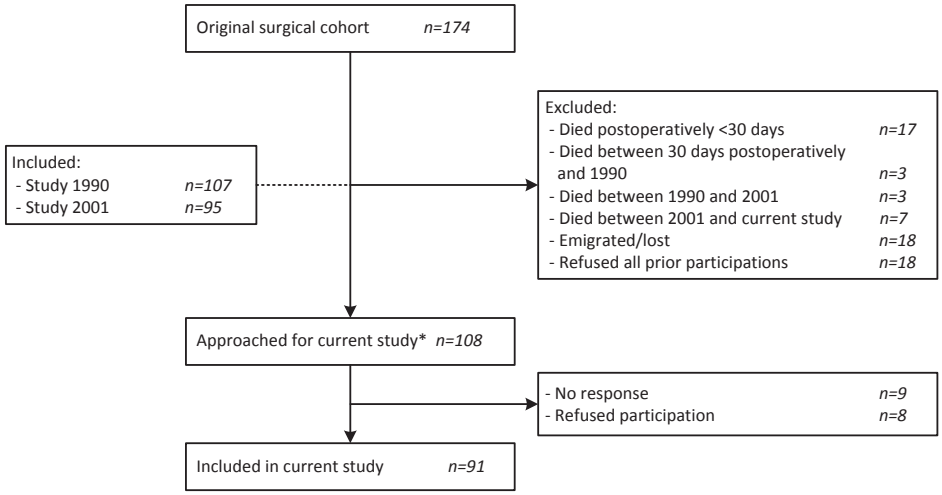


Figure 1. Flow chart of the study patients.
One patient died shortly after participation in the study. We used the in-hospital-examination results for this study, and scored him as deceased in the survival analysis. *Patients who were alive, traceable, and participated in the studies of 1990, 2001 or both.

Table 1. Baseline characteristics of the study patients.

	Total	1990	2001	2012	No third study*	P-value†
	n = 174	n = 107	n = 95	n = 91	n = 83	
Male	96 (55%)	64 (60%)	57 (60%)	56 (62%)	40 (48%)	0.077
Age at study (yrs)	-	19.2 [14.2-23.7]	29.2 [24.5-33.5]	39.6 [35.2-43.8]	-	-
Age at operation (yrs)	2.3 [0.5-6.9]	3.4 [0.6-7.1]	2.1 [0.6-6.5]	2.9 [0.5-6.5]	1.9 [0.5-7.1]	0.664
Age at operation <1 year	60 (34%)	34 (32%)	33 (35%)	30 (33%)	30 (36%)	0.660
Pre-op RV systolic pressure (mmHg)	70 [47-83]	69 [42-85]	68 [42-82]	68 [42-82]	70 [54-85]	0.371
Pre-op Qp/Qs ratio	2.0 [1.7-2.8]	2.0 [1.7-2.8]	2.0 [1.7-2.9]	2.0 [1.7-2.8]	2.1 [1.6-2.8]	0.916
Type of VSD						
Perimembranous	134 (77%)	91 (85%)	78 (82%)	74 (81%)	60 (72%)	0.157
Muscular	8 (5%)	1 (1%)	2 (2%)	2 (2%)	6 (7%)	0.154
Non-isolated VSD	56 (32%)	32 (30%)	29 (31%)	27 (30%)	30 (36%)	0.363
Previous PA banding	15 (9%)	6 (6%)	4 (4%)	6 (7%)	9 (11%)	0.318
Hypothermia during surgery						
Temperature < 20°C	70 (40)	38 (35)	37 (39)	33 (36)	37 (45)	0.285
Temperature 20-35°C	101 (58)	67 (63)	56 (59)	56 (62)	45 (54)	-
Temperature unknown	3 (2)	2 (2)	2 (2)	2 (2)	1 (1)	-
RV-incision	82 (47)	54 (50%)56 (52)	46 (48)	46 (51)	36 (43%)	0.344
VSD closure with patch	155 (89)	95 (89)	86 (91)	80 (88)	75 (90)	0.605
Post-operative arrhythmia < 30 days						
Tachyarrhythmia	10 (6)	5 (5)	4 (4)	4 (4)	6 (7)	0.522
Heart block	9 (5)	2 (2)	3 (3)	3 (3)	6 (7)	0.313
Cardiac arrest	3 (2)	-	-	-	3 (4)	-

Values are n (%) or median (interquartile range). *Including deceased and emigrated patients. †2012 vs. no third study.
PA = pulmonary artery; RV = right ventricular; VSD = ventricular septal defect

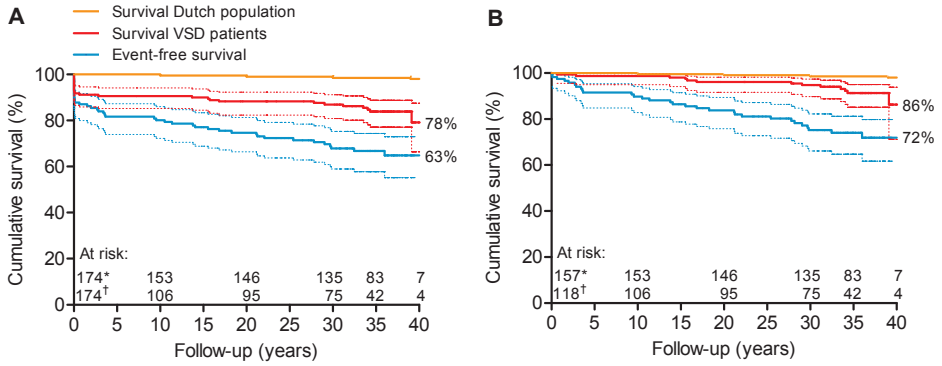


Figure 2. Cumulative Survival and Event-Free Survival of VSD Patients With and Without Early Post-Operative Mortality and Events

Kaplan-Meier curves for survival and event-free survival of patients after surgical closure of ventricular septal defect (VSD), including early mortality and events within 30 days after surgery (A), and after exclusion of early mortality and events (B). Seventeen patients died within 30 days after surgery and 14 died during follow-up of the following causes: arrhythmia (n = 4), heart failure (n = 1), endocarditis (n = 1), valvular surgery (n = 1), pulmonary hypertension (n = 1), noncardiac cause (n = 4), and unknown (n = 2). The dashed lines depict 95% confidence intervals. Survival curve of Dutch population represents survival from age 3 to 43 years. *Number of patients at risk for survival. †Number of patients at risk for event-free survival.

Survival

Information on survival was available for 156 patients (90%). Cumulative survival after surgical closure, including early post-operative mortality, was 89% at 10 years, 87% at 20 years, 85% at 30 years, and 78% at 40 years, which was significantly lower than in the general Dutch population of comparable age (Figure 2A). Thirty-one patients died, with 17 deaths occurring within 30 days of surgery. Cumulative survival after successful surgery, excluding early post-operative mortality, was 99% at 10 years, 96% at 20 years, 95% at 30 years, and 86% at 40 years, which was slightly lower than the general Dutch population (Figure 2B). Successful surgery was defined as the group without early post-operative mortality. In the last 10 years, 8 patients died. One patient died of ventricular fibrillation 34 years after surgery at 34 years of age. He had received a pacemaker for SND 20 years earlier. One patient who had developed moderate aortic stenosis had sudden death, presumably due to an arrhythmia, 39 years after surgery at the age of 49 years. One patient died of heart failure as a result of severely dilated cardiomyopathy, 28 years after surgery, at the age of 28. There were 3 noncardiac deaths, attributable to breast cancer, lung cancer, and alcohol abuse 29, 33, and 31 years after surgery, respectively. The cause of death was unknown for 2 patients, who died 34 and 42 years after surgery, respectively. Cumulative survival rates of isolated versus nonisolated VSD patients up to 39 years after surgery were comparable (93% vs. 88%) (Figure 3A).

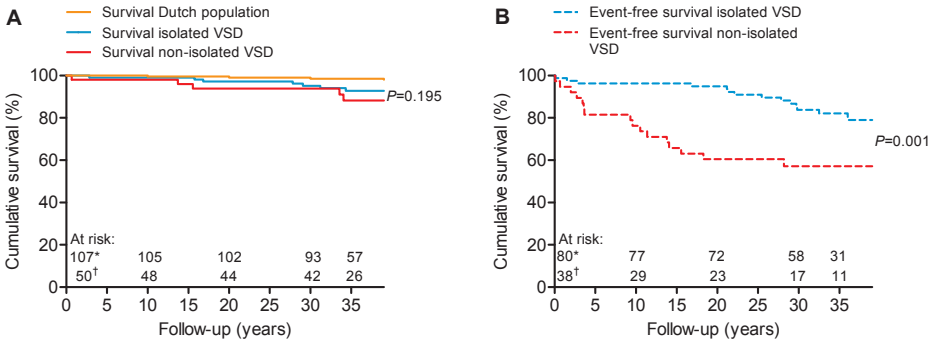


Figure 3. Cumulative Survival and Event-Free Survival of Isolated and Nonisolated VSD Patients.
Kaplan-Meier curves for survival (A) and event-free survival (B) of patients with isolated and nonisolated ventricular septal defect (VSD) (mortality, n = 7/7; cardiac reintervention, n = 2/12; arrhythmia, n = 9/3; endocarditis, n = 2/2; heart failure, n = 3/1, respectively). Patients who died <30 days after surgery are excluded from this figure. *Number of isolated VSD patients at risk. †Number of nonisolated VSD patients at risk.

Adverse events

Cumulative survival free of adverse events was 63% at 40 years (Figure 2A). When early post-operative mortality was excluded, event-free survival was 72% (Figure 2B). The event-free survival at 40 years was significantly better in isolated versus nonisolated VSD patients (79% vs. 57%, respectively) (Figure 3B).

Reinterventions

Cumulative incidence of late reinterventions at 40 years of follow-up was 12% (Figure 4B). An overview of the reinterventions is summarized in Table 2. Arrhythmias. Cumulative incidence of late symptomatic arrhythmias including pacemaker implantation at 40 years was 13% (Figure 4C). In the last decade studied, 7 patients developed new symptomatic arrhythmias: 1 patient had recurrent atrial flutter and fibrillation, treated with electrical cardioversion and catheter ablation; 1 patient who had a pacemaker for 19 years had recurrent atrial fibrillation treated with electrical cardioversion; 1 patient had atrial fibrillation treated with verapamil; and 1 patient had paroxysmal atrioventricular reentrant tachycardia. The cumulative incidence of late pacemaker implantation, including ICD in 2 patients, was 7% at 40 years. In the last decade studied, 3 pacemakers were implanted: 1 for SND, 1 for severe bradycardia, and 1 for complete heart block. The last patient received a biventricular ICD because of ventricular tachycardias and diminished ejection fraction due to dilated cardiomyopathy. During total follow-up, 3 patients developed complete heart block.

Table 2. Types of late cardiac reinterventions

First decade		**Second Decade**	
Residual VSD	2	Resection aortic (re)coarctation	3
Resection pulmonary stenosis	2	Balloon dilation aortic (re)coarctation	2
Resection aortic coarctation	1	Residual VSD	1
Resection subvalvular aortic stenosis	1	Surgery for restenosis aortic valve	1
Closure patent ductus arteriosus	1	Aortic root replacement	1
False aneurysm ascending aorta 1	1	Aortic valve replacement	1
Closure sternal dehiscence	1	Pulmonary valve replacement	1
		Balloon dilation pulmonary stenosis	1
Third Decade		**Fourth Decade**	
Bentall procedure	1	Stenting aortic recoarctation	1
		Aortic valve replacement	1
		Mitral valve replacement	1

Information on late cardiac reinterventions (beyond 30 days after surgery) was available for 118 patients. Fourteen patients underwent 1 or more reinterventions.
VSD = ventricular septal defect.

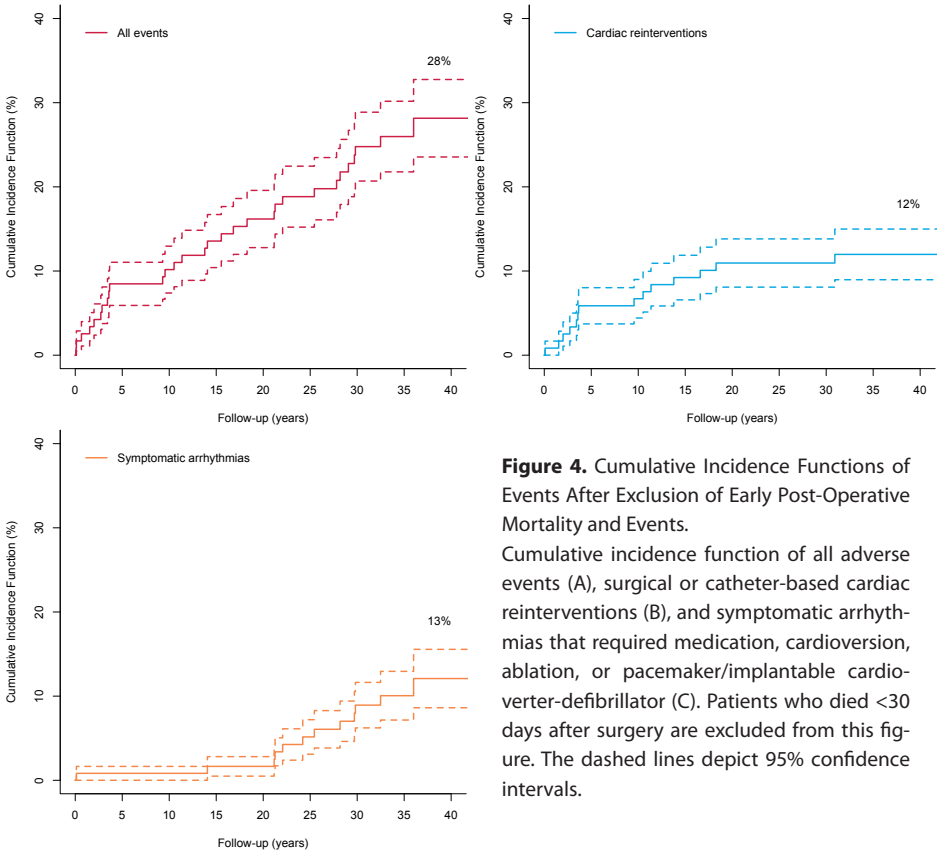


Figure 4. Cumulative Incidence Functions of Events After Exclusion of Early Post-Operative Mortality and Events.
Cumulative incidence function of all adverse events (A), surgical or catheter-based cardiac reinterventions (B), and symptomatic arrhythmias that required medication, cardioversion, ablation, or pacemaker/implantable cardioverter-defibrillator (C). Patients who died <30 days after surgery are excluded from this figure. The dashed lines depict 95% confidence intervals.

Endocarditis

Cumulative incidence of late endocarditis at 40 years was 4%. During the last 10 years, 1 patient was diagnosed with pacemaker endocarditis caused by Staphylococcus aureus, which required treatment with antibiotic drugs and replacement of the pacemaker system.

Heart failure

Cumulative incidence of late heart failure at 40 years was 4%. During the last decade studied, 3 patients developed heart failure. One of them died during hospitalization, 1 was admitted to the hospital several times, and 1 was hospitalized for heart failure triggered by a pneumonia. One of these patients developed heart failure 9 years after epicardial pacemaker implantation, and 1 had diminished LV function before pacemaker implantation.

Electrocardiography and Holter monitoring

The ECG and Holter findings are summarized in Table 3. None of the patients had ventricular pauses longer than 3 s.

Cardiopulmonary exercise testing

Table 3 shows the results of bicycle ergometry. Of the 33 patients with a diminished exercise capacity (i.e., workload <85% of expected), 6 (18%) had 1 or more reinterventions compared with 1 (3%) in the group with normal exercise capacity (p = 0.049). No differences were found with regard to current age, surgical characteristics, isolated versus nonisolated VSD, QRS duration, or ventricular function.

Table 3. Standard 12-lead and 24-h Holter electrocardiogram, bicycle ergometry and echocardiography.

	1990	2001	2012	P value	P value
Electrocardiography	**n = 107**	**n = 95**	**n = 79**	**2012 vs. 1990**	**2012 vs. 2001**
Rhythm					
Sinus	104 (97%)	86 (91%)	72 (91%)	0.125	1.0
Atrial	1 (1%)	2 (2%)	2 (3%)	1.0	1.0
Nodal	1 (1%)	3 (3%)	1 (1%)	1.0	1.0
Pacemaker	1 (1%)	4 (4%)	4 (5%)	1.0	1.0
Atrial flutter	0	0	0	-	-
PR interval (mean ms ± SD)	147 ± 29	151 ± 28	159 ± 30	**<0.001**	**0.001**
PR ≥200 ms (%)	4 (5%)	7 (8%)	6 (9%)	0.219	1.0
QRS duration (mean ms ± SD)	101 ± 20	113 ± 27	117 ± 27	**<0.001**	**0.010**
QRS duration ≥120 ms	21 (25%)	29 (32%)	25 (34%)	0.070	1.0
QRS duration ≥180 ms	0 (0%)	2 (2%)	1 (1%)	1.0	1.0
24-hour Holter	**n = 103**	**n = 92**	**n = 68**		

Table 3. (continued)

	1990	2001	2012	P value	P value
Electrocardiography	**n = 107**	**n = 95**	**n = 79**	**2012 vs. 1990**	**2012 vs. 2001**
Supraventricular arrhythmias	21 (20%)	25 (27%)	25 (37%)	0.052	0.286
Sinus node disease	21 (20%)	8 (9%)	4 (6%)	**0.013**	0.289
SVT	0	19 (21%)	22 (32%)	**<0.001**	0.093
Paroxysmal atrial fibrillation	0	0	1 (1%)	-	-
Paroxysmal atrial flutter	0	0	0	-	-
VT 3-10 complexes	6 (6%)	2 (2%)	3 (4%)	0.625	1.0
VT >10 complexes	0	0	0	1.0	1.0
Bicycle ergometry	**n = 103**	**n = 93**	**n = 69**		
Maximal heart rate (%)	89 ± 9	88 ± 10	88 ± 12	0.190	**0.018**
Maximal workload (%)	94 ± 19	91 ± 24	87 ± 19	**0.001**	**0.012**
Workload <85%	30 (29%)	37 (40%)	33 (48%)	**0.017**	**0.017**
Arrhythmias	5 (5%)	10 (11%)	5 (7%)	1.0	0.754
Peak VO_2 (%)	-	-	87 ± 20	-	-
Echocardiographic parameters	**n = 107**	**n = 95**	**n = 76**		
LA end-systolic dimension (mm)	32 ± 5	37 ± 6	38 ± 6	**<0.001**	0.145
LV end-systolic dimension (mm)	32 ± 5	34 ± 5	33 ± 6	0.981	**0.003**
LV end-diastolic dimension (mm)	49 ± 6	52 ± 5	50 ± 6	0.481	**<0.001**
LV fractional shortening (%)	34 ± 6	34 ± 7	35 ± 8	0.416	0.567
Fractional shortening <30%	19 (19%)	24 (27%)	19 (26%)	0.664	1.0
LV posterior wall dimension (mm)	9 ± 2	10 ± 2	8 ± 2	0.791	**0.005**
Aorta end-diastolic dimension (mm)	30 ± 5	33 ± 5	33 ± 5	<0.001	0.394
AR				**0.022**	0.109
None-trace	95 (89%)	79 (83%)	59 (79%)		
Mild-moderate	12 (11%)	16 (17%)	16 (21%)		
Severe	-	-	-		
MR				0.267	1.0
None-trace	91 (87%)	84 (88%)	69 (92%)		
Mild-moderate	14 (13%)	11 (12%)	6 (8%)		
Severe	-	-	-		
PR				**0.012**	**0.006**
None-trace	81 (78%)	68 (72%)	66 (89%)		
Mild-moderate	23 (22%)	27 (28%)	7 (10%)		
Severe	-	-	1 (1%)		
TR				0.286	0.210
None-trace	63 (62%)	41 (43%)	40 (53%)		
Mild-moderate	38 (38%)	54 (57%)	34 (46%)		
Severe	-	-	1 (1%)		

Values are n, n (%), or mean SD. *Atrial, nodal, and pacemaker rhythm were excluded from analysis. †Pacemaker rhythm was excluded from analysis. ‡Significance test was based on log-transformed values. §Significance test was based on binary variables (none–trace vs. mild–severe).
LA = left atrium; LV = left ventricular; SVT = supraventricular tachycardia; VT = ventricular tachycardia.

Echocardiography

Echocardiographic findings are summarized in Tables 3 and 4. Systolic LV function was mildly impaired in 11 patients (14%), moderately impaired in 3 (4%), and severely impaired in 2 (3%). The percentage of patients with impaired systolic LV function was 14% in 2001 and 21% in 2012 ($p = 0.180$). Normal diastolic LV function was observed in 63 patients (89%), pseudonormal diastolic function in 6 (8%), and restrictive relaxation pattern in 2 (3%). Systolic RV function was mildly impaired in 10 patients (13%) and moderately impaired in 3 (4%). The percentage of patients with impaired systolic RV function increased significantly over the last decade of study from 1% to 17% ($p = 0.001$). Patients with impaired systolic RV function more often had an elevated estimated RV systolic pressure than patients with normal systolic RV function (42% vs. 12%, $p = 0.036$), more often had a pacemaker (23% vs. 3%, $p = 0.033$), and more often had impaired systolic LV function (69% vs. 11%, $p < 0.001$). Diastolic LV function did not differ significantly between patients with impaired or normal systolic RV function. There were no significant differences in systolic biventricular function between patients with isolated and nonisolated VSD, with and without RV incision, or with and without VSD patch. The percentage of patients with mild or moderate aortic regurgitation increased significantly over the last 20 years from 11% in 1990 to 21% in 2012 ($p = 0.039$).

NT-proBNP measurement

NT-proBNP was measured in 68 patients. The median level was 11.6 pmol/l (IQR: 7.0 to 19.8 pmol/l), with an elevated level (>14.0 pmol/l) measured in 26 patients (38%). The highest value was 56.5 pmol/l, measured in a woman with an isolated VSD, in sinus rhythm, and without clinical signs of heart failure. Median NT-proBNP was comparable between patients with an isolated VSD ($n = 50$) and those with a nonisolated VSD ($n = 18$; 11.2 pmol/l [IQR: 6.9 to 18.4 pmol/l] vs. 14.3 pmol/l [IQR: 6.8 to 28.1 pmol/l], $p = 0.436$). Patients with impaired systolic RV function ($n = 8$) tended to have a higher NT-proBNP than patients with normal RV function ($n = 59$; 16.2 pmol/l [IQR: 12.9 to 26.6 pmol/l] vs. 11.1 pmol/l [IQR: 6.4 to 19.5 pmol/l], $p = 0.063$). No relationships were found with systolic LV function, ventricular dimensions, age at operation, current age, or exercise capacity.

Subjective health status assessment

Seventy four patients completed the SF-36 health survey. The results are depicted in Figure 5. Patients obtained significantly better scores than the reference population on all scales except for general health perceptions, which were comparable ($p = 0.089$). The patients' results were comparable with their own results 10 years earlier, except for mental health, which they now rated better ($85 \pm 13\%$ vs. $80 \pm 11\%$, $p = 0.030$).

Table 4. Additional diagnostic test results performed only in 2012

Parameter	n	Median (IQR)	Abnormal, n (%)*
LV EF (%)	38	54 [49-61]	9 (24)
E/A ratio	72	1.3 [1.1-1.7]	2 (3)
E/E' ratio	71	8.5 [6.3-10.0]	5 (7)
Deceleration time (ms)	72	185 [158-218]	20 (28)
RV basal dimension (mm)	65	40 [34-46]	26 (40)
RV longitudinal dimension (mm)	64	77 [69-84]	12 (19)
TAPSE (mm)	61	19 [18-22]	3 (5)
RV fractional area change, %	49	40 (37–43)	7 (14)
Estimated RV systolic pressure, mm Hg	53	28 (24–35)	10 (19)

* According to the reference values in the guidelines (09,10). Right ventricular dimensions were measured during end-diastolic phase.
IQR = interquartile range; LVEF = left ventricular ejection fraction; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion.

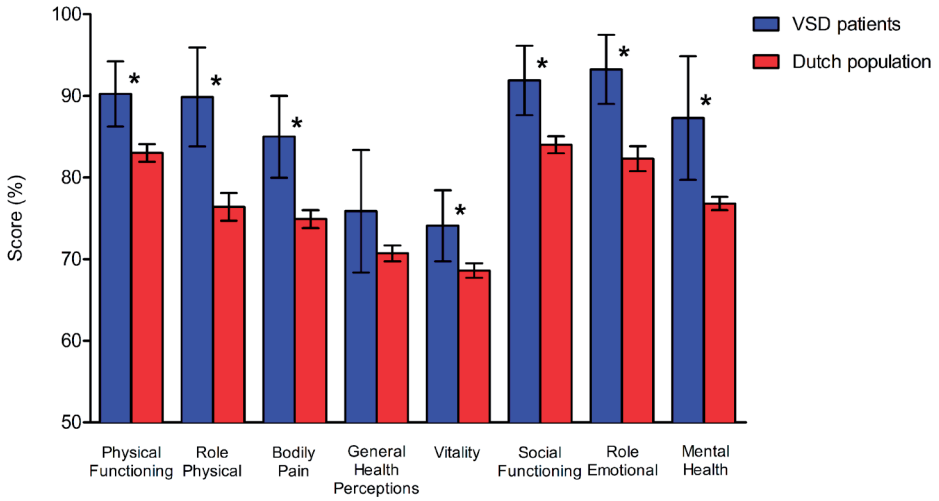


Figure 5. Results of SF-36 for VSD patients and the reference Dutch population.
Higher scores represent more favorable subjective health status. A high score on the bodily pain scale indicates subject was free from pain. Error bars show 95% confidence interval.
*p < 0.01. SF-36 = 36-item short-form health survey; VSD = ventricular septal defect.

Determinants of clinical outcome

Higher pre-operative systolic RV pressure tended to be a determinant of mortality (hazard ratio [HR]: 1.02; 95% confidence interval [CI]: 1.00 to 1.04). Univariable regression analyses identified nonisolated VSD, early post-operative arrhythmias, and aortic cross-clamp time as determinants of late events, including mortality. In multivariable regression analysis with these determinants, patients with nonisolated VSD or patients with longer aortic cross-clamp time had higher risk for events (HR: 2.84 [95% CI: 1.23 to

6.53]; HR: 1.47 per 10 min [95% CI: 1.22 to 1.99 per 10 min], respectively). Early postoperative arrhythmias showed a trend toward predicting later events (HR: 2.59 [95% CI: 0.92 to 7.29]). Patients with a complete heart block in the early post-operative period more often developed symptomatic arrhythmias during follow-up (HR: 9.7 [95% CI: 2.1 to 44.6]). No other baseline characteristics were significant determinants of outcome.

DISCUSSION

In this unique longitudinal cohort study of VSD patients who underwent surgical repair at a young age, survival up to 40 years was relatively good but lower than in the general Dutch population. Although morbidity was substantial, especially among patients with nonisolated VSD, the reported subjective health status was even better than normative data.

Mortality and adverse events

Cumulative survival 40 years after surgical VSD closure was 78% in our cohort. One-half of these deaths occurred within 30 days after surgery. Currently, pulmonary artery banding is performed only rarely, and advances in surgical and anesthesiology techniques and improvements in peri-operative care have greatly reduced peri-operative mortality.[14] In addition, the care during follow-up is better organized today. Therefore, these early results are not applicable to patients who have undergone surgery in more recent years. With the exclusion of in-hospital operative mortality, however, cumulative survival in our cohort was 86% at 40 years, which was still slightly lower than in the general population. In more than one-half of the cases, late mortality was cardiac related: cardiac arrest/sudden death, reoperation, and heart failure (Central Illustration). Cumulative survival was similar between patients with isolated and nonisolated VSD. Morbidity was higher in patients with nonisolated VSD and was dominated by reinterventions for concomitant lesions, for example, aorta-related problems or pulmonary stenosis.

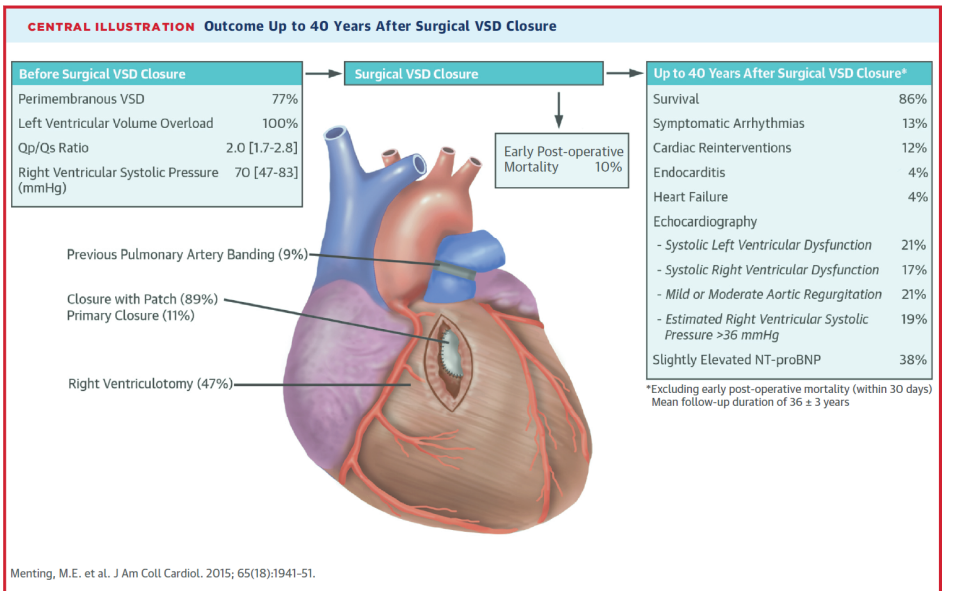
Health status and ventricular function

Most of our patients rated their physical functioning better than the reference population; however, their maximal workload at exercise testing was clearly lower than the reference population, with almost one-half of the patients having a diminished maximal workload. Furthermore, the maximal workload decreased over the last decades studied. The median peak VO2 of 87% in our study population was a bit higher than the 73% in the study by Kempny et al.[15] This difference could probably be explained by the fact that they included patients who underwent exercise testing as part of their ongoing

outpatient care, whereas our study included many patients who had been discharged from routine clinical follow-up.

The occurrence of aortic regurgitation appears to be an important issue after VSD surgery. In our cohort, 1 patient developed severe aortic regurgitation that necessitated aortic valve replacement, and in the other patients, the prevalence of aortic regurgitation nearly doubled over the last 20 years of the study, from 11% in 1990 to 21% in 2012.

CENTRAL ILLUSTRATION **Outcome Up to 40 Years After Surgical VSD Closure**



Menting, M.E. et al. J Am Coll Cardiol. 2015; 65(18):1941-51.

A cohort of 174 consecutive patients who underwent surgical closure of a ventricular septal defect (VSD) between 1968 and 1980 were examined. The surgical characteristics and the findings on clinical outcome up to 40 years are depicted in this figure. NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Systolic LV function remained stable over the last decade of study, but impaired systolic RV function increased. In our cohort, systolic RV dysfunction was not related to VSD patch or RV incision, but the vast majority of patients with systolic RV dysfunction had systolic LV dysfunction and more often had elevated RV systolic pressure. This relationship between RV and LV dysfunction could be explained in part by the presence of a pacemaker in a quarter of patients with RV dysfunction or by systolic ventricular interaction. In the case of systolic LV dysfunction, pulmonary pressure increases, which results in reduction of RV contractility. Moreover, ventricular interaction is mediated by forces at the interventricular septum and mechanical coupling through shared myocardial fibers:

When the LV becomes more spherical, the fibers of the interventricular septum become less oblique, which reduces and impairs RV contractile function.[16,17] Systolic ventricular interaction is also observed in other congenital heart defects.[18,19] Another explanation for the higher prevalence of RV dysfunction over time may be the use of a more sophisticated echocardiographic assessment to facilitate the detection of dys-

function. Using tissue Doppler imaging, Klitsie et al.[20] found a systolic RV impairment up to 20 months after surgical VSD closure in children. Although subclinical RV impairment may not be of direct clinical relevance, it could be a first sign of systolic RV dysfunction and does stress the importance of detailed evaluation of RV function after VSD surgery.

NT-proBNP levels were elevated in more than onethird of the patients. This is striking, because the majority of patients were asymptomatic and had normal systolic biventricular function. No studies were found in the published data on BNP levels in adults after surgical VSD closure, and only a few in children,[21] which reported mildly increased levels. Prospective studies are necessary to elucidate the prognostic value of BNP in these patients.

Arrhythmias

In the last 10 years of the study, 4 patients developed supraventricular arrhythmias, and 3 required pacemaker implantation. Cumulative incidence of late symptomatic arrhythmias at 40 years was 13%. This was much lower than the incidence after surgical VSD closure at adult age[22] but higher than in patients who underwent surgery after 1980.[14,23] The incidence of arrhythmias after surgical closure of an atrial septal defect at young ages is higher.[24] Recently, interest has been generated in development of percutaneous techniques to close VSDs; however, this technique is not implemented in routine clinical practice and has even ceased in most clinics because of the high rate of post-procedural heart block (up to 8%).[4,25] This is higher than the incidence in our cohort after surgical closure at a young age (3%), as well as at an adult age.[22,23]

Subjective health status assessment

A remarkable finding of the SF-36 results was that patients reported a more favorable functioning than the reference Dutch population on 7 of the 8 scales and comparable functioning on 1 scale (general health perceptions). These propitious results for VSD patients may be attributable to different frames of reference than the normal population, more adequate coping with the disadvantageous consequences of the congenital heart defect at advanced age, overcompensation, or social desirability.[26]

Determinants of clinical outcome

Although numbers in our study were relatively small, patients with early post-operative arrhythmia tended to develop more late events. In another cohort of patients with surgically repaired VSD, transient and complete heart blocks were a risk factor for late mortality.[27] In that study, a substantial percentage of deceased patients had not received a pacemaker because either pacemakers had not been developed at that time or they were only newly available. The relation between early post-operative arrhythmias and arrhythmias during follow-up was also described after surgery at young age for other

congenital heart defects.[24,28] The relation may be explained by surgical damage to the conduction system or by post-operative scar tissue and fibrosis. Early arrhythmias might therefore reveal patients at risk for late complications. A simple concomitant cardiac lesion and longer aortic cross-clamp time during surgery were determinants of late events. The fact that patients with a concomitant cardiac lesion have a greater risk of events appears directly related to the relatively higher number of reinterventions in this group.

Study limitations

Although the number of patients was relatively small, we report results of a longitudinal follow-up of consecutive patients without selection bias related to disease severity. After a median follow-up of 36 years, we gathered medical information on 84% of the eligible patients. We found no significant differences in baseline characteristics between participating and nonparticipating patients. Therefore, we believe that we have minimized selection bias.

Diagnostic methods have changed over time. For comparisons of echocardiographic data with previous studies, we had to use the same methods as were used in the past, which may not be considered current state of the art. However, we also performed and reported innovative diagnostic methods available in the current era.

CONCLUSIONS

Survival up to 40 years after successful surgical VSD closure is good but slightly lower than in the general Dutch population. Although many patients have been discharged from routine follow-up at outpatient clinics, morbidity is substantial, especially in patients with nonisolated VSD. There is concern about systolic LV and RV dysfunction, which were observed in 21% and 17% of patients, respectively, and about occurrence of aortic regurgitation, which almost doubled over the last 20 years of the study. Early postoperative arrhythmia is a borderline determinant and aortic cross-clamp time a significant determinant of late events. Therefore, clinical follow-up with long intervals seems advisable. Despite the reported morbidity, the subjective health status is excellent.

ACKNOWLEDGEMENTS

The authors thank Elisabeth E.M. Konings and Maarten A. Slager for their contribution to data collection and Sara J. Baart for her contribution to statistical analysis.

Online appendix: Additional information on statistical analysis

Changes in patient characteristics since the follow-up study in 1990 and 2001 were evaluated by estimating a trend using mixed models which take missing values into account. For the continuous variables, a trend was estimated using linear mixed models. When the distribution of the variables deviated from normality, log-transformations were applied. For the binary variables, generalized linear mixed models were estimated with a logit-link function. The variables with three categories (aortic, mitral, pulmonary and tricuspid regurgitation) were recoded as binary variables (none-trace vs. mild-severe).

Univariable and multivariable Cox regression analyses were used to identify determinants of the predefined adverse events: all-cause mortality, arrhythmias, reinterventions, heart failure and endocarditis. The following baseline characteristics were included as determinants in the analyses: non-isolated VSD, age at repair, era of repair, preoperative systolic RV pressure, pulmonary-systemic flow ratio, preoperative palliation, temperature during surgery, RV incision, early postoperative arrhythmias, and aortic cross-clamp time. Baseline characteristics that turned out to be significant in the univariable Cox regression analysis, were implanted in the multivariable Cox regression model. For every ten events, one characteristic could be implemented in the multivariable Cox regression model.

Perspectives

Competency in medical knowledge: Surgical closure represents the standard approach to management of patients with congenital VSD, but the incidence of postoperative right ventricular systolic dysfunction has increased over time.

Translational outlook: Longer-term follow-up studies of a larger number of patients could better define the risks of heart failure, arrhythmias, and death in the years after repair of congenital VSD.

REFERENCES

1. van der Linde D, Konings EE, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol* 2011;58:2241–7.
2. Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol* 2002; 39:1890–900.
3. Minette MS, Sahn DJ. Ventricular septal defects [published correction appears in Circulation 2007;115:e205*]. Circulation* 2006;114:2190–7.
4. Penny DJ, Vick GW 3rd. Ventricular septal defect. *Lancet* 2011;377:1103–12.
5. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, et al. Outcome of patients after surgical closure of ventricular septal defect at young age: longitudinal follow-up of 22-34 years. *Eur Heart J* 2004;25: 1057–62.
6. Meijboom F, Szatmari A, Utens E, et al. Longterm follow-up after surgical closure of ventricular septal defect in infancy and childhood. *J Am Coll Cardiol* 1994;24:1358–64.
7. van Rijen EH, Utens EM, Roos-Hesselink JW, et al. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. *Eur Heart J* 2003;24:673–83.
8. Kugler J. Sinus node dysfunction. In: Garson A BJ, McNamara DG, editors. The Science and Practice of Pediatric Cardiology. 1st edition. Philadelphia, PA: Lea & Febiger, 1990:1751–85.
9. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440–63.
10. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;23:685–713, quiz 786–8.
11. Lancellotti P, Tribouilloy C, Hagendorff A, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation, part 1: aortic and pulmonary regurgitation (native valve disease). *Eur J Echocardiogr* 2010;11:223–44.
12. Lancellotti P, Moura L, Pierard LA, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation, part 2: mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr* 2010;11:307–32.
13. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 1998;51:1055–68.
14. Scully BB, Morales DL, Zafar F, McKenzie ED, Fraser CD Jr., Heinle JS. Current expectations for surgical repair of isolated ventricular septal defects. *Ann Thorac Surg* 2010;89:544–9, discussion 550–1.

15. Kempny A, Dimopoulos K, Uebing A, et al. Reference values for exercise limitations among adults with congenital heart disease: relation to activities of daily life: single centre experience and review of published data. *Eur Heart J* 2012;33: 1386–96.

16. Santamore WP, Dell'Italia LJ. Ventricular interdependence: significant left ventricular contributions to right ventricular systolic function. Prog Cardiovasc Dis 1998;40:289–308. 17. Schwarz K, Singh S, Dawson D, Frenneaux MP. Right ventricular function in left ventricular disease: pathophysiology and implications. *Heart Lung Circ* 2013;22:507–11.

18. Kempny A, Diller GP, Orwat S, et al. Right ventricular-left ventricular interaction in adults with Tetralogy of Fallot: a combined cardiac magnetic resonance and echocardiographic speckle tracking study. *Int J Cardiol* 2012;154: 259–64.

19. Menting ME, Eindhoven JA, van den Bosch AE, et al. Abnormal left ventricular rotation and twist in adult patients with corrected tetralogy of Fallot. *Eur Heart J Cardiovasc Imaging* 2014;15: 566–74.

20. Klitsie LM, Kuipers IM, Roest AA, et al. Disparity in right vs left ventricular recovery during follow-up after ventricular septal defect correction in children. *Eur J Cardiothorac Surg* 2013;44:269–74.

21. Eindhoven JA, van den Bosch AE, Boersma E, Roos-Hesselink JW. The usefulness of brain natriuretic peptide in simple congenital heart disease: a systematic review. *Cardiol Young* 2013; 23:315–24.

22. Mongeon FP, Burkhart HM, Ammash NM, et al. Indications and outcomes of surgical closure of ventricular septal defect in adults. *J Am Coll Cardiol Intv* 2010;3:290–7.

23. Bol Raap G, Meijboom FJ, Kappetein AP, Galema TW, Yap SC, Bogers AJ. Long-term follow-up and quality of life after closure of ventricular septal defect in adults. *Eur J Cardiothorac Surg* 2007;32:215–9.

24. Cuypers JA, Opic P, Menting ME, et al. The unnatural history of an atrial septal defect: longitudinal 35 year follow up after surgical closure at young age. *Heart* 2013;99:1346–52.

25. Dumitrescu A, Lane GK, Wilkinson JL, Goh TH, Penny DJ, Davis AM. Transcatheter closure of perimembranous ventricular septal defect. *Heart* 2007;93:867.

26. van Rijen EH, Utens EM, Roos-Hesselink JW, et al. Current subjective state of health, and longitudinal psychological well-being over a period of 10 years, in a cohort of adults with congenital cardiac disease. *Cardiol Young* 2005; 15:168–75.

27. Moller JH, Patton C, Varco RL, Lillehei CW. Late results (30 to 35 years) after operative closure of isolated ventricular septal defect from 1954 to 1960. *Am J Cardiol* 1991;68:1491–7.

28. Cuypers JA, Eindhoven JA, Slager MA, et al. The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years. *Eur Heart J* 2014;335:1666–74.

4

Pulmonary stenosis: update on diagnosis and therapeutic options

Judith Anne Adriane Ellen Cuypers, Maarten Witsenburg,
Denise van der Linde, Jolien W. Roos-Hesselink

Heart 2013 Mar;99(5):339-47

Pulmonary stenosis (PS) accounts for approximately 8% of all congenital heart defects.[1] Valvular PS is usually an isolated defect, but it can be associated with other congenital heart defects, such as atrial septal defect (ASD), ventricular septal defect (VSD), and persistent ductus arteriosus. Combined valvular and infundibular PS can be part of tetralogy of Fallot (ToF). The clinical presentation of PS may vary from critical stenosis in the newborn, to asymptomatic mild stenosis without need for therapy throughout life. The need for treatment of critical PS in the newborn is obvious, but the optimal timing, type of treatment, and follow-up strategy for the asymptomatic patient is less well defined.

EPIDEMIOLOGY

PS occurs in about 1 per 2000 live births worldwide.[1] The prevalence seems to be steadily increasing over time (figure 1A). There is a slightly higher birth prevalence in Asia as compared to Europe and the USA[1] (figure 1B). The underlying cause is not well known, but should be sought in genetic, environmental, and dietary factors. There is increasing evidence that epigenetic modifications play an important role in certain diseases apart from genetics, and this might also be true for PS.[w1 w2] Since an increasing number of patients had surgical or interventional repair during childhood, more and more adults will be seen with long term residual lesions like pulmonary regurgitation (PR) and restenosis.

MORPHOLOGICAL CLASSIFICATION AND AETIOLOGY

PS can be valvular, subvalvular (infundibular) or supravalvular (figure 2A). Valvular stenosis is by far the most common form.

Valvular PS

In valvular PS, the pulmonary valve usually has a dome-like shape with a narrow central opening (figure 2B). Rudimentary raphes can be seen. Less often, the valve is dysplastic, with myxomatous thickened leaflets. The latter is associated with Noonan syndrome (table 1). In ToF there often is a stenotic bicuspid or unicuspid pulmonary valve. Valvular PS can also be associated with other congenital heart defects such as ASD, Ebstein's anomaly, double outlet right ventricle, and transposition of the great arteries.

Subvalvular PS

Subvalvular PS can be infundibular or subinfundibular. Infundibular PS is usually seen as part of ToF, while isolated infundibular PS is very rare. Secondary infundibular hypertrophy may occur in valvular PS: because the right ventricular (RV) outflow tract

(infundibulum) is a circular muscular structure, reactive RV hypertrophy can cause a dynamic outflow obstruction. Subinfundibular PS is also known as 'double chambered right ventricle' (DCRV). In that case, the RV cavity is divided into a high pressure inlet

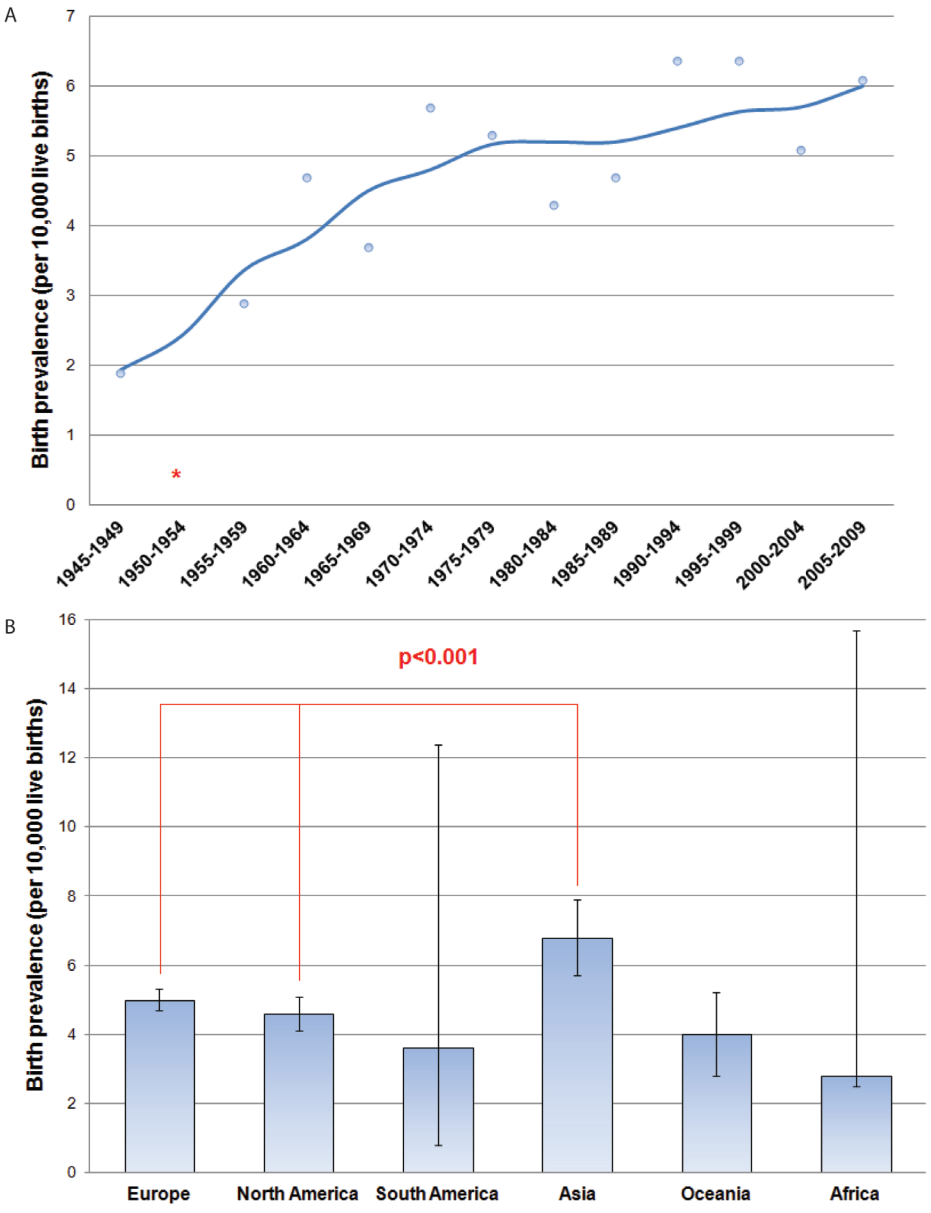


Figure 1. Birth prevalence of pulmonary stenosis.
A. Time course of birth prevalence until 2010.
B. Reported birth prevalence per continent. Adapted with permission from van der Linde, *et al*, [1].

part and a low pressure outlet part, by anomalous muscle bundles. This can be either a hypertrophied moderator band or local hypertrophy that may develop as the consequence of a high velocity jet of a small VSD, directed at the opposing RV wall. A DCRV can be misinterpreted as RV hypertrophy due to, for example, pulmonary hypertension. In contrast to most other causes of right ventricular outflow tract (RVOT) obstruction, a DCRV can be progressive in adult life.

Supravalvular PS

Supravalvular PS can be isolated, but is often associated with other cardiac or extracardiac abnormalities. It is described in several syndromes, including Williams–Beuren, Noonan, Allagile, DiGeorge, and Leopard syndrome (table 1). Furthermore, it can occur in the clinical picture of congenital rubella syndrome. The stenosis can be located in the common pulmonary trunk, the bifurcation or the pulmonary branches.

CLINICAL PRESENTATION

In the newborn with a critical PS, the suprasystemic RV pressure may result in RV dilatation and failure with severe tricuspid regurgitation (TR) and cyanosis due to right-to-left shunting over the foramen ovale or an ASD. These infants may present in heart failure and will often be duct dependent. However, most patients with mild to moderate PS are asymptomatic and will be discovered by a murmur during routine physical examination

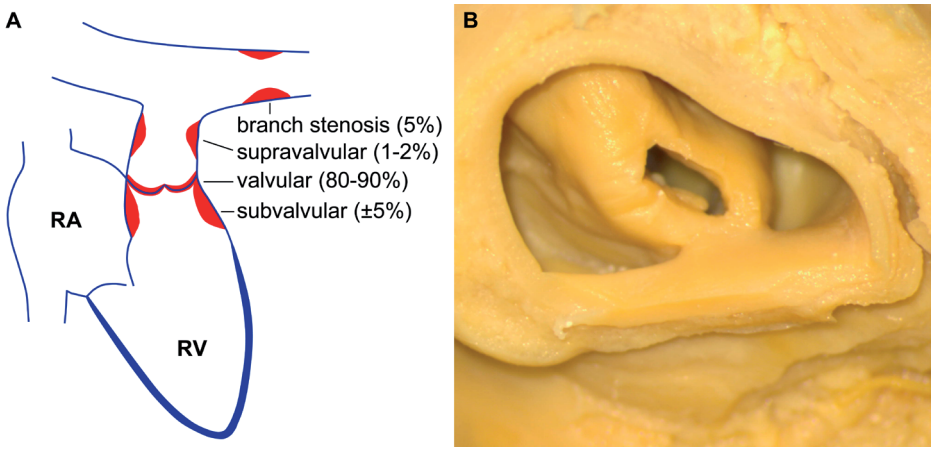


Figure 2. Morphology of pulmonary stenosis.
A. schematic representation of different types of pulmonary stenosis. RA: right atrium, RV: right ventricle.
B. doming pulmonary valve. *Courtesy of Dr. M.M. Bartelings and Dr. M.R.M. Jongbloed, Department of Anatomy & Embryology, Leiden University Medical Centre, the Netherlands*

in infancy or childhood. There can be mild exertional dyspnoea and fatigue. In untreated severe PS, the inability to increase pulmonary blood flow during exercise can lead to chest pain or syncope.

Table 1. Common genetic syndromes associated with pulmonary stenosis

Syndrome	Genetic defect	Cardiac features	Non-cardiac features
Noonan	PTPN11, SOS1, aberrant RAS-MAPK-signalling, heterogeneous trait	dysplastic pulmonary valve stenosis, supravalvular pulmonary stenosis, hypertrophic cardiomyopathy	short stature, hypertelorism, downward eye slant, low set ears
Williams-Beuren	7Q11.23 deletions, autosomal dominant trait	supravalvular aortic or pulmonary stenosis	elfin face, short stature, impaired cognition and development, endocrine disorders, genitourinary abnormalities
Leopard	PTPN11, RAF-1, autosomal dominant trait	electrocardiographic abnormalities, supravalvular or valvular pulmonary stenosis	lentigines, ocular hypertelorism, abnormal genitalia, retardation of growth, deafness
DiGeorge (velocardiofacial)	22Q11 deletion, autosomal dominant trait	conotruncal defects such as Tetralogy of Fallot, interrupted aortic arch, truncus arteriosus, vascular rings and ASD/VSD	hypertelorism, low set and posteriorly rotated ears, palatal abnormalities, micrognatia. Developmental delay, hypoplastic thymus, hypocalcemia, variety of immunological abnormalities
Allagile	JAG-1 , NOTCH-2, dominant trait	peripheral pulmonary stenosis	facial dysmorphias (triangular face, wide nasal bridge, deep set eyes), intrahepatic cholestasis, butterfly vertebrae
Keutel	MGP-mutations autosomal recessive trait	multiple peripheral pulmonary stenosis	abnormal cartilage calcifications, brachytelephalangysm, subnormal IQ, hearing loss
Congenital rubella	-	peripheral pulmonary stenosis, open ductus Botalli	congenital cataract/glaucoma, deafness, pigmentary retinopathy

DIAGNOSTIC TOOLS

ECG

In patients with mild PS the ECG can be normal, perhaps showing only a more pronounced right-ward axis deviation. In children and adolescents a right axis up to −100° to −110° can be completely normal.[w3] However, in more severe stenosis, RV hypertrophy, further rightward axis deviation, high R wave amplitude in lead V1 and deep S waves in the left precordial leads, with an R:S ratio <1 in V6, can be seen.[w4]

ECHOCARDIOGRAPHY

Transthoracic two dimensional (2D) echocardiography and Doppler imaging is the clinical standard to detect PS and quantify its severity. For visualisation of the pulmonary valve, the parasternal short axis view and alternatively the anterior angulated subcostal or subxyphoid view are used (figure 3). These latter views are very useful in neonates and children, in whom the distances are small. Furthermore, in adults it is sometimes possible to obtain a parasternal long axis image by rotation of the probe by 90° and angulating towards the right shoulder. In the parasternal short axis view, a thickened and

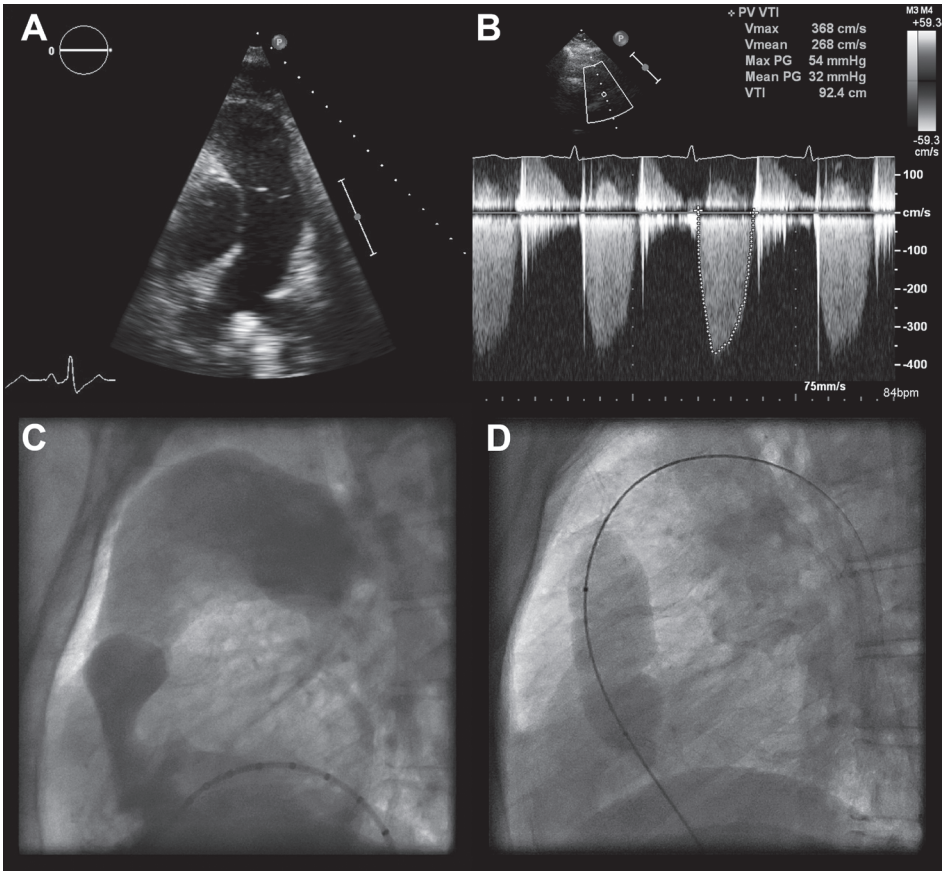


Figure 3. Echocardiographic and angiographic images of pulmonary stenosis
A. two-dimensional parasternal short axis view of a doming pulmonary valve.
B. corresponding Doppler image showing moderate pulmonary stenosis.
C. cineangiographic frame showing doming of the pulmonary valve and hyperkinetic contraction of the infundibular myocardium.
D. cineradiographic frame showing balloon dilatation of the stenotic pulmonary valve. Note the "waisting" of the balloon at the site of stenosis.

often dome shaped pulmonary valve can be seen (figure 3A). Peak and mean gradients can be measured by Doppler imaging. The orientation of the RVOT in the chest and the posterior direction of the pulmonary artery make it relatively easy to align the echo beam to the pulmonary flow, so off-angle interrogation is not a real problem in valvular and supravalvular stenosis. Continuous wave Doppler imaging can best be obtained with the sample volume located just distally to the tips of the pulmonary valve. Pulsed wave Doppler is useful to discriminate between subvalvular, valvular and supravalvular stenosis. In DCRV, however, alignment problems can be an issue, making it difficult to measure the true gradient. Double checking with RV systolic pressure estimates from the TR gradient will prevent underestimation of the true gradient. Both in multilevel stenosis and more than mild regurgitation, the modified Bernouilly equation will overestimate the real gradient. Here too, the TR gradient will give a better estimate of the true gradient. PS is graded as mild, moderate or severe (figure 4).[2] Accompanying PR can be visualised with colour Doppler and continuous wave Doppler techniques. PR severity can be estimated by the jet length and width compared to the annular diameter and RVOT on colour Doppler imaging. This is sometimes difficult to assess, especially in eccentric PR. Diastolic retrograde flow in the pulmonary artery branches, however, is always a sign of severe PR. This should always be looked for in particular. A PR pressure half time <100 ms is also an indicator of haemodynamically significant PR. Semiquantitative assessment of PR by the PR index (ratio of PR duration to diastolic duration) can be useful.[3] A PR index <0.77 yields 100% sensitivity and 85% specificity for identifying patients with a significant PR (ie, >24.5% regurgitation). In severe PR, RV diastolic function can become restrictive. Although this reflects abnormal haemodynamics, its effect is beneficial: the high end-diastolic RV pressure causes end-diastolic antegrade flow over the pulmonary valve and thereby limits the amount of PR.

Quantitative assessment of RV volume and function by 2D echocardiography is limited. Three dimensional (3D) echocardiography can accurately estimate RV volume

	Mild	Moderate	Severe
Peak Doppler velocity (m/s)	< 3	3 - 4	> 4
Peak Doppler gradient (mmHg)	< 36	36 - 64	> 64
Mean Doppler gradient (mmHg)			> 40
Always check tricuspid regurgitation gradient to rule out overestimation of pulmonary stenosis gradient			

Figure 4. Severity grading of pulmonary stenosis

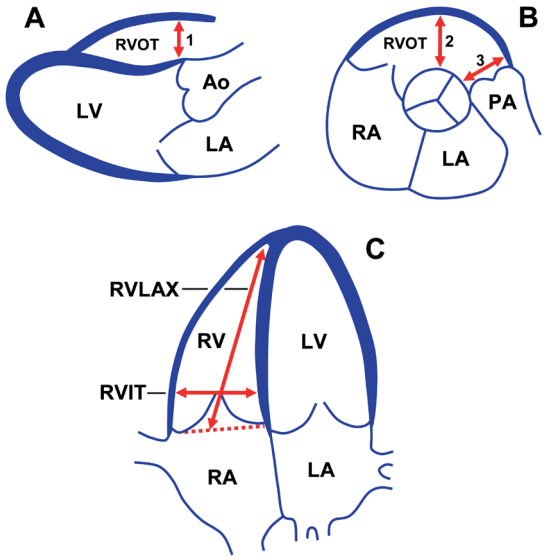


Figure 5. Echocardiographic measurements of right ventricular dimensions
1. Parasternal long axis view. 2. Parasternal short axis view. 3. Apical four chamber view.
RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium; Ao, aorta; PA, pulmonary artery; RVOT, right ventricular outflow tract; RVIT, right ventricular inflow tract; RVLAX, right ventricular long axis.

and ejection fraction,[4 w5] but it has limitations due to a limited acoustic window. Qualitative assessment is hampered by subjectivity, but can be used to estimate dilatation and deterioration of function over time. Routine work-up of the right heart includes parasternal long and short axis views for measurements of RV inflow and outflow dimensions (figure 5) and assessment of the tricuspid and pulmonary valve, and the apical four chamber view for long and short axis dimensions, tricuspid annular plane systolic excursion (TAPSE), and fractional area change.

MRI

MRI is useful for studying the anatomy of the RVOT, pulmonary artery and its branches, using cine and phase contrast techniques and 3D gadolinium imaging. The precise location of the stenosis can be visualised, which is valuable in distinguishing between subvalvular, valvular and supravalvular stenosis especially. Flow artefacts in gradient echo images can be indicative of stenosis or regurgitation. Velocity mapping, based on the principle of phase shift between stationary and moving tissue, which can be translated into voxel velocity at any point of the cardiac cycle, can be used to study the peak velocity of flow over the pulmonary valve. Because this technique detects the velocity of the fastest protons in the flow, the maximum velocity measured by MRI is often higher than that measured by echo Doppler, in which the mean velocity of many erythrocytes is calculated. A major drawback of velocity mapping MRI techniques is that the technique is based on laminar flow, and is detrimentally affected by turbulent flow patterns such as in valvular stenosis. Consequently, for determination of flow velocities,

echocardiography is the technique of choice. Flow volumes, however, can be accurately assessed by MRI. This is especially useful for determination of the regurgitant volume in PR after a prior intervention. MRI is considered the gold standard for assessment and quantification of (right) ventricular volume, mass and function. It is not bothered by the geometric assumptions that are unavoidable in echocardiography. Limitations of cardiac MRI are its incompatibility with most pacemakers and other metal devices, the requirement of breath holds, and a regular heart rhythm. Furthermore, its availability is still limited and costs are high, and claustrophobia may make a patient unsuitable for MRI.

Multislice CT

Multislice CT (MSCT) might be the superior diagnostic technique to study the anatomy of the RVOT and the pulmonary arterial tree especially, but it lacks possibilities for volumetric and functional assessment. For routine follow-up, MRI is preferred over MSCT where possible, because of the ionising radiation of the latter, especially where young patients are concerned. Moreover, for image acquisition with MSCT, a low heart rate is required. Cardiac catheterisation and angiography This has been the classic way of determining the severity of PS. Pressure gradients can be measured directly and angiography represents anatomy accurately (figure 3). Nowadays, cardiac catheterization is used for invasive treatment, because the diagnosis and severity of stenosis

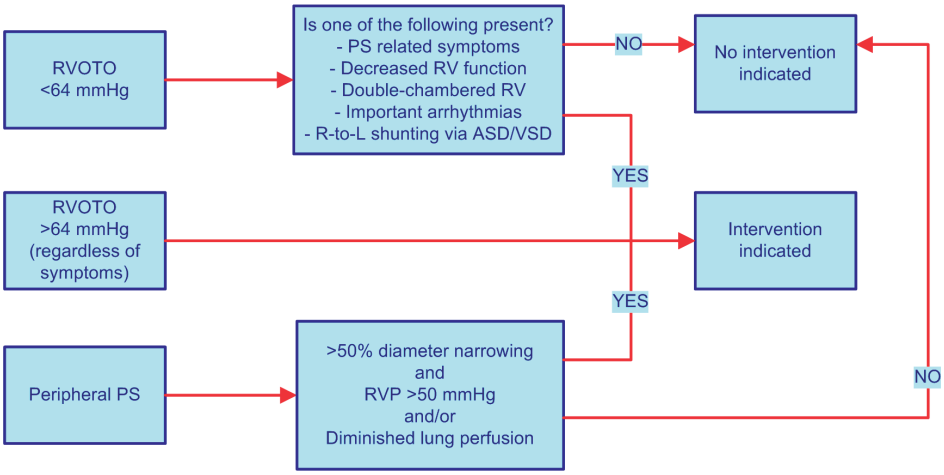


Figure 6. Indications for intervention in pulmonary stenosis(A) and regurgitation after previous treatment (B). In asymptomatic patients in whom valve replacement is the only option, the treshold for intervention is higher: surgery should be performed in the presence of a systolic RV-pressure > 80 mmHg (TR velocity > 4.3 m/s).
RV, right ventricle; RVOTO, right ventricular outflow tract obstruction; RVP, right ventricular systolic pressure; PS, pulmonary stenosis; PR, pulmonary regurgitation; TR, tricuspid regurgitation.

will already have been assessed by echocardiography. For comparison with the older literature, on which guidelines are still partly based, translating the Doppler derived peak instantaneous gradient into the peak-to-peak invasive gradient becomes relevant. Although overestimation of the gradient by Doppler is less likely to occur in pulmonary valve stenosis than in aortic stenosis, in case of doubt severity confirmation by invasive measurement is warranted.

TREATMENT

Indications

The goal of treatment is relief of the RVOT obstruction, thereby alleviating the pressure overloaded RV. Any obstruction in the RVOT and/or pulmonary valve with a Doppler derived peak instantaneous gradient >64 mm Hg (peak velocity >4 m/s) should be repaired. Indications for treatment in moderate PS or peripheral pulmonary artery stenosis are summarised in figure 6.5 In case of asymptomatic valvular stenosis in which balloon valvuloplasty is not possible, surgical repair should be performed in the presence of a systolic RV pressure >80 mm Hg (TR velocity >4.3 m/s).

Choice of treatment

Since balloon pulmonary valvuloplasty (BPV) was introduced in the 1980s, it has rapidly replaced surgical valvotomy as the preferred treatment. If there is a hypoplastic pulmonary annulus or a severely dysplastic valve, or if the stenosis is infundibular or associated with other lesions which have to be repaired, the result may be limited and surgical treatment will often be necessary.

Balloon pulmonary valvuloplasty

Venous access is usually achieved via the femoral vein, but access through the jugular, axillar or hepatic veins is possible in the case of occluded femoral veins. The valve is dilated with a balloon sized 1.2–1.4 times the pulmonary annulus. The procedure is considered successful when the invasive gradient is reduced to <30 mm Hg. In experienced hands the risk of death or major complications is very low, 0.24% and 0.35%, respectively.[w6] Complications, including transient bradycardia and hypotension during balloon inflation, transient or permanent right bundle branch block or atrioventricular block, balloon rupture, tricuspid papillary muscle rupture, and tears in the pulmonary artery have been reported, but all are rare. Development of post-procedural infundibular stenosis may occur, but this usually resolves over time. Rarely, β-blocker treatment is necessary for this dynamic RVOT obstruction after balloon valvulotomy.

Surgical repair

Many different approaches have been used to repair valvular PS. The initial surgical correction consisted of a closed valvulotomy, first performed in 1948 by Lord Brock. Afterwards the procedure evolved to open valvulotomy, initially using inflow occlusion and later on cardiopulmonary bypass. Nowadays, an open commissurotomy or valvulotomy is performed, in which the pulmonary trunk is opened through a vertical incision. If present, the fused commissures of the valve are opened by incision. Valvular tissue is excised only when other methods fail to achieve a wide opening. The same goes for the use of a transannular patch of autologous pericardium. In isolated valvular PS, the perioperative risk is very low, and the risk of death approaches zero.[6] As initial treatment, valve replacement is rare.

Redo intervention and future options

In patients with significant residual PS after BPV, a redo BPV can be performed with a larger balloon. If this is still unsuccessful, surgical intervention will be necessary. Sometimes pulmonary valve replacement cannot be avoided. Then implantation of a non-mechanical valve is preferred, because the risk of thrombosis in pulmonary mechanical valves is higher than in mechanical valves in the aortic position. Our preference is implantation of a pulmonary homograft, but availability of homografts can be limited. Other surgeons might prefer the use of other bioprosthetic valves. Surgical valve replacement may also be necessary in the case of severe, haemodynamically significant PR after BPV or previous surgery. In patients who have already received a non-mechanical valve, stenosis or regurgitation can develop over time. In those patients, percutaneous valve implantation may be an option. For PR after correction with a transannular patch, percutaneous intervention is not possible yet, but new devices are being developed. The first in-human implantation of a new, self-expandable valve has been reported.[7]

Late outcome

Unoperated patients

The natural history of patients with mild PS is usually benign. In the Second Natural History study,[8] patients with an invasive peak-to-peak gradient ≤25 mm Hg had normal survival and no progression of their stenosis in 25 years of follow-up; patients with a gradient between 25–49 mm Hg had a 20% chance of ever needing an intervention; and the majority of patients with a gradient ≥50 mm Hg experienced progressive stenosis and required intervention. There was no advantage in delaying intervention in the latter patient group.

Patients after surgical correction

Overall survival of patients after surgical correction of valvular PS is good, with survival rates of 90–96% 25 years after surgery (table 2).[9–13 w7] If surgery is performed during childhood then survival is comparable to the normal population, while if repair of the stenosis is performed at adult age a 70% 25 year survival is described.[8] Although survival is good, these patients do have residual lesions. Postoperative PR is common, especially if a transannular patch is used. Because PR is usually tolerated well for many years, re-intervention is not often required in the first decades after surgery. In the long run, however, PR can lead to irreversible RV myocardial damage. Therefore, postoperative PR should be followed carefully. Indications for reintervention are summarised in figure 6.

Patients after balloon valvuloplasty

Long term outcome and survival after BPV are good, as is summarised in table 2.9 [12–16 w8–w18] At mid-term follow-up (<2 years), restenosis, defined as an invasive gradient >50 mm Hg, is observed in 8–10% of patients. In the absence of severe annular hypoplasia and valvular dysplasia, this can be treated with a repeat BPV using a larger balloon with good success rates. Risk factors for restenosis are use of a relatively small balloon (balloon:annulus ratio <1.2) and an immediate invasive post-BPV gradient of ≥30 mm Hg. In the long term follow-up, the freedom of reintervention is reported as 88% and 84% at 5 and 10 years, respectively. Surgical intervention could be avoided in nearly all patients. PR was present in 40–90% of patients, with increasing prevalence over time. However, RV volume overload does not seem to be a major problem. The risk of significant PR seems to be related to younger age at treatment and smaller body surface area (BSA), more severe PS, use of a large or non-compliant balloon, and low residual gradient at the time of BPV.

CLINICAL FOLLOW-UP

Patients with PS require lifelong follow-up with regular echocardiographic imaging, checking for the degree of PR, RV pressure, size and function and TR, unless their stenosis is mild (<36 mm Hg) and stable. Attention should also be paid to the occurrence of arrhythmias. Follow-up frequency depends on the severity of the lesion. Patients with mild PS, whether untreated or residual, require follow-up only once every 5 years. Patients with moderate PS or PR should be checked annually, including echocardiographic imaging every 2 years.

Table 2. Post-interventional follow-up in patients with valvular pulmonary stenosis: an overview of published studies

Author	Intervention	Intervention period	Number of patients	Age at intervention (years)	Male (%)	Follow-up (years)	Pre-inventional gradient (mmHg) *	Post- inventional gradient (mmHg) *	Early mortality (<30 days)	Late survival	Re-intervention #	Time to re-intervention (years) #	Moderate to severe PR
Kopecky et al. (1988)	Surgery	1956-1967	191	13.6 ± 13.1	52%	24 ± 4	118 ± 48 (C)	51 ±16 (C)	4.2%	90%	2.6% S	12 (4-21)	1%
O'Connor et al. (1992)	Surgery	1978 - 1982	20	4.7 ± 0.8	—	11.7 ± 0.5	74 ± 4.4 (C)	16 ± 1.5 (C)	—	—	—	—	45%
Earing et al. (2005)	Surgery	1951 - 1982	53	10 ± 13	57%	33 (18-51)	—	—	—	96.7%	52.8% (25% S, 56% R, 19% O)	34 (4-44)	43%
Roos-Hesselink et al. (2006)	Surgery	1968 - 1980	90	5.5 (0-14)	—	27 (22-33)	95 ± 39 (C)	—	2.2%	93%	15.6% (40% S, 60% R)	S: 50% 2-3, 50% 16-18. R: 16-24	37%
Voet et al. (2010)	Surgery	1960 - 2009	79	5 (0-39)	54%	22.5 (0-45)	97.4 ± 48.5 (C)	9.7 ± 6.1 (E)	2.5%	96.2%	20.3% (81% R, 19% O)	—	59%
Peterson et al. (2003)	Surgery	1969 - 2000	54	3.0 ± 3.7	—	9.8 ± 6.1	64.8 ± 30.8 (E)	17.4 ± 14.7 (E)	—	—	5.6% S	2-7	45%
McCrindle et al. (1991)	BVP	1981-1986	46	4.6 ± 1.9	37%	4.6 (0.3-56)	70 ± 36 (C mean)	23 ± 14 (C mean)	—	—	8.7% S	—	2.2%
O'Connor et al. (1992)	BVP	1982 - 1986	20	4.3 ± 0.8	—	5.3 ± 0.3	76 ± 5 (C mean)	35 ± 3.2 (C mean)	—	—	—	—	0%
Kaul et al. (1993)	BVP	1985 - 1991	40	27.6 (18-56)	40%	2 ± 1	107 ± 29 (C)	37 ± 25 (C)	—	—	2.5% O	Immediate (rescue)	0%
Masura et al. (1993)	BVP	—	34	— (children)	—	5.2 ± 0.8	74 ± 24 (C mean)	36 ± 26 (C mean)	0%	95%	23.5% S	—	17.6%
Ray et al. (1993)	BVP	1986-1991	139	14.9 ± 9.4	55%	1.3 ± 1	116.3 ± 49 (C)	54.4 ± 51.9 (C)	0.7%	99.3%	5% S	—	2.2%
Witsenburg et al. (1993)	BVP	1984 - 1990	92	5.9 (0.8-17.9)	51%	3 ± 1.7	61 ± 34 (C mean)	27 ± 20 (C mean)	—	—	4.3% S	—	0%
McCrindle et al. (1994)	BVP	1981-1986	533	3.7 (0.01-55)	—	2.8 (1-8.7)	74 ± 37 (C mean)	29 ± 22 (C mean)	—	—	16% S	—	7%

Table 2. Post-interventional follow-up in patients with valvular pulmonary stenosis: an overview of published studies (continued)

Author	Intervention	Intervention period	Number of patients	Age at intervention (years)	Male (%)	Follow-up (years)	Pre-inventional gradient (mmHg) *	Post- inventional gradient (mmHg) *	Early mortality (<30 days)	Late survival	Re-intervention #	Time to re-intervention (years) #	Moderate to severe PR
Chen et al. (1996)	BVP	1985-1995	53	26 ± 11	66%	6.9 ± 3.1	91 ± 46 (C)	38 ± 32 (C)	—	—	17% S	—	0%
Mendelsohn et al. (1996)	BVP	1983 - 1993	55	2.5 (0.3-21)	—	4.6 ± 2.3	63.5 ± 24.8 (C mean)	26.7 ± 12.9 (C mean)	0%	100%	2% S	—	—
Rao et al. (1998)	BVP	1983 - 1994	85	7 ± 6.4	51%	7 (3-10)	87 ±38 (C mean)	26 ±22 (C mean)	—	—	16% N	—	8%
Berman et al. (1999)	BVP	1985 - 1998	107	1 (0.28 – 17)	—	7.2 (0.5-10)	—	19 (no SD) (C)	0.9%	99.1%	5.6% (83% S, 17% R)	—	5.6%
Jarrar et al. (1999)	BVP	1987 - 1996	62	13.5 ± 10.5	52%	6.4 ± 3.4	98 ± 40 (C)	32 ± 23 (C)	1.5%	98.5%	4.8% S	—	10%
Gupta et al. (2001)	BVP	Before 1996	96	10.9 ± 11.0	67%	4.9 ± 2.7	111 ± 41 (C)	43 ± 32 (C)	—	—	—	—	4.2%
Peterson et al. (2003)	BVP	1969 - 2000	92	3.2 ± 3.2	—	5.4 ± 3.8	66.2 ± 21.4 (E)	23.8 ± 15.8 (E)	—	—	15.2% (93% S, 7% R)	—	11%
Fawzy et al. (2007)	BVP	1985 - 2003	90	23 ± 9	45%	10 ± 3.9	105 ± 39 (C)	34 ± 26 (C)	0%	100%	6% S	0.5-1	2.2%
Karagoz et al. (2009)	BVP	1988 - 2008	50	0.02 (0 – 0.23)	50%	6.1 (0.02 -18)	80 (15-125) (E mean)	22 (7-98) (E mean)	0%	89%	30% S	—	36%
Voet et al. (2010)	BVP	1987 - 2009	139	3 (0-61)	44%	6 (0-21)	79.5 ± 24.5 (E mean)	24.5 ± 20.8 (E mean)	1.4%	98.6%	9.4% (85% S, 15% O)	—	35.8

Values are expressed as mean ± standard deviation (SD) or median (range).

— = not reported; BVP = balloon valvuloplasty.

** (C) indicates catheter-derived peak-to-peak pressure gradient; (E) indicates peak gradient measured by Doppler echocardiography; "mean" indicates that the mean gradient was measured.*

 # S expresses that restenosis was the indication; R expresses that regurgitation was the indication; O expresses that other reasons were the indication; N expresses that the indication for re-intervention was not specified.

ENDOCARDITIS PROPHYLAXIS

Prophylactic use of antibiotics to prevent bacterial endocarditis is considered unnecessary, except in patients who have a valvular prosthesis, whether it is mechanical, autologous or biological.

PREGNANCY AND RECURRENCE RISK

Because the survival of patients with PS is good, many will reach reproductive age and will want to start a family. Questions about the haemodynamic burden of pregnancy, the impact on ventricular function, and the recurrence of PS in the offspring will thus be frequently encountered.

Recurrence risk

In isolated, non-syndromic PS the recurrence risk is reported to be 1.7–3.7%.[17 w19 w20] In syndromic PS the recurrence risk will be higher, depending on the inheritance pattern of the specific syndrome. While the underlying genetic defect has been identified for the various syndromes associated with PS (table 1), this remains unknown for isolated valvular PS. Referral to the clinical genetics department should be offered to patients considering reproduction, especially when other family members also have a congenital defect.

Pregnancy in PS

In women with mild-to-moderate PS, either native or after previous correction, pregnancy is tolerated well. In severe PS, however, pregnancy may lead to right sided heart failure, due to the increased haemodynamic burden of pregnancy with an increase in cardiac output of 30–50%. Furthermore, atrial arrhythmias occur more frequently during pregnancy, especially in women with a previous history of such arrhythmias. These complications can occur regardless of the functional class before pregnancy. A decrease in ventricular function may occur and does not always resolve after pregnancy. In a Dutch retrospective study of 81 pregnancies in 51 women with mostly mild PS (New York Heart Association (NYHA) functional class I (almost 90% of patients) or II), cardiac complications occurred in 11 pregnancies (14%): two showed persisting deterioration of NYHA class (I>II), and in nine cases palpitations or arrhythmias were reported, but not investigated further. In a large review of the literature regarding cardiac and non-cardiac complications in pregnancy in women with congenital heart disease,18 there appeared to be no cardiac complications in women with PS, although the rate of hypertensive pregnancy complications was higher than in the general population. Taking all this

into account, there seem to be no grounds for discouragement of pregnancy in women with asymptomatic mild-to-moderate PS with a normal ventricular function, exercise tolerance and oxygen uptake. In women showing signs of reduced exercise tolerance or ventricular impairment, correction of the stenosis before conception should be considered. In severe PS, women should undergo correction before conception or they should be counselled against pregnancy. Women who are only discovered to have a significant PS during pregnancy should be followed in a tertiary centre. In the rare case of progressive right heart failure during pregnancy, BPV is the best treatment option. BPV can be performed with relatively low risk for the mother and child.[19] Open heart surgery in pregnancy has a high risk of fetal complications or death, up to 30%.[w21 w22]

Pregnancy in PR

PR is often well tolerated in pregnancy. A London study of 76 pregnancies in 47 women with variable degrees of residual haemodynamic lesions of the RVOT showed that even in those with moderate-to- severe PR the pregnancy outcome was good. Predictors for right heart failure were twin pregnancy, branch PS, RV systolic dysfunction, and RV hypertrophy.[20]

Delivery

There will hardly ever be a cardiological indication for delivery by caesarean section. Unless women are in overt heart failure, vaginal delivery is safe.

EXERCISE AND SPORTS

Patients with mild PS and those without significant residual lesions after previous correction can live normal lives, without any exercise restriction. They should be allowed to participate in competitive sports. Patients with moderate PS and normal biventricular function can participate in moderate levels of exercise, and should be encouraged to do so. They should avoid competitive and static sports. In patients with severe PS, the stenosis must be resolved before they can resume unrestricted physical activity. While awaiting intervention they should be restricted to low intensity sports.

Patients with significant residual PR and RV dilatation should be considered for pulmonary valve replacement before increasing their level of physical activity. Timing of such an intervention depends on (systolic) ventricular function, volume and cardiac reserve, and their deterioration in time.

CONCLUSION

PS is a congenital heart defect with widely variable presentation. It usually can be treated well, with low risk. Nevertheless, patients can have or develop residual lesions and therefore most of them require lifelong cardiological follow-up.

Acknowledgements
The authors wish to thank R Frowijn for his support in editing the illustrations.

Pulmonary stenosis: key points

- The clinical picture of pulmonary stenosis (PS) varies widely, from critical stenosis in the newborn to lifelong asymptomatic mild stenosis.
- The birth prevalence of PS seems to be increasing gradually and is highest in Asia.
- PS can be part of an inheritable syndrome; if not, recurrence risk is 1.7–3.5%.
- First choice treatment is balloon pulmonary valvuloplasty. It can be performed with low risk and has good long term results.
- Patients with mild PS do not need exercise restrictions. Patients with more severe stenosis should avoid competitive and static sports.
- Pregnancy in women with PS is generally well tolerated. The vast majority can go safely through pregnancy and delivery as long as adequate pre-pregnancy counselling and specialised high quality care during pregnancy and delivery are offered.

REFERENCES

1 van der Linde D, Konings EE, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol* 2011;58:2241–7.

‣ An excellent review of all available evidence on the worldwide birth prevalence of congenital heart disease.

2 Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr* 2009;10:1–25.

3 Li W, Davlouros PA, Kilner PJ, et al. Doppler-echocardiographic assessment of pulmonary regurgitation in adults with repaired tetralogy of Fallot: comparison with cardiovascular magnetic resonance imaging. *Am Heart J* 2004;147:165–72.

‣ Describes PR index as a very useful echocardiography tool for daily practice.

4 van der Zwaan HB, Geleijnse ML, McGhie JS, et al. Right ventricular quantification in clinical practice: two-dimensional vs. three-dimensional echocardiography compared with cardiac magnetic resonance imaging. *Eur J Echocardiogr* 2011;12:656–64.

5 Baumgartner H, Bonhoeffer P, De Groot NM, et al. ESC guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J* 2010;31:2915–57.

6 Kouchoukos NT, Blackstone EH, Doty DB, et al. Kirklin/Barratt-Boyes cardiac surgery, 3rd revised edn. Elsevier Health Sciences.

‣ Nice overview of congenital cardiac surgery in a classic textbook.

7 Schievano S, Taylor AM, Capelli C, et al. First-in-man implantation of a novel percutaneous valve: a new approach to medical device development. *EuroIntervention* 2010;5:745–50.

‣ These new developments in percutaneous valves might be promising but they first have to prove themselves.

8 Hayes CJ, Gersony WM, Driscoll DJ, et al. Second natural history study of congenital heart defects. Results of treatment of patients with pulmonary valvar stenosis. *Circulation* 1993;87(2 Suppl):I28–37.

‣ Much cited classic reference on the long term outcome in PS patients.

9 O'Connor BK, Beekman RH, Lindauer A, et al. Intermediate-term outcome after pulmonary balloon valvuloplasty: comparison with a matched surgical control group. *J Am Coll Cardiol* 1992;20:169–73.

10 Earing MG, Connolly HM, Dearani JA, et al. Long-term follow-up of patients after surgical treatment for isolated pulmonary valve stenosis. *Mayo Clin Proc* 2005;80:871–6.

11 Roos-Hesselink JW, Meijboom FJ, Spitaels SE, et al. Long-term outcome after surgery for pulmonary stenosis (a longitudinal study of 22–33 years). *Eur Heart J* 2006;27:482–8.

12 Voet A, Rega F, de Bruaene AV, et al. Long-term outcome after treatment of isolated pulmonary valve stenosis. *Int J Cardiol* 2012;156:11–15.

‣ Very recent overview of the long term results of both BPV and surgery.

13 Peterson C, Schilthuis JJ, Dodge-Khatami A, et al. Comparative long-term results of surgery versus balloon valvuloplasty for pulmonary valve stenosis in infants and children. *Ann Thorac Surg* 2003;76:1078–82; discussion 1082–3.

14 McCrindle BW. Independent predictors of long-term results after balloon pulmonary valvuloplasty. Valvuloplasty and Angioplasty of Congenital Anomalies (VACA) Registry Investigators. *Circulation* 1994;89:1751–9.

‣ Large multicentre registry on BPV in over 500 patients.

15 Berman W Jr, Fripp RR, Raisher BD, et al. Significant pulmonary valve incompetence following oversize balloon pulmonary valveplasty in small infants: a long-term follow-up study. *Catheter Cardiovasc Interv* 1999;48:61–5; discussion 66.

16 Fawzy ME, Hassan W, Fadel BM, et al. Long-term results (up to 17 years) of pulmonary balloon valvuloplasty in adults and its effects on concomitant severe infundibular stenosis and tricuspid regurgitation. *Am Heart J* 2007;153:433–8.

17 Driscoll DJ, Michels VV, Gersony WM, et al. Occurrence risk for congenital heart defects in relatives of patients with aortic stenosis, pulmonary stenosis, or ventricular septal defect. *Circulation* 1993;87(2 Suppl):I114–20.

18 Drenthen W, Pieper PG, Roos-Hesselink JW, et al. Outcome of pregnancy in women with congenital heart disease: a literature review. *J Am Coll Cardiol* 2007;49:2303–11.

‣ A nice, recent overview on pregnancy outcomes in congenital heart disease patients. No cardiac events occurred in 100 pregnancies in PS patients.

19 Regitz-Zagrosek V, Blomstrom LC, Borghi C, et al. ESC guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during pregnancy of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:3147–97.

20 Greutmann M, Von Klemperer K. Pregnancy outcome in women with congenital heart disease and residual haemodynamic lesions of the right ventricular outflow tract. *Eur Heart J* 2010;31:1764–70.

‣ This study shows that the haemodynamic burden of PR is tolerated well in pregnancy, except when additional risk factors are present.

ONLINE ONLY REFERENCES:

w1. Mitchell, M.E., Sander, T.L., Klinkner, D.B., et al., The molecular basis of congenital heart disease. *Semin Thorac Cardiovasc Surg*, 2007. 19(3): p. 228-37.

w2. Huang, J.B., Liu, Y.L., Sun, P.W., et al., Molecular mechanisms of congenital heart disease. *Cardiovasc Pathol*, 2010. 19(5): p. e183-93.

w3. Rijnbeek, P.R., Witsenburg, M., Schrama, E., et al., New normal limits for the paediatric electrocardiogram. *Eur Heart J, 2001*. 22(8): p. 702-11.

w4. Bassingthwaighte, J.B., Parkin, T.W., Dushane, J.W., et al., The Electrocardiographic and Hemodynamic Findings in Pulmonary Stenosis with Intact Ventricular Septum. *Circulation*, 1963. 28: p. 893-905.

w5. van der Zwaan, H.B., Helbing, W.A., McGhie, J.S., et al., Clinical value of real-time three-dimensional echocardiography for right ventricular quantification in congenital heart disease: validation with cardiac magnetic resonance imaging. *J Am Soc Echocardiogr*, 2010. 23(2): p. 134-40.

w6. Stanger, P., Cassidy, S.C., Girod, D.A., et al., Balloon pulmonary valvuloplasty: results of the Valvuloplasty and Angioplasty of Congenital Anomalies Registry. *Am J Cardiol*, 1990. 65(11): p. 775-83.

w7. Kopecky, S.L., Gersh, B.J., McGoon, M.D., et al., Long-term outcome of patients undergoing surgical repair of isolated pulmonary valve stenosis. Follow-up at 20-30 years. *Circulation*, 1988. 78(5 Pt 1): p. 1150-6.

w8. McCrindle, B.W. and J.S. Kan, Long-term results after balloon pulmonary valvuloplasty. *Circulation,* 1991. 83(6): p. 1915-22.

w9. Kaul, U.A., Singh, B., Tyagi, S., et al., Long-term results after balloon pulmonary valvuloplasty in adults. *Am Heart J*, 1993. 126(5): p. 1152-5.

w10. Masura, J., Burch, M., Deanfield, J.E., et al., Five-year follow-up after balloon pulmonary valvuloplasty. *J Am Coll Cardiol*, 1993. 21(1): p. 132-6.

w11. Ray, D.G., Subramanyan, R., Titus, T., et al., Balloon pulmonary valvoplasty: factors determining short- and long-term results. *Int J Cardiol*, 1993. 40(1): p. 17-25.

w12. Witsenburg, M., Talsma, M., Rohmer, J., et al., Balloon valvuloplasty for valvular pulmonary stenosis in children over 6 months of age: initial results and long-term follow-up. *Eur Heart J,* 1993. 14(12): p. 1657-60.

w13. Chen, C.R., Cheng, T.O., Huang, T., et al., Percutaneous balloon valvuloplasty for pulmonic stenosis in adolescents and adults. *N Engl J Med*, 1996. 335(1): p. 21-5.

w14. Mendelsohn, A.M., Banerjee, A., Meyer, R.A., et al., Predictors of successful pulmonary balloon valvuloplasty: 10-year experience. *Cathet Cardiovasc Diagn*, 1996. 39(3): p. 236-43.

w15. Rao, P.S., Galal, O., Patnana, M., et al., Results of three to 10 year follow up of balloon dilatation of the pulmonary valve. *Heart*, 1998. 80(6): p. 591-5.

w16. Jarrar, M., Betbout, F., Farhat, M.B., et al., Long-term invasive and noninvasive results of percutaneous balloon pulmonary valvuloplasty in children, adolescents, and adults. *Am Heart J*, 1999. 138(5 Pt 1): p. 950-4.

w17. Gupta, D., Saxena, A., Kothari, S.S., et al., Factors influencing late course of residual valvular and infundibular gradients following pulmonary valve balloon dilatation. *Int J Cardiol*, 2001. 79(2-3): p. 143-9.

w18. Karagoz, T., Asoh, K., Hickey, E., et al., Balloon dilation of pulmonary valve stenosis in infants less than 3 kg: a 20-year experience. *Catheter Cardiovasc Interv*, 2009. 74(5): p. 753-61.

w19. Drenthen, W., Pieper, P.G., Roos-Hesselink, J.W., et al., Non-cardiac complications during pregnancy in women with isolated congenital pulmonary valvar stenosis. *Heart*, 2006. 92(12): p. 1838-43.

w20. Nora, J.J. and A.H. Nora, Recurrence risks in children having one parent with a congenital heart disease. *Circulation*, 1976. 53(4): p. 701-2.

w21. Weiss, B.M., von Segesser, L.K., Alon, E., et al., Outcome of cardiovascular surgery and pregnancy: a systematic review of the period 1984-1996. *Am J Obstet Gynecol*, 1998. 179(6 Pt 1): p. 1643-53.

w22. John, A.S., Gurley, F., Schaff, H.V., et al., Cardiopulmonary bypass during pregnancy. *Ann Thorac Surg*, 2011. 91(4): p. 1191-6.

w23. Campbell, M., Natural history of congenital pulmonary stenosis. *Br Heart J*, 1969. 31(3): p. 394.

w24. Gatzoulis, M.A., Clark, A.L., Cullen, S., et al., Right ventricular diastolic function 15 to 35 years after repair of tetralogy of Fallot. Restrictive physiology predicts superior exercise performance. *Circulation*, 1995. 91(6): p. 1775-81.

w25. Inglessis, I. and M.J. Landzberg, Interventional catheterization in adult congenital heart disease. *Circulation,* 2007. 115(12): p. 1622-33.

w26. Jurcut, R., Giusca, S., La Gerche, A., et al., The echocardiographic assessment of the right ventricle: what to do in 2010? *Eur J Echocardiogr*, 2010. 11(2): p. 81-96.

w27. Odenwald, T. and A.M. Taylor, Pulmonary valve interventions. *Expert Rev Cardiovasc Ther,* 2011. 9(11): p. 1445-57.

w28. Rao, P.S., Percutaneous balloon pulmonary valvuloplasty: state of the art. *Catheter Cardiovasc Interv*, 2007. 69(5): p. 747-63.

w29. Rowland, D.G., Hammill, W.W., Allen, H.D., et al., Natural course of isolated pulmonary valve stenosis in infants and children utilizing Doppler echocardiography. *Am J Cardiol*, 1997. 79(3): p. 344-9.

w30. Silvilairat, S., Cabalka, A.K., Cetta, F., et al., Outpatient echocardiographic assessment of complex pulmonary outflow stenosis: Doppler mean gradient is superior to the maximum instantaneous gradient. *J Am Soc Echocardiogr*, 2005. 18(11): p. 1143-8.

w31. Warnes, C.A., Williams, R.G., Bashore, T.M., et al., ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*, 2008. 52(23): p. e143-263.

w32. Boyle, D.M., P. Morton, and J.F. Pantridge, The Electrocardiogram in Pulmonary Valve Stenosis with Intact Ventricular Septum. *Br Heart J,* 1964. 26: p. 477-80.

5

The unnatural history of pulmonary stenosis: outcome up to 40 years after surgical repair

Judith A.A.E. Cuypers, MD; Myrthe E. Menting, MD; Petra Opić, MSc, Elisabeth M.W.J. Utens, PhD; Willem A. Helbing, MD, PhD; Maarten Witsenburg, MD, PhD; Annemien E. van den Bosch, MD, PhD; Ron T. van Domburg, PhD; Sara J. Baart, MSc; Eric Boersma, PhD; Folkert J. Meijboom, MD, PhD; Ad J.J.C. Bogers, MD, PhD; Jolien W. Roos-Hesselink, MD, PhD

Submitted

ABSTRACT

Purpose

To provide prospective information on long-term outcome after surgical correction of valvular pulmonary stenosis (PS).

Methods

Eighty-nine consecutive patients operated for PS during childhood between 1968-1980 in our center are followed longitudinally for 37±3.4 years, including extensive in-hospital examination every 10 years.

Results

Survival information was available in 93% of the original 89 patients. Cumulative survival was 97% at 20 years and 93% at 40 years. Excluding perioperative mortality (< 30 days), survival was 95% at 40 years. Of 46 eligible survivors, 29 participated in the in-hospital examination, 15 gave permission to use their hospital records (96% participation). Cumulative event-free survival was 67% after 40 years: 25% needed a reintervention, 12% underwent pacemaker implantation and 9% had supraventricular arrhythmias. Early reinterventions were mainly for residual PS, late reinterventions for pulmonary regurgitation. Subjective health status was good. Exercise capacity was normal in 74% (median 96 [82-107]% of expected). RV and LV dysfunction was found in 13% and 41% respectively. The use of a transannular patch (TAP) and younger age at surgery were predictive for late events (HR 3.02 [95%CI: 1.09-8.37] and HR 0.81/year [95%CI 0.66-0.98] respectively). Use of inflow occlusion compared to cardiopulmonary bypass showed a trend towards more re-interventions (HR 3.19 [95%CI: 0.97-10.47]).

Conclusion

Survival up to 40 years after successful PS repair is nearly normal. Subjective health status is good and there is a low incidence of arrhythmias. Reinterventions, however, are necessary in one quarter and in the last decade a substantial number of patients developed LV dysfunction.

INTRODUCTION

Valvular pulmonary stenosis (PS) is a relatively common congenital heart defect, occurring in about 1 in 2000 live births worldwide.[1] Birth prevalence seems to be increasing, mainly in Asia,[1] but this may be an effect of better recognition due to improved diagnostic tools. Survival after surgical correction, which has been performed since the mid 1950's, is very good, with reported survival rates up to 96% after 25 years.[2-4] Nowadays, balloon pulmonary valvuloplasty has largely replaced surgical correction as the first choice treatment. There are still many patients, however, who underwent surgical correction in the past. They may encounter residual problems like pulmonary regurgitation (PR), which has been reported increasingly as follow-up duration is increasing,[2] and may require reintervention. Also arrhythmias and deterioration in ventricular function have been reported.[3-5] Reports on long-term outcome have been mainly of retrospective nature, and moreover results beyond 25 years are hardly documented in literature.[5] Therefore, we aim to describe survival and morbidity in our cohort of patients that underwent surgical correction of their PS before 1980. This study is unique, as it prospectively followed a cohort of consecutively operated patients for 30-40 years, with extensive in-hospital examination every ten years.[3]

METHODS

Study patients

The 89 consecutive patients who underwent surgical correction for valvular PS in our institution between 1968 and 1980 at an age <15 years, were included in this longitudinal study. The cohort was first studied in 1990 and again in 2001. Survival status of all 89 patients of the original cohort was obtained from the Dutch National Population Registry. In 1990, erroneously, 36 patients were not invited for the first follow-up study.[3] In 2001, efforts were made to trace them, but most were lost to follow-up or did not respond to the invitation. To allow comparison of repeated measurements, all surviving patients who had participated in one or both of the previous follow-up studies were invited to participate in the current, third, detailed in-hospital examination (n=46). Baseline characteristics, surgical procedure, and earlier results have been reported previously.[3] The present study protocol was approved by the institutional Medical Ethics Committee (2010-015). Written informed consent was obtained from all study participants.

Survival and adverse events

Survival status of the whole surgical cohort was obtained from the Dutch National Population Registry and compared to the survival of the reference, age-matched Dutch

population.[6] Adverse events included cardiac reinterventions (surgical or percutaneous), symptomatic arrhythmias (requiring medication, cardioversion or ablation), pacemaker or ICD implantation, stroke, heart failure (requiring medication or hospital admission) and endocarditis. All events were assessed by 2 independent investigators (JC, MM).

Clinical and subjective health status assessment

Medical examination included history, physical examination, 12-lead electrocardiography (ECG), 24-hour ambulatory Holter monitoring, 2D-echocardiography, cardiopulmonary exercise testing and NT-proBNP measurement.

If a patient was unwilling or unable to visit the hospital, a questionnaire was sent to obtain information on morbidity and subjective health-status, and to receive permission for the use of information from their medical records. Participants completed the 36-item short-form healthy survey (SF-36) and results were compared to those of the normative, age-matched Dutch population.[7]

Electrocardiography and Holter monitoring

Standard 12-lead surface ECGs were analyzed for rhythm, PR interval and QRS duration. ECGs with pacemaker rhythm were excluded from analysis of conduction times. A 24-hour Holter monitoring was performed with a Cardio Perfect Holter DR180+ three channel recorder (Welch Allyn Cardio Control, NorthEast Monitoring, Maynard, MA, USA).

Echocardiography

A complete two-dimensional transthoracic Doppler echocardiography was performed using the iE33 xMATRIX X5-1 system (Philips Medical Systems, Best, the Netherlands). Cardiac dimensions and function were measured according to the current guidelines.[8] Right ventricular (RV) and left ventricular (LV) function were assessed visually to allow comparison with the two previous studies. Additionally, more objective measures including RV fractional area change (FAC), S' of the lateral tricuspid annulus and Simpson biplane method were measured to quantify ventricular function. Measurements were obtained by 2 independent observers (JC, MM).

Cardiopulmonary exercise testing

Maximal work load and peak oxygen consumption were assessed by cardiopulmonary exercise testing (CPET) using a bicycle ergometer with gradual workload increments of 20 Watts per minute (Ramp protocol) and compared to the values of normal individuals corrected for age, gender, height and weight. The ratio of minute ventilation to carbon dioxide production (VE/VCO2) was assessed at maximum workload. Performance was considered maximal when a respiratory quotient (RER) of ≥ 1.1 was reached. Maximal work load of <85% was considered abnormal.

NT-proBNP measurement

Venous blood samples were collected after 30 minutes of rest. Plasma NT-proBNP was assessed by electrochemiluminescence immunoassays (Elecsys, Roche Diagnostics, Basel, Switzerland). The normal value for NT-proBNP in our hospital is <14 pmol/L.

Statistical analysis

Continuous data are presented as mean with standard deviation (SD), or median with interquartile range [Q1-Q3] depending on the data distribution. Categorical data are presented as frequencies and percentages. Changes in patient characteristics since the follow-up studies in 1990 and 2001 were evaluated by estimating a trend using mixed models which take missing values into account. Differences between independent subgroups are evaluated by Mann-Whitney-U tests (continuous data), and by Chi^2 or Fisher's exact tests (categorical data). To quantify correlations between two variables, the Spearman correlation test was used.

Cumulative survival and event-free survival of all patients, and of patients with successful PS repair (i.e. excluding postoperative mortality <30 days) were determined by the Kaplan-Meier method. Cumulative event incidences were estimated with the Kaplan-Meier method. In case of sufficient event numbers, univariable and multivariable Cox regression analyses were used to identify determinants of predefined adverse events: all-cause mortality, arrhythmias, reinterventions, heart failure and endocarditis. For the mixed models we used SAS software (version 9.3). All other statistical analyses were performed using the Statistical Package for Social Sciences (version 21, SPSS Inc., Chicago, IL). The statistical tests were two-sided and $P<0.05$ was considered statistically significant.

RESULTS

Survival

Survival status could be obtained in 84 of the 89 patients (93%). Two patients died early due to postoperative complications a third died 10 months postoperatively due to perioperative brain injury.[3] There were 3 late deaths, respectively 24, 25 and 31 years after operation. One 29 year old patient died in a car accident, one 38 year old died unexpectedly during his sleep and the third died due to myocardial infarction, aged 37. Cumulative survival was 97%, 94% and 93% at 20, 30 and 40 years of follow-up, respectively (Figure 1). Excluding early postoperative mortality, survival was 99%, 96% and 95% at 20, 30 and 40 years of follow-up.

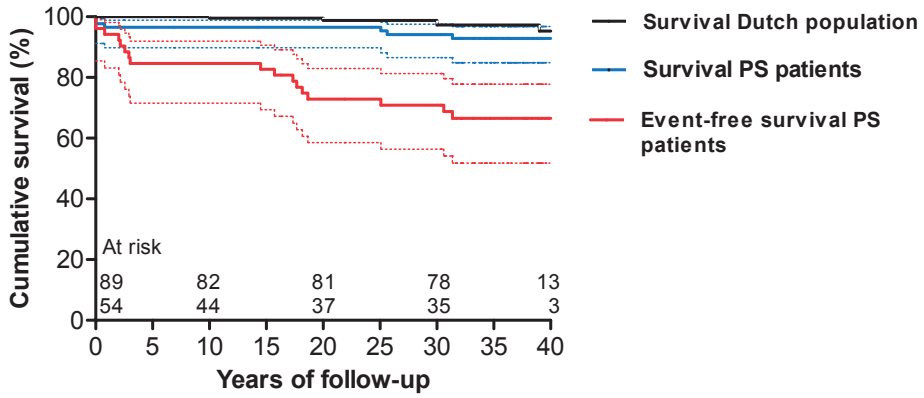


Figure 1. Survival and event-free survival of PS patients compared to the general Dutch population.

Study patients

Of the 46 eligible patients 44 (96%) were included: 29 (66%) participated in-hospital and 15 (34%) completed the questionnaire and gave permission to use the hospital records of their regular clinical follow-up. For the current study, the median post-operative follow-up was 36 years [34-39](range 31-43). The baseline characteristics of the participants are shown in table 1.

Table 1. Baseline characteristics

Baseline characteristics	Original cohort (n = 89)	1990 (n = 44)	2001 (n = 37)	participants 2012 (n = 44)*
Male (%)	53	52	49	49
Palliation (%)	3.4	4.5	5.4	4.4
Patch (%)	20	32	32	29
RV incision (%)	35	55	46	51
Cardiopulmonary bypass (%)	46	66	62	67
Inflow occlusion (%)	53	32	38	32
Hypothermia (%)	73	89	89	87
Aortic clamping (%)	45	71	60	67
Age at operation (years)	5.6 [2.1-8.3]	4.7 [1.2-7.7]	4.6 [1.1-7.5]	5.1 [1.1-7.8]
Temperature during surgery (°C)	30 [28-33]	30 [28-32]	29 [28-32]	29 [28-32]
Aortic cross clamp time (minutes)	20 [7-37]	18 [5-35]	15 [5-27]	18 [7-38]
Preop. systolic RV pressure (mmHg)	106 [90-140]	119 [95-149.5]	112 [95-144]	112 [90-144]
Follow-up duration (years)	-	14.7 [12.6-17.7]	25.5 [23.8-29.4]	36.3 [33.5-39.1]
Age at study (years)	-	18.9 [16-24]	29.8 [27.1-35.8]	39.4 [36.9-45.4]

RV= right ventricle. *Participants in 2012 took part in one or both previous studies.

Adverse events

Cumulative event free survival was 85%, 73%, 71% and 67% at 10, 20, 30 and 40 years. The most frequent event was reoperation. There we no discrepancies between assessments of the 2 evaluators regarding post-surgical events.

Reinterventions: 25% of the patients needed a reintervention: one patient had a re-thoracotomy 2 days postoperatively for unspecified postoperative complications. He died shortly thereafter. Five patients needed a reoperation for residual PS, at 2, 2, 2.5, 3 and 17 years after operation. Four patients needed pulmonary valve replacement (PVR) for severe PR after 18,18,19 and 30 years. One patient had a balloon dilatation of residual PS at the age of 16. One patient underwent ASD closure 3 years after the pulmonary valvotomy.

Arrhythmias: cumulative incidence after 40 years of follow-up was 9%: three patients had atrial flutter at 16, 18 and 21 years follow-up. One of them developed recurrent atrial fibrillation afterwards for which an atrioverter ICD was implanted at the age of 30. One other patient had atrial fibrillation at the age of 19. There were no symptomatic ventricular arrhythmias.

Pacemaker implantation was necessary in 12%: in 2 patients for sick sinus syndrome at 17 and 19 years of follow-up; in the third for 2nd degree AV-block at the age of 48, 38 years after operation.

No patient developed endocarditis, stroke or heart failure.

Subjective health status assessment

On all SF-36 domains patients scored at least as good as the normative population. On social functioning, role limitations due to emotional problems and mental health perception, patients even scored significantly better (Figure 2).

Electrocardiography and Holter monitoring

The ECG and Holter findings are summarized in Table 2. There was no clinically significant increase in conduction delay or sinus node dysfunction. None of the patients had ventricular pauses >3 seconds. There was no progression of SVT or VT on Holter monitoring since 2001. None of the patients showed sustained VTs.

Echocardiography

Table 2 focusses on the comparison with the previous investigations of the same patients. Table 3 describes the state-of-the-art echo measurements, only assessed in 2012. The decline in ventricular function was found by both visual assessment and semi-quantitative assessment (RV FAC and LVEF). No correlation between diminished RV and LV function was observed. There were no significant associations between severity of valvular regurgitation and any parameter of RV and LV function, although there was a

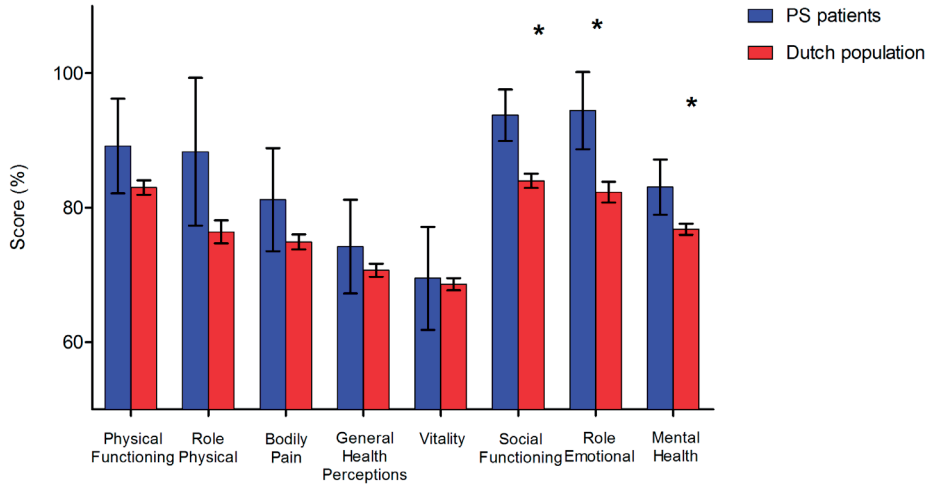


Figure 2. SF-36 results for PS patients and the general Dutch population.
Higher scores indicate more favorable status. *P<0.001.

trend towards lower LVEF in patients with severe PR (p=0.062). Patients with a transannular patch repair (TAP) had lower TAPSE (16.5 versus 19 mm, p=0.031) and RV S' (9.6 versus 12.1 cm/s, p=0.032) than patients without.

Patients operated at normothermia had higher RV FAC (56 versus 45%, p=0.017) and temperature during surgery was related to TAPSE (p=0.013, ρ=0.491).

RV S' was higher in patients operated at older age (p=0.007, ρ=0.548) and with longer follow-up (p=0.049, ρ=0.414).

Patients with TAP tended to have severe PR or PVR more often than patients without (67% versus 27%, p=0.056). There was no difference in deterioration of LV function in patients with and without severe PR.

Cardiopulmonary exercise testing

Table 2 shows the results of CPET. Median maximal workload was 96 [82-107]% of expected. Twenty-six percent of the patients had a diminished exercise capacity (<85% of expected), this did not deteriorate over the last 10 years. Exercise capacity was related to LVEF (p=0.024, ρ=0.516). Exercise capacity was related to temperature during surgery (p=0.032, ρ=0.422). Exercise capacity was better in patients without TAP (103% vs 81%, p=0.027), without RV incision (104 versus 89%, p=0.036) and without prior palliation (97% versus 69%, p=0.009) and tended to be better in patients who were operated at younger age (p=0.069, ρ=0.342).

Peak oxygen uptake was higher in patients without a patch (97% versus 73%, p=0.014) and lower in patients with diminished TAPSE (72% versus 97%, p=0.023).

Table 2. Diagnostic measurements

	1990	2001	2012	
Electrocardiography	**n = 33**	**n = 36**	**n = 35**	**p-value**
Rhythm				
Sinus	29 (88%)	34 (94%)	31 (88%)	0.83
Atrial	4 (12%)	0	1 (3%)	0.109
Pacemaker	0	2 (6%)	3 (9%)	0.127
PR interval (ms)	150 [130-160]	149 [137-160]	151 [142-178]	0.0039
PR ≥200 ms (%)	0	2 (6%)	2 (6%)	0.2421
QRS duration (ms)	90 [80-100]	100 [96-114]	103 [96-121]	**0.0001**
QRS duration ≥120 ms	3 (9%)	8 (24%)	8 (25%)	0.1009
QRS duration ≥180 ms	0	0	0	-
24-hour Holter	**n = 40**	**n = 34**	**n = 28**	
Supraventricular arrhythmias				
Sinus node disease	13 (33%)	12 (35%)	6 (21%)	0.3558
SVT	5 (13%)	4 (12%)	8 (29%)	0.1117
Paroxysmal atrial fibrillation	0	0	0	-
Paroxysmal atrial flutter	0	0	0	-
VT 3-10 complexes	2 (5%)	1 (3%)	2 (7%)	0.7404
VT >10 complexes	1 (3%)	0	0	-
Bicycle ergometry	**n = 42**	**n = 34**	**n = 31**	
Maximal heart rate (%)	94 [89-98]	94 [88-96]	92 [86-96]	0.24
Maximal exercise capacity (%)	102 [90-115]	91 [84-98]	96 [82-107]	**0.005**
Exercise capacity <85%	8 (19%)	8 (24%)	8 (26%)	0.4101
Arrhythmias	7 (17%)	3 (9%)	2 (6%)	0.1595
VO_2 max (%)	-	-	86 [73-105]	-
RER max	-	-	1.33 [1.24-1.42]	-
VE/VCO2 max			32.2 [28.3-34.9]	
Echocardiographic parameters	**n = 43**	**n = 36**	**n = 32**	
LA end-systolic dimension (mm)	32 [25-35]	37 [32-40]	38 [32-42]	**<0.0001**
LV end-systolic dimension (mm)	25 [26-32]	32 [27-34]	30 [26-34]	0.21
LV end-diastolic dimension (mm)	44 [40-48]	47 [43-50]	47 [44-50]	0.015
LV fractional shortening (%)	37 [30-42]	35 [28-39]	35 [30-43]	0.309
Fractional shortening <30%	8 (20%)	11 (31%)	6 (19%)	0.8214
RV systolic function normal	-	35 (95%)	19 (58%)	-
LV systolic function normal	-	35 (95%)	21 (64%)	-
PS peak velocity (m/s)	-	1.8 [1.5-2.1]	1.8 [1.7-2.1]	-
TR peak velocity (m/s)	-	2.5 [2.2-2.7]	2.5 [2.4-2.7]	-
PR >mild	19 (44)	15 (43)	13 (41)	0.7172
TR >mild	3 (9)	4 (13)	3 (11)	0.7232

SVT= supraventricular tachycardia; VT= ventricular tachycardia; RER= respiratory exchange ratio; RA= right atrium; RV= right ventricular; LA= left atrium; LV= left ventricular; FS= fractional shortening; AR= aortic valve regurgitation; MR= mitral valve regurgitation; PR= pulmonary valve regurgitation; PS= pulmonary stenosis; TR= tricuspid valve regurgitation.
Categorical data are presented as n (%); continuous data as median [interquartile range].

Table 3. Echocardiographic parameters only available in 2012

	Median	Q1-Q3	Abnormal (n, %)	Cutt-off value for normal
TAPSE (mm)	19	17-20.5	5 (17)	≥16
RV FAC (%)	46	39-53	4 (13)	≥35%
RV S'	10.9	9.6-13.3	6 (26)	≥10 cm/s
LV EF (%)	55	49-63	9 (41)	male ≥52%, female ≥54%
E/A ratio	1.3	1.1-1.8	2 (6)	0.7-3.1
E/E' ratio	8	6.4-12.3	4 (12,5)	<15
DET (ms)	204	165-243	15 (48)	139-219
Estimated SRVP (mmHg)	31	25-35	13 (52)	<30 mmHg

TAPSE= tricuspid annular plane systolic excursion; RV= right ventricular; FAC= fractional area change; S'= lateral wall pulse tissue Doppler S wave; LV EF= left ventricular ejection fraction by Simpson's method; DET= deceleration time; SRVP= systolic right ventricular pressure.

Table 4. Predictors of the clinical end points all events and reintervention

ALL EVENTS (n = 17)	p-value	HR	CI
Univariate analysis			
Use of a transannular patch	0.034	3.020	(1.089-8.371)
Age at operation	0.042	0.857	(0.738-0.994)
RV incision	0.812		
Prior palliation	<0.001	35.549	(5.747-219.908)
Inflow occlusion (no CPB)	0.105		
Aortic cross clamp time	0.770		
Preoperative RV pressure	0.726		
Multivariate analysis			
Age at operation	0.148	0.9	(0.8-1.0)
Prior palliation	0.001	24.1	(3.7-156.4)
REINTERVENTIONS (n = 12)	**p-value**	**HR**	**CI**
Use of a transannular patch	0.015	4.611	(1.342-15.841)
Age at operation	0.033	0.805	(0.659-0.982)
RV incision	0.790		
Prior palliation	1.000		
Inflow occlusion (no CPB)	0.055	3.192	(0.973-10.470)
Aortic cross clamp time	0.734		
Preoperative RV pressure	0.482		

RV= right ventricle.

NT-proBNP measurement

Median NT-proBNP level was 13.2 [IQR 10.1-23.7] pmol/L. A mildly elevated NT-proBNP level (>14.0) was measured in 48%. NT-proBNP was not related to LV or RV function, severity of PR, exercise capacity or any of the baseline characteristics. All 3 patients with more than mild tricuspid regurgitation had a higher NT-proBNP (29.3 versus 13.2 pmol/l, p=0.046). NT-proBNP levels correlated with lower S' of the RV lateral wall (p=0.019, ρ=-0.507).

Predictor analyses

Results of the baseline parameters Cox regression analysis are shown in Table 4. The limited number of events prevented separate testing of all outcomes. Patients who were operated at older age, who had prior palliation and in whom a patch was used to relieve the PS, were more likely to have an event. Adjusting for age at operation, prior palliation remained a statistically significant predictor for events (p=0.001, HR 24.080 (3.7-156.4)). Younger age at surgery and TAP were associated with a higher incidence of reintervention. Cardiac arrest by use of inflow occlusion showed a trend towards more reinterventions. The use of a RV incision or a more severe PS preoperatively did not predict outcome.

DISCUSSION

This prospective longitudinal study of PS patients operated at young age shows that survival is excellent and comparable to the normal Dutch population. However, event-free survival is only 67% at 40 years, with 25% of the patients needing at least one reintervention. There was a low incidence of arrhythmias and no endocarditis or heart failure occurred. Unexpectedly, we found a deterioration in LV function in more than 40% of the patients, which was associated with a lower exercise capacity.

Mortality and late events

Our study shows that mortality remains low up to 40 years after operation. Previous reports have shown good survival after successful repair of PS up to 30 years of follow-up,[2] however, longer studies were not available until now. Half of the mortality was due to perioperative complications. When perioperative mortality is excluded, the survival is even comparable to the normal population. Nowadays, with most PS patients being treated percutaneously, early mortality is even lower.[2]

Late mortality in patients with congenital heart disease is typical due to heart failure or arrhythmias,[9] as was found in Fallot patients operated in the same era.[10] Heart failure was not found in our population, although there is ventricular dysfunction and PR in a substantial number of patients. Fatal arrhythmia is only suspected in one of our patients. This patient died suddenly and was not known to have diminished ventricular function and had only mild PR.

Morbidity is mainly due to the need for reintervention, with residual PS being the main reason for reintervention in the first decades, while reintervention for PR was typically seen later on. The reintervention rate after balloon valvuloplasty is reported to be lower (2.5-30%),[2] but follow-up is inevitably shorter. In comparison with tetralogy of Fallot, the reintervention rate of PS patients seems to be lower.[10, 11] We found a reintervention rate

of 25% after 40 years in PS patients versus 44% in Fallot patients, while others report reintervention rates between 2-20% after PS repair[2] and 21-50% after Fallot repair.[11, 12] One PS study reports reinterventions up to 59%, but this study also included the very early era.[4] In our study 33% of the reinterventions was performed for PR and in addition 25% now has moderate to severe PR, probably needing reintervention in the future. This underscores the need for lifelong follow-up after PS repair.

Subjective health status

Overall, exercise capacity in our patients was good, and better than reported by Kempny et al.[13] Still, one quarter of our patients had a mildly diminished exercise capacity. Their subjective health status, however, is comparable to or even better than normative data. The higher scores in our group may be due to different frames of reference, overcompensation, and social desirability.[14]

Arrhythmia

Arrhythmias are not frequently reported to be a major problem in patients post PS repair. In our group, they occurred in only 9%, and consisted of supraventricular arrhythmias only. This is much lower than reported by Earing et al, who described clinically significant arrhythmias (both supraventricular and ventricular) in 38%. None of our patients had ventricular arrhythmias, neither clinically nor on Holter recording. Although QRS duration increased mildly over time, none had a QRS duration >180 ms, which is recognized as a risk factor for ventricular arrhythmias and sudden cardiac death in Fallot patients [15]. AV-conduction delay was not a major problem in our patients. AV-conduction intervals on ECG did not increase over time, and pacemakers were implanted for sick sinus syndrome and AV block only after earlier episodes of SVT.

Ventricular function and PR

While almost every patient in our cohort had a normal ventricular function 10 years ago, a substantial number developed ventricular dysfunction in the last decade, concerning both the right and especially the left ventricle. Regarding the RV, we were not surprised to find a deterioration over time, as this is also observed in Fallot patients, who in part suffer from the same residual problems. Zdradzinski et al reported similar RV function and volumes in patients after surgical PS repair as in Fallot patients.[16] In our study, the amount of RV dysfunction in PS patients was less than in Fallot patients, studied in a comparable manner and after a comparable follow-up.[10] Puranik et al. also found a worse ventricular function (on CMR) in Fallot patients compared to PS patients with the same amount and duration of PR.[17] This was related to the presence of an acontractile patch in the RVOT. Others reported larger RV volumes, worse RV EF and more PR in Fallot patients compared to PS patients treated with balloon valvuloplasty.[18, 19] Also in our study TAPSE

and RV lateral S', measures of RV function, were better in patients without a patch. In conclusion, the RV in PS patients seems better than in Fallot, but also hampered by the presence of a TAP.

The observed deterioration in LV function is harder to explain. Our first thought, of having become more critical in visual assessment of ventricular function, seems to be offset by the results of the semi-quantitative assessments confirming diminished LV function. In addition, diminished LV function was found to be associated with diminished exercise capacity, so this seems clinically relevant. Is this deterioration of LV function due to suboptimal techniques of cardiac arrest and cardio-protection during surgery in the earliest surgical era? We did not find a difference in LV function between patients that were operated using inflow obstruction or cardiopulmonary bypass, or between those operated in the earliest years compared to those who were operated in the later years, to underscore this argument. We assumed a contribution of ventricular-ventricular interaction, but were not able to show an association between diminished RV and LV function in our relatively small group.

A substantial number of our patients had more than mild PR, but this did not deteriorate over the last decade. PR is known to be tolerated well for a long time, and timing of PVR remains difficult. The goal is to prevent irreversible deterioration of ventricular function. Most recommendations on when to intervene for PR are based on findings in Fallot patients [20]. In the absence of more specific literature, we tend to apply the same recommendations in post-PS patients. Because deterioration of RV function may be present in completely asymptomatic patients, regular follow-up seems indicated.

Predictors for late events

Although the amount of events in our study group was too small to test for different events separately, we were able to show that the use of palliation prior to the PS repair, the use of a TAP and repair at younger age were related to more events.

CONCLUSION

Survival up to 40 years after successful repair of PS is nearly as good as survival in the general population. Subjective health status is very good. There is a low incidence of arrhythmias. Reinterventions, however, are necessary in one quarter of the patients and function of both right and left ventricle need careful attention.

Study limitations

The number of patients in this study is limited. Nevertheless, we were able to gather medical information on 44 (96%) of the 46 approached patients, of whom we have data

over time. Moreover, this is the only cohort worldwide that is being followed consequently every 10 years, regardless of whether patients are still followed in the outpatient clinic.

Due to the limited number of events in our cohort, we were only able to perform univariable testing for predictors of outcomes.

Diagnostic methods have changed inevitably over the last decades. For comparison with data of the previous study in this cohort, we used the same methods as were used in the past. Additionally, we performed and reported all up-to-date diagnostic methods which were available in 2012.

Aknowledgements

We thank Lisanne Konings and Maarten Slager for their valuable help in data collection, entry and analysis.

REFERENCES

1. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2011 Nov 15;58(21):2241-7.
2. Cuypers JA, Witsenburg M, van der Linde D, Roos-Hesselink JW. Pulmonary stenosis: update on diagnosis and therapeutic options. *Heart*. 2013 Mar;99(5):339-47.
3. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, vanDomburg RT, vanRijen EH, Utens EM, et al. Long-term outcome after surgery for pulmonary stenosis (a longitudinal study of 22-33 years). *Eur Heart J*. 2006 Feb;27(4):482-8.
4. Voet A, Rega F, de Bruaene AV, Troost E, Gewillig M, Van Damme S, et al. Long-term outcome after treatment of isolated pulmonary valve stenosis. *Int J Cardiol*. 2012 Apr 5;156(1):11-5.
5. Earing MG, Connolly HM, Dearani JA, Ammash NM, Grogan M, Warnes CA. Long-term follow-up of patients after surgical treatment for isolated pulmonary valve stenosis. *Mayo Clin Proc*. 2005 Jul;80(7):871-6.
6. Continuous quality of life survey of the Dutch population. In: NCBoS, editor. The Hague/Heerlen: Sdu Publisher.
7. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol*. 1998 Nov;51(11):1055-68.
8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015 Mar;16(3):233-70.
9. Oechslin EN, Harrison DA, Connelly MS, Webb GD, Siu SC. Mode of death in adults with congenital heart disease. *Am J Cardiol*. 2000 Nov 15;86(10):1111-6.
10. Cuypers JA, Menting ME, Konings EE, Opic P, Utens EM, Helbing WA, et al. Unnatural history of tetralogy of Fallot: prospective follow-up of 40 years after surgical correction. *Circulation*. 2014 Nov 25;130(22):1944-53.
11. Hickey EJ, Veldtman G, Bradley TJ, Gengsakul A, Manlhiot C, Williams WG, et al. Late risk of outcomes for adults with repaired tetralogy of Fallot from an inception cohort spanning four decades. *Eur J Cardiothorac Surg*. 2009 Jan;35(1):156-64; discussion 64.
12. Bacha EA, Scheule AM, Zurakowski D, Erickson LC, Hung J, Lang P, et al. Long-term results after early primary repair of tetralogy of Fallot. *J Thorac Cardiovasc Surg*. 2001 Jul;122(1):154-61.
13. Kempny A, Dimopoulos K, Uebing A, Moceri P, Swan L, Gatzoulis MA, et al. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life—single centre experience and review of published data. *Eur Heart J*. 2012 Jun;33(11):1386-96.
14. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, et al. Current subjective state of health, and longitudinal psychological well-being over a period of 10 years, in a cohort of adults with congenital cardiac disease. *Cardiol Young*. 2005 Apr;15(2):168-75.

15. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, et al. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet*. 2000 Sep 16;356(9234):975-81.

16. Zdradzinski MJ, Qureshi AM, Stewart R, Pettersson G, Krasuski RA. Comparison of long-term postoperative sequelae in patients with tetralogy of Fallot versus isolated pulmonic stenosis. *Am J Cardiol*. 2014 Jul 15;114(2):300-4.

17. Puranik R, Tsang V, Lurz P, Muthurangu V, Offen S, Frigiola A, et al. Long-term importance of right ventricular outflow tract patch function in patients with pulmonary regurgitation. *J Thorac Cardiovasc Surg*. 2012 May;143(5):1103-7.

18. Luijnenburg SE, de Koning WB, Romeih S, van den Berg J, Vliegen HW, Mulder BJ, et al. Exercise capacity and ventricular function in patients treated for isolated pulmonary valve stenosis or tetralogy of Fallot. *Int J Cardiol*. 2012 Jul 26;158(3):359-63.

19. Mercer-Rosa L, Ingall E, Zhang X, McBride M, Kawut S, Fogel M, et al. The impact of pulmonary insufficiency on the right ventricle: a comparison of isolated valvar pulmonary stenosis and tetralogy of fallot. *Pediatr Cardiol*. 2015 Apr;36(4):796-801.

20. Piazza L, Chessa M, Giamberti A, Bussadori CM, Butera G, Negura DG, et al. Timing of pulmonary valve replacement after tetralogy of Fallot repair. *Expert Rev Cardiovasc Ther*. 2012 Jul;10(7):917-23.

6

Unnatural history of tetralogy of Fallot: prospective follow-up of 40 years after surgical correction

Judith A.A.E. Cuypers, MD; Myrthe E. Menting, MD; Elisabeth E.M. Konings, MSc; Petra Opić, MSc; Elisabeth M.W.J. Utens, PhD; Willem A. Helbing, MD, PhD; Maarten Witsenburg, MD, PhD; Annemien E. van den Bosch, MD, PhD; Mohamed Ouhlous, MD, PhD; Ron T. van Domburg, PhD; Dimitris Rizopoulos, PhD; Folkert J. Meijboom, MD, PhD; Eric Boersma, PhD; Ad J.J.C. Bogers, MD, PhD; Jolien W. Roos-Hesselink, MD, PhD

Circulation. 2014;130:1944-1953.

ABSTRACT

Background

Prospective data on long-term survival and clinical outcome beyond 30 years after surgical correction of tetralogy of Fallot are nonexistent.

Methods and Results

This longitudinal cohort study consists of the 144 patients with tetralogy of Fallot who underwent surgical repair at <15 years of age between 1968 and 1980 in our center. They are investigated every 10 years. Cumulative survival (data available for 136 patients) was 72% after 40 years. Late mortality was due to heart failure and ventricular fibrillation. Seventy-two of 80 eligible survivors (90%) participated in the third in-hospital investigation, consisting of ECG, Holter, echocardiography, cardiopulmonary exercise testing, N-terminal pro-brain natriuretic peptide measurement, cardiac magnetic resonance (including dobutamine stress testing), and the Short Form-36 questionnaire. Median follow-up was 36 years (range, 31–43 years). Cumulative event-free survival was 25% after 40 years. Subjective health status was comparable to that in the normal Dutch population. Although systolic right and left ventricular function declined, peak exercise capacity remained stable. There was no progression of aortic root dilation. A previous shunt operation, low temperature during surgery, and early postoperative arrhythmias were found to predict late mortality (hazard ratio, 2.9, 1.1, and 2.5, respectively). An increase in QRS duration and a deterioration of exercise tolerance and ventricular dysfunction did not predict mortality. Insertion of a transannular patch was a predictor for late arrhythmias (hazard ratio, 4.0; 95% confidence interval, 1.2–13.4).

Conclusions

Although many patients needed a reoperation or developed arrhythmias, late mortality was low, and the clinical condition and subjective health status of most patients remained good. Previous shunt, low temperature during surgery, and early postoperative arrhythmias were found to predict late mortality.

INTRODUCTION

Tetralogy of Fallot (ToF) is the most prevalent form of cyanotic congenital heart diseases.[1] Although mortality was substantial in the earliest era of surgical correction,[2] survival has improved dramatically over the years: 90% of patients are currently alive 30 years after successful surgical correction at a young age.[3-6] Despite these satisfactory results, survival up to 30 years is lower than in the normal population, and little is known about long-term functional outcome and life expectancy beyond 30 years. [5, 7]

Although anatomic correction and physiological correction have been achieved, complications such as pulmonary regurgitation leading to right ventricular (RV) dysfunction, recurrent obstruction of the RV outflow tract, arrhythmias, sudden death, and aortic dilation and regurgitation are found in late survivors.[1, 8, 9]

Information on outcome after correction beyond 30 years is limited and has mostly been collected retrospectively. Most previous studies focused on a selection of patients regularly seen at the outpatient clinic, which may lead to selection bias. Our study is part of a unique ongoing longitudinal follow-up that started in 1990. The patients are investigated in hospital every 10 years.[10, 11] The aim of the present study is to provide data on survival and clinical course, including late sequelae, in survivors up to 40 years after initial correction and to detect predictors for outcome.

METHODS

Study patients

All consecutive patients who underwent surgical correction for ToF (excluding pulmonary atresia) in our institution between 1968 and 1980 at <15 years of age were included in this longitudinal study. The cohort was first studied in 1990, and the second follow-up was performed in 2001. For the current third follow-up, survival status of the patients was obtained from the Dutch National Population Registry. All patients who were alive and had participated in 1 or both of the earlier follow-up studies were invited for the third in-hospital investigation in 2011 to 2012. Detailed information describing the baseline characteristics, surgical procedure, and 10- and 20-year follow-up results has been reported previously.[10, 11] The study protocol was approved by the institutional Medical Ethics Committee (2010-015). Written informed consent was obtained from all study participants.

Survival and adverse events

Survival was compared with the survival of the reference, age-matched Dutch population. Adverse events were defined as all-cause mortality, cardiac reinterventions (both percu-

taneous and surgical), symptomatic arrhythmias (needing medication or an intervention), stroke, heart failure (needing medication or hospital admission), and endocarditis.

Clinical assessment

Medical examination included history, physical examination, subjective health status assessment (Short Form-36), standard 12-lead ECG, 24-hour ambulatory Holter monitoring, 2-dimensional echocardiography, cardiopulmonary exercise testing, N-terminal pro-brain natriuretic peptide (NT-proBNP) measurement, and cardiac magnetic resonance (CMR) imaging with dobutamine stress testing unless contraindicated.

If a patient was unwilling or unable to visit the outpatient clinic, a questionnaire was sent to obtain information on morbidity and subjective health status and to receive permission for the use of information from medical records.

Subjective health status assessment

The scores on the 36-item short-form healthy survey (Short Form-36) of all study participants were compared with results of the normative Dutch population[12] and with their own results from 2001.

ECG and Holter monitoring

Standard 12-lead surface ECGs were analyzed for rhythm, PR interval, and QRS duration. ECGs with pacemaker rhythm were excluded from comparison of conduction times. A 24-hour Holter monitoring was performed with a Cardio Perfect Holter DR180+ 3-channel recorder (Welch Allyn Cardio Control, NorthEast Monitoring, Maynard, MA).

Echocardiography

A complete 2-dimensional transthoracic Doppler echocardiography was performed with the iE33 xMATRIX X5-1 system (Philips Medical Systems, Best, the Netherlands). Cardiac dimensions and function were measured according to the current guidelines.[13, 14] RV function was assessed visually to allow comparison with the 2 previous studies. Additionally, more objective measures, including fractional area change and tricuspid annular plane systolic excursion, were measured to quantify RV function.

Cardiopulmonary exercise testing

Maximal workload and oxygen consumption (VO_2max) were assessed by cardiopulmonary exercise testing using a bicycle ergometer with gradual workload increments of 20 W/min (ramp protocol) and compared with the values of normal individuals corrected for age, sex, height, and weight. The ratio of minute ventilation to carbon dioxide production (VE/VCO_2) was assessed at the anaerobic threshold and at maximum workload. Performance was considered maximal when a respiratory quotient of ≥ 1.1 was reached.

NT-proBNP measurement

Peripheral venous blood samples were collected after 30 minutes of rest. Plasma NT-proBNP levels were determined with the use of the commercially available electrochemiluminescence immunoassay Elecsys (Roche Diagnostics, Basel, Switzerland). The normal value for NT-proBNP in our hospital is <14 pmol/L.

CMR imaging with dobutamine

CMR imaging was performed with a Signa 1.5-T whole-body scanner (GE Medical Systems, Milwaukee, WI) with dedicated phased array cardiac surface coils. Details of the MR sequence used have been reported previously.[15] Images were collected at rest and after low-dose (7.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and high-dose (20 $\mu g \cdot kg^{-1} \cdot min^{-1}$) dobutamine administration. Contraindications for the use of dobutamine were previous sustained ventricular tachycardia (VT), frequently recurrent supraventricular tachycardia, and inflow or outflow obstruction of the ventricles. For CMR analyses, a commercially available Advanced Windows workstation (GE Medical Systems) was used, equipped with Q-mass (version 5.2, Medis Medical Imaging Systems, Leiden, the Netherlands). The ventricular volumetric data set was quantitatively analyzed by a single investigator (J.A.A.E.C.) using manual outlining of endocardial borders in end systole and end diastole, excluding large trabeculae (visible on 3 subsequent slices) and the papillary muscles from the blood volume. Biventricular end-diastolic volume, end-systolic volume, ejection fraction (EF), and valvular regurgitation fractions were calculated and compared with reference values.[16]

Statistical analysis

For the descriptive data analyses, we used the Statistical Package for Social Sciences (version 20.0, SPSS, Inc, Chicago, IL). Continuous data are presented as mean with standard deviation or median with interquartile range. Categorical variables are presented as frequencies and percentages. For comparison of continuous variables between independent groups, the Student unpaired t test was used; for repeated measures, the paired t test or Wilcoxon signed-rank test were performed. Frequencies of unpaired data were compared by use of the $\chi 2$ test or Fisher exact test when applicable, and for paired data, the McNemar test was used. To quantify correlations between 2 variables, we used the Pearson correlation test or Spearman correlation test. For advanced statistical analyses of the longitudinal and survival data, the R software version 3.0.1 package was used (www.r-project.org). Univariable and multivariable Cox proportional hazard regression analyses were used to identify predictors for the predefined events: all-cause mortality, arrhythmias or pacemaker implantation, and pulmonary valve replacement (PVR). The following covariates were included in the models: early postoperative arrhythmias, temperature during surgery, palliative shunt before corrective surgery, insertion of a transannular patch, age at operation, and era of operation (before or after 1975). Because

of the low frequencies for the aforementioned events, we used a penalized likelihood approach for estimating the Cox model.[17] To account for missing covariate data, we used a multiple imputation approach.[18] Wald tests were used to assess which covariates were most associated with the risk of each event. Time-dependent Cox regression analysis was used to assess the effects of the time-dependent covariates: QRS duration, VT on Holter, exercise capacity, and left ventricular (LV) fractional shortening on outcome. For description of survival of the total cohort and the Dutch reference population, the Kaplan–Meier method was used. Cumulative event incidences were computed with the use of a nonparametric estimator of cumulative incidence functions. All statistical tests were 2 sided, and the level of significance was at $P<0.05$.

RESULTS

Study patients

The original study cohort consisted of 144 consecutive patients who underwent surgical correction of ToF between 1968 and 1980. Baseline characteristics are presented in Table 1. Further baseline and surgical details have been reported previously.[10, 11]

For the present study 36 years (range, 31–43 years) after correction, 80 patients were eligible. Of them, 72 (90%) were included: 53 (66%) participated in-hospital and 19 (24%) gave permission to use the hospital records of their regular clinical follow-up. There were no differences in baseline characteristics between the participating and nonparticipating patients.

Table 1. Baseline characteristics.

	Total	**1990**	**2001**	**2012**	**No third study***	**P-value†**
	n = 144	**n = 79**	**n = 79**	**n = 72**	**n = 72**	
Male, n (%)	87 (60%)	46 (58%)	44 (56%)	42 (58%)	45 (63%)	0.609
Age at study, yrs (IQR)	-	18.5 [15.1-23.2]	30.4 [26.3-35.6]	39.8 [36.1-45.5]	-	-
Age at operation, yrs (IQR)	4.6 [1.7-6.6]	4.3 [1.4-6.5]	4.3 [1.4-6.6]	3.8 [1.4-6.6]	4.9 [1.8-7.2]	0.163
Prior palliation, n(%)	50 (35%)	25 (32%)	25 (32%)	20 (28%)	30 (42%)	0.080
Transannular patch, n(%)	87 (60%)	48 (55%)	47 (54%)	48 (67%)	44 (51%)	0.488
Hypothermia, n(%)						
Temperature <20°C	43 (30%)	25 (32%)	27 (34%)	24 (33%)	19 (26%)	0.746
Temperature 20-35°C	89 (62%)	52 (66%)	50 (63%)	47 (65%)	42 (58%)	
Temperature unknown	12 (8%)	2 (2%)	2 (3%)	1 (1%)	11 (15%)	

* Including deceased and emigrated patients.
† 2012 vs. no third study.

Survival

Survival status was obtained in 136 patients (94%). Eight patients moved abroad and were untraceable. Cumulative survival after surgical correction was 83% after 10 years, 81% after 20 years, 78% after 30 years, and 72% after 40 years (Figure 1). In total, 35 of the 144 patients died, 23 within 30 days after surgery. Of the hospital survivors, cumulative survival was 98% after 10 years, 96% after 20 years, 92% after 30 years, and 86% after 40 years. In patients who survived 30 days postoperatively, incident mortality rate was 0.29 per 100 patient-years. In the last 10 years, 6 patients died. Three patients died of end-stage heart failure 26, 28, and 38 years after surgery at 31, 32, and 51 years of age, respectively. Two of them had nonsustained VTs on Holter in 1990 or 2001. In 1 of these patients, death was triggered by an infection. Two other patients died of ventricular fibrillation 24 and 34 years after surgery at 28 and 41 years of age, respectively. One patient died after a shooting incident.

Adverse events

Cumulative event-free survival after 40 years was 25% (Figure 2). In the last 10 years, 35 patients (49% of the participants) were hospitalized at least once.

Reinterventions

The cumulative incidence of reinterventions after 35 years of follow-up was 44% (Figure 3). In the last decade, 32 patients required ≥1 reinterventions: PVR (n=20); closure of a ventricular septal defect (n=8); balloon dilation of the pulmonary artery or branch (n=6); aorta-related reoperation (n=3), including 1 elective aortic arch replacement because of an aneurysm (aortic diameter, 57 mm); and infundibulectomy (n=1).

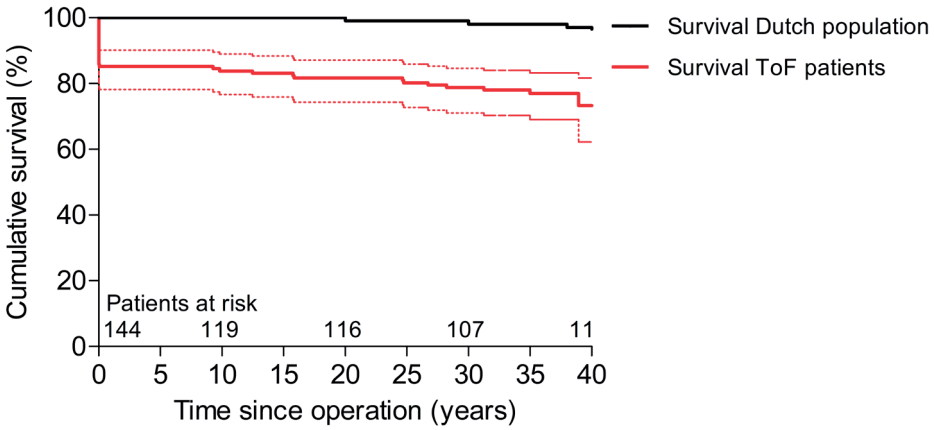


Figure 1. Survival of the cohort and the general Dutch population.
Kaplan Meier plot describing survival in the studied cohort compared to the Dutch reference population.

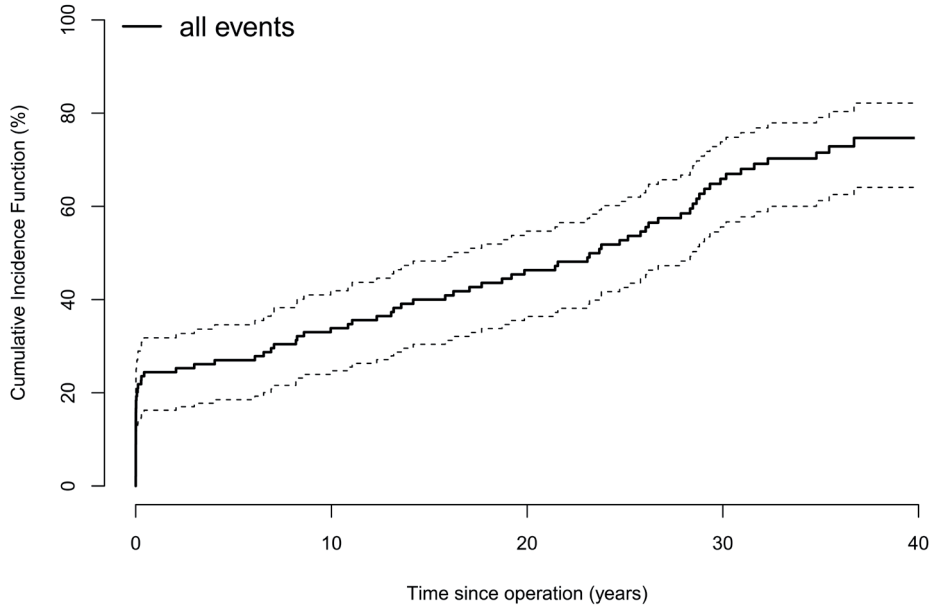


Figure 2. Cumulative incidence of all events.

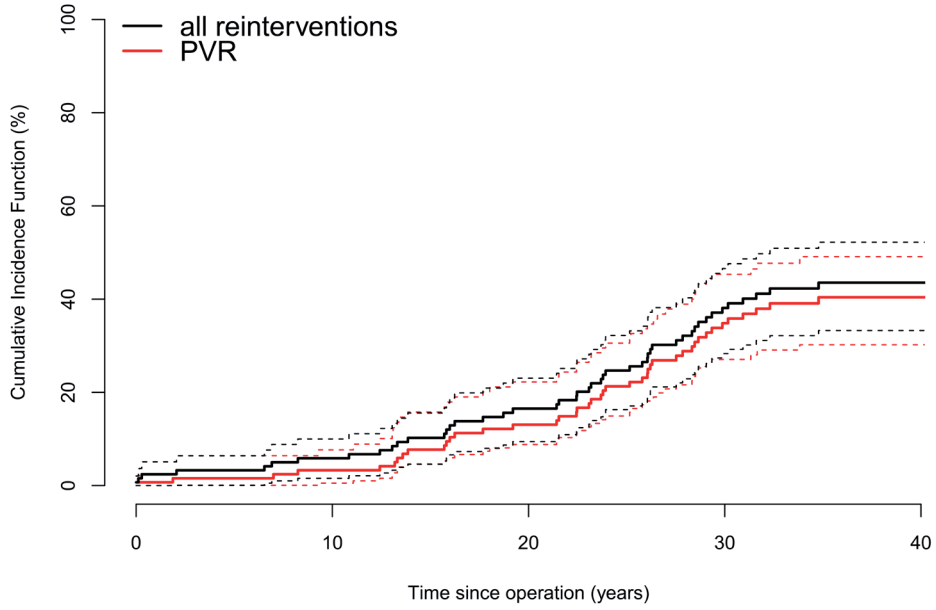


Figure 3. Cumulative incidence of PVR and all reintervention.

Pulmonary valve replacement

Despite a rather conservative approach to PVR in our center,[11] the cumulative incidence of PVR was 40% at 35 years (Figure 3). Of the participating patients, 35 underwent PVR at a median of 24 years (interquartile range, 16–29 years) after the initial correction. In the last decade, surgical PVR was performed in 19 patients for the first time, 2 of whom underwent transcatheter PVR later. One patient underwent transcatheter PVR after receiving a surgical homograft in 2000.

Arrhythmias

The cumulative incidence of symptomatic arrhythmias was 17% at 35 years (Figure 4). In the last decade, 5 patients had new symptomatic arrhythmias; 3 patients had atrial fibrillation and needed electric cardioversion. One of them underwent catheter ablation afterward. One patient had atrial flutter, and 1 patient was treated for arrhythmias of unknown origin in another hospital. In the last decade, 2 patients received a pacemaker and 2 received an implantable cardioverter-defibrillator (ICD). Both ICDs were implanted for secondary prevention after the patients experienced sustained VTs. One other patient had an ICD indication because of recurrent VTs but has refused implantation. Thirty-five years after surgical correction, the cumulative incidences of pacemaker and ICD implantation were 10% and 5% respectively.

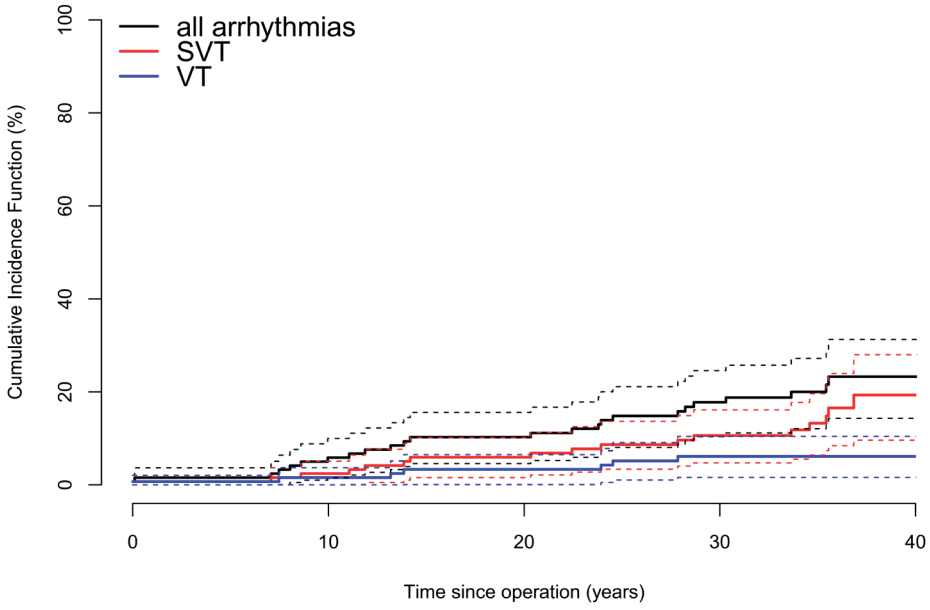


Figure 4. Cumulative incidences of SVT, VT and all arrhythmias, including implantation of pacemaker and ICD.

Heart Failure

The cumulative incidence of heart failure at 35 years of follow-up was 3%.

Stroke

In the last decade, 4 patients had a transient ischemic attack. Two of them had an open foramen ovale.

Endocarditis

Two patients were diagnosed with endocarditis: 1 had bacteremia with Streptococcus oralis 5 years after ICD implantation, which resolved on antibiotics only after the ICD had been removed. The other had bacteremia with Streptococcus sanguis 21 years after pulmonary homograft implantation. The patient was treated with antibiotics and remained free of recurrent bacteremia afterward.

Subjective health status assessment

Patients scored significantly better on the domains of role limitations resulting from physical or emotional problems, bodily pain, and social functioning compared with normative data (Figure 5). In direct comparison with their own previous results, patients showed a less favorable general health perception (P=0.042) than 10 years ago.

ECG and Holter monitoring

The ECG and Holter findings are summarized in Table 2. None of the patients had ventricular pauses >3 seconds.

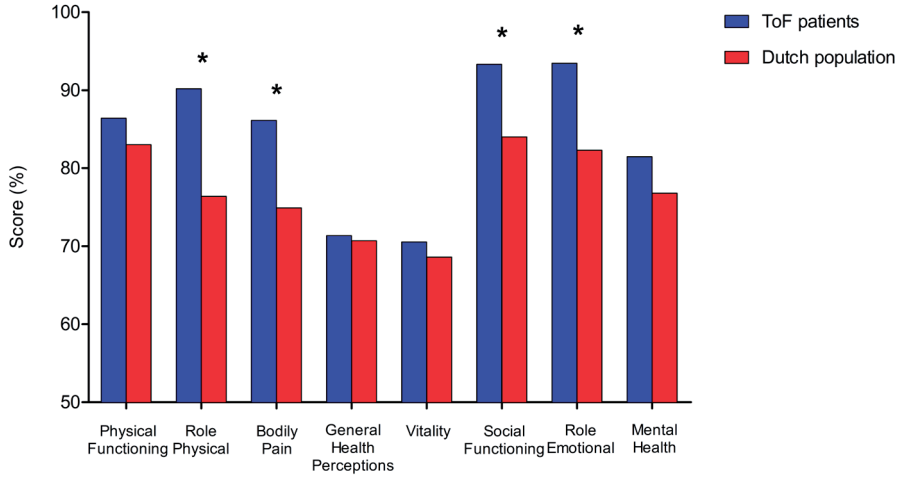


Figure 5. Results of SF-36 for ToF patients and the normal Dutch population. Higher scores indicate more favorable subjective health status. *P < 0.001.

Echocardiography

Echocardiographic findings are summarized in Tables 2 through 4. The systolic function of both ventricles diminished in the last 10 years. In 21 patients (40%), the estimated RV pressure was >40 mm Hg, but in all but 3 patients, this was completely attributable to residual pulmonary stenosis. Normal diastolic LV function was observed in 35 patients (55%), impaired relaxation in 13 (20%), pseudonormal diastolic filling in 2 (3%), and restrictive relaxation pattern in 14 (22%). There was no progression of aortic root dilation in the last decade. No correlations were found between pulmonary regurgitation or tricuspid regurgitation and right atrial dilation, RV dilation, or RV function.

Cardiopulmonary exercise testing

Table 2 shows the results of bicycle ergometry. Forty percent of the patients had a reduced exercise capacity (<85% of expected workload). These patients did not significantly differ from those with a normal test result with regard to age at the time of operation, current age, or findings at echocardiography and CMR (dimensions and ventricular function).

NT-proBNP measurement

Median NT-proBNP level was 16.4 pmol/L (interquartile range, 6.7–32.0 pmol/L). An elevated NT-proBNP level (>14.0 pmol/L) was measured in 58% of the patients. NT-proBNP (logarithmic) correlated modestly with echocardiography-derived LV end-systolic dimension (r=0.31, P=0.03) and CMR-derived LV end-diastolic volume (r=0.36, P=0.01). No correlations were found with age at operation, current age, exercise capacity, or RV dimensions.

CMR imaging

CMR was performed in 49 of the 72 patients (68%). Contraindications for CMR were either the presence of a pacemaker or ICD or claustrophobia. The results of CMR are summarized in Table 5. RV and LV end-diastolic dilation was observed in 15 patients (31%) and 2 patients (4%), respectively. In 23 patients (47%), RV EF was diminished, and in 14 (29%) patients, LV EF was diminished. RV EF correlated with LV EF (r=0.54, P<0.001). Thirty patients consented to dobutamine stress. In 5 of them, dobutamine administration was terminated before the dose was increased because of adverse effects: increase in ventricular extrasystoles, ventricular bigeminy, nonsustained VT, symptomatic blood pressure drop, and anxiety. All of these effects recovered spontaneously. LV EF and RV EF increased significantly after administration of 7.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine (P<0.001 for both), but after a dose of 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$, there was no further increase (P=0.4 and P=0.9, respectively).

Table 2. Diagnostic measurements.

				P-value*	
	1990	**2001**	**2012**	**2012 vs. 1990**	**2012 vs. 2001**
Electrocardiography	**n = 79**	**n = 79**	**n = 70**		
Rhythm					
Sinus	66 (84%)	69 (87%)	58 (83%)	0.7	0.3
Atrial	6 (8%)	5 (6%)	4 (6%)	0.7	1.0
Atrial flutter	1 (1%)	3 (4%)	0	-	-
Atrial fibrillation	0	0	1 (1%)	-	-
Nodal	1 (1%)	0	0	-	-
Pacemaker	5 (6%)	2 (3%)	7 (10%)	1.0	0.1
PR interval (mean ms ± SD)	159±32	162±27	173±41	**0.008**	**0.02**
PR >200 ms (%)	3 (4%)	4 (6%)	11 (18%)	**0.02**	0.1
QRS duration (mean ms ± SD)	120±29	135±32	144±32	**<0.001**	**<0.001**
QRS duration >120 ms	27 (39%)	46 (62%)	46 (72%)	**<0.001**	0.1
QRS duration >180 ms	1 (1%)	6 (8%)	8 (13%)	0.1	0.2
24-hour Holter	**n = 70**	**n = 76**	**n = 56**		
Supraventricular arrhythmias	15 (21%)	44 (59%)	29 (52%)	**0.03**	1.0
Sinus node disease	12 (17%)	20 (27%)	14 (25%)	0.5	1.0
SVT	7 (10%)	27 (36%)	19 (34%)	0.3	0.8
Paroxysmal atrial fibrillation	1 (1%)	1 (1%)	1 (2%)	1.0	1.0
Paroxysmal atrial flutter	0	1 (1%)	0	-	-
VT 3-10 complexes	7 (10%)	9 (12%)	10 (18%)	1.0	0.4
VT >10 complexes	0	1 (1%)	1 (2%)	-	1.0
Bicycle ergometry	**n = 73**	**n = 71**	**n = 52**		
Maximal heart rate (mean % ± SD)	86±11	89±10	86±12	0.7	**0.04**
Maximal exercise capacity (mean % ± SD)	88±17	83±16	89±18	0.6	**0.02**
Exercise capacity <85%	26 (36%)	39 (55%)	21 (40%)	1.0	0.3
Arrhythmia	14 (19%)	17 (24%)	12 (23%)	0.2	0.6
VO_2 max (%)	-	-	81±17	-	-
RER max	-	-	1.4±0.2	-	-
VE/VCO_2 - anaerobic treshold	-	-	27.0±4.0	-	-
VE/VCO_2 - max workload	-	-	29.5±4.1	-	-
Echocardiographic parameters	**n = 79**	**n = 79**	**n = 70**		
RA dilation	35 (44%)	65 (82%)	59 (86%)	**<0.001**	0.7
RV dilation	72 (91%)	56 (71%)	62 (89%)	0.7	**0.01**
LA dilation	3 (4%)	12 (15%)	23 (34%)	**<0.001**	**0.01**
LV dilation	1 (1%)	7 (9%)	7 (10%)	0.4	1.0
RV systolic function normal	-	54 (78%)	19 (28%)	-	**<0.001**
LV systolic function normal	76 (96%)	70 (90%)	34 (50%)	**<0.001**	**<0.001**
FS <20%	3 (4%)	7 (10%)	6 (9%)	0.6	0.7
Valve regurgitation (>trace)					
AR	4 (5%)	15 (19%)	19 (28%)	**<0.001**	0.1
MR	0	6 (8%)	13 (19%)	**0.004**	**0.004**

Table 2. Diagnostic measurements. (continued)

				P-value*	
	1990	**2001**	**2012**	**2012 vs. 1990**	**2012 vs. 2001**
PR	65 (82%)	62 (79%)	43 (62%)	**0.002**	**0.001**
TR	45 (57%)	49 (62%)	49 (71%)	0.1	0.4
Vmax PR (m/s)	1.8	1.8	2.0	**0.007**	0.1
Vmax TR (m/s)	2.7	2.8	2.7	0.6	0.7
LA diameter (mm)	32±6	37±7	39±6	**<0.001**	**0.001**
LV diameter (mm)	44±6	49±6	48±7	**<0.001**	0.7
Aortic diameter (mm)	32±6	37±6	36±5	**0.002**	0.08

SVT = supraventricular tachycardia; VT = ventricular tachycardia; RER = respiratory exchange ratio; RA = right atrium; RV = right ventricle; LA = left atrium; LV = left ventricle; FS = fractional shortening; AR = aortic regurgitation; MR = mitral regurgitation; PR = pulmonary regurgitation; TR = tricuspid regurgitation; Vmax = maximal velocity found with Doppler echocardiography.

* *P*- values are displayed only for measures performed in two or all three studies.

Predictor analyses

Results of the baseline parameters Cox regression analysis are presented in Table 5. Early postoperative arrhythmias, a palliative shunt before initial correction, and lower temperature during surgery were predictive of mortality. In the time-dependent Cox regression analyses, no predictors for mortality were found. Increase in QRS duration and decrease in maximally achieved workload during cardiopulmonary exercise testing over time were predictive for PVR (hazard ratio, 1.14 per 10-millisecond increase, P=0.023; and hazard ratio, 0.961, P=0.001, respectively) but not for mortality. Ventricular dysfunction on echocardiogram or arrhythmias on Holter in 1990 or 2001 did not predict adverse outcome. After adjustment for changes in QRS duration, exercise capacity, VTs on Holter, and LV fractional shortening, patients without a previous palliative shunt still showed a trend toward lower all-cause mortality (hazard ratio, 0.22; P=0.064). The presence of a supraventricular arrhythmia on ECG in 1990 or 2001 predicted mortality (hazard ratio, 13.9, P=0.016; and hazard ratio, 14.5, P=0.004, respectively).

DISCUSSION

In this unique prospective, longitudinal cohort study of an unselected cohort of ToF patients with detailed clinical evaluation and analysis of predictors for outcome, we found that late mortality up to 40 years was low. Early postoperative arrhythmias were found to be a new predictor for late mortality. Although morbidity was substantial, the subjective health status was excellent, and objective exercise capacity remained stable.

Table 3. Additional diagnostic test results performed only in 2012: Echocardiography

	Median	IQR	Abnormal (n, %)*
PR Vmax (m/s)	2.0	[1.7-2.3]	17 (46%)
TAPSE (mm)	18	[16-22]	10 (16%)
RV FAC (%)	38	[32-48]	15 (33%)
LV EF (%)	51	[45-57]	15 (42%)
E/A ratio	1.4	[1.0-1.8]	6 (9%)
E/E' ratio	9.4	[8.0-12.6]	6 (10%)
DET (ms)	190	[160-240]	27 (43%)
IVC collapse > 50% (n, %)	60 (94%)		
HV ratio S>D (n, %)	7 (15%)		

DET indicates deceleration time; FAC, fractional area change; HV S/D ratio, hepatic vein ratio of systolic to diastolic wave; IQR, interquartile range; IVC, inferior vena cava; LV EF, left ventricular ejection fraction; PR, pulmonary regurgitation; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; and Vmax, maximal velocity found with Doppler echocardiography.
*According to the reference values in the guidelines for structural heart disease.[13,14]

Table 4. Additional diagnostic test results performed only in 2012:

Cardiac Magnetic Resonance imaging	At rest n = 49	7.5 µg/kg/min dobutamine n = 30	20 µg/kg/min dobutamine n = 26	p-value rest vs 7.5 µg/kg/min	p-value 7.5 vs. 20 µg/kg/min
LV EDV/BSA (mL/m^2)	74 [64-86]	70 [62-84]	60 [55-71]	0.071	<0.001
LV ESV/BSA (mL/m^2)	29 [22-37]	16 [13-22]	12 [10-17]	<0.001	<0.001
LV EF (%)	61 [54-69]	77 [74-83]	80 [74-84]	<0.001	0.247
RV EDV/BSA (mL/m^2)	96 [81-120]	92 [79-121]	89 [75-109]	0.417	<0.001
RV ESV/BSA (mL/m^2)	49 [36-63]	36 [28-49]	35 [25-42]	<0.001	0.048
RV EF (%)	49 [45-59]	63 [53-69]	64 [57-70]	<0.001	0.939

BSA indicates body surface area; EDV, end-diastolic volume; EF, ejection fraction ESV, end-systolic volume; FAC, fractional area change; LV, left ventricular; and RV, right ventricular.

Mortality and major events

In the total cohort, cumulative survival 40 years after surgical correction was 72%, with one fifth of deaths occurring within 30 days after surgery. In the hospital survivors, cumulative survival was 86% after 40 years of follow-up. This is only slightly lower than survival in the general Dutch population. The causes of late death in our cohort were heart failure and arrhythmia, which is in accordance with the literature.[3, 4, 19, 20] Morbidity was substantial in our population; only one quarter of the patients were free from events after 40 years. Reinterventions were required in nearly half of the patients, mostly PVR. This is considerably more than reported in other studies, probably reflecting the earlier era of initial operation and longer duration of follow-up in our study.[6, 19, 21]

Table 5. Predictors of the clinical endpoints all-cause mortality, arrhythmias/PM implantation and PVR.

	Univariable model			Multivariable model		
Endpoint	**HR**	**CI**	**P-value**	**HR**	**CI**	**P-value**
All-cause mortality						
Early postoperative arrhythmias	3.33	[1.60-6.95]	**0.001**	2.52	[1.18-5.36]	**0.017**
Temperature during surgery (per °C decrease)	1.18	[1.05-1.30]	**0.003**	1.14	[1.01-1.28]	**0.029**
Prior shunt	1.64	[0.85-3.23]	0.144	2.94	[1.32-6.25]	**0.008**
Transannular patch	1.27	[0.62-2.61]	0.518	0.74	[0.36-1.53]	0.419
Age at operation	0.90	[0.81-1.01]	0.071	0.89	[0.76-1.03]	0.118
Operated after 1975	0.93	[0.47-1.84]	0.833	0.54	[0.24-1.20]	0.131
Arrhythmias/PM implantation						
Early postoperative arrhythmias	4.36	[1.57-12.10]	**0.005**	3.68	[1.29-10.52]	**0.015**
Temperature during surgery (per °C decrease)	1.00	[0.90-1.12]	0.923	1.01	[0.89-1.14]	0.906
Prior shunt	2.17	[0.91-5.00]	0.080	1.96	[0.68-5.56]	0.213
Transannular patch	5.91	[1.37-25.47]	**0.017**	3.99	[1.19-13.41]	**0.026**
Age at operation	1.00	[0.86-1.15]	0.947	0.95	[0.79-1.15]	0.621
Operated after 1975	0.58	[0.25-1.38]	0.219	0.41	[0.16-1.03]	0.059
Pulmonary valve replacement						
Early postoperative arrhythmias	1.90	[0.79-4.57]	0.149	1.33	[0.55-3.25]	0.525
Temperature during surgery (per °C decrease)	1.09	[1.00-1.16]	**0.045**	1.02	[0.93-1.11]	0.650
Prior shunt	1.64	[0.86-3.13]	0.133	2.50	[1.00-6.25]	**0.049**
Transannular patch	6.40	[2.26-18.10]	**<0.001**	3.50	[1.39-8.86]	**0.008**
Age at operation	0.91	[0.82-1.01]	0.087	0.92	[0.79-1.05]	0.215
Operated after 1975	2.72	[1.29-5.76]	**0.009**	1.88	[0.84-4.20]	0.126

CI = confidence interval; HR = hazard ratio; PM = pacemaker.

Health status assessment

Exercise capacity was clearly impaired in our ToF patients but remained stable in the last 10 years. The lowest VO_2max in our study population was 51% of the predicted value. This is still considerably higher than the 36% described by Giardini et al[22] as a cutoff value for greater risk of cardiac-related death. Remarkably, patients themselves reported favorable physical functioning and even less interference from physical problems in their work and daily activities than the reference Dutch population. This is in contrast to earlier reports by Knowles et al,[23] who reported less favorable results in ToF patients compared with their healthy siblings. The better scores in our group may be due to different frames of reference, overcompensation, and social desirability.[24] Over time, our patients showed a decrease in general health perception scores, which can be related to age because this effect also is seen in the general population.[12]

Arrhythmias

Arrhythmias and sudden death are important late complications.[4,8,25] We found a lower prevalence of arrhythmias than described by Khairy et al.[25] In our study, supraventricular

arrhythmias were common on Holter, but only 5 patients had symptomatic arrhythmias. The prevalence of SVT on Holter did not increase in the last decade and did not predict outcome. In addition, an increase in QRS duration did not predict arrhythmias or mortality. However, strikingly, 2 of the 3 patients with an atrial arrhythmia (atrial flutter) on ECG in 2001 died during the last 10 years. Their atrial arrhythmia could have been an indicator of worsening hemodynamics, but none of these patients had more than mild RV dysfunction, and only 1 had LV dysfunction in 2001. It seems that these supraventricular arrhythmias should not be considered insignificant.

Ventricular function

Late deterioration of RV and LV function has been an increasing concern.[26, 27] Indeed, this was found in our study because systolic RV function was impaired in >75% and systolic LV function in 50% of the patients. Moreover, diastolic LV dysfunction was found often. The deterioration of LV function could be explained by adverse ventricular-ventricular interaction associated with RV dilation, which influences LV twist.[28] We found a significant association between RV and LV dysfunction. In addition, we found a modest but significant correlation between LV dimensions and NT-proBNP levels. In other studies, NT-proBNP levels correlated with both LV and RV dimensions and LV function.[29] Whether NT-pro-BNP predicts clinical outcome remains to be established. Administration of dobutamine during CMR led to an increase in RV EF and LV EF at a low dose, but no further increase was observed at a high dose. As described by Parish et al. who found a similar stress response,[30] this is caused mainly by the lack in further decrease of RV end-systolic volume, indicating diminished contractile reserve. Because this is not apparent at rest, dobutamine stress CMR may contribute to the decision making in terms of intervention such as timing of PVR in these patients.[31]

Aortic dilation

Dilation of the ascending aorta is found in 15% to 87% of the ToF patients [32] presumably inherent to volume overload resulting from the original overriding position of the aorta. Additionally, intrinsic vascular wall properties could play a role. We found aortic root dilation (≥40 mm) in 24% of our patients at the last follow-up. The long-term risk of aortic dilation in ToF patients has not been clarified yet. In our longitudinal follow-up, the aortic diameter did not increase over time, and until now, no aortic dissection occurred. However, in 1 patient, the aortic arch was electively replaced because of an aortic diameter of 57 mm.

Predictors for late events

Patients with a palliative shunt before initial correction, that is, Waterston shunt, Blalock-Taussig shunt, or Potts anastomosis, were more at risk of dying or needing PVR than

patients without them. Because in our cohort the use of a palliative shunt was related to the era of surgery rather than to anatomy, selection bias regarding more or less favorable anatomy is very unlikely. Therefore, our study supports early initial correction without previous shunt if the patient's condition tolerates.

Mortality was higher in patients who experienced early postoperative arrhythmias. In addition, these patients had a higher risk of late arrhythmias or pacemaker implantation. The occurrence of early arrhythmias and their relation to the increased risk of death and permanent pacing have previously been described in small series and, on the basis of our results, seem to have clinical relevance.[33, 34] More attention for these early postoperative arrhythmias and their underlying mechanism is needed and may attribute to risk stratification for preventive interventions such as ICD implantation.

A QRS duration >180 milliseconds and an increase in QRS duration over time have been recognized as predictors for VT and late sudden death.[4, 35] Our study showed a steady increase in QRS duration over time. However, all patients with a QRS duration >180 milliseconds in 1990 or 2001 are still alive, and QRS duration could not be identified as predictor for mortality in our study.

Although the numbers in our study are small, supraventricular arrhythmias on ECG in 1990 or 2001 seem to be predictive of mortality. The importance of atrial arrhythmias as a predictor for outcome has been suggested before. However, the exact mechanism remains to be elucidated.[8]

The insertion of a transannular patch has received much attention as a possible cause of pulmonary regurgitation and long-term morbidity. Our results confirm the association of a transannular patch with PVR but not with mortality. These results are similar to the results of the study by Lindberg et al.[36] Furthermore, we found an association between the use of a transannular patch and the occurrence of late arrhythmias. Nowadays, surgeons tend to use smaller transannular patches to minimize pulmonary regurgitation and its long-term sequelae. Whether this will result in better outcome has to be established.

Study limitations

Although the number of patients in this study is relatively small, we report the results of a longitudinal follow-up of consecutive patients without selection bias related to disease severity. After a median follow-up of 36 years, we gathered medical information on 72 of the approached patients (90%). We found no significant differences in baseline characteristics between participating and nonparticipating patients; therefore, we believe that we have minimized selection bias.

From 1968 to 1980, the era in which our cohort was operated on, the standard surgical policy gradually changed from secondary correction after previous shunting, use of a large transannular patch, and surgery at very low temperature to primary correction

at higher temperatures. These factors were accounted for in our analyses of predictors for outcome. We believe that there is no bias concerning temperature during surgery, but we cannot completely exclude that the use of a previous shunt was related to more complex anatomy.

Diagnostic methods have been changed during the last 36 years. For comparing echocardiography data of the present study with the previous studies, we had to use the same methods used in the past. Some of these techniques are not seen as being up-to-date. However, we also performed and reported innovative diagnostic methods available in 2012.

CONCLUSIONS

Long-term survival after successful surgical correction of ToF in childhood is good. Morbidity, however, is substantial, with almost half of the patients needing at least 1 reintervention. There is concern about the deterioration of both RV and LV function. Nevertheless, the clinical condition and subjective health status of most patients remain good, and aortic dimensions did not increase over time.

ACKNOWLEDGMENTS

We thank Eleni-Rosalina Andrinopoulou for her contribution to statistical analysis and preparation of figures.

REFERENCES

1. Apitz C, Webb GD, Redington AN. Tetralogy of Fallot. *Lancet*. 2009;374:1462–1471.
2. Lillehei CW, Cohen M, Warden HE, Read RC, Aust JB, Dewall RA, Varco RL. Direct vision intracardiac surgical correction of the tetralogy of Fallot, pentalogy of Fallot, and pulmonary atresia defects; report of first ten cases. *Ann Surg*. 1955;142:418–442.
3. Nollert G, Fischlein T, Bouterwek S, Böhmer C, Klinner W, Reichart B. Long-term survival in patients with repair of tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. *J Am Coll Cardiol*. 1997;30:1374–1383.
4. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosenthal M, Nakazawa M, Moller JH, Gillette PC, Webb GD, Redington AN. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet.* 2000;356:975–981.
5. Murphy JG, Gersh BJ, Mair DD, Fuster V, McGoon MD, Ilstrup DM, McGoon DC, Kirklin JW, Danielson GK. Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. *N Engl J Med.* 1993;329:593–599.
6. Hickey EJ, Veldtman G, Bradley TJ, Gengsakul A, Manlhiot C, Williams WG, Webb GD, McCrindle BW. Late risk of outcomes for adults with repaired tetralogy of Fallot from an inception cohort spanning four decades. *Eur J Cardiothorac Surg*. 2009;35:156–164.
7. Hickey EJ, Veldtman G, Bradley TJ, Gengsakul A, Webb G, Williams WG, Manlhiot C, McCrindle BW. Functional health status in adult survivors of operative repair of tetralogy of Fallot. *Am J Cardiol*. 2012;109:873–880.
8. Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of Fallot: correlations with clinical, exercise, and echocardiographic findings. *Circulation*. 1995;91:2214–2219.
9. Bouzas B, Kilner PJ, Gatzoulis MA. Pulmonary regurgitation: not a benign lesion. *Eur Heart J*. 2005;26:433–439.
10. Meijboom F, Szatmari A, Deckers JW, Utens EM, Roelandt JR, Bos E, Hess J. Cardiac status and health-related quality of life in the long term after surgical repair of tetralogy of Fallot in infancy and childhood. *J Thorac Cardiovasc Surg.* 1995;110(pt 1):883–891.
11. Meijboom FJ, Roos-Hesselink JW, McGhie JS, Spitaels SE, van Domburg RT, Utens LM, Simoons ML, Bogers AJ. Consequences of a selective approach toward pulmonary valve replacement in adult patients with tetralogy of Fallot and pulmonary regurgitation. *J Thorac Cardiovasc Surg*. 2008;135:50–55.
12. Aaronson NK, Muller M, Cohen PD, Essink-Bot ML, Fekkes M, Sanderman R, Sprangers MA, te Velde A, Verrips E. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol*. 1998;51:1055–1068.
13. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing Group, American Society of Echocardiography's Guidelines and Standards Committee, European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European

Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.

14. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685–713; quiz 786.
15. van den Berg J, Hop WC, Strengers JL, de Jongste JC, van Osch-Gevers L, Meijboom FJ, Pattynama PM, Bogers AJ, Helbing WA. Clinical condition at mid-to-late follow-up after transatrial-transpulmonary repair of tetralogy of Fallot. *J Thorac Cardiovasc Surg*. 2007;133:470–477.
16. Alfakih K, Plein S, Thiele H, Jones T, Ridgway JP, Sivananthan MU. Normal human left and right ventricular dimensions for MRI as assessed by turbo gradient echo and steady-state free precession imaging sequences. *J Magn Reson Imaging*. 2003;17:323–329.
17. Therneau T GP. Modeling Survival Data: Extending the Cox Model. New York, NY: Spring-Verlag; 2000.
18. Van Buuren S. Flexible Imputation of Missing Data. Boca Raton, FL: CRC Press; 2012.
19. Nørgaard MA, Lauridsen P, Helvind M, Pettersson G. Twenty-tothirty- seven-year follow-up after repair for tetralogy of Fallot. *Eur J Cardiothorac Surg*. 1999;16:125–130.
20. Oechslin EN, Harrison DA, Connelly MS, Webb GD, Siu SC. Mode of death in adults with congenital heart disease. *Am J Cardiol*. 2000;86:1111–1116.
21. Bacha EA, Scheule AM, Zurakowski D, Erickson LC, Hung J, Lang P, Mayer JE Jr, del Nido PJ, Jonas RA. Long-term results after early primary repair of tetralogy of Fallot. *J Thorac Cardiovasc Surg*. 2001;122:154–161.
22. Giardini A, Specchia S, Tacy TA, Coutsoumbas G, Gargiulo G, Donti A, Formigari R, Bonvicini M, Picchio FM. Usefulness of cardiopulmonary exercise to predict long-term prognosis in adults with repaired tetralogy of Fallot. *Am J Cardiol*. 2007;99:1462–1467.
23. Knowles R, Veldtman G, Hickey EJ, Bradley T, Gengsakul A, Webb GD, Williams WG, McCrindle BW. Functional health status of adults with tetralogy of Fallot: matched comparison with healthy siblings. *Ann Thorac Surg*. 2012;94:124–132.
24. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Current subjective state of health, and longitudinal psychological well-being over a period of 10 years, in a cohort of adults with congenital cardiac disease. *Cardiol Young*. 2005;15:168–175.
25. Khairy P, Aboulhosn J, Gurvitz MZ, Opotowsky AR, Mongeon FP, Kay J, Valente AM, Earing MG, Lui G, Gersony DR, Cook S, Ting JG, Nickolaus MJ, Webb G, Landzberg MJ, Broberg CS; Alliance for Adult Research in Congenital Cardiology (AARCC). Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. *Circulation.*2010;122:868–875.
26. Broberg CS, Aboulhosn J, Mongeon FP, Kay J, Valente AM, Khairy P, Earing MG, Opotowsky AR, Lui G, Gersony DR, Cook S, Ting JG, Webb G, Gurvitz MZ; Alliance for Adult Research in Congenital Cardiology (AARCC). Prevalence of left ventricular systolic dysfunction in adults with repaired tetralogy of Fallot. *Am J Cardiol*. 2011;107:1215–1220.

27. Diller GP, Kempny A, Liodakis E, Alonso-Gonzalez R, Inuzuka R, Uebing A, Orwat S, Dimopoulos K, Swan L, Li W, Gatzoulis MA, Baumgartner H. Left ventricular longitudinal function predicts life-threatening ventricular arrhythmia and death in adults with repaired tetralogy of Fallot. *Circulation*. 2012;125:2440–2446.

28. Menting ME, Eindhoven JA, van den Bosch AE, Cuypers JA, Ruys TP, van Dalen BM, McGhie JS, Witsenburg M, Helbing WA, Geleijnse ML, Roos-Hesselink JW. Abnormal left ventricular rotation and twist in adult patients with corrected tetralogy of Fallot. *Eur Heart J Cardiovasc Imaging*. 2014;15:566–574.

29. Eindhoven JA, van den Bosch AE, Ruys TP, Opić P, Cuypers JA, McGhie JS, Witsenburg M, Boersma E, Roos-Hesselink JW. N-terminal pro-Btype natriuretic peptide and its relationship with cardiac function in adults with congenital heart disease. *J Am Coll Cardiol*. 2013;62:1203–1212.

30. Parish V, Valverde I, Kutty S, Head C, Qureshi SA, Sarikouch S, Greil G, Schaeffter T, Razavi R, Beerbaum P. Dobutamine stress MRI in repaired tetralogy of Fallot with chronic pulmonary regurgitation: a comparison with healthy volunteers. *Int J Cardiol*. 2013;166:96–105.

31. Luijnenburg SE, Mekic S, van den Berg J, van der Geest RJ, Moelker A, Roos-Hesselink JW, Bogers AJ, de Rijke YB, Strengers JL, Mulder BJ, Vliegen HW, Helbing WA. Ventricular response to dobutamine stress relates to the change in peak oxygen uptake during the 5-year follow-up in young patients with repaired tetralogy of Fallot. *Eur Heart J Cardiovasc Imaging*. 2014;15:189–194.

32. Mongeon FP, Gurvitz MZ, Broberg CS, Aboulhosn J, Opotowsky AR, Kay JD, Valente AM, Earing MG, Lui GK, Fernandes SM, Gersony DR, Cook SC, Ting JG, Nickolaus MJ, Landzberg MJ, Khairy P; Alliance for Adult Research in Congenital Cardiology (AARCC). Aortic root dilatation in adults with surgically repaired tetralogy of Fallot: a multicenter cross-sectional study. *Circulation*. 2013;127:172–179.

33. Dodge-Khatami A, Miller OI, Anderson RH, Gil-Jaurena JM, Goldman AP, de Leval MR. Impact of junctional ectopic tachycardia on postoperative morbidity following repair of congenital heart defects. *Eur J Cardiothorac Surg*. 2002;21:255–259.

34. Cuypers JA, Opić P, Menting ME, Utens EM, Witsenburg M, Helbing WA, van den Bosch AE, Ouhlous M, van Domburg RT, Meijboom FJ, Bogers AJ, Roos-Hesselink JW. The unnatural history of an atrial septal defect: longitudinal 35 year follow up after surgical closure at young age. *Heart*.2013;99:1346–1352.

35. Gatzoulis MA, Till JA, Somerville J, Redington AN. Mechanoelectricalinteraction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. *Circulation*. 1995;92:231–237.

36. Lindberg HL, Saatvedt K, Seem E, Hoel T, Birkeland S. Single-center 50 years' experience with surgical management of tetralogy of Fallot. *Eur J Cardiothorac Surg*. 2011;40:538–542.

7

The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years

Judith A.A.E. Cuypers, Jannet A. Eindhoven, Maarten A. Slager, Petra Opić, Elisabeth M.W.J. Utens, Willem A. Helbing, Maarten Witsenburg, Annemien E. van den Bosch, Mohamed Ouhlous, Ron T. van Domburg, Dimitris Rizopoulos, Folkert J. Meijboom, Ad J.J.C. Bogers and Jolien W. Roos-Hesselink

European Heart Journal. 2014 Jul 1;35(25):1666-74

ABSTRACT

Aims

To describe long-term survival, clinical outcome and ventricular systolic function in a longitudinally followed cohort of patients after Mustard repair for transposition of the great arteries (TGA). There is serious concern about the long-term outcome after Mustard repair.

Methods and results

This longitudinal single-center study consisted of 91 consecutive patients, who underwent Mustard repair before 1980, at age <15 years, and were evaluated in-hospital every 10 years. Survival status was obtained of 86 patients. Median follow-up was 35 (IQR 34–38) years. Cumulative survival was 84% after 10 years, 80% after 20 years, 77% after 30 years, and 68% after 39 years. Cumulative survival free of events (i.e. heart transplantation, arrhythmias, reintervention, and heart failure) was 19% after 39 years. Reinterventions were mainly required for baffle-related problems. Supraventricular and ventricular arrhythmias occurred in 28 and 6%of the patients, respectively. Pacemaker and/or ICD implantation was performed in 39%. Fifty survivors participated in the current in-hospital investigation including electrocardiography, 2D-echocardiography, cardiopulmonary-exercise testing, NT-proBNP measurement, Holter monitoring, and cardiac magnetic resonance. Right ventricular systolic function was impaired in all but one patient at last follow-up, and 14% developed heart failure in the last decade. NT-proBNP levels [median 31.6 (IQR 22.3–53.2) pmol/L] were elevated in 92% of the patients. Early postoperative arrhythmias were a predictor for late arrhythmias [HR 3.8 (95% CI 1.5–9.5)], and development of heart failure [HR 8.1 (95% CI 2.2–30.7)]. Also older age at operation was a predictor for heart failure [HR 1.26 (95% CI 1.0–1.6)].

Conclusion

Long-term survival after Mustard repair is clearly diminished and morbidity is substantial. Early postoperative arrhythmias are a predictor for heart failure and late arrhythmias.

INTRODUCTION

The survival of patients with transposition of the great arteries (TGA) has improved dramatically after introduction of the atrial switch procedures described by Senning in 1959[1] and Mustard in 1964.[2] At that time, the choice was made in our center to preferentially apply the Mustard procedure. Although the Mustard procedure has reasonably good outcome during the first two decades of life,[3] late sequelae are frequently encountered including arrhythmias, baffle-related complications, and right ventricular (RV) dysfunction leading to heart failure.[3–5] Since the mid-1980s, the Mustard procedure has been replaced by the arterial switch operation.[6] Nevertheless, cardiologists continue to see older patients after Mustard repair.[4,5] The cumulative survival after atrial switch is ≈ 80% after 25 years.[3–5,7,8] The morphologic right ventricle supporting the systemic circulation remains an important concern and may cause a high burden of morbidity and premature mortality from heart failure.[9]

So far, reliable information on outcome beyond 30 years is limited. The aim of this study is to assess survival, occurrence of arrhythmias and systemic ventricular dysfunction, and clinical course over a time span of nearly 40 years. This study is unique by its longitudinal design and extensive in-hospital investigations every 10 years.

METHODS

Study population

All 91 consecutive patients who underwent Mustard repair for transposition of the great arteries in our institution between 1973 and 1980, at age <15 years, were included in this longitudinal study. In 36 patients, additional VSD closure or relief of pulmonary stenosis was performed in the same procedure. These patients are referred to as 'complex TGA'. The cohort was first studied in 1990,[10] and the second follow-up was performed in 2001.[3] All patients who were alive and had participated in one or both of the previous studies were invited to participate in the current third study. Survival status was obtained from the Dutch National Population Registry. Patients were invited to participate and were seen at the outpatient clinic of Erasmus Medical Center between April 2011 and March 2012. Detailed information describing the baseline characteristics, surgical procedure, and 10-year and 20-year follow-up results has previously been reported.[3,10] The study protocol was approved by the institutional Medical Ethics Committee (2010–15). Written informed consent was obtained from all study participants.

Adverse events

Survival was compared with the expected survival of the normal, age matched Dutch population. Major events were defined as: all-cause mortality; heart transplantation (HTx); cardiac reinterventions; symptomatic arrhythmias, or heart failure. Arrhythmias were defined as symptomatic if antiarrhythmic medication was prescribed, cardioversion or catheter based or surgical ablation had been applied, or pacemaker/ICD implantation was performed. Heart failure was defined as hospitalization for heart failure or initiation of heart-failure medication.

Clinical assessment

All participating patients underwent extensive medical examination including history, physical examination, standard 12-lead electrocardiography (ECG), 24 h ambulatory Holter monitoring, 2D-echocardiography, bicycle ergometry with maximum oxygen consumption (VO2 max), NT-proBNP measurement, and if possible cardiac magnetic resonance (CMR) imaging.

If a patient was unwilling or unable to visit the outpatient clinic, an additional questionnaire was sent to obtain information on morbidity, and to receive permission for the use of information from their medical record.

Electrocardiography and 24 h Holter monitoring

Standard 12-lead surface ECGs were analyzed for rhythm, PR interval, and QRS duration. A 24 hour Holter monitoring was performed with a Cardio Perfect Holter DR180+ three-channel recorder (Welch Allyn Cardio Control, North East Monitoring, Maynard, MA, USA). Sinus node disease (SND) was defined according to the Kugler criteria, as described previously.[10]

Echocardiography

A detailed two-dimensional transthoracic echocardiogram was performed using the commercially available IE33 system (Philips Medical Systems, Best, the Netherlands). Cardiac dimensions and function were measured according to the current guidelines.[11,12] Right ventricular systolic function was also assessed visually ('eyeballing') to make a comparison with the two previous studies possible. Right ventricular systolic function was graded as normal or mildly, moderately or severely impaired. Additionally, more objective measures including fractional area change (FAC), S' of the tricuspid annulus, and tricuspid annulus plane systolic excursion (TAPSE) were used to quantify RV function. Elevated pulmonary pressure was defined as early diastolic pulmonary regurgitation flow velocity of >2.5 m/s or, in the absence of (sub)pulmonary obstruction, mitral regurgitation flow velocity >3.0 m/s. The presence of baffle leakage or stenosis

was assessed with colour Doppler echocardiography. All measures were obtained by two independent observers.

Bicycle ergometry

Maximal workload and maximal oxygen consumption (VO_2 max) were assessed by bicycle ergometry with gradual workload increment of 20Watts per min (Ramp protocol), and compared with that of normal individuals corrected for age, gender, body height, and weight. The ratio of minute ventilation to carbon dioxide production (VE/VCO_2) was assessed at the anaerobic threshold and at maximum workload. Performance was considered maximal when a respiratory quotient (RER) of >1 was reached.

NT-proBNP measurement

Peripheral venous blood samples were collected after 30 min rest. Plasma NT-proBNP levels were determined with the use of the commercially available electrochemiluminesence immunoassay Elecsys (Roche Diagnostics, Basel, Switzerland). The reference value of normal for NT-proBNP in our hospital is <0,14 pmol/L.

Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging was performed using a Signa 1.5-Tesla whole-body scanner (GE Medical Systems, Milwaukee, WI, USA) with dedicated phased-array cardiac surface coils. Details of the used MR sequence have been reported previously.[13] For CMR analyses, a commercially available Advanced Windows workstation (GE Medical Systems) was used, equipped with Q-mass version 5.2 (Medis Medical Imaging Systems, Leiden, the Netherlands). Ventricular volume was quantified using manual outlining of endocardial borders, excluding large trabeculae and the papillary muscles from the blood volume, in end-systole and end-diastole.

Statistical analysis

For the descriptive data analyses, we used the Statistical Package for Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA). Continuous data are presented as mean ± SD, or median with interquartile range (IQR) depending on data distribution. Categorical variables are presented as frequencies and percentages. For comparison of continuous variables between independent groups, the Student's unpaired t-test was used. For paired groups, the paired Student's t-test or Wilcoxon signed-rank test were performed. Frequencies of unpaired data were compared with use of the Chi^2 test or Fisher's exact test when applicable, and for paired data the McNemar test was used. To quantify correlations between two variables, the Pearson correlation test or Spearman correlation test was used.

For advanced statistical analyses of the longitudinal and survival data, the R software version 3.0.1 package was used (available at www.r-project.org). Univariable and multivariable Cox proportional hazard regression analyses were used to identify predictors for the predefined adverse events: all-cause mortality and HTx; arrhythmia or pacemaker implantation; heart failure, and need for reinterventions. The following baseline covariates were included in the models: age at operation, era of Mustard operation (before or after the median, 1977), simple vs. complex TGA, temperature during surgery, and early postoperative arrhythmias, defined as any arrhythmia within 30 days after Mustard repair. Clinical parameters from 1990 and 2001 that were included in the models comprised: QRS duration; exercise capacity; RV systolic function and severity of tricuspid regurgitation on echocardiography; signs of SND, VT, or SVT on Holter. Due to the low frequencies of the aforementioned events, a penalized likelihood approach was used in the multivariable Cox model.[14] To account for missing covariate data, we used a multiple imputation approach.[15] Wald tests were used to assess which covariates were most associated with the risk of each event. In addition, time-dependent Cox regression analysis was used to assess the effects of the time-dependent covariates QRS duration, exercise capacity, and ECG rhythm on outcome.

Cumulative survival plots and cumulative event incidences for the predefined adverse events were calculated using the Kaplan–Meier method. The survival of Mustard patients was compared with the expected survival of the normal Dutch population. The Mantel and Haenszel log-rank test was used to compare survival curves. All statistical tests were two-sided and a P-value of < 0.05 was considered significant.

Table 1. Baseline characteristics

	Total	**1990**	**2001**	**2012**
	n = 91	**n = 58**	**n = 54**	**n = 50**
Male (%)	65%	69%	70%	64%
Age at time of study (years)	—	14.1 [12.8-17.5]	25.8 [24.5-30.1]	35.8 [34.4-40.1]
Age at operation (years)	0.7 [0.3 - 3.2]	0.7 [0.3-2.5]	0.7 [0.3-2.5]	0.7 [0.4-2.5]
Prior palliation (n, %)	83 (91%)	55 (95%)	52 (96%)	47 (94%)
Follow-up since surgery (years)	—	13 [12 – 16]	25 [24 – 28]	35 [34 – 38]
Hypothermia during surgery:				
Temperature <20°C (n, %)	60 (66%)	44 (76%)	40 (74%)	37 (74%)
Temperature 20-35°C (n)	22 (24%)	11 (19%)	11 (20%)	10 (20%)
Temperature unknown (n)	9 (`10%)	3 (5%)	3 (6%)	3 (6%)
Complex TGA (%)	40%	36%	33%	36%
Pacemaker before 1990 (n, %)	12 (13%)	8 (14%)	8 (15%)	6 (12%)

TGA=transposition of the great arteries

RESULTS

Study population

The original study cohort consisted of 91 patients. Baseline characteristics are presented in Table 1. An overview of the patient participation for the current study is presented in Figure 1. Median age at operation was 0.7 (IQR 0.4–2.5) years. Age at current study did not differ significantly between patients operated before and after 1977 (28.0±15.9 vs. 31.1 years, P = 0.257). There were no differences in baseline characteristics between the current participating and non-participating patients.

Survival

Survival status was obtained of 86 (95%) patients. Cumulative survival without HTx was 84% at 10 years, 80% at 20 years, 77% at 30 years, and 68% after 39 years (Figure 2). Five patients moved abroad and were untraceable. The median postoperative follow-up was 35 (IQR 34–38) years. Twenty-two patients died: five patients died within 30 days after surgery. Until the first follow-up study in 1990, 13 patients died, 7 of whom suddenly without evidence of prior heart failure or arrhythmias.[10] In the following decade, two patients died of heart failure.[3] In the last decade, two patients died, both of ventricular

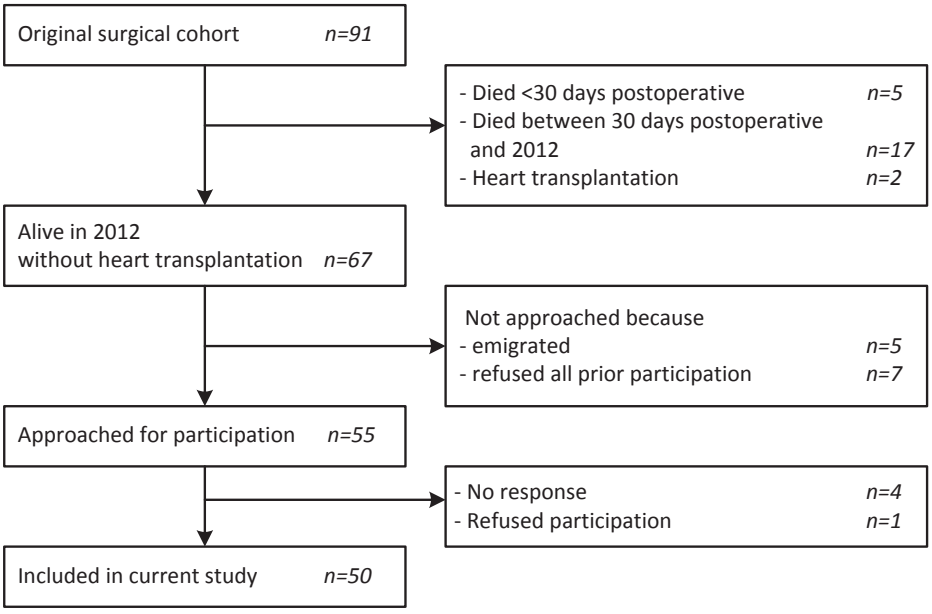


Figure 1. Flow chart of the study population.

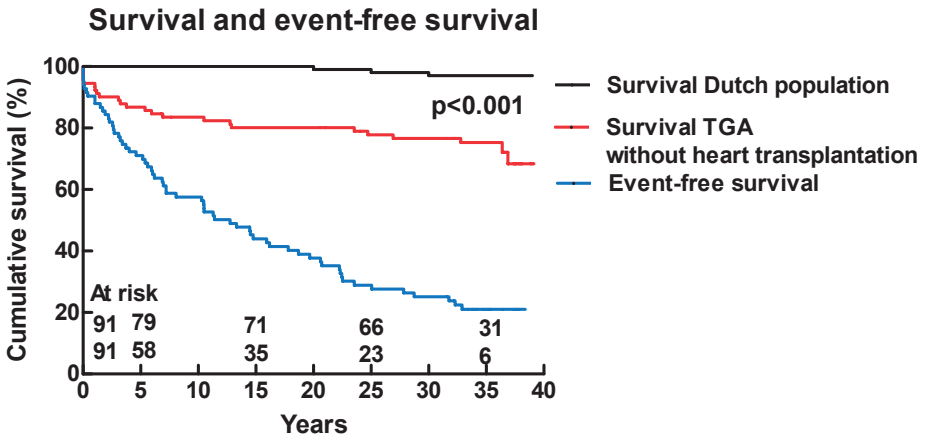


Figure 2. Kaplan Meier survival curves for survival without heart transplantation and event-free survival, i.e. free of heart transplantation, cardiac reinterventions, symptomatic arrhythmias, heart failure or death. Survival without heart transplantation was compared to the survival of the Dutch population.

fibrillation (VF). One patient died of VF during exercise, without previous signs of heart failure. This patient had showed nonsustained VT on Holter in 1990, but never had experienced symptomatic arrhythmias. The other patient developed VF in hospital, shortly after ICD implantation, before threshold testing could be performed. Resuscitation was not successful. He had received the ICD because of severely impaired RV systolic function. No differences in survival and event-free survival between patients with simple or complex TGA were observed (Figure 3). Two patients underwent successful HTx for failure of the systemic right ventricle, respectively 26 and 37 years after Mustard correction.

Adverse events

During total follow-up, 66 patients had at least one of the pre-defined adverse events, with a subsequent cumulative event-free survival of 19% after 39 years (Figure 2).

Reinterventions

In the last decade, three patients (6%) underwent catheter intervention for inferior baffle stenosis. In one of them, reintervention for superior baffle stenosis was performed in the same procedure. One patient had an acute myocardial infarction at the age of 45 years, for which she underwent a successful percutaneous coronary intervention. During total follow-up, 27 patients (cumulative incidence of 46%) required reintervention, mainly for baffle stenosis or leakage (n = 19). The median time between Mustard repair and first baffle reintervention was 14.8 (IQR 10.3–20.6) years.

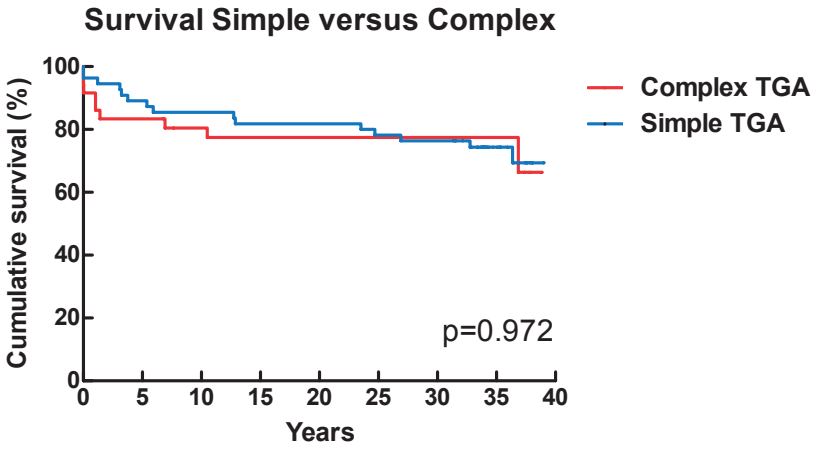


Figure 3. Survival for complex versus simple TGA
Kaplan Meier curves for survival without heart transplantation of patients with complex TGA (n=36) versus simple TGA (n=55).

Arrhythmias

In the last decade, two patients (4%) developed atrial fibrillation (AF), two patients (4%) had atrial flutter, one patient (2%) had VF, and two (4%) experienced both VT and SVT. The cumulative incidence of SVT was 28% and of VT/VF was 6% during total follow-up. In total, pacemaker implantation was performed in 19 patients (cumulative 33%) and ICD implantation in three patients (6%). One patient received an ICD for primary prevention, and the other two for secondary prevention.

Heart failure

In the last 10 years, 7 patients (14%) developed heart failure of whom five needed hospital admission. During total follow-up, 12 patients (23%) developed heart failure; 2 of them died and 2 underwent HTx.

History and clinical evaluation

The median age at the time of the current study was 36 (IQR 34–40) years with a median postoperative follow-up of 35 (IQR 34–38) years. Median oxygen saturation was 97 (IQR 96–99)%. Twenty-six patients (52%) used cardiac medication comprising: ACE-inhibitors (n = 16), beta-blockers for heart failure (n = 2) or arrhythmia (n = 9), digoxin (n = 6), or other antiarrhythmic drugs (n = 5). One patient was treated for pulmonary arterial hypertension with sildenafil. A total of 22 patients (44%) had at least one hospital admission in the last decade. No paradoxical embolic events occurred. Seven women had 13 successful pregnancies. Three patients refrained from pregnancy after careful counselling regarding the possible risks posed by their cardiac status.

Electrocardiography and 24 h Holter

The results are summarized in Table 2. The majority of patients were in sinus rhythm (66%).QRS duration increased significantly over time (Figure 4). On Holter, no significant bradycardia (ventricular pauses longer than three seconds) or sustained VTs were observed. None of the patients with non-sustained VT (16%) was symptomatic. There were no differences in the incidence of supraventricular or ventricular arrhythmias between patients with simple and complex TGA (P = 0.4).

Echocardiography

The systemic RV function deteriorated over time (Table 2). At last follow-up, only one patient (2%) had a good RV systolic function. Right ventricular systolic dysfunction was mild in 11 patients (23%), moderate in 28 (60%), and severe in 7 (15%). Both RV FAC and TAPSE were decreased in the majority of patients (Table 3). TDI S′ was below 10 cm/s in all but one patient. Lower RV FAC was correlated with a larger RV annulus dimension (r = -.35, P = 0.03). There was no difference in RV systolic function or a difference in deterioration of RV systolic function over time between patients with simple or complex TGA. To investigate the impact of pregnancy on deterioration of RV systolic function, we compared changes in RV systolic function between women with and without previous pregnancy. No significant differences were found. More patients developed regurgitation of the aortic, pulmonary, and tricuspid valve. Severe tricuspid regurgitation was not significantly associated with diminished RV systolic function. Eight patients (16%) had elevated pulmonary arterial pressures. Neither pulmonary nor mitral regurgitation peak velocities were related to the severity of RV dilation or RV systolic dysfunction. In 18 patients, residual lesions were found comprising mild obstruction of the inferior baffle (n = 4), pulmonary venous baffle (n = 4) or both (n = 2), pulmonary valve stenosis (n = 9), baffle leakage (n = 2), residual VSD (n = 1), and residual ASD (n = 1). All lesions were well tolerated and did not require intervention.

Bicycle ergometry

Maximal exercise capacity was decreased but remained stable over the last 10 years (Table 2). Sixty-nine percent achieved a VO_2 max <85% of the predicted value. During exercise, six patients had an increase in ventricular extrasystoles; in two patients, these were multifocal. No SVT or VT was observed.

NT-proBNP

Median NT-proBNP level was 31.6 (IQR 22.3–53.2) pmol/L. An elevated NT-proBNP level was observed in 92% of the patients. NT-proBNP correlated with age (r = 0.5, P = 0.01) and there was a trend with RV FAC (r = -.33, P = 0.059) and RV annulus dimension (r = 0.30, P = 0.063). Patients with pacemaker rhythm or AF had significantly higher NT-

Table 2. Diagnostic tests

	1990 (10)	2001 (3)	2012	P-value*	
	n = 58	n = 54	n = 50	2012 vs. 1990	2012 vs. 2001
12-lead electrocardiogram	**n = 58**	**n = 54**	**n = 47**		
Rhythm					
- Sinus rhythm	40 (69%)	34 (63%)	31 (66%)	0.4	1.0
- Atrial rhythm	6 (10%)	5 (9%)	5 (11%)	0.7	0.7
- Atrial fibrillation / flutter	1 (2%)	0	3 (6%)	0.2	0.2
- Nodal rhythm	7 (12%)	7 (13%)	1 (2%)	0.2	**0.03**
- Pacemaker rhyhtm	4 (7%)	8 (15%)	7 (15%)	0.5	1.0
PR interval (ms)	162±42	165±23	175±43	**< 0.001**	**0.02**
PR interval >200 ms	1 (2%)	1 (3%)	7 (21%)	**0.03**	0.1
QRS duration (ms)	94±11	110±17	117±19	**<0.001**	**0.001**
QRS duration >120 ms	0	11 (25%)	13 (33%)	**0.01**	0.5
RBBB	5 (9%)	9 (17%)	20 (40%)	**<0.001**	**0.001**
24-hour Holter ECG n = 57		**n = 50**	**n = 37**		
Mean heart rate (bpm)	-	-	73±14	-	-
Maximum heart rate (bpm)	-	-	132±28	-	-
Minimum heart rate (bpm)	-	-	44±10	-	-
Sinus node disease	18 (32%)	30 (60%)	19 (51%)	**0.003**	0.3
Paroxysmal AF/flutter	1 (2%)	0	4 (9%)	0.3	0.5
VT 3-10 complexes	3 (5%)	4 (8%)	6 (16%)	0.1	0.5
VT >10 complexes	0	0	0	-	-
Bicycle ergometry	**n = 49**	**n = 49**	**n = 36**		
Maximum workload (%)	84 [74-93]	74 [64-84]	73 [68-87]	**0.001**	1.0
Maximum heart rate (%)	86 [80-90]	87 [79-92]	85 [76-92]	0.2	**0.02**
VO_2 max (%)	-	-	69 [54-80]	-	-
RER max	-	-	1.3[1.3-1.4]	-	-
VE/VCO2 - anaerobic threshold			28.3[25.8-33.8]		
VE/VCO2 – max workload			29.3[28.7-38.6]		
Echocardiogram	**n = 58**	**n = 53**	**n = 47**		
RV systolic function normal	40 (69%)	3 (6%)	1 (2%)	**<0.001**	0.3
Valve regurgitation (>trace)					
- Aortic regurgitation	4 (7%)	5 (9%)	7 (15%)	**0.03**	0.2
- Mitral regurgitation	8 (14%)	12 (23%)	11 (23%)	0.3	0.7
- Pulmonary regurgitation	15 (26%)	27 (51%)	27 (57%)	**<0.001**	0.3
- Tricuspid regurgitation	36 (62%)	45 (85%)	43 (92%)	**0.001**	0.2
Severe tricuspid regurgitation	1 (2%)	10 (19%)	17 (38%)	**<0.001**	0.1
Mitral regurgitation vmax (m/s)	2.9	2.5	2.8	0.7	0.4
Pulmonary regurgitation vmax (m/s)	1.9	1.9	2.0	0.1	0.9

bpm: beats per minute, RER: respiratory exchange ratio, SVT: supraventricular tachycardia, vmax: maximum velocity, VT: ventricular tachycardia.
Values are presented as mean±SD, median [IQR] or n (%).
* p-values are displayed only for measurements performed in two or all three studies

proBNP levels than patients with sinus or atrial rhythm [134.3 (IQR 44.4–230.5) vs. 28.6 (IQR 21.9–40.4) pmol/L, P = 0.006].

Cardiac magnetic resonance imaging

Cardiac magnetic resonance was performed in 24 patients (48%). The reasons for not performing CMR in the others were the presence of a pacemaker (n = 16), refusal (n = 7), and claustrophobia (n = 3). The results of CMR are summarized in Table 3. Median RV ejection fraction was 47 (IQR 28–71)%. Patients with complex TGA had a higher LVEF (67 vs. 58%, P = 0.007) and RVEF (56 vs. 43%, P = 0.005) than patients with simple TGA.

Predictor analyses

Results of Cox regression analyses are presented in Table 4. Patients operated before 1977 more often died, but needed fewer reinterventions than patients operated after 1977. Early post-operative arrhythmias were predictive for arrhythmias and for development of heart failure during follow-up. Using a time-dependent Cox regression model, early postoperative arrhythmias were predictive for heart failure independent of changes in QRS duration, exercise capacity, and loss of sinus rhythm over the three study moments. No clinical parameters derived from ECG, echocardiography, Holter, and bicycle ergometry in 1990 and 2001 were predictive for outcome.

DISCUSSION

This longitudinal study, evaluating Mustard patients systematically every 10 years for nearly 40 years, shows that patients operated in the 1970s have an acceptable survival and remain in remarkably stable clinical condition despite substantial morbidity and compromised ventricular systolic function. Although ventricular systolic function shows a further decline over time and arrhythmias are often encountered, exercise capacity remains stable.

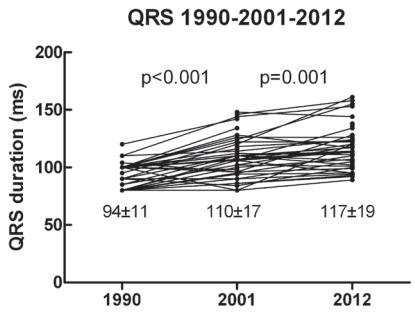


Figure 4. QRS duration over time
The course of QRS duration over time for each participant

Table 4. Predictors for clinical endpoints; all-cause mortality, reinterventions, heart failure and arrhythmias

	Univariable model			Multivariable model		
Endpoint	**HR**	**CI**	**p-value**	**HR**	**CI**	**p-value**
All-cause mortality						
Early postoperative arrhythmias	2.04	[0.76 - 5.50]	0.158	1.50	[0.55 - 4.10]	0.432
Temperature during surgery	1.15	[1.04 - 1.26]	**0.004**	1.05	[0.95 - 1.17]	0.328
Complex or simple TGA	0.99	[0.43 - 2.25]	0.972	1,00	[0.44 - 2.30]	0.995
Age at operation	1.11	[0.95 - 1.28]	0.182	0.97	[0.80 - 1.17]	0.738
Operated before 1977	4.26	[1.44 - 12.60]	**0.009**	2.89	[1.00 - 8.33]	**0.049**
Reintervention						
Early postoperative arrhythmias	0.50	[0.12 - 2.09]	0.343	1.23	[0.62 - 0.36]	0.739
Temperature during surgery	0.97	[0.88 - 1.08]	0.589	1.03	[0.90 - 1.18]	0.622
Complex or simple TGA	1.35	[0.64 - 2.86]	0.428	1.33	[0.63 - 2.81]	0.450
Age at operation	0.88	[0.73 - 1.08]	0.239	0.99	[0.77 - 1.28]	0.944
Operated before 1977	0.37	[0.18 - 0.78]	**0.008**	0.34	[0.14 - 0.84]	**0.020**
Heart failure						
Early postoperative arrhythmias	3.00	[0.81 - 11.12]	0.100	8.13	[2.15 - 30.72]	**0.002**
Temperature during surgery	1.02	[0.89 - 1.18]	0.760	0.92	[0.77 - 1.11]	0.393
Complex or simple TGA	0.70	[0.22 - 2.19]	0.695	1.26	[0.38 - 4.19]	0.706
Age at operation	1.23	[1.01 - 1.50]	**0.038**	1.26	[1.01 - 1.56]	**0.041**
Operated before 1977	1.22	[0.39 - 3.86]	0.730	0.57	[0.15 - 2.07]	0.391
Arrhythmias						
Early postoperative arrhythmias	4.62	[1.96 - 10.90]	**<0.001**	3.82	[1.54 - 9.49]	**0.004**
Temperature during surgery	1.11	[1.02 - 1.21]	**0.012**	1.05	[0.95 - 1.17]	0.331
Complex or simple TGA	1.12	[0.53 - 2.36]	0.765	1.42	[0.65 - 3.09]	0.378
Age at operation	1.18	[1.03 - 1.35]	**0.019**	1.09	[0.91 - 1.29]	0.356
Operated before 1977	1.95	[0.96 - 3.98]	0.065	1.10	[0.48 - 2.51]	0.829

CI= 95% Confidence Interval; HR= Hazard Ratio; TGA= Transposition of the great arteries

Survival and major events

Survival in our cohort is clearly worse than in the general Dutch population. So far, results after the arterial switch operation are better, but follow-up in these patients is still inevitably shorter.[16–18] Survival seems comparable to patients after the Senning operation however, only follow-up of no longer than 20 year has been described for Senning patients.[19] In contrast to findings by Lange et al.,[8] survival rates of patients with simple and complex TGA were similar in our study. At 25-year follow-up, there was a difference in event-free survival between simple and complex TGA. This difference disappeared over the last 10 years. While in the previous decade, heart failure was the main cause of death, ventricular arrhythmias were the sole cause in the last decade. Ventricular arrhythmias are associated with impaired systemic ventricular systolic function in Mustard patients.[20] One of our patients had VF despite having only mild systolic ventricular dysfunction. Survival results were not as bad as we expected, based on the findings in this

cohort 10 years ago. However, morbidity was substantial. Baffle-related complications are the most frequent cause of reintervention, which has been described by Horer et al.[7] However, as only three baffle-related reinterventions were performed in the last 10 years, baffle problems seem to have been addressed effectively in the previous decades and new stenosis are not often encountered.

Systemic right ventricular systolic dysfunction

Progressive decline in systemic RV systolic function is confirmed by our study and remains the major concern in Mustard patients. Tricuspid regurgitation increased in line with further deterioration of RV systolic function and dilation of the ventricle. The degree of RV systolic dysfunction was correlated with NT-proBNP levels, a known marker of prognosis in acquired heart failure.[21] Decline in RV systolic function seems to be confirmed by CMR-derived ejection fraction, although normal values for these subaortic RVs are not available. Nevertheless, the median RVEF in our patients is lower than the RVEF measured in the younger patients with systemic RVs described by Dobson et al.[22] As the benefit of conventional heart failure medication for failing subaortic RVs is limited,[23,24] we expect that more patients will qualify for heart transplantation in the future.

Interestingly, patients with complex TGA had a higher LV and RV ejection fraction on CMR than those with simple TGA. Possibly, the presence of a residual LV outflow tract obstruction with subsequent higher systolic LV pressure causing a more favourable position of the interventricular septum improves ventricular interaction and thereby ventricular systolic function. However, regarding our CMR results, our study population was small and data will have to be confirmed by larger studies.

Arrhythmias

In the last decade, the incidence of SVTs has doubled. This is worrisome, as Kammeraad et al.[25] showed that SVTs are a predictor of sudden cardiac death. The occurrence of atrial macro-re-entry tachycardia could be related to extensive atrial scar tissue, since patients with a systemic RV without atrial scarring (i.e. congenitally corrected TGA) have significantly less SVTs.[22] Also increase in atrial pressure caused by ongoing decline in RV systolic function could induce AF. Although Holter recordings did not show an increase in ventricular arrhythmias, five patients experienced them and two of them died. This urges the question whether more patients with systemic RV systolic dysfunction should receive an ICD for primary prevention. Decisions on this topic are difficult, because in these young patients inappropriate shocks are known to occur more often and consequent psychological problems are of major concern.[26,27] Moreover, lead implantation may lead to obstruction in relatively narrow superior systemic venous baffles.[28] Additionally, lead renewal may be necessary over time in these relatively young patients, which has a significant morbidity. On the other hand, two patients died because of VF in the

last decade, which probably could have been prevented by an ICD in one. Sinus-node disease has been a major concern and the main reason for pacemaker implantation in Mustard patients.[29] Although more than half of our patients showed signs of SND on Holter, only two additional pacemakers were implanted for this indication. Moreover, there was no further loss of sinus rhythm on ECG. Therefore, SND appears to be primarily a problem of the earlier decades after surgery.

Functional capacity

Exercise capacity is clearly impaired in our cohort of patients, but remained stable in the last 10 years. This impaired exercise capacity and lower VO_2 max are in line with the reference values for patients after atrial switch operation described by Kempny et al.[30] Exercise capacity could be limited by several factors: failure to increase ventricular stroke volume due to impaired myocardial contractile reserve, the inability to augment ventricular filling because of noncompliant baffles or inadequate coronary flow reserve in the hypertrophic RV, and chronotropic incompetence, which is a known problem in Mustard patients.[31] In our patients, the maximum heart rate during exercise testing declined over the last 10 years .

Predictors for late events

Older age at time of Mustard repair was associated with a higher chance of developing heart failure. This emphasizes the importance of early surgery, which became standard in the last era of Mustard repair. In patients who are operated at an older age, the prolonged presence of cyanosis may negatively affect the ventricular myocardium. Mortality was significantly higher in the patients operated before 1977 than in those patients operated after 1977. This could reflect improvement in experience, in surgical techniques, and in the quality of perioperative care. Early postoperative arrhythmias predicted the development of late arrhythmias and also the occurrence of heart failure in our cohort. Sarkar et al.[32] found early post-operative arrhythmias to be associated with late sudden death and childhood junctional rhythm in Mustard patients was a predictor for late SVTs in the study of Puley et al.[33] Possibly, the relation between early and late arrhythmias can be explained by surgical damage to the conduction system and the presence of post-operative scar tissue and fibrosis. The relation between early arrhythmias and heart failure is new and needs attention. As patients with early arrhythmias receive a pacemaker more often, ventricular function could be hampered by longstanding abnormal ventricular activation.[34] Also the use of negative inotropic antiarrhythmic drugs could have had a negative effect on RV function. For example, 20% of our patients used a beta-blocker. On the other hand, perhaps the occurrence of early post-operative arrhythmias is an independent sign of a compromised haemodynamic or anatomic situation. Further studies should investigate the exact role and predictive value of these early arrhythmias.

Study limitations and advantages

Although the number of patients in this study is limited, we report the follow-up of a consecutive cohort of operated patients, without selection bias related to disease severity. After a follow-up of nearly 40 years, we gathered medical information on 50 (91%) of the 55 approached patients. We found no significant differences in baseline characteristics between participating and non-participating patients. Therefore, we are confident that there was no selection bias and consider the patients who participated in this study as a non-selected population. Most other studies report on selected patients, still regularly seen at the adult outpatient clinic, while we approached the total patient population operated in the pre-defined time period to visit the hospital.

Assessment of RV function with the use of echocardiography is difficult in the normal heart, and even more difficult in Mustard patients.[35] Normal values for subaortic RVs are not available. The same holds for CMR. Cardiac magnetic resonance is an elegant technique to assess RV volume and function, also in Mustard patients. However, a substantial amount of the Mustard patients has a pacemaker, which makes it impossible to perform a CMR. Even with the use of MRI compatible pacemakers, the intracardiac leads will continue to cause artefacts in the area of interest and thus accurate assessment of RV function in these patients remains difficult.

Diagnostic methods have been changed inevitably over the last decades. Therefore, for comparison to data of the previous studies, we used the same methods as were used in the past. In addition, we performed and reported all up-to-date diagnostic methods which were available in 2012. We believe that this study provides unique data, because this is the only study to examine the same cohort of Mustard patients longitudinally.

CONCLUSIONS

Forty years after Mustard repair, two-third of our original cohort are still alive. There is a progressive decline in RV systolic function and an increasing incidence of arrhythmias and heart failure. However, functional capacity remains stable.

REFERENCES

1. Senning A. Surgical correction of transposition of the great vessels. *Surgery* 1959;45: 966–980.
2. Mustard WT. Successful two-stage correction of transposition of the great vessels. *Surgery* 1964;55:469–472.
3. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, van Domburg R, van Rijen EH, Utens EM, McGhie J, Bos E, Bogers AJ, Simoons ML. Decline in ventricular function and clinical condition after Mustard repair for transposition of the great arteries (a prospective study of 22–29 years). *Eur Heart J* 2004;25:1264–1270.
4. Oechslin E, Jenni R. 40 years after the first atrial switch procedure in patients with transposition of the great arteries: long-term results in Toronto and Zurich. *Thorac Cardiovasc Surg* 2000;48:233–237.
5. Moons P, Gewillig M, Sluysmans T, Verhaaren H, Viart P, Massin M, Suys B, Budts W, Pasquet A, De Wolf D, Vliers A. Long term outcome up to 30 years after the Mustard or Senning operation: a nationwide multicentre study in Belgium. *Heart* 2004;90: 307–313.
6. Jatene AD, Fontes VF, Paulista PP, Souza LC, Neger F, Galantier M, Sousa JE. Anatomic correction of transposition of the great vessels. *J Thorac Cardiovasc Surg* 1976;72: 364–370.
7. Horer J, Herrmann F, Schreiber C, Cleuziou J, Prodan Z, Vogt M, Holper K, Lange R. How well are patients doing up to 30 years after a mustard operation? *Thorac Cardiovasc Surg* 2007;55:359–364.
8. Lange R, Horer J, Kostolny M, Cleuziou J, Vogt M, Busch R, Holper K, Meisner H, Hess J, Schreiber C. Presence of a ventricular septal defect and the Mustard operation are risk factors for late mortality after the atrial switch operation: thirty years of follow-up in 417 patients at a single center. *Circulation* 2006;114:1905–1913.
9. Piran S, Veldtman G, Siu S, Webb GD, Liu PP. Heart failure and ventricular dysfunction in patients with single or systemic right ventricles. *Circulation* 2002;105:1189–1194.
10. Meijboom F, Szatmari A, Deckers JW, Utens EM, Roelandt JR, Bos E, Hess J. Longterm follow-up (10 to 17 years) after Mustard repair for transposition of the great arteries. *J Thorac Cardiovasc Surg* 1996;111:1158–1168.
11. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ, Chamber Quantification Writing Group, American Society of Echocardiography's Group, Standards Committee, European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440–1463.
12. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;23:685–713; quiz 786–688.

13. van den Berg J, Hop WC, Strengers JL, de Jongste JC, van Osch-Gevers L, Meijboom FJ, Pattynama PM, Bogers AJ, Helbing WA. Clinical condition at mid-to-late follow-up after transatrial-transpulmonary repair of tetralogy of Fallot. *J Thorac Cardiovasc Surg* 2007;133:470–477.

14. Therneau T, Grambsch P. Modeling Survival Data: Extending the Cox Model. NewYork: Springer Verlag, 2000.

15. Buuren S. Flexible Imputation of Missing Data. Boca Raton: Chapman & Hall/CRC Press; 2012.

16. Khairy P, Clair M, Fernandes SM, Blume ED, Powell AJ, Newburger JW, Landzberg MJ, Mayer JE Jr. Cardiovascular outcomes after the arterial switch operation for D-transposition of the great arteries. *Circulation* 2013;127:331–339.

17. Ruys TP, van der Bosch AE, Cuypers JA, Witsenburg M, HelbingWA, Bogers AJ, van Domburg R, McGhie JS, Geleijnse ML, Henrichs J, Utens E, Van der Zwaan HB, Takkenberg JJ, Roos-HesselinkJW. Long-termoutcome and quality of life after arterial switch operation: a prospective study with a historical comparison. *Congenit Heart Dis* 2013;8:203–210.

18. Tobler D, Williams WG, Jegatheeswaran A, Van Arsdell GS, McCrindle BW, Greutmann M, Oechslin EN, Silversides CK. Cardiac outcomes in young adult survivors of the arterial switch operation for transposition of the great arteries. *J Am Coll Cardiol* 2010;56:58–64.

19. Roubertie F, Thambo JB, Bretonneau A, Iriart X, Laborde N, Baudet E, Roques X. Late outcome of 132 Senning procedures after 20 years of follow-up. *Ann Thorac Surg* 2011;92:2206–2213; discussion 2213-2204.

20. Schwerzmann M, Salehian O, Harris L, Siu SC, Williams WG, Webb GD, Colman JM, Redington A, Silversides CK. Ventricular arrhythmias and sudden death in adults after a Mustard operation for transposition of the great arteries. *Eur Heart J* 2009; 30:1873–1879.

21. Eindhoven JA, van den Bosch AE, Ruys TP, Opić P, Cuypers JA, McGhie JS, Witsenburg M, Boersma E, Roos-Hesselink JW. N-terminal pro-B-type natriuretic peptide and its relationship with cardiac function in adults with congenital heart disease. *J Am Coll Cardiol* 2013;62:1203–1212.

22. Dobson R, Danton M, Nicola W,Hamish W. The natural and unnatural history of the systemic right ventricle in adult survivors. *J Thorac Cardiovasc Surg* 2013;145: 1493–1501; discussion 1501-1493.

23. van der Bom T, Winter MM, Bouma BJ, Groenink M, Vliegen HW, Pieper PG, van Dijk AP, Sieswerda GT, Roos-Hesselink JW, Zwinderman AH, Mulder BJ. Effect of valsartan on systemic right ventricular function: a double-blind, randomized, placebo-controlled pilot trial. *Circulation* 2013;127:322–330.

24. Winter MM, Bouma BJ, Groenink M, Konings TC, Tijssen JG, van Veldhuisen DJ, Mulder BJ. Latest insights in therapeutic options for systemic right ventricular failure: a comparison with left ventricular failure. *Heart* 2009;95:960–963.

25. Kammeraad JA, van Deurzen CH, Sreeram N, Bink-Boelkens MT, Ottenkamp J, Helbing WA, Lam J, Sobotka-Plojhar MA, Daniels O, Balaji S. Predictors of sudden cardiac death after Mustard or Senning repair for transposition of the great arteries. *J Am Coll Cardiol* 2004;44:1095–1102.

26. Opić P, Utens EM, Moons P, Theuns DA, van Dijk AP, Hoendermis ES, Vliegen HW, de Groot NM, Witsenburg M, Schalij M, Roos-Hesselink JW. Psychosocial impact of implantable cardioverter defibrillators (ICD) in young adults withTetralogy of Fallot. *Clin Res Cardiol* 2012;101:509–519.

27. Yap SC, Roos-Hesselink JW, Hoendermis ES, Budts W, Vliegen HW, Mulder BJ, van Dijk AP, Schalij MJ, Drenthen W. Outcome of implantable cardioverter defibrillators in adults with congenital heart disease: a multi-centre study. *Eur Heart J* 2007;28: 1854–1861.

28. Bottega NA, Silversides CK, Oechslin EN, Dissanayake K, Harrison JL, Provost Y, Harris L. Stenosis of the superior limb of the systemic venous baffle following a Mustard procedure: an under-recognized problem. *Int J Cardiol* 2012;154:32–37.

29. Dos L, Teruel L, Ferreira IJ, Rodriguez-Larrea J, Miro L, Girona J, Albert DC, Goncalves A, Murtra M, Casaldaliga J. Late outcome of Senning and Mustard procedures for correction of transposition of the great arteries. *Heart* 2005;91:652–656.

30. Kempny A, Dimopoulos K, Uebing A,Moceri P, SwanL, GatzoulisMA, DillerGP. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life—single centre experience and review of published data. *Eur Heart J* 2012;33:1386–1396.

31. Fredriksen PM, Pettersen E, Thaulow E. Declining aerobic capacity of patients with arterial and atrial switch procedures. *Pediatr Cardiol* 2009;30:166–171.

32. Sarkar D, Bull C, Yates R, Wright D, Cullen S, Gewillig M, Clayton R, Tunstill A, Deanfield J. Comparison of long-term outcomes of atrial repair of simple transposition with implications for a late arterial switch strategy. *Circulation* 1999;100 (19 suppl):II176–II181.

33. Puley G, Siu S, Connelly M, Harrison D,Webb G, WilliamsWG, Harris L. Arrhythmia and survival in patients .18 years of age after the mustard procedure for complete transposition of the great arteries. *Am J Cardiol* 1999;83:1080–1084.

34. Nothroff J, Norozi K, Alpers V, Arnhold JO, Wessel A, Ruschewski W, Buchhorn R. Pacemaker implantation as a risk factor for heart failure in young adults with congenital heart disease. *Pacing Clin Electrophysiol* 2006;29:386–392.

35. Iriart X, Horovitz A, van Geldorp IE, Barnetche T, Lederlin M, De Guillebon M, Reant P, Lafitte S, Thambo JB. The role of echocardiography in the assessment of right ventricular systolic function in patients with transposition of the great arteries and atrial redirection. *Arch Cardiovasc Dis* 2012;105:432–441.

8

Sports participation in adults with congenital heart disease

Petra Opić, Elisabeth M.W.J. Utens, Judith A.A.E. Cuypers, Maarten Witsenburg, Annemien van den Bosch, Ron van Domburg, Ad J.J.C. Bogers, Eric Boersma, Antonio Pelliccia, Jolien W. Roos-Hesselink

International Journal of Cardiology 2015 May 6;187:175-82

ABSTRACT

Background

It is unclear whether sports participation in adults with repaired congenital heart disease is safe and has benefits.

Methods

Congenital heart disease (ConHD) patients who underwent corrective surgery for Atrial Septal Defect, Ventricular Septal Defect, Pulmonary Stenosis, Tetralogy of Fallot or Transposition of the Great Arteries in our center between 1968 and 1980 were included, and participated in our longitudinal follow-up study with serial evaluations in 2001 and 2011. At both time points patients filled in questionnaires on sports participation, subjective physical functioning and quality of life. Exercise testing, echocardiogram and 24-hour continuous ambulatory ECG-monitoring were performed in both 2001 and 2011. All clinical events (re-intervention, arrhythmia, heart failure) were prospectively recorded.

Results

No relationship was found between practicing sports and the occurrence of sudden death, PVCs or SVTs. Patients with moderate/complex forms of ConHD practiced fewer hours of sports compared with the general Dutch normative population. Patients with both simple and moderate/complex ConHD who practiced sports showed a higher exercise capacity. More favorable subjective physical functioning was found for moderate/complex patients who practiced sports.

Conclusions

Adults with repaired ConHD are less often involved in sports than the Dutch general population. The patients that were engaged in sports show a higher exercise capacity than those who did not. Sports participation in patients with ConHD was not associated with an increased incidence of adverse cardiac events.

INTRODUCTION

Since the first surgical techniques for patients with congenital heart disease (ConHD) became available some 55 years ago, virtually every area of medical care has evolved substantially. These improvements led to an increased survival for patients with ConHD, with over 90% of infants reaching adulthood nowadays.[1]

Sports participation in adults with ConHD is a relatively new territory and many physicians are having difficulty in advising their patients. The first concern is the safety of the patients, and the fear exists that exercise training and competitive sports participation may increase the risk of adverse events, including sudden death. In this field, however, there is a paucity of prospective data and controversial opinions still exist concerning the safety for these patients to be regularly engaged in sports.[2,3]

Participation in sports can have beneficial effects on quality of life, as was recently shown in a multicenter randomized controlled trial for adolescents with ConHD, and also for ischemic heart disease and heart failure.[4-6] Moreover, adolescents overall do not achieve the 60 min of recommended daily moderate to vigorous physical activity.[7] The recent RCT showed that practicing sports reduced passive leisure time spending.[4]

We therefore planned the present study to investigate the clinical consequences of sports participation in adults with repaired ConHD, with particular emphasis on the occurrence of adverse cardiac events, but also assessing the cardiovascular functional capacity, the patients' physical fitness and quality of life. To this scope, we took advantage of the long-standing follow-up program, which includes consecutive ConHD patients operated at the Erasmus Medical Center between 1968 and 1980, and extensively followed-up every 10 years.

METHODS

Inclusion criteria

The original cohort consisted of all consecutive patients who underwent surgical correction for Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), Pulmonary Stenosis (PS), Tetralogy of Fallot (ToF) or Transposition of the Great Arteries (TGA) between 1968 and 1980 in the Erasmus MC, and were younger than 15 years at the time of surgery. This patient cohort has been investigated in 1991, in 2001, and again in 2011. The baseline characteristics and medical and psychosocial results of these investigations have been reported previously.[8-13]

The target population of the third follow-up (conducted in 2011) consisted of the 362 patients who had previously participated in 2001. Of these patients, 10 died (i.e., 6 cardiac-related, 3 unknown, 1 accident), 1 underwent heart transplantation and 22

patients were lost to the follow-up. Of the remaining 329 eligible patients, 245 patients (already examined in 2001) agreed to participate and represent the study population of the current analysis in 2011. The flow-chart describing the plan of the study is shown in Figure 1. No differences were found in baseline characteristics between the patients who participated again in 2011 and those who did not.

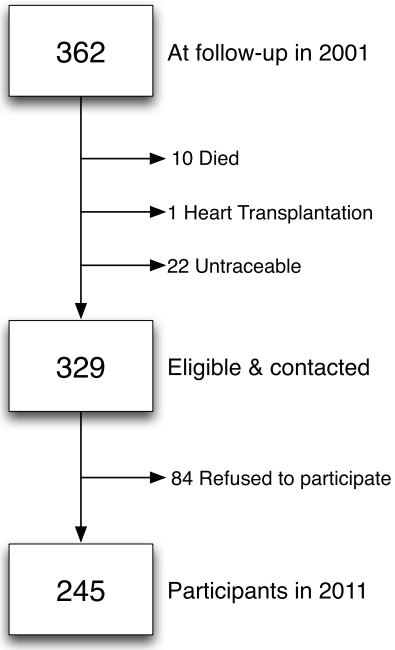


Figure 1. Flow-chart of patient inclusion

Assessment procedure

All patients were invited to the outpatient clinic for cardiac and psychological examination and were informed of the study project. During the outpatient visit, patients underwent a cardiac examination which consisted of 24-hour Holter monitoring, an electrocardiogram, an echocardiogram and exercise testing. The participation in exercise programs, sports and psychosocial characteristics were assessed by questionnaires, which are described in detail below. The questionnaires were administered verbally for patients who had difficulty reading or understanding the written questions. The research protocol was approved by the institutional ethical committee of the Erasmus MC and all patients included in the present analysis provided written informed consent.

Questionnaires and normative groups

Sports participation was assessed using the same general questionnaire on leisure activities in 2001 and 2011 which is based on the Dutch Central Bureau of Statistics (CBS).[10,14,15] In addition, in 2011, four items of the "Baecke questionnaire", widely used for assessing habitual physical activity in epidemiological studies[16] were used. Sports participation was defined as any form of solitary or group physical activities outside of regular walking and cycling throughout the day. In order to make comparison with the general Dutch population possible, the types of sports were classified according to the CBS, which was also used to obtain normative values for the average Dutch population (data retrieved in 2012).[17] Specifically, the categories "Extensive" (more than 5 h of sports per week), "Little/ Moderate" (in between 1 and 5 h of sports per week) and "None" (up to 1 h or less of sports per week) were used. The physiologic types of sports that patients in our study were practicing (listed in Table 3) were classified according to Mitchell et al.[18]

This classification shows the percentage of patients practicing dynamic and static sports in different intensities.

According to the classification adopted at the American Heart Association Task Force on Adults with CHD,[19] patients with repaired ASD, VSD and PS were classified as simple ConHD (unless they had complications such as severe ventricular dysfunction),while patients with ToF or TGA (all operated with a Mustard repair) were classified as moderate to complex ConHD.

Clinical events were defined as surgical/transcatheter re-intervention, ICD implantation, pacemaker implantation, heart failure or symptomatic and clinically relevant arrhythmia. Arrhythmias (supraventricular tachycardia or ventricular tachycardia) were defined as clinically relevant if anti-arrhythmic medication was needed, cardioversion or catheter-based or surgical ablation had been applied, or hospitalization was necessary. Data on events were collected from patient records, and classified by the first and last authors.

Maximal *exercise capacity* was assessed by bicycle ergometry and was compared with that of normal individuals corrected for age, gender, body height and weight.[20] Gradual increments of workload of 20 Watts per minute were used. Exercise capacity <85% of the predicted value was considered to be decreased. VO2 max was also measured in the evaluation of 2011, but not in 2001.

Subjective physical functioning[21] was assessed by the physical functioning scale of the SF-36. This scale measures the amount of limitation in physical activities due to health problems. Good reliability and validity for the Dutch version of the SF-36 have been reported.[22]

Self-perceived quality of life was assessed by the Linear Analogue Scale (LAS) for Quality of Life. The LAS has been proven valid, reliable, and sensitive for the ConHD population.[23] This instrument was not used in 2001 and therefore no historical comparison can be made.

Statistical analyses

Continuous data are presented by means ± SD. In case of a skewed distribution (significant Kolmogorov–Smirnov test or highly skewed histogram by visual inspection), medians and interquartile ranges [IQR] (Q1–Q3) are displayed. The SF36 Physical Functioning scale is analyzed with means ± SD according to its manual.[22] To assess differences between ConHD diagnostic groups (simple versus moderate/complex), t-tests or Mann–Whitney-U tests were utilized. Longitudinal comparison was assessed by paired sample t-tests or Wilcoxon signed-rank tests.

Categorical variables are represented by percentages. When comparing categorical variables between ConHD diagnostic groups (simple versus moderate/complex ConHD), Chi-square tests or Fisher exact tests were used. Longitudinal (repeated measures)

comparison of categorical variables was analyzed by the McNemar test for 2 × 2 paired tables.

Univariate Cox regression was used to assess the association between death and ConHD, and to assess the association between death and practicing sports in 2001. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported. Univariate logistical regression analyses were applied to assess the association between arrhythmias and sports participation in 2011 (yes/no), adjusted for age, gender, complexity of ConHD, and systemic ventricular function in 2011. We report odds ratios (ORs) and corresponding 95% confidence intervals. Only variables that had a p-value of <0.1 were used in the multivariate regression. Multivariate logistical regression was applied to PVCs (127 cases) adjusting for complexity of congenital heart disease, systemic ventricular function and sports (yes/no), SVTs (69 cases) adjusting for age and gender and VTs (23 cases) adjusting for complexity of congenital heart disease, systemic ventricular function, exercise capacity and sport (yes/no).

Two-tailed probability values of <0.05 were considered statistically significant. The statistical program IBM SPSS Statistics for Mac, Version 20.0 (released 2011) was used for all statistics. Figures were made using GraphPad Prism version 6.0a for Mac, GraphPad Software (released July 18, 2012), La Jolla, California, USA.

RESULTS

Baseline characteristics in 2001

The baseline characteristics of the patients included in this analysis are shown in Table 1. Patients with simple ConHD who were not practicing sports were smoking more cigarettes per day compared with those who were practicing sports (hours) (20 [14–20] vs. 10 [4–15], p = 0.009), and showed a significantly lower exercise capacity (% predicted of norm) (89.6 ± 21.9 vs. 97.5 ± 15.2, p = 0.008). Patients with moderate/complex ConHD who were not practicing sports in 2001 were significantly older (years) (29.5 [24.2–35.0] vs. 26.7 [23.7–29.3], p = 0.036), had a significantly lower exercise capacity (% predicted of norm) (75.3 ± 17.2 vs. 84.1 ± 21.0, p = 0.047), had a higher average heart rate (beats per minute) (76.0 [72.0–80.0] vs. 71.0 [66.8–77.5], p=0.021) and showed worse results on subjective physical functioning (QoL score) (95.0 [75.0–100.0] vs. 95.0 [90.0–100.0], p = 0.039) compared with patients who were practicing sports in 2001.

Mortality or arrhythmias

Of the 362 patients evaluated in 2001, 10 patients died and 1 patient underwent heart transplantation over the follow-up period of 10 years. Clinical characteristics of these 11 patients are reported in Table 2. We found an association between the presence of

Table 1. Patient characteristics in 2001

	Total	Simple ConHD		p	Moderate/complex ConHD		p
		No sports	Sports		No sports	Sports	
	n = 245	n = 74	n = 91		n = 45	n = 35	
Age in 2001 (years)	29.7 [26.5-34.8]	31.6 [28.0-36.1]	30.1 [27.7-35.2]	0.161	29.5 [24.2-35.0]	26.7 [23.7-29.3]	0.036
Age at first surgery	4.6 [1.1-1.3]	5.5 [1.8-8.8]	5.7 [2.1-8.9]	0.814	3.2 [0.7-6.5]	1.2 [0.5-3.1]	0.059
Gender							
Male	52.2 (128)	45.9 (34)	51.6 (47)	0.466	62.2 (28)	54.3 (19)	0.474
Female	47.8 (117)	54.1 (40)	48.4 (44)		37.8 (17)	45.7 (16)	
Smoking							
Yes	22.6 (55)	27.0 (20)	18.9 (17)	0.215	20.5 (9)	25.7 (9)	0.580
Amount/day	10 [5-20]	20 [14-20]	10 [4-15]	0.009	4 [3-12]	7 [3-15]	0.478
SYSVF							
Good	80.8 (189)	90.1 (64)	94.1 (80)	0.628	59.1 (26)	55.9 (19)	0.866
Mild	9.8 (23)	8.5 (6)	4.7 (4)		13.6 (6)	20.6 (7)	
Moderate	6.0 (14)	1.4 (1)	1.2 (1)		15.9 (7)	14.7 (5)	
Bad	3.4 (8)	0.0 (0)	0.0 (0)		11.4 (5)	8.8 (3)	
Exercise capacity	79.1 ± 19.3	89.6 ± 21.9	97.5 ± 15.2	0.008	75.3 ± 17.2	84.1 ± 21.0	0.047
Holter data							
Average beats per minute	75.0 [69.0-81.0]	76.0 [70.0-82.2]	76.5 [69.0-81.8]	0.624	76.0 [72.0-80.0]	71.0 [66.8-77.5]	0.021
SVT	0.4 (1)	0.0 (0)	0.0 (0)	-	2.2 (1)	0.0 (0)	1.000
PVC > 10 complexes	0.0 (0)	0.0 (0)	0.0 (0)	-	0.0 (0)	0.0 (0)	-
VT	4.5 (11)	2.7 (2)	2.2 (2)	1.000	8.9 (4)	8.6 (3)	1.000
Medication							
Any medication	4.9 (10)	96.8 (61)	97.4 (74)	1.000	94.1 (32)	87.1 (27)	0.413
Aspirin	0.5 (1)	1.6 (1)	0.0 (0)	0.453	0.0 (0)	0.0 (0)	-
Calcium antagonist	0.0 (0)	0.0 (0)	0.0 (0)	-	0.0 (0)	0.0 (0)	-
Betablocker	1.0 (2)	0.0 (0)	1.3 (1)	1.000	0.0 (0)	3.2 (1)	0.477

Table 1. Patient characteristics in 2001 (continued)

	Total	Simple ConHD		p	Moderate/complex ConHD		p
		No sports	Sports		No sports	Sports	
	n = 245	n = 74	n = 91		n = 45	n = 35	
Nitrate	0.0 (0)	0.0 (0)	0.0 (0)	-	0.0 (0)	0.0 (0)	-
Anti-arrhythmics	0.5 (1)	0.0 (0)	0.0 (0)	-	2.9 (1)	0.0 (0)	1.000
Digitalis	2.0 (4)	1.6 (1)	0.0 (0)	0.453	5.9 (2)	3.2 (1)	1.000
Duretics	0.0 (0)	0.0 (0)	0.0 (0)	-	0.0 (0)	0.0 (0)	-
ACE inhibitor	2.5 (5)	1.6 (1)	1.3 (1)	1.000	2.9 (1)	6.5 (2)	0.602
Cholesterol lowering	0.0 (0)	0.0 (0)	0.0 (0)	-	0.0 (0)	0.0 (0)	-
Oral anticoagulation	0.5 (1)	0.0 (0)	0.0 (0)	-	2.9 (1)	0.0 (0)	0.475
Physical Functioning	95.0 [90.0-100.0]	95.0 [90.0-100.0]	100.0 [93.8-100.0]	0.152	95.0 [75.0-100.0]	95.0 [90.0-100.0]	0.039

Abbreviations: Complex ConHD = Tetralogy of Fallot (ToF) & Transposition of the Great Arteries (TGA); ConHD = Congenital Heart Disease; Exercise capacity is expressed in % of expected; NYHA = New York Heart Association; PVC = Premature ventricular complex; Simple ConHD = Atrial Septal Defect (ASD) & Ventricular Septal Defect (VSD) & Pulmonary Stenosis (PS); SVT = supraventricular tachycardia; SYSVF = systemic ventricular function; VT = Ventricular tachycardia;
Data are expressed as proportion and (actual number).
Holter data has been recorded for 24 hours, amount of SVT, PVC and VT's reported are per 24 hours.

Table 2. Data on patients that died between 2001 and 2011

Age	Gender	ConHD	Surgery	BMI	Hypertension	Hrs of sports/week	Type of sport	Cause of death	ECG + Pacemaker	Systemic ventricular function	Systemic AV-valve	Pulmonary valve	Arrhythmias	Other
51	F	Fallot	1968	18	No	0	No	Heart failure	Endocardial VVI since 1990 (no ICD)	Bad	No regurgitation	No regurgitation	Sick-Sinus Syndrome	
28	M	VSD	1980	18	No	0	No	Heart failure, cardiac arrest	SR	Moderately reduced	No regurgitation	No regurgitation	No	
41	M	TGA (Mustard)	1973	21	No	0	No	Untreatable VF by ICD	Epicardial VVI since 1996 (ICD)	Bad	Severe regurgitation	Moderate regurgitation	Sick-Sinus Syndrome	
41	M	Fallot	1988	32	No	1-5	Jogging	Directly after jogging	Endocardial DDD since 1981 (no ICD)	Mildly reduced	N/A	Severe regurgitation	Sick-Sinus Syndrome	No pulmonary homograft because of high surgery risk
45	F	ASD	1972	25	Yes	1-5	Unknown	Unknown	SR	Good	Mild regurgitation	No regurgitation	No	
33	M	TGA (Mustard)	1974	28	No	0-1	Tennis	During tennis	SR	Mildly reduced	N/A	Moderate regurgitation	No	Mild baffle stenosis
32	F	Fallot	1974	19	No	0-1	Hiking, walking	Heart failure	SR RBTB	Good	No regurgitation	No regurgitation	No	
28	M	Fallot	1978	27	No	0-1	Surfing	VF	SR RBTB	Good	No regurgitation	N/A	No	
52	M	VSD	1968	27	No	5+	Fitness, rowing, running	Unknown	SR RBTB	Good	Mild regurgitation	Light regurgitation	No	
32	M	Fallot	1980	32	No	5+	Fitness, soccer	Shot to death	SR RBTB	Mildly reduced	Mild regurgitation	N/A	No	

Abbreviations: ASD = Atrial Septal Defect; AV-valve = Atrioventricular valve; BMI = Body Mass Index; ConHD = Congenital heart disease; ECG = Electrocardiogram; Fallot = Tetralogy of Fallot; ICD = Implantable Cardioverter Defibrillator; N/A = Not Available; RBTB = Right Ventricular Bundle Branch Block; TGA = transposition of the Great Arteries (all Mustard surgery); VF = Ventricular Fibrillation; VSD = Ventricular Septal Defect. Hours of sports is expressed in hours per week.

moderate/complex ConHD and the occurrence of death (HR [95% CI]: 4.3 [1.1–16.6], p = 0.036). We found no relationship between practicing sports and the occurrence of death (HR [95% CI]: 0.6 [0.2–2.3], p=0.482). The changes in sports participation in patients in the period from 2001 to 2011 are shown in Fig. 2.

We also did not find a relationship between sports participation and the occurrence of PVCs (OR [95% CI]: 0.3 [0.1–1.05], p = 0.06), SVTs (OR [95% CI]: 0.9 [0.5–1.5], p = 0.572) or the average heart rate (R^2 = .008, $F(1,224)$= 1.8, p =0.181). There was a negative association between sports participation and the occurrence of VTs (OR [95% CI]: 0.3 [0.1–0.7], p = 0.010); however, this association disappeared after adjustment for potential confounders (OR [95% CI]: 0.5 [0.2–1.4], p = 0.169).

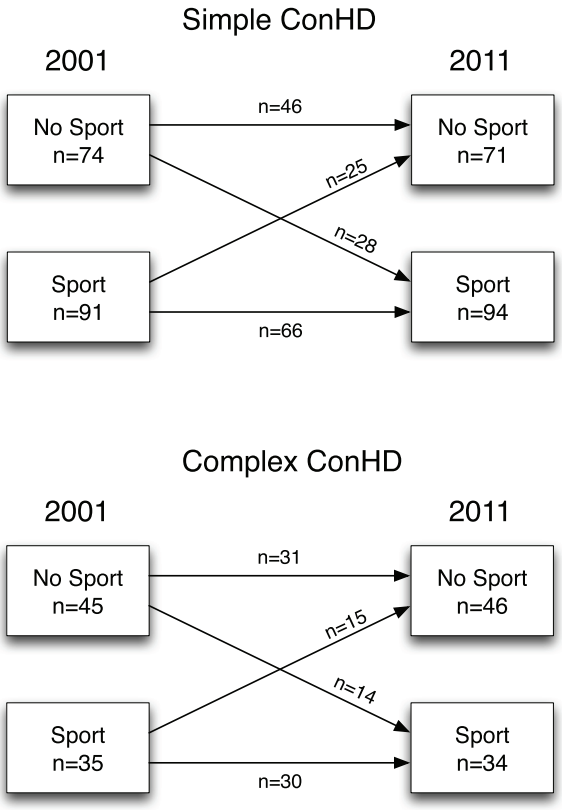


Figure 2. Flowchart of sport participation between 2001 and 2011.
Abbreviations: ConHD = Congenital Heart Disease;
The category "No sports" contains patients who never practiced any sports and patients who stopped practicing sports between 2001 and 2011. The category "Sports" contains patients who remained practising sports between 2001 and 2011, and patients who started practicing sports between 2001 and 2011.

Characteristics of sports participation in patients with ConHD in 2011

The types of sports participated by patients in 2011 are listed in Table 3. More than half of the patients were involved in high-dynamic sports (57.9%).

Table 3. Type of sports participation of ConHD patients in 2011

Increasing static component	Low 36.8%	Moderate 5.3%	High 57.9%
High 30.9%	23.0%	1.3%	6.6%
Moderate 43.4%	4.6%	3.3%	35.5%
Low 25.7%	9.2%	0.7%	15.8%

Increasing dynamic component

Data is for total ConHD group. Table based on the study of Mitchell et al. [18]

Fig. 3 shows sports participation in patients with ConHD in 2011 compared with normative data derived from the general population. Specifically, patients with moderate/complex ConHD practiced fewer hours of sports in comparison with the normal population. Both simple and moderate/complex ConHD patients were underrepresented in the 'Extensive' sports category compared with the general Dutch population.

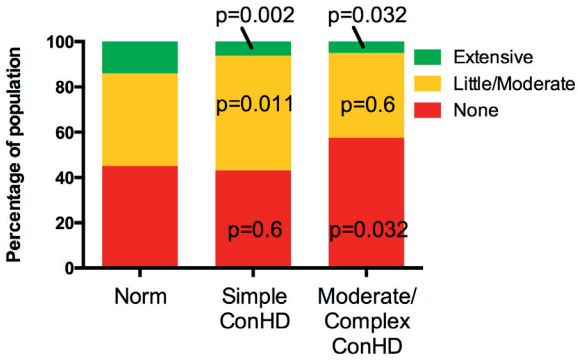


Figure 3. Sports participation in 2011 versus normative data
Abbreviations: Extensive = 5 or more hours per week; Little/Moderate = In between 1 and 5 hours of sports per week; More than 5 hours of sports per week; None = Up to 1 hour or less of sports per week. Categories are based on normative data derived from the Dutch Central Bureau of statistics [15].

Fig. 4 shows that patients who practiced sports had a significantly higher exercise capacity compared with patients who did not practice any sport.

Table 4 shows that patients with simple ConHD who were not practicing sports had a worse exercise capacity than patients who were practicing sports (86.6±18.2 vs.

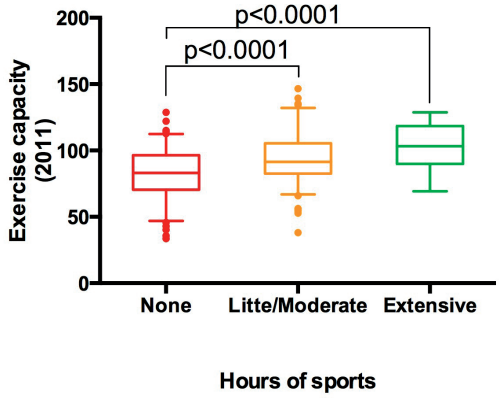


Figure 4. Relationship between exercise capacity and hours of sports practiced
Abbreviations: Extensive = 5+ hours of sports per week; Little/Moderate = 1 to 5 hours of sports per week; None = Up to 1 hour or less of sports per week. The X-axis represents the hours of sports practiced in 2011. On the Y-axis the exercise capacity is shown. Practicing > 5 hours/week sports per week or more results in a better exercise capacity.

96.8±19.2, p=0.001). The same influence was observed for moderate/complex patients (75.9 ± 19.3 vs. 90.1 ± 19.2, p = 0.003).

The total sports group showed a lower incidence of ventricular tachycardia (14.5% vs. 4.7%, p=0.008, not in the table) and fewer premature ventricular complexes (64.2% vs. 49.2%, p = 0.023, not in the table).

In addition, patients with moderate/complex ConHD who were not practicing sports showed a worse exercise capacity compared with those who were practicing sports (90.0 [75.0–95.0] vs. 95.0 [89.7–100.0], p-value = 0.001).

Patients with moderate/complex ConHD who were practicing sports showed a significantly higher Physical Functioning compared with patients who did not practice sports (95.0 [89.7–100.0] vs. 90.0 [75.0–95.0], p = 0.001). No differences were found on quality of life (according to the LAS instrument).

Clinical consequences of sports participation over time

Over the period of 10 years, 22.5% of the patients showed deterioration in systemic ventricular function, while 69.6% remained stable. In 7.9% of the patients, an improvement in systemic ventricular function was observed. The patients who practiced sports, more often remained stable (77.0% vs. 61.0%, overall p-value= 0.031).

When looking at subjective physical functioning over time, deterioration was seen in the group of patients that stopped practicing sports between 2001 and 2011 (95.0 [85.0–100.0] vs. 92.5 [75.0–100.0], p = 0.035). Systemic ventricular function did not deteriorate in patients who stopped practicing sports over time compared with patients who remained practicing sports (20.9% vs. 30.6%, p = 0.276).

These influences were observed only when the data were analyzed for the overall patient's cohort, and were lost when looking separately at simple and moderate/complex ConHD.

Major complications between 2001 and 2011

Table 5 lists the major complications that occurred between 2001 and 2011. In total, 46 patients had only events before the first assessment in 2001. These patients were excluded from analysis. A total of 26 patients had one or more major cardiac events. There were no significant differences between patients who did or did not practice sports.

Table 4. Results in 2011

	2011							
	Total	Simple ConHD		p	Moderate/complex ConHD		p
		No sports	Sports		No sports	Sports	
	n = 245	n = 74	n = 91		n = 45	n = 35	
Exercise capacity	89.2 ± 20.3	86.6 ± 18.2	96.8 ± 19.2	0.001	75.9 ± 19.3	90.1 ± 19.2	0.003
SYSVF							
Good	66.1 (156)	82.8 (53)	86.0 (80)	0.564	24.4 (11)	35.3 (12)	0.173
Mild	22.9 (54)	15.6 (10)	12.9 (12)		48.9 (22)	29.4 (10)	
Moderate	7.6 (18)	0.0 (0)	1.1 (1)		15.6 (7)	29.4 (10)	
Bad	3.4 (8)	1.6 (1)	0.0 (0)		11.1 (5)	5.9 (2)	
Holter data							
Average beats per minute	73.0 [68.0-79.0]	74.0 [69.0-79.3]	72.0 [68.0-79.0]	0.491	73.5 [69.3-80.8]	74.0 [65.0-78.0]	0.352
PVC > 10 complexes	56.2 (127)	51.6 (32)	44.4 (40)	0.384	81.8 (36)	63.3 (19)	0.074
SVT	28.2 (69)	25.4 (18)	30.9 (29)	0.438	34.8 (16)	17.6 (6)	0.090
VT	9.4 (23)	7.0 (5)	2.1 (2)	0.121	26.1 (12)	11.8 (4)	0.113
Physical Functioning	95.0 [85.0-100.0]	95.0 [80.0-100.0]	100.0 [90.0-100.0]	0.122	90.0 [75.0-95.0]	95.0 [89.7-100.0]	0.001
LAS	80.0 [75.0-88.0]	80.0 [74.0-85.0]	80.5 [75.0-90.0]	0.062	80.0 [74.3-85.0]	83.0 [75.0-89.0]	0.105

Abbreviations: Complex ConHD = Tetralogy of Fallot (ToF) & Transposition of the Great Arteries (TGA); ConHD = Congenital Heart Disease; Exercise capacity is expressed in % of expected workload; LAS = Linear Analogue Scale; PVC = Premature ventricular complex; Simple ConHD = Atrial Septal Defect (ASD) & Ventricular Septal Defect (VSD) & Pulmonary Stenosis (PS); SVT = supra-ventricular tachycardia; SYSVF = systemic ventricular function; VT = Ventricular tachycardia. Data are expressed as n(%).
Holter data has been recorded for 24 hours, amount of SVT, PVC and VT's reported are per 24 hours.

Table 5. Clinical events between 2001 – 2011

	Major events between 2001 - 2011						
	Total	Simple ConHD		p	Moderate/complex ConHD		p
		No sports	Sports		No sports	Sports	
	n = 245	n = 74	n = 91		n = 45	n = 35	
Major events							
Overall	10.6 (26)	8.5 (6)	5.3 (5)	0.425	19.6 (9)	17.6 (6)	0.828
Arrhythmia	6.5 (16)	5.6 (4)	4.3 (4)	0.726	10.9 (5)	8.8 (3)	1.000
Pacemaker implantation	2.9 (7)	2.8 (2)	0.0 (0)	0.184	8.7 (4)	2.9 (1)	0.388
Surgical reintervention	2.4 (6)	2.8 (2)	0.0 (0)	0.184	4.3 (2)	5.9 (2)	1.000
ICD implantation	1.6 (4)	1.4 (1)	1.1 (1)	1.000	4.3 (2)	0.0 (0)	0.505
Heart failure	1.2 (3)	0.0 (0)	0.0 (0)	-	6.5 (3)	0.0 (0)	0.258

Abbreviations: Complex ConHD = Tetralogy of Fallot (ToF) & Transposition of the Great Arteries (TGA); ConHD = Congenital Heart disease; ICD = Implantable Cardioverter Defibrillator; Simple ConHD = Atrial Septal Defect (ASD) & Ventricular Septal Defect (VSD) & Pulmonary Stenosis (PS). Data are expressed as n(%); One person can have multiple major complications.

DISCUSSION

Our study shows that sports participation in adults with ConHD has a positive influence on exercise capacity, both in patients with simple and moderate/complex ConHD, without conveying major negative consequences such as death or arrhythmias. In the patients with moderate/complex ConHD a positive influence on subjective physical function was also observed.

Sports participation in patients with ConHD

Almost half of the adults with ConHD included in the present analysis were engaged in sports. Compared with the general Dutch population, the patients with ConHD, and especially those with moderate/complex ConHD, practice sports for fewer hours per week. Our findings are in line with two previous studies,[24,25] and in contrast only with Immer et al. who unexpectedly reported a higher rate of sports participation in patients with simple and complex forms of ConHD compared with the general population.[26] Patients with more complex forms of ConHD are known to have a reduced exercise capacity.[27] This finding is the most logic explanation why complex patients (as shown in our study) are less often involved in sports. They are probably limited in their possibility to sport, based on their reduced physical capacities. However, it has been shown that children and adolescents with ConHD were able to improve their peak oxygen uptake with an exercise program, so the depressed exercise capacity may partially be explained by the absolute lack of exercise, mostly based on fear for complications or negative impact on cardiac function.[6,24,25,27-30] We found that practicing sports did increase exercise capacity in patients with ConHD, including those with the more complex lesions.

Indeed, we found not only a positive influence on exercise capacity but also on subjective physical functioning, including the patients with more complex ConHD. Previous studies have shown ambiguous results, with some studies reporting that an active lifestyle in ConHD patients has a positive influence on exercise capacity or peak oxygen uptake and perceived physical functioning,[6,25,31,32] while other studies found no relationship.[29,33]

Safety

The results on safety in this article should be interpreted with caution due to the small sample size. The rare case of a young man with an operated Tetralogy of Fallot dying suddenly at the sports field is a dramatic and emotional event that raises a number of questions regarding the safety of sports participation and explains the implementation of strict regulations.[34] On the other hand, many patients with moderate/complex ConHD can and do participate in sports without major problems and can even reach the highest level of achievement. For instance, Shaun White, also operated for Tetralogy of Fallot won Olympic gold twice on snowboarding.[35] Proper studies on safety are lacking and are difficult to perform.

In our prospective observational cohort, we found no significant relation between sports participation and sudden cardiac death or other adverse events such as ominous arrhythmias. Moreover, we found less ventricular ectopic beats and short VTs on Holter ECG monitoring in patients that were actively engaged in sports and a trend for a favorable influence on ventricular function. Of course, there may be a bias selection in sports, usually compromising the individuals in better conditions, but nevertheless these patients seem not to be at higher risk.

We found high scores on subjective physical functioning in patients with ConHD, with the possible consequence of overestimating their physical capabilities. This might indeed imply that they might choose a sport that can potentially be harmful. In our study, over 50% was engaged in high-dynamic sports and a small subset of patients (6.6%) practiced sports both at the highest static and dynamic level. Despite participation in these demanding sports, we found no negative influence on ventricular function or clinical events. Our study supports the concept that sports participation in patients with Con HD can be approached with more confidence and may imply more beneficial consequences than believed in the past. Our findings open also the question of the appropriateness of the current restrictive guidelines regarding sports participation in these patients.[36]

Recommendations

Although our study shows no overall increased risk of cardiac complications and death, recommendation for practicing sports should take into account the unique medical his-

tory of the patient. Advice on the type of sport should be based on the personal situation and anticipated effort levels, and if needed can be supervised by a physician first.[6,37,38] In a recent publication, Budts et al. have published a 6-step evaluation in order to be able to advise patients for a high, moderate or low intensity sport.[39] Takken et al. have published guidelines for children with ConHD on physical activity, recreational sports and exercise training.[36] Solid programs of sports participation with medical supervision as described successfully for patients with heart failure may be necessary also for our (adult) patients with ConHD.

Limitations of the study

Although this is the first report based on longitudinal data, no firm conclusions on safety can be drawn due to the relatively small size of the patient population. Larger series and longer follow-up are clearly warranted to consolidate our positive experiences regarding the low mortality and better ventricular function associated with sports participation. Our findings open also the discussion regarding less conservative rules regarding sports participation in these patients.

The patients included in this study had one of the following diagnoses: ASD, VSD, PS, ToF or TGA, therefore, the obtained results may not be applicable to all forms of ConHD. The results of the safety of sports from the logistic regression (mortality, heart frequency and arrhythmias) should be drawn with caution since our data is based on an observational cohort and selection bias may exist. Patients participating in sports may have been in better health condition at baseline. We tried to avoid this bias by dividing the group into patients with simple and moderate/complex heart disease, but still a bias cannot be ruled out. Also, the study design in 2001 did not anticipate these analyses on sports behavior in 2011. Therefore, patients were not instructed in 2001 to write down the dates in which they changed or stopped to practice sports, nor did they wear an accelerometer to objectify duration and intensity of sports participation. Therefore, in the "No sports" category patients who did practice sports for a certain amount of hours prior to the assessment in 2011 could have been included.

Lastly, a questionnaire on sports participation (without objective measurement) unfortunately does not always reflect reality. Furthermore, duration of sports does not equal intensity. Outcome on these questionnaires should be interpreted bearing this in mind.

CONCLUSION

The results of this study suggest that sports participation in patients with congenital heart disease does not increase the risk of arrhythmias or sudden cardiac death. Patients

with congenital heart disease who participate in sports have better subjective and objective (physical) functioning than those who do not.

REFERENCES

1 M.E. Brickner, L.D. Hillis, R.A. Lange, Congenital heart disease in adults. First of two parts, *N. Engl. J. Med*. 342 (2000) 256–263.

2 L. Swan, W.S. Hillis, Exercise prescription in adults with congenital heart disease: a long way to go, *Heart* 83 (2000) 685–687.

3 P. Moons, E. De Volder,W. Budts, et al.,What do adult patients with congenital heart disease know about their disease, treatment, and prevention of complications? A call for structured patient education, *Heart* 86 (2001) 74–80.

4 K. Dulfer, N. Duppen, N.A. Blom, et al., Effect of exercise training on sports enjoyment and leisure-time spending in adolescents with complex congenital heart disease: the moderating effect of health behavior and disease knowledge, *Congenit. Heart Dis.* 9 (2014) 415–423.

5 C.J. Lavie, R.V. Milani, Adverse psychological and coronary risk profiles in young patients with coronary artery disease and benefits of formal cardiac rehabilitation, *Arch. Intern. Med*. 166 (2006) 1878–1883.

6 P.M. Fredriksen, N. Kahrs, S. Blaasvaer, et al., Effect of physical training in children and adolescents with congenital heart disease, *Cardiol. Young* 10 (2000) 107–114.

7 D. Arvidsson, F. Slinde, L. Hulthén, J. Sunnegårdh, Physical activity, sports participation and aerobic fitness in children who have undergone surgery for congenital heart defects, *Acta Paediatr*. 98 (2009) 1475–1482.

8 E.M. Utens, F.C. Verhulst, R.A. Erdman, et al., Psychosocial functioning of young adults after surgical correction for congenital heart disease in childhood: a followup study, *J. Psychosom. Res*. 38 (1994) 745–758.

9 E.M. Utens, F.C. Verhulst, F.J. Meijboom, et al., Behavioural and emotional problems in children and adolescents with congenital heart disease, *Psychol. Med*. 23 (1993) 415–424.

10 E.H. van Rijen, E.M. Utens, J.W. Roos-Hesselink, et al., Psychosocial functioning of the adult with congenital heart disease: a 20–33 years follow-up, *Eur. Heart J*. 24 (2003) 673–683.

11 E.H. van Rijen, E.M. Utens, J.W. Roos-Hesselink, et al., Medical predictors for psychopathology in adults with operated congenital heart disease, *Eur. Heart J*. 25 (2004) 1605–1613.

12 J. Roos-Hesselink, M.G. Perlroth, J. McGhie, S. Spitaels, Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlationswith clinical, exercise, and echocardiographic findings, *Circulation* 91 (1995) 2214–2219.

13 J.W. Roos-Hesselink, F.J.Meijboom, S.E. Spitaels, et al., Decline in ventricular function and clinical condition after mustard repair for transposition of the great arteries (a prospective study of 22–29 years), *Eur. Heart J*. 25 (2004) 1264–1270.

14 P. Opić, J.W. Roos-Hesselink, J.A. Cuypers, et al., Psychosocial functioning of adults with congenital heart disease: outcomes of a 30–43 year longitudinal follow-up, *Clin. Res. Cardiol*. 104 (2015) 388–400.

15 Dutch Central Bureau of Statistics, http://statline.cbs.nl 2012 (Accessed August 9, 2014).

16 J.A. Baecke, J. Burema, J.E. Frijters, A short questionnaire for the measurement of habitual physical activity in epidemiological studies, *Am. J. Clin. Nutr*. 36 (1982) 936–942.

17 Dutch Central Bureau of Statistics, Leisure Table, http://statline.cbs.nl/StatWeb/publication/?DM=SLNL&PA=60029NED&D1=1-2,5,9-10,14-15,20-21,43-44,46-47,56-57&D2=0-2,21-22&D3=8-14&VW=T2012 (Accessed August 21, 2012).

18 J.H.Mitchell,W. Haskell, P. Snell, S.P. Van Camp, Task force 8: classification of sports, *J. Am. Coll. Cardiol*. 45 (2005) 1364–1367.

19 C.A. Warnes, R.G. Williams, T.M. Bashore, et al., ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). Developed in collaboration with the American Society of Echocardiography, Heart RhythmSociety, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, *J. Am. Coll. Cardiol*. 52 (2008) e143–e263.

20 K.Wasserman, Principles of Exercise Testing and Interpretation, Lea & Febiger, Philadelphia, 1994.

21 J.E. Ware, C.D. Sherbourne, The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection, *Med. Care* 30 (1992) 473–483.

22 N.K. Aaronson, M. Muller, P.D. Cohen, et al., Translation, validation, and norming of the Dutch language version of the SF-36 health survey in community and chronic disease populations, *J. Clin. Epidemiol*. 51 (1998) 1055–1068.

23 P. Moons, K. Van Deyk, L. De Bleser, et al., Quality of life and health status in adults with congenital heart disease: a direct comparison with healthy counterparts, *Eur. J. Cardiovasc. Prev. Rehabil*. 13 (2006) 407–413.

24 K. Gierat-Haponiuk, I. Haponiuk, M. Chojnicki, R. Jaworski, S. Bakuła, Exercise capacity and the quality of life late after surgical correction of congenital heart defects, *Kardiol. Pol*. 69 (2011) 810–815.

25 R. Buys, A. Van De Bruaene, W. Budts, C. Delecluse, L. Vanhees, In adults with atrial switch operation for transposition of the great arteries low physical activity relates to reduced exercise capacity and decreased perceived physical functioning, *Acta Cardiol.* 67 (2012) 49–57.

26 F.F. Immer, S.M. Althaus, P.A. Berdat, H. Saner, T.P. Carrel, Quality of life and specific problems after cardiac surgery in adolescents and adults with congenital heart diseases, *Eur. J. Cardiovasc. Prev. Rehabil*. 12 (2005) 138–143.

27 P.M. Fredriksen, G. Veldtman, S. Hechter, et al., Aerobic capacity in adults with various congenital heart diseases, *Am. J. Cardiol*. 87 (2001) 310–314.

28 P.M. Fredriksen, E. Pettersen, E. Thaulow, Declining aerobic capacity of patients with arterial and atrial switch procedures, *Pediatr. Cardiol*. 30 (2009) 166–171.

29 A. Gratz, J. Hess, A. Hager, Self-estimated physical functioning poorly predicts actual exercise capacity in adolescents and adults with congenital heart disease, *Eur. Heart J*. 30 (2009) 497–504.

30 A. Kempny, K. Dimopoulos, A. Uebing, et al., Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life — single centre experience and review of published data, *Eur. Heart J*. 33 (2012) 1386–1396.

31 A. Hager, J. Hess, Comparison of health related quality of life with cardiopulmonary exercise testing in adolescents and adults with congenital heart disease, *Heart* 91 (2005) 517–520.

32 J. Lemmer, G. Heise, A. Rentzsch, et al., Right ventricular function in grown-up patients after correction of congenital right heart disease, *Clin. Res. Cardiol*. 100 (2011) 289–296.

33 J. Müller, J. Hess, A. Hager, Minor symptoms of depression in patients with congenital heart disease have a larger impact on quality of life than limited exercise capacity, *Int. J. Cardiol*. 154 (2012) 265–269.

34 John McCall rugby field death, http://www.telegraph.co.uk/news/uknews/1457993/Rugby-boy-18-dies-after-World-Cup-game-collapse.html (Accessed August 9, 2014).

35 Shaun White, website http://www.shaunwhite.com (Accessed August 9, 2014).

36 T. Takken, A. Giardini, T. Reybrouck, et al., Recommendations for physical activity, recreation sport, and exercise training in paediatric patients with congenital heart disease: a report from the Exercise, Basic & Translational Research Section of the European Association of Cardiovascular Prevention and Rehabilitation, the European Congenital Heart and Lung Exercise Group, and the Association for European Paediatric Cardiology, *Eur. J. Prev. Cardiol*. 19 (2012) 1034–1065.

37 H. Baumgartner, P. Bonhoeffer, N.M. De Groot, et al., ESC guidelines for the management of grown-up congenital heart disease (new version 2010), *Eur. Heart J*. 31 (2010) 2915–2957.

38 G.P. Diller, K. Dimopoulos, D. Okonko, et al., Heart rate response during exercise predicts survival in adults with congenital heart disease, *J. Am. Coll. Cardiol*. 48 (2006) 1250–1256.

39 W. Budts, M. Börjesson, M. Chessa, et al., Physical activity in adolescents and adults with congenital heart defects: individualized exercise prescription, *Eur. Heart J*. 34 (2013) 3669–3674.

9

Sexual functioning is impaired in adults with congenital heart disease

Petra Opić, Jolien W. Roos-Hesselink, Judith A.A.C. Cuypers, Maarten Witsenburg, Annemien E. van den Bosch, Ron T. van Domburg, Ad J.J.C. Bogers, Elisabeth M.W.J. Utens

International Journal of Cardiology. 2013 Oct 9;168(4):3872-7

ABSTRACT

Background

To investigate the overall sexual functioning and disease specific sexual problems in congenital heart disease (ConHD) patients, for both genders and different cardiac diagnostic groups, and compare these with Dutch normative data. Also disease specific sexual problems were investigated.

Methods

From a longitudinal cohort of patients, operated for ConHD between 1968 and 1980, 254 patients (median age: 40, 53.4% male) were included in this study: atrial septal defect (n=72), ventricular septal defect (n=71), pulmonary stenosis (n=30), tetralogy of Fallot (n=53) and transposition of the great arteries (n=28). Patients completed internationally validated, generic questionnaires and also disease specific instruments on sexual functioning.

Results

Patients showed a delay in starting sexual activities compared with peers. Females with ConHD scored significantly worse compared with normative data on all scales of sexual functioning, indicating a broad range of sexual problems and 15% showed clinical levels of sexual dysfunction. Of the males, 14% suffered from erectile dysfunction. Males with ConHD scored worse on erectile function, orgasmic function and satisfaction regarding their sexual life compared with normative data. No differences were found between the different cardiac diagnoses. The majority of patients reported disease specific worries and fears about the use of contraceptives, heredity, pregnancy and delivery. Patients indicated to have been suboptimally informed about sexuality in early adolescence.

Conclusions

This study shows that sexual functioning is impaired in adults with ConHD. Providing information to patients about sexuality, pregnancy, delivery and heredity should be improved, and given at young age.

INTRODUCTION

The number of adults with congenital heart disease (ConHD) is steadily increasing due to the successes of pediatric cardiology and open-heart surgery. This nascent demographic phenomenon is creating major issues concerning the optimal medical and psychological management of these patients.[1-3] Adults with ConHD have very specific needs, both on medical and psychosocial topics. Previous studies concerning psychosocial well-being and quality of life in adult ConHD patients have largely neglected sexual functioning and only very few studies have reported on this topic.[4]

As part of a longitudinal study following a large cohort of consecutive patients operated for ConHD at young age, we investigated sexual functioning 30-43 years after cardiac surgery. Sexual functioning was assessed with both internationally validated instruments and disease-specific questionnaires, for males and females separately.
The aims of this study are:

1. To investigate the overall sexual functioning, for both sexes and different cardiac diagnostic groups, and compare this with the general population.
2. To investigate disease specific problems in sexual functioning.

METHODS

Inclusion criteria

The original cohort exists of all consecutive patients who underwent their first open heart surgery for Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), Pulmonary Stenosis (PS), Tetralogy of Fallot (ToF) or Transposition of the Great Arteries (TGA) between 1968 and 1980 in the Erasmus Medical Center, and were younger than 15 years at the time of surgery. This cohort has already been investigated in 1990/1991 and in 2000/2001. The baseline characteristics, medical and psychosocial results of these investigations have been reported in detail previously.[5-10]

The target population of this third follow-up (2010-2011) consisted of the 412 patients who participated in the previous 2 follow-ups. Of these patients, ten had died (causes: 6 cardiac-related, 3 unknown, 1 accident), 1 underwent heart transplantation and 28 patients were untraceable. Of the remaining 373 eligible patients, 102 refused to participate in this study due to practical reasons (work, distance to hospital), leading to a response rate of 73%.

Patient sample

Of the 271 patients who participated and completed psychological instruments, 17 patients refused to complete the questionnaires on sexual functioning. Patients were

classified into 2 groups of disease severity according to the classification adopted at the American Heart Association Task Force on Adults with CHD.[11] Patients with corrected ASD, VSD and PS were classified as simple ConHD (unless they had complications such as severe ventricular dysfunction), while patients with ToF or TGA (all operated with a Mustard repair) were classified as moderate to complex ConHD.

Assessment procedure

The research protocol was approved by the institutional ethical committee and complies with the 1975 Declaration of Helsinki. All patients were approached uniformly and invited to visit the hospital for extensive cardiac and psychological examination. All participating patients signed informed consent before participating. During their visit, a cardiologist performed the cardiac and medical examination. The semi-structured interview and psychological questionnaires were completed during the hospital visit. Due to practical reasons (work, children), 20 patients completed the questionnaires at home. The questionnaires were administered verbally for patients who had difficulty reading or understanding the questionnaires.

Instruments and normative groups

The Female Sexual Function Index (FSFI) is a multidimensional and standardized self-report questionnaire used to assess 6 domains of sexual functioning in females.[12] The FSFI has shown good discriminative validity between females with and without sexual problems.[12-14]

The Female Sexual Distress Scale-Revised (FSDS-R) is a 12 item self-report questionnaire used to assess sexual related personal distress indicating sexual dysfunction. The FSDSR measures the psychological distress encountered during sexual intercourse.[12-15]

If a patient scores within the clinical range on both the FSFI and the FSDSR, this is classified as a DSM-IV sexual disorder. Normative data for both the FSFI and FSDSR were derived from Kuile et al.[12] Normative data on sexual dysfunctions in the general Dutch population were derived from the Rutgers Foundation.[16]

The International Index of Erectile Function (IIEF) is a multidimensional self-report questionnaire that measures erectile function and sexual functioning in males.[17] Normative data for the IIEF questionnaire was derived from Rosen et al.[17] Normative data on erectile dysfunction in the general Dutch population was derived from the Rutgers Foundation.[17]

The ConHD Specific Problems related to Sexual Functioning (CSSP) is a structured self-report specifically designed for this study by 2 congenital cardiologists and a psychologist specialized in ConHD to assess the impact of ConHD on sexual functioning (unpublished questionnaire Utens et al. 2010). Normative data on general sexual functioning of the Dutch population was derived from the Rutgers Foundation.[16,18]

Statistical analyses

Categorical variables are represented by frequencies and percentages. Where appropriate, a chi-square test or Fisher's exact test was used when comparing frequencies. Data on generic questionnaires (FSFI, FSDSR, IIEF) were analyzed conform to international manuals using means and standard deviations.[12,17] Data on disease-specific questionnaires are represented with medians and interquartile ranges because of the skewed nature of the data. Comparison of continuous variables between simple and moderate/complex ConHD was made with Student's T-tests, comparison between ASD, VSD, PS, ToF and TGA groups was made by one-way ANOVA tests. In case of a skewed distribution, Mann-Whitney-U tests resp. Wilcoxon signed rank tests were used. Univariate binary logistic regression (forced entry model) was used to test for effects of medication on erectile function and for the effects of educational level, occupational level and income on sexual dysfunctions in both men en women. Two-tailed probability values of <0.05 were considered statistically significant. The statistical packages IBM SPSS Statistics for Mac version 19.0 (Release 19.0.0) and R (64 bit) for Mac, version 2.14.2 were used to perform the calculations.

RESULTS

Baseline characteristics

The baseline characteristics of the 254 included patients (53.5% male, median age 40 years) are summarized in Table 1. A total of 97% was heterosexual, 2% was homosexual and 1% was bisexual. The majority of patients were married, and 84.5% reported to be sexually active. Patients with moderate/complex ConHD used cardiac medication significantly more often than the patients with simple ConHD ($p=0.004$) and, on average, had a worse systemic ventricular function ($p<0.001$).

Gender specific sexual functioning compared to normative data

Females (FSFI and FSDSR) (Figure 1)

On all sexual functioning scales (FSFI questionnaire), females with ConHD scored significantly worse compared to normative data, indicating a broad range of sexual problems; with younger females showing worse outcome compared to older females (groups based on median age of 39 years) ($p<0.0001$). However, on the FSDS-R scale assessing sexual distress indicating pathological sexual dysfunction, females obtained similar results compared to normative data. A pathological sexual disorder (defined on both clinical levels on the FSFI and FSDS-R) was present in 14.6% of our female patients compared to 17.7% in the reference group ($p=0.5$).[18]

Table 1. Baseline characteristics

		ConHD classification			ConHD diagnosis					
	Total	Simple	Moderate/ complex	p	ASD	VSD	PS	ToF	TGA	p
Variable	**n = 254**	**n = 173**	**n = 81**		**n = 72**	**n = 71**	**n = 30**	**n = 53**	**n = 28**	
Age	40 [36-45]	40 [37-45]	38 [34-41]	**0.000**	43 [39-47]	39 [35-43]	39 [37-45]	40 [35-45]	36 [33-38]	**0.000**
Gender										
Male	53.5	50.3	60.5	0.129	37.5	60.6	56.7	56.6	67.9	**0.022**
Female	46.5	49.7	39.5		62.5	39.4	43.3	43.4	32.1	
Marital status										
Unmarried	16.7	15.6	19.0	0.504	19.4	14.1	10.0	15.7	25.0	0.535
Cohabitants	21.0	20.2	22.8	0.644	19.4	16.9	30.0	25.5	17.9	0.546
Married	62.3	64.2	58.2	0.367	61.1	69.0	60.0	58.8	57.1	0.726
Medication										
No medication	76.5	82.1	64.3	**0.004**	76.6	84.8	88.5	72.7	50.0	**0.004**
Aspirin	4.9	3.8	7.1	0.287	4.7	1.5	7.7	9.1	3.8	0.327
Calcium antagonist	0.9	0.6	1.4	0.524	-	1.5	-	-	3.8	0.447
Betablocker	7.5	5.8	11.4	0.136	7.8	6.1	-	6.8	19.2	0.150
Nitrate	-	-	-	-	-	-	-	-	-	-
Anti-arrhythmics	2.2	1.9	2.9	0.646	3.1	-	3.8	2.3	3.8	0.426
Digitalis	0.9	-	2.9	0.095	-	-	-	-	7.7	**0.026**
Duretics	3.1	2.6	4.3	0.680	1.6	4.5	-	-	11.5	0.080
ACE inhibitor	8.0	3.8	17.1	**0.001**	1.6	7.6	-	9.1	30.8	**0.000**
Cholesterol lowering	3.1	2.6	4.3	0.680	4.7	-	3.8	6.8	-	0.160
Oral anticoagulation	4.9	3.2	8.6	0.083	4.7	3.0	-	2.3	19.2	**0.028**
Systemic ventricular function										
Good	62.9	86.4	29.8	**0.000**	92.4	80.0	75.0	46.3	-	**0.000**
Mildly impaired	24.8	11.9	42.9	**0.000**	7.6	15.0	25.0	48.1	33.3	**0.000**
Moderately impaired	7.9	-	19.0	**0.000**	-	-	-	-	53.3	**0.000**
Severely impaired	4.5	1.7	8.3	**0.035**	-	5.0	-	5.6	13.3	0.052

Data are presented as n %, unless indicated otherwise. Continuous data are presented as median [interquartile range (IQR)]

ASD = Atrial Septal Defect, PS = Pulmonary Stenosis, TGA = Transposition of the Great Arteries, ToF = Tetralogy of Fallot, VSD = Ventricular Septal Defect

In-between ConHD diagnostic groups: No difference was found on either of the questionnaires between diagnostic groups.

Effect of systemic ventricular function: Univariate logistic regression showed no significant effects of systemic ventricular function on the prevalence of sexual disorders in females (FSDSR, FSFI and clinical score).

Effects of socio-economic status: Univariate logistic regression showed no significant effects of occupational level, educational level and income on the prevalence of sexual disorders in females (FSDSR, FSFI and clinical score).

Males (IIEF) (Figure 2)

Males with ConHD scored worse on erectile function, orgasmic function, intercourse satisfaction and overall satisfaction compared to normative data. This result indicates a broad range of sexual problems. A total of 13.7% of males scored within the clinical range of having erectile dysfunction. This is more than twice as high as in normative data stratified by age (5.9%, p=0.002). Patients with erectile dysfunction were not significantly older than patients without (p=0.8). The use of beta-blockers did not have an effect on erectile function in this population (p=0.9).

Diagnostic groups: No difference was found between the different ConHD diagnoses.

Effect of systemic ventricular function: Univariate logistic regression showed no significant effects of systemic ventricular function on the prevalence of sexual disorders in males (IIEF and clinical score).

Effects of socio-economic status: Univariate logistic regression showed no significant effects of occupational level, educational level and income on the prevalence of sexual disorders in males (erectile disorders on the IIEF).

Disease specific problems related to sexual functioning (Table 2 – Table 4)

Gender specific sexual aspects are shown in Table 2. Females had their first menstrual period at a median age of 13 years, which is comparable to the general Dutch population. Cardiac complaints worsened in 11% of females during menses. Menstrual complaints mainly consisted of pain (41.7%) and excessive blood loss (35.1%). A total of 19.8% required medical treatment for menstrual related problems.

Problems before, during and after sexual activity (Table 3)

Patients in our study were on average 18 years old when they first had sexual intercourse. On average, they had 1 sexual partner during the past 3 months. Roughly a quarter of patients (24.7%) had sexual intercourse between zero and one time per month, 23.3% had sexual intercourse between 2 and 3 times per month, almost a third (28.4%) had sexual intercourse four to nine times per month and the rest (11.4%) had sexual intercourse more than nine times per month.

Table 2. Female disease specific sexually related aspects, fears & worries

	Total N=118		ConHD classification				p
			Simple N=86		Moderate/complex N=32		
	N	%	N	%	N	%	
At what age did you get your first menstrual period?							
Age (median [IQR])	13 [12-14]		13 [12-14]		13 [12-14]		0.5
Do you get more complaints from your ConHD or do the complaints change before or after your menstrual period?							
Yes	13	11.0	9	10.5	4	12.5	0.7
Have you ever experienced one of the following complaints?							
>5 weeks between menses	11	9.5	10	11.8	1	3.2	0.3
<5 weeks between menses	7	6.1	7	8.4	-	-	0.2
Excessive bloodloss	40	35.1	27	32.5	13	41.9	0.3
Painful menses	48	41.7	36	42.9	12	38.7	0.7
6 months no menses	14	12.4	12	14.5	2	6.7	0.3
Spotting	5	11.6	10	12.2	4	12.9	1.0
Did you ever need medical attention for menstrual complaints?							
Yes	23	19.8	17	20.0	6	19.4	0.9
Are you (pre)menopausal?							
Yes	19	16.5	17	20.5	2	6.3	0.1
Age (median [IQR])	45 [42-47]		45 [42-47]		44 [42-44]		0.5
Are you receiving medical treatment for your (pre)menopause?							
Yes	3	2.6	2	2.4	1	3.1	1.0

Data are displayed as n %, unless indicated otherwise.
IQR = Interquantile Range

The majority (76.5%) of patients felt satisfied with their overall physical appearance. Obesity was the main reason why some of the patients felt dissatisfied. When rating the appearance of their scar, patients scored a 6 on a scale from 1 to 10 (1 = ugly, 10 = beautiful). The surgical scar made 11.4% of patients feel ashamed and less attractive during sexual activity. This was reported significantly more often by females (17.5% versus 6.2% in males, p=0.004).

Of all patients, 11.7% reported having problems with sexual activities because of their ConHD. This was observed more frequently in females compared with males (16.2% versus 7.7%, p=0.037), and more frequently in moderate/complex ConHD patients compared with simple ConHD patients (21.8% versus 7.1%, p=0.001). In addition, 11.6% of all patients reported that their ConHD had a great influence on starting and maintaining a relationship. Remarkably this was reported significantly more often in the simple ConHD group compared to the moderate/complex ConHD group (17.5% versus 8.9%, p=0.048). Overall, patients did not have to prematurely cease with sexual activity due to heart complaints.

About 1 in every 5 patients reported not having enjoyed sexual activity (18.6%), having feelings of insecurity (15.7%) or felt unable to achieve sexual arousal during sexual activity (19.5%) within the last month. Not enjoying sexual activity was reported more often by females compared to males (25.5% versus 13.1%, p=0.015).

About 1 in 4 patients worry about their sex life (23.8%). This was reported more frequently by females (30.8% versus 18.0%, p=0.021).

A total of 7.8% of patients reported having been forced to perform sexual activity against their will. This finding was higher in females compared to males (11.3% versus 4.6%, p=0.05).

When asked to rate the information provided by physicians about sexuality and ConHD, patients scored a 2.0 on average on a 1-10 Likert scale (1 = not being informed about the influence of sexuality on ConHD, 10 being optimally informed). Almost half of the patients (45%) rated the provided information on the possible side effects of sex on their heart condition as 1, and 68% of patients scored ≤5 (unsatisfactory).

Contraceptives, pregnancy and heredity (Table 4)

Patients began using contraceptives at a median age of 18 years. The most used contraceptive was the condom, followed by oral contraceptives and sterilization. 10.9% of

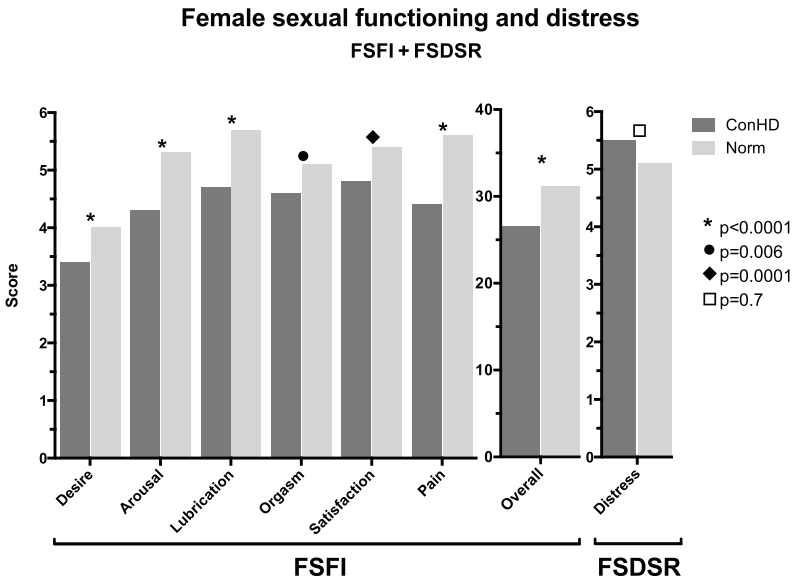


Figure 1.

ConHD = all congenital heart diseases together; Norm = normative data.

A high score indicates favorable sexual functioning. On the distress scale, a high score indicates high distress. Data are presented using means.

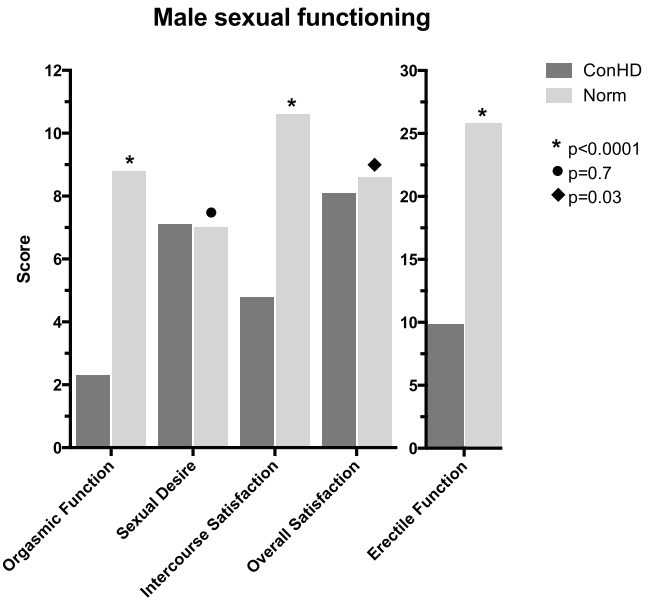


Figure 2.
ConHD = all congenital heart diseases together; Norm = normative data.
A high score indicates favorable sexual functioning. Data are presented using means

males were sterilized, versus 5.9% of females (p=0.166). A minority of patients (4.7%) became pregnant while using contraception.

The vast majority of patients (86.2%) never discussed the possible side effects of different methods of contraceptives with their physicians. There was a strong gender difference in information received from the physician; with females asking and receiving more information. Despite this, only 20% of women reported to have received information from their physicians regarding the use of contraceptives. Of this group, 56% had to actively ask for this information. Females reported having a greater fear of being infertile compared to males (26.2% versus 12.0%, p = 0.007). In addition, females reported experiencing more feelings of fear concerning the heredity of their ConHD (64.5% versus 41.0%, p<0.0001). The fear of harmful effects of their heart disease on the outcome of their child was reported by 34.5% of patients. This was reported significantly more often in patients with moderate/complex ConHD (43.7% versus 30.3%, p=0.05). Patients with moderate/complex ConHD also had significantly more fears of not having enough energy to raise children (16.9% versus 4.6%, p=0.002) and fears of a lower life expectancy as a disability to fully raise children (19.7% versus 5.9%, p=0.002). ConHD was a limiting factor in the decision of having children in 14.6% of patients, mostly in females compared with males (22.2% versus 7.6% p=0.002) and in patients with moderate/complex ConHD compared with simple ConHD patients (22.2% versus 11.0%, p=0.027).

A total of 21.3% of females feared that pregnancy would have a negative influence on their heart or on their overall clinical condition. This was found more often in females with moderate/complex ConHD ($p<0.0001$). In addition, some of the females feared that delivery would have a negative effect on their heart (28.0%) and overall health (21.5%). Both of these findings were higher in females with moderate/complex ConHD group compared to females with simple ConHD ($p<0.0001$).

DISCUSSION

The present study shows a broad range of sexual problems in both men and women with ConHD. Concern over sexual health appeared to be stronger in women. Sexual functioning was significantly impaired compared to normative data. Our female patients reported a wide range of problems, including a lower sexual desire, less arousal, and more pain during sexual intercourse. The proportion of male patients with erectile dysfunction was more than twice as high as in the general population. Male sexual functioning was clearly impaired as to satisfaction regarding intercourse and orgasmic function.

No differences were found between cardiac diagnostic groups on generic questionnaires into sexual functioning. However, disease-specific instruments showed that patients with moderate/complex ConHD viewed their ConHD as a limiting factor in having children. Concerns included not having enough energy in raising children, having a lower life expectancy, potentially harmful effects of the pregnancy on their child, their heart and overall health.

Disease specific problems related to sexual functioning

An important issue is whether the surgical scar influences personal feelings and hereby indirectly the sexual functioning of patients. Some patients indicated that the scar was part of their body and a symbol that their life had been saved. Earlier in life about half of patients from this same cohort reported to have been troubled by their scar.[8] Now, 10 years later, during the third follow-up of this cohort, a minor proportion of patients still felt ashamed because of their scar and felt less attractive. This was especially seen in females. However, compared to the 2 previous follow-ups, these numbers seem to have declined. A possible explanation is that with older age, patients seem to have accepted the scar and find it less important. This hypothesis is supported by Horner et al.[19] who described that patients reported to conceal or hide their scars mostly during adolescence. Most problems were observed around 20 years of age, the age that many people start a relationship. This may imply that the desire of young females to correct

Table 3. Male and female disease specific fears and worries

	Total N=254		ConHD classification					Gender				
			Simple N=173		Moderate/complex N=81		p	Male N=136		Female N=118		p
	N	%	N	%	N	%		N	%	N	%	
How old were you when you first had sexual intercourse?												
(median [IQR])	18 [16-20]		18 [16-20]		18 [16-20]		0.8	18 [16-20]		18 [16-20]		0.8
In the past three months, how many sexual partners have you had?												
Sexual partners (median [IQR])	1 [1-1]		1 [1-1]		1 [1-1]		0.5	1 [1-1]		1 [1-1]		0.2
In the past month, how often did you have sexual intercourse?												
None - One	67	24.7	51	28.0	16	18.0	0.1	40	27.6	27	24.1	0.2
Two to three	63	23.2	44	24.2	19	21.3	0.6	29	20.0	34	27.0	0.2
Four to nine	77	28.4	**44**	**24.2**	**33**	**37.1**	**0.027**	41	28.3	36	28.6	1.0
Above nine	31	11.4	25	13.7	6	6.7	0.1	16	11.0	15	11.9	0.8
Are you satisfied with your overall appearance?												
Satisfied	202	76.5	134	74.9	68	80.0	0.4	114	80.9	88	71.5	0.075
Neutral	41	15.5	31	17.3	10	11.8	0.2	19	13.5	22	17.9	0.3
Dissatisfied	21	8.0	14	7.8	7	8.2	0.9	8	5.7	13	10.6	0.1
Please rate on a scale from 1 to 10 how you feel about the appearance of your scar												
(median [IQR])	6 [4-8]		6 [4-8]		6 [5-8]		0.1	6 [5-8]		6 [4-8]		0.2
During sexual activity, do you experience any of the following complaints because of your heart disease?												
Fear of rejection	10	3.7	5	2.7	5	5.6	0.3	5	3.4	5	4	1.0
Fear of excessive tiredness	12	4.4	7	3.8	5	5.6	0.5	6	4.1	6	4.8	1.0
Fear of infarction	9	3.3	6	3.3	3	3.4	1.0	4	2.8	5	4.0	0.7
Fear of sudden death	6	2.2	3	1.6	3	3.4	0.4	2	1.4	4	3.2	0.4
Ashamed/less attractive because of scars	31	11.4	21	11.5	10	11.2	0.9	**9**	**6.2**	**22**	**17.5**	**0.004**
Do you have problems before, during or after sexual intercourse because of your heart disease?												
Yes	29	11.7	**12**	**7.1**	**17**	**21.8**	**0.001**	**10**	**7.7**	**19**	**16.2**	**0.037**
My heart disease plays a major influence on the starting and maintaining of a relationship												

Table 3. Male and female disease specific fears and worries (continued)

	Total N=254		ConHD classification					Gender				
			Simple N=173		Moderate/complex N=81		p	Male N=136		Female N=118		p
	N	%	N	%	N	%		N	%	N	%	
(Entirely) true	29	11.6	**15**	**8.9**	**14**	**17.5**	**0.048**	15	11.4	14	12.0	0.9
(Entirely) false	220	88.3	**154**	**91.1**	**66**	**82.5**		117	88.6	103	88.1	
My heart disease has a big influence on my sexual life												
(Entirely) true	24	9.6	13	7.6	11	13.8	0.1	11	8.3	13	11.1	0.4
(Entirely) false	226	90.4	157	92.4	69	86.3		122	91.7	104	88.9	
I cannot fully enjoy my sexual life because of my heart disease												
(Entirely) true	14	5.6	8	4.7	6	7.5	0.4	6	4.5	8	6.8	0.4
(Entirely) false	236	94.4	162	95.3	74	92.5		127	95.5	109	93.2	
Do you have to stop prematurely with sexual activities because of heart complaints?												
No	231	93.9	159	94.6	72	92.3	0.5	122	93.8	109	94.0	1.0
Rarely	13	5.3	7	4.2	6	7.7	0.3	7	5.4	6	5.2	0.9
Often	1	0.4	1	0.6	-	-	1.0	1	0.8	-	-	1.0
Almost always	1	0.4	1	0.6	-	-	1.0	-	-	1	0.9	0.5
In the past month, how often did you not enjoy sexual activity?												
Occasionally/Often	44	18.6	33	20.5	11	14.7	0.3	**17**	**13.1**	**27**	**25.5**	**0.015**
In the past month, how often did you feel insecure about sexual intercourse?												
Occasionally/Often	37	15.7	28	17.5	9	12.0	0.3	17	13.2	20	18.9	0.2
In the past month, how often did you not get aroused during sexual activity?												
Occasionally/Often	45	19.5	33	20.6	12	16.9	0.5	**11**	**8.7**	**34**	**32.4**	**0.000**
In the past month, how often were you afraid to have sexual intercourse?												
Occasionally/Often	7	3.0	5	3.1	2	2.8	1.0	2	1.6	5	4.7	0.3
In the past month, how often were you worried about your sex life?												
Occasionally/Often	56	23.8	38	23.5	18	24.7	0.8	**23**	**18.0**	**33**	**30.8**	**0.021**
Were you ever forced to sexual activities against your will?												

Table 3. Male and female disease specific fears and worries (continued)

	Total N=254		ConHD classification					Gender				
			Simple N=173		Moderate/complex N=81		p	Male N=136		Female N=118		p
	N	%	N	%	N	%		N	%	N	%	
Yes	19	7.8	11	6.6	8	10.3	0.3	**6**	**4.6**	**13**	**11.3**	**0.051**
Are you using any sleep medication, or medication to calm you down?												
Yes	15	6	8	4.7	7	8.9	0.2	8	6	7	6	
How well are you informed about the influence of sexual activities on your heart disease?												
(median [IQR])	2 [1-6]		2 [1-6]		2 [1-6]		0.8	2 [1-5]		2 [1-7]		0.064
Would you like to receive more information about the possible influence of sexual activities on your heart disease?												
Yes	42	17.2	27	16.4	15	19.0	0.6	24	18.5	18	15.8	0.6
No	95	38.9	64	38.8	31	39.2	0.9	54	41.5	41	36.0	0.4
Not interested	107	43.9	74	44.8	33	41.8	0.7	52	40.0	55	48.2	0.2

Data are displayed as n %, unless indicated otherwise.
IQR = Interquantile Range

Table 4. Facts and concerns regarding contraceptives, pregnancy and heredity

	Total N=254		ConHD classification					Gender				
			Simple N=173		Moderate/complex N=81		p	Male N=136		Female N=118		p
	N	%	N	%	N	%		N	%	N	%	
How old were you when you started to use contraceptives?												
Age in years (median [IQR])	18 [16-19]		18 [16-19]		18 [16-20]		0.5	**18 [17-20]**		**17 [16-19]**		**0.036**
Have you ever had an unplanned pregnancy despite the use of contraceptives?												
Yes	11	4.7	9	5.6	2	2.7	0.5	4	3.3	7	6.2	0.4
Have you ever had an unplanned pregnancy without the use of contraceptives?												
Yes	7	3.0	6	3.7	1	1.4	0.4	6	4.9	1	0.9	0.1
Did your physician give you information about the possible side effects that different contraceptives may have?												
Physician started conversation	14	6.3	11	7.1	3	4.3	0.6	**3**	**2.7**	**11**	**9.6**	**0.050**
I asked it myself	17	7.6	**7**	**4.5**	**10**	**14.5**	**0.009**	**3**	**2.7**	**14**	**12.3**	**0.010**
Never spoke about it	193	86.2	137	88.4	56	81.2	0.1	**104**	**94.5**	**89**	**78.1**	**0.000**
Would you like to receive more information about the possible side effects of different contraceptives?												
I would like more information	28	12.7	**13**	**8.4**	**15**	**22.4**	**0.004**	**7**	**6.4**	**21**	**18.9**	**0.005**
I have enough information	66	29.9	45	29.2	21	31.3	0.8	29	26.4	37	33.3	0.3
No interest	127	57.5	**96**	**62.3**	**31**	**46.3**	**0.026**	**74**	**67.3**	**53**	**47.7**	**0.003**
If you have sexual intercourse, how often do you use a condom?												
Never	156	70.6	115	74.2	41	62.1	0.071	**77**	**64.2**	**79**	**78.2**	**0.022**
Rarely	10	4.5	4	2.6	6	9.1	0.069	5	4.2	5	5.0	1.0
Sometimes	13	5.9	12	7.7	1	1.5	0.1	10	8.3	3	3.0	0.1
Often	11	5.0	7	4.5	4	6.1	0.7	5	4.2	6	5.9	0.5
Always	31	14.0	**17**	**11.0**	**14**	**21.2**	**0.045**	**23**	**19.2**	**8**	**7.9**	**0.016**
In the past month, how often did you worry about the ability to have children?												
Never	210	90.1	144	90.0	66	90.4	1.0	115	91.3	95	88.8	0.5
Occasionally	13	5.6	9	5.6	4	5.5	1.0	7	5.6	6	5.6	1.0
Often	10	4.3	7	4.4	3	4.1	1.0	4	3.2	6	5.6	0.5

Table 4. Facts and concerns regarding contraceptives, pregnancy and heredity (continued)

	Total N=254		ConHD classification					Gender				
			Simple N=173		Moderate/complex N=81		p	Male N=136		Female N=118		p
	N	%	N	%	N	%		N	%	N	%	
Have you ever been afraid of infertility?												
Yes	42	18.8	33	21.4	9	12.9	0.1	**14**	**12.0**	**28**	**26.2**	**0.007**
Have you ever been afraid about the heredity of your heart disease?												
Yes	117	52.2	74	48.4	43	60.6	0.089	**48**	**41.0**	**69**	**64.5**	**0.000**
Have you ever been afraid of any harmful effects of your heart disease on your child?												
Yes	77	34.5	**46**	**30.3**	**31**	**43.7**	**0.050**	37	32.2	40	37.0	0.4
Have you ever been afraid of not having enough energy to raise a child?												
Yes	19	8.6	**7**	**4.6**	**12**	**16.9**	**0.002**	7	6.1	12	11.2	0.2
Have you ever been afraid of a possible lower life expectancy while raising children?												
Yes	23	10.3	**9**	**5.9**	**14**	**19.7**	**0.002**	13	11.1	10	9.3	0.7
Do you feel your heart disease is a limiting factor in having children?												
Yes	33	14.6	**17**	**11.0**	**16**	**22.2**	**0.027**	**9**	**7.6**	**24**	**22.2**	**0.002**
Are you afraid that pregnancy can have a negative influence on your heart?												
Yes	23	21.3	**9**	**11.5**	**14**	**46.7**	**0.000**	-	-	23	21.3	
Are you afraid that pregnancy can have a negative effect on your overall health?												
Yes	23	21.3	**8**	**10.3**	**15**	**50.0**	**0.000**	-	-	23	21.3	
Are you afraid that the delivery of your child will have a negative influence on your heart?												
Yes	30	28.0	**12**	**15.6**	**18**	**60.0**	**0.000**	-	-	30	28.0	
Are you afraid that the delivery of your child will have a negative influence on your overall health?												
Yes	23	21.5	**8**	**10.4**	**15**	**50.0**	**0.000**	-	-	23	21.5	

Data are displayed as n %, unless indicated otherwise.
IQR = Interquantile Range

their scar by plastic surgery should be taken seriously, but does seem age-related and is often not a problem after 10 years.

Patients from our study lost their virginity at a significantly older age compared to the general Dutch population.[18] It has been reported that a lower educational level is associated with an early age of losing virginity.[18] Taking into account the lower educational level of the present cohort,[7] the significantly older age when losing virginity is even more noticeable. In our opinion this finding can be explained by possible overprotection from parents.[20] In addition, the later age at which patients become independent and gain autonomy could play a role.[21-23] Finally, feelings of uncertainty or feelings about being less attractive might play a role here. Previously, during the second follow-up of this study at a younger age, our patients reported feeling limited due to their surgical scars. This could also have contributed to fear of rejection, which may cause patients to become sexually active at a later age.

Gender-specific sexual functioning

In our study we found that female patients had their first menstrual period at a median age of 13 years, which is in line with literature and normative data.[18,24] There was no difference between simple and moderate/complex ConHD patients.

Although females obtained significantly worse outcomes on the FSFI compared to normative data, the prevalence of sexual disorders in females (14.6% had clinical range on both the FSFI and FSDSR) did not differ from the general Dutch population. A possible explanation for this is that the FSDSR instrument is not sensitive enough to measure distress in females with ConHD. In contrast to the study of Reid et al.[25] we did not find that females with a moderate/complex ConHD had significantly more sexual partners indicating promiscuity. This could however be explained by the age difference: the patients in our study are older.

Of the male patients, 13.7% experienced a clinical level of erectile dysfunction, which is higher than reported previously using the same instruments in ConHD patients,[26] and over twice as high as in the general Dutch population.[18]

Contraceptives, pregnancy and heredity

This study also shows areas in outpatient care to which more attention should be paid. Only a minority of patients (13.8%) reported to have been fully informed about how sexuality, pregnancy, and contraceptives can influence their heart and overall general health.[27-30] 20% of females reported to have been informed regarding contraceptives by their physician. Studies have shown poor knowledge about contraceptives with many misconcepts.[31-32] Of course, at the age of 40, this probably is not a big issue anymore, but there seems to be a clear need for counseling provided at a younger age, preferably

before puberty. Information could be provided by pediatric cardiologists, but also by nurse practitioners or patient organizations.

Clinical implications

Since this cohort has reached the age of 30-56 years, and most patients have children, the need for sexually oriented information may have disappeared, and may be higher in younger patients. Patients reported to have had worries and fears in the past about the heredity of ConHD, harmful effects on the unborn child and infertility. Patients were also worried about the harmful effects of pregnancy and delivery on their own heart and overall health.[19,25,28] Caregivers should bear in mind that patients wish to receive information about contraceptives and sexual activities.[32] Therefore, we would recommend that patients receive disease specific information regarding sexual activities at young age, before planning to have children. Considering that most hospitals have combined transfer of patients from pediatric to adult clinics, this would provide a perfect opportunity to counsel patients about this problem, for instance by a nurse practitioner. Highlighted topics should at least include the safe use of contraceptives, sexual activities, pregnancy and delivery.

Strengths and study limitations

This study is the first to report on gender-specific sexual functioning in a systematically followed consecutive series of 30-56 year old patients. Both internationally validated generic questionnaires and disease specific instruments were used to measure sexual functioning for both genders. Where possible, outcomes were compared to normative data. Unfortunately, data on sexual functioning in males is scarce. There was no Dutch IIEF data of male reference groups for the Netherlands. Therefore, IIEF normative data from the USA was used. The patients included in this study all had the diagnosis of ASD, VSD, PS, ToF or TGA, and all were followed in an adult tertiary care center in the Netherlands. Therefore, the obtained results may not be applicable for all ConHD patients, nor in all countries worldwide. The FSDSR instrument may not have been specific enough to detect clinical levels of problems with sexuality in females.

Future recommendations

With increasing age, it can be expected that erectile disorders and menopausal complaints in ConHD patients may worsen. Systematic follow-up of sexual function is therefore recommended in this population since the present patients with ConHD already show high levels of sexual dysfunction. Attention for and information on sexual functioning should be organized for adolescents with ConHD. The extent in which these findings can be extrapolated to other heart conditions is unknown and should be investigated.

CONCLUSIONS

Sexual functioning in ConHD adults has largely been neglected in psychosocial research. Our study shows that sexual functioning is hampered substantially in adults with ConHD. Importantly, providing information to patients about sexuality, pregnancy, delivery and heredity should be improved and given at a younger age to assure the best holistic care.

ACKNOWLEDGEMENTS

The authors gratefully thank the participating patients for their contribution to this study, and the staff of the outpatients' clinic for adults with ConHD (Erasmus Medical Center, Rotterdam, the Netherlands) for including and motivating the patients. Also, thanks are extended to Michael Cramer, for his valuable assistance in the preparation of this manuscript.

REFERENCES

1. van der Linde D, Konings EE, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol* 2011; 58:2241-7.
2. Brickner ME, Hillis LD, Lange RA. Congenital heart disease in adults. First of two parts. *N Engl J Med* 2000; 342:256-63.
3. Warnes CA. The adult with congenital heart disease: born to be bad? *J Am Coll Cardiol* 2005; 46:1-8.
4. Moons P, Van Deyk K, Marquet K, De Bleser L, Budts W, De Geest S. Sexual functioning and congenital heart disease: Something to worry about? *Int J Cardiol* 2007; 121:30-5.
5. Utens EM, Verhulst FC, Erdman RA, et al. Psychosocial functioning of young adults after surgical correction for congenital heart disease in childhood: a follow-up study. *J Psychosom Res* 1994; 38:745-58.
6. Utens EM, Verhulst FC, Meijboom FJ, et al. Behavioural and emotional problems in children and adolescents with congenital heart disease. *Psychol Med* 1993; 23:415-24.
7. van Rijen EH, Utens EM, Roos-Hesselink JW, et al. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. *Eur Heart J* 2003; 24:673-83.
8. van Rijen EH, Utens EM, Roos-Hesselink JW, et al. Medical predictors for psychopathology in adults with operated congenital heart disease. *Eur Heart J* 2004; 25:1605-13.
9. Roos-Hesselink J, Perlroth MG, McGhie J, Spitaels S. Atrial arrhythmias in adults after repair of tetralogy of Fallot. Correlations with clinical, exercise, and echocardiographic findings. *Circulation* 1995; 91:2214-9.
10. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, et al. Decline in ventricular function and clinical condition after Mustard repair for transposition of the great arteries (a prospective study of 22-29 years). *Eur Heart J* 2004; 25:1264-70.
11. Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008; 52:e143-263.
12. ter Kuile M, Brauer M, Laan E. De Female Sexual Function Index (FSFI) en de Female Sexual Distress Scale (FSDS): Psychometrische eigenschappen in een Nederlandse populatie. *Tijdschrift voor Seksuologie* 2009; 33-3:207-222
13. Meston CM. Validation of the Female Sexual Function Index (FSFI) in women with female orgasmic disorder and in women with hypoactive sexual desire disorder. *J Sex Marital Ther* 2003; 29:39-46.
14. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. *J Sex Marital Ther* 2005; 31:1-20.

15. Derogatis L, Clayton A, Lewis-D'Agostino D, Wunderlich G, Fu Y. Validation of the female sexual distress scale-revised for assessing distress in women with hypoactive sexual desire disorder. *J Sex Med* 2008; 5:357-64.

16. de Graaf H, Kruijer H, van Acker J, Meijer S. Seks onder je 25ste (2012). 1st ed. Rutgers WPF/Soa Aids Nederland. Eburon, Delft.

17. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997; 49:822-30.

18. Bakker F, Vanwesenbeeck I. Sexuele gezondheid in Nederland 2006. 1st ed. Rutgers Nisso Groep 2006. Eburon, Delft.

19. Horner T, Liberthson R, Jellinek MS. Psychosocial profile of adults with complex congenital heart disease. *Mayo Clin Proc* 2000; 75:31-6.

20. Ong L, Nolan RP, Irvine J, Kovacs AH. Parental overprotection and heart-focused anxiety in adults with congenital heart disease. *Int J Behav Med* 2011; 18:260-7.

21. Kovacs AH, Sears SF, Saidi AS. Biopsychosocial experiences of adults with congenital heart disease: review of the literature. *Am Heart J* 2005; 150:193-201.

22. Simko LC, McGinnis KA, Schembri J. Educational needs of adults with congenital heart disease. *J Cardiovasc Nurs* 2006; 21:85-94.

23. Kokkonen J, Paavilainen T. Social adaptation of young adults with congenital heart disease. *Int J Cardiol* 1992; 36:23-9.

24. Vigl M, Kaemmerer M, Niggemeyer E, et al. Sexuality and reproductive health in women with congenital heart disease. *Am J Cardiol* 2010; 105:538-41.

25. Reid GJ, Siu SC, McCrindle BW, Irvine MJ, Webb GD. Sexual behavior and reproductive concerns among adolescents and young adults with congenital heart disease. *Int J Cardiol* 2008; 125:332-8.

26. Vigl M, Hager A, Bauer U, et al. Sexuality and subjective wellbeing in male patients with congenital heart disease. *Heart* 2009; 95:1179-83.

27. Hargrove A, Penny DJ, Sawyer SM. Sexual and reproductive health in young people with congenital heart disease: a systematic review of the literature. *Pediatr Cardiol* 2005; 26:805-11.

28. Uzark K, VonBargen-Mazza P, Messiter E. Health education needs of adolescents with congenital heart disease. *J Pediatr Health Care* 1989; 3:137-43.

29. Kamphuis M, Verloove-Vanhorick SP, Vogels T, Ottenkamp J, Vliegen HW. Disease-related difficulties and satisfaction with level of knowledge in adults with mild or complex congenital heart disease. *Cardiol Young* 2002; 12:266-71.

30. Verstappen A, Pearson D, Kovacs AH. Adult congenital heart disease: the patient's perspective. *Cardiol Clin* 2006; 24:515-29, v.

31. Rogers P, Mansour D, Mattinson A, O'Sullivan JJ. A collaborative clinic between contraception and sexual health services and an adult congenital heart disease clinic. *J Fam Plann Reprod Health Care* 2007; 33:17-21.

32. Kaemmerer M, Vigl M, Seifert-Klauss V, et al. Counseling reproductive health issues in women with congenital heart disease. *Clin Res Cardiol* 2012; 101:901-7.

10

Long-term outcome and quality of life after arterial switch operation. A prospective study with a historical comparison.

T.P.E. Ruys, A.E. van den Bosch, J. A. A. E. Cuypers, M. Witsenburg, W.A. Helbing, A.J.J.C. Bogers, R. van Domburg, J.S. McGhie, M.L. Geleijnse, J. Henrichs, E. Utens, H.B. Van der Zwaan, J.J.M. Takkenberg, J.W. Roos-Hesselink

Congenital Heart Disease. 2013 May-Jun;8(3):203-10

ABSTRACT

Aim

To describe the long-term cardiological and psychological results of our first surgical cohort of arterial switch operation (ASO) patients and compare the results with our earlier series of Mustard patients.

Methods

Twenty-four survivors of ASO operated in our centre (1985-1990) were evaluated by ECG, echocardiography, MRI, exercise-testing, 24-hour Holter-monitoring and health-related quality of life questionnaire. The results were compared with 58 adult Mustard patients who were evaluated in 2001 using the same study-protocol.

Results

ASO was performed at a median age of 13 days and Mustard operation at 2 years. Median follow-up was 22 (range 20-25) and 25 years (22-29), respectively. After ASO survival was better ($p=0.04$). The event-free survival after 22 years was 77% after ASO versus 44% after Mustard ($p=0.03$). Good systemic ventricular function was present in 93% after ASO versus 6% after Mustard ($p<0.01$). Exercise capacity in ASO was 85% of predicted, compared to 72% in Mustard patients ($p=0.01$). Aortic regurgitation was found in 21% of in ASO versus 16% in Mustard patients. Arterial switch patients versus Mustard patients reported significantly better quality of life and less somatic complaints.

Conclusion

The progression made in surgical treatment for transposition of the great arteries from Mustard to ASO has had a positive impact on survival, cardiac function, exercise capacity, and also self-reported quality of life and somatic complaints. Longer follow-up is warranted to monitor aortic regurgitation.

INTRODUCTION

Complete transposition of the great arteries (TGA) is one of the most common cyanotic congenital heart diseases.[1] Until three decades ago, atrial repair (Mustard or Senning) was the only surgical option. Long-term follow-up showed considerable ongoing mortality and morbidity mainly caused by progressive right systemic ventricular failure.[2]

Nowadays, the arterial switch operation (ASO),has become the established surgical correction.[3] Operative survival after arterial switch in the current era is good, with a operative mortality rate of 5% to 6%.[4-5] Mid- and long-term follow-up studies are also encouraging, however, the oldest survivors of ASO at most centers are young adults.[6-10] The aim of this study was to describe the long-term cardiac outcome and quality of life in our first surgical cohort of arterial switch patients and compare the results with the outcome data of our series of Mustard patients.

METHODS

Study protocol

Simple TGA was defined as TGA without concomitant abnormalities or minor concomitant abnormalities (atrial septal defect, ventricular septal defect not requiring surgical patch closure or a persisting arterial duct); others were defined as complex TGA. Major events were defined as death, cardiac transplantation, re-intervention (surgery or catheter intervention), pacemaker implantation or hospital admission for arrhythmia, endocarditis or heart failure.

The protocol included physical examination, 12-lead electrocardiography (ECG), 24-hour Holter monitoring, echocardiography, cardiac magnetic resonance imaging (MRI), bicycle exercise test, N-terminal pro-Brain Natriuretic Peptide measurements (NT pro BNP) and quality of life assessment (short form 36). The results of the ASO group were compared with patients after Mustard procedure operated between 1973 and 1980, who were studied in 2001 after a comparable follow-up at a comparable age, using the same protocol except for MRI and NT-proBNP measurements.[2-11]

Echocardiography

Transthoracic two-dimensional echocardiography studies were performed using the iE33 ultrasound system (Philips Medical Systems, Best, the Netherlands). Systemic ventricular systolic function was visually graded as normal, moderate or poor. Left ventricular end-systolic dimension and left ventricular end-diastolic dimension were measured using the standard parasternal long axis. Diastolic function was obtained by measurements of transmitral inflow pattern. Valvular stenosis and regurgitation severity

were graded according to current guidelines.[12-13] Body surface area was derived with the DuBois formula and aortic diameter was corrected for body surface.[14] Aortic root dilatation at the sinuses of Valsalva was defined as an aortic root diameter ratio above the upper limit of 1.3 of predicted.

MRI

MRI was performed using a Signa 1.5 Tesla MR imaging system (General Electric, Milwaukee, WI, USA). The cardiovascular magnetic resonance imaging studies were analyzed on an Advanced Windows workstation (General Electric Medical Systems, Milwaukee, WI, USA), equipped with Q-mass (version 5.2, Medis Medical Imaging Systems, Leiden, the Netherlands). The ventricular volumetric data set was quantitatively analyzed using manual outlining of endocardial and epicardial borders in end systole and end diastole.[15]

Exercise capacity

Maximal exercise capacity was obtained using bicycle ergometry. The exercise capacity measured was indexed for age, sex and body height, standardized for the Dutch population.

NT-proBNP

Peripheral venous blood was collected from each patient and analyzed using the electrochemiluminescence immunoassay kit (Elecsys 2010, Roche Diagnostics GmbH, Mannheim, Germany). NT-proBNP <15 pmol/L was defined as normal.

Short Form 36

Health-related quality of life was assessed using the Dutch Short-Form 36.[16] Higher scores indicate a better quality of life. Effect sizes were expressed in terms of Cohen's *d*, (small effects: $d<0.3$., medium effects: $0.3<d<0.8$, large effects: $d>0.08$). The scores of the arterial switch patients were compared to the Mustard patients and also to an age- and gender-specific Dutch population sample.[17]

Behavioural/emotional problems

Behavioural/emotional problems were assessed using a screening list for psychopathology: the Adult Self-Report (ASR) (Achenbach & Rescorla, 2003) and its previous version (Young Adult Self-Report (Achenbach, 1997), respectively. Age-equivalent Dutch population data on the ASR (n=938) was derived from Vanheusden et al.[18] For historical comparisons, 88 common items of the ASR and Young Adult Self-Report were used.

Patients

Between 1985 and 1990, 75 consecutive patients underwent ASO successfully in our institute. Forty-five patients were referred from other countries in Europe and could not be traced for adequate follow-up. Baseline characteristics and survival data of all other 30 patients were obtained by chart review and by contacting the civil registry. Twenty-nine (Dutch) survivors were invited to participate in this follow-up study in 2009. Institutional board review was obtained (NL26121.078.08) and participating patients provided informed consent. Five patients refused to participate, thus this cohort comprised 24 patients.

Control Groups

In 2001 an extensive study of Mustard patients was performed with survival data available in all 91 patients and 58 patients participated in the in-hospital protocol. These 58 patients serve as the Mustard control group. The results of these Mustard patients were described previously in detail and are presented in the tables.[2]

The scores of the SF 36 and the Adult Self-Report were compared to the Mustard patients and also with the Dutch population sample. Additionally, for comparison of echocardiographic measurements, we studied 23 gender- and age matched healthy controls.

Statistical methods

Continuous data are presented as mean with standard deviation and were compared with the Student-T or Mann-Whitney test. Discrete variables are presented in absolute numbers and percentages and were analysed using the chi-square or Fischer's exact test and Mann-Whitney test for ranked discrete data. Cumulative survival rates were calcu-

Table 1. Baseline characteristics of arterial switch population and Mustard population.

	ASO 30	**Mustard 58**	**p value**
Male	17 (57)	40 (69)	0.26
Age at operation	13 days	2 years	<0.01
Rashkind septostomy	12 (40)	41 (71)	<0.01
Simple TGA	17 (57)	22 (38)	0.1
With IVS	16 (53)		
With VSD without patch	1 (4)		
Complex TGA	13 (43)	36 (62)	
TGA with VSD with patch	7 (23)		
TGA with DORV and/or aortic pathology	6 (20)		

All data are number of patients (%) IVS intact ventricular septum VSD ventricular septal defect DORV double outlet right ventricle.

lated with the Kaplan-Meier method and the Tarone-Ware test was used to compare the ASO and Mustard patients. The level of significance was $p < 0.05$ (two sided). The data were analyzed with the SPSS version 16.0 software (SPSS Inc., Somers, NY).

RESULTS

Baseline characteristics of the 30 patients after ASO are shown in Table 1. Thirteen patients had complex TGA (43%), of which 2 patients with hypoplastic right ventricle (one with hypoplastic aorta). Lecompte's manoeuvre was applied in 70% of cases; the main reason not to apply the Lecompte's manoeuvre was side to side position of the aorta and pulmonary artery. The coronary pattern was left anterior descending artery and circumflex from the left coronary sinus and right coronary artery from the right coronary sinus in 50% of the patients; all other had various other coronary patterns.

Survival

One patient with hypoplastic right ventricle and hypoplastic aorta died at 18 months of age, no specific cause could be identified by autopsy. Overall cumulative survival rate of the arterial switch patients was 97% at 25 years after operation while in Mustard patients this was 77% (Figure 1).

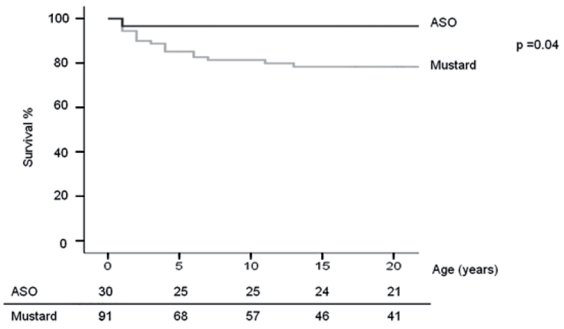
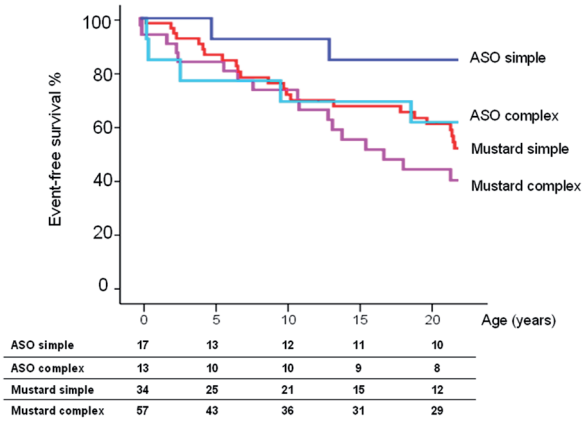


Figure 1. Cumulative survival after transposition of the great arteries. ASO: patients with arterial switch operation studied in 2009; Mustard: patients after Mustard operation, studied in 2001.

Reinterventions

Twelve re-interventions were performed in 6 arterial switch patients, mainly for pulmonary artery stenosis: reoperation (n=7), balloon dilatation (n=3) and one reoperation for residual atrial septal defect and ventricular septal defect. One patient with complex TGA suffered from ventricular tachycardia (VT) at age 19, treated by ablation and Implantable Cardioverter Defibrillator (ICD) implantation. No interventions for neo-aortic regurgita-



ASO simple	17	13	12	11	10
ASO complex	13	10	10	9	8
Mustard simple	34	25	21	15	12
Mustard complex	57	43	36	31	29

Figure 2. Event-free survival after transposition of the great arteries. Events were defined as reintervention, heart failure, or arrhythmias.

tion or coronary obstruction or hospital admission for heart failure were necessary. At 22 years follow-up the overall event-free survival was 77% in arterial switch patients versus 44% in Mustard patients p=0.03.(Figure 2) Event-free survival was 88% for simple TGA and 62% for complex TGA for patients who underwent ASO (p=0.15). In complex TGA patients there were 0.036 events per patient year, this was 0.006 events per patient year in simple TGA patients.

Follow-up study

Twenty-four arterial switch patients participated in our in-hospital prospective follow-up study with a median age at follow-up of 22 years (IQR 20-24), of which 63% was male.

Electrocardiography and 24 hours monitoring

All 24 patients were in sinus rhythm at follow-up. One patient needed anti-arrhythmic medication and received an ICD. Voltage criteria for LV hypertrophy or dilatation were found in 47%. Nineteen patients had Holter-monitoring. In 3 patients, non-sustained VT's were documented, of which 2 had VTs shorter than 10 beats. None of the arterial switch patients had supraventricular arrhythmias.

Echocardiographic findings

Echocardiography was performed in 23 of the 24 arterial switch patients. Mild or moderate neo-aortic regurgitation was present in 17% and 4%, respectively, whereas no severe neo-aortic regurgitation was found. Mild neo-aortic stenosis was observed in one patient. Increased peak flow velocity (>2.0 m/s) was found across the pulmonary artery in 43% of the patients, the highest velocity found was 3.8 m/s. By detailed inspection of the images, it was concluded that anatomical deformities were responsible for 50% of

Table 2. Echocardiography findings in arterial switch patients.

Echocardiogram	ASO 23	Controls 23	**p-value**
LVEDD mm	52 ± 6	49 ± 4	0.09
LVESD mm	32 ± 5	29 ± 3	0.06
FS %	37 ± 7	38 ± 5	0.35
IVS ED mm	9 ± 1	9 ± 1	0.93
PW ED mm	8 ± 1	8 ± 1	0.48
Aortic sinus mm	33 ± 6	26 ± 3	< 0.01
Aortic sinus ratio	1.1 ± 0.15	0.9 ± 0.08	< 0.01
E m/s	0.9 ± 0.3	0.8 ± 0.2	0.06
A m/s	0.4 ± 0.1	0.4 ± 0.1	0.21
E/A ratio	2.3 ± 0.9	2.2 ± 0.5	0.65
DET msec	193 ± 51	202 ± 30	0.47

Echocardiography: All data are mean ± standard deviation. ASO patients with Arterial Switch Operation, LVESD Left ventricular end-systolic dimension, LVEDD left ventricle end-diastolic dimension, FS fractional shortening, IVSED end-diastolic thickness of the interventricular septum, LVPWED end-diastolic thickness of the posterior wall, E early component of the transmitral inflow pattern, A late component of the transmitral inflow pattern, DET deceleration time of E.

Table 3. Overview outcome after surgery for transposition of the great arteries.

	ASO (2009)	**Mustard (2001)**	**p- value**
NYHA class I	100%	24%	< 0.01
Sinus rhythm	100%	63%	< 0.01
Sinus node disease	0%	43%	< 0.01
Normal systemic ventricular function	93%	4%	< 0.01
Maximum heart rate reached during exercise testing	89%	84%	0.12
Exercise tolerance % of expected	88%	72%	0.03
Exercise capacity below 85 % of predicted value	53%	76%	0.05

ASO = arterial switch operation, Mustard = Mustard correction.

obstructions; whereas surgery related obstruction (suture line or Lecompte's manoeuvre) was responsible for the other 50%. Mild pulmonary regurgitation was found in 42%, severe pulmonary regurgitation in 4%.

Systemic ventricular function was judged to be normal in 93% and no diastolic dysfunction was found. Mean fractional shorting was 37%, which was comparable with the healthy controls (Table 2).

Physical capacity

Results are presented in Table 3. Two patients needed medication; the patient with the ICD received beta-blockers, whereas another patient was treated with ACE-inhibitors because of moderate LV dysfunction.

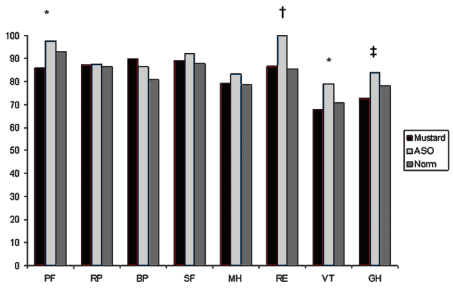


Figure 3. Quality of life: SF-36. PF, physical functioning; RP role limitations due to physical; health problems; BP, bodily pain; SF, social functioning; MH, general mental health; RE, role limitations due to emotional problems; VT, vitality; GH, general health perceptions; ASO, patients with arterial switch operation; Mustard, patients after Mustard operation; Norm, normal Dutch population matched for sex and age.[20] * Significant difference between ASO vs. Mustard and vs. Norm. † Significant difference between ASO vs. Norm. ‡ Significant difference between ASO vs. Mustard.

Twenty patients underwent exercise testing. No arrhythmias occurred. One patient had a rate- depended right bundle branch block during exercise and 3 patients (20%) showed ST alterations (downslope ST depression > 2 mm), but with additional testing no coronary artery obstruction was found (2 MIBI scans and CT angiogram).

MRI

Magnetic resonance imaging was performed in 13 arterial switch patients (54%). Reasons for not participating in the MRI were: claustrophobia (5), refused (5) and ICD (1). The mean ejection fraction measured with MRI was 66% for the left ventricle and 62% for the right ventricle. One patient had a left ventricle ejection fraction of 41%. The neo-aortic root had a mean diameter of 39 mm (range 30 to 49 mm), 44% of the patients had a neo-aortic root diameter of more than 40 mm.

Table 4. Differences in mean behavioural/emotional problems scale scores between ASO patients and Mustard patients.

	Problems Scores		
ASR scales	**Switch (n = 17)[a] M (SD)**	**Mustard (n = 55)[a] M (SD)**	**p-value**
Anxious/Depressed	4.1 (4.3)	5.9 (5.2)	0.19
Withdrawn	1.9 (2.0)	3.1 (2.6)	0.90
Somatic Complaints	2.3 (3.3)	3.6 (3.1)	0.04
Thought Problems	1.8 (2.4)	2.0 (2.1)	0.45
Attention Problems	3.4 (2.1)	3.5 (2.4)	0.98
Aggressive Behavior	1.9 (1.8)	2.8 (2.3)	0.15
Rule-Breaking Behavior	2.4 (1.8)	2.8 (2.3)	0.95
Intrusive	2.0 (2.2)	2.3 (2.0)	0.48
Internalizing Problems	8.4 (8.8)	12.6 (9.1)	0.05
Externalizing Problems	6.4 (4.0)	7.8 (5.3)	0.47

[a] Data on behavioural/emotional problems was available in 17 arterial switch patients and 55 Mustard patients

ASR = Adult Self-Report

NT-proBNP

NT-proBNP was measured in 18 arterial switch patients. Mean NT-proBNP was 10.1 pmol/L ± 12.2. Three patients had an elevated NT-proBNP level, of which 2 patients (21.4 and 23.3 pmol/L) had normal LV function. Their exercise capacity was 82 and 84% of predicted. The patient with the ICD had a moderate LV dysfunction and a NT-proBNP level of 52.2 pmol/L.

Quality of life

Eighteen patients completed the quality of life questionnaires. Outcomes are presented in Figure 3. Arterial switch patients scored better than the normal Dutch population on the scales physical functioning, vitality and role limitations due to emotional problems ($p < 0.01$). Compared to Mustard patients, arterial switch patients scored better in the sub domains physical functioning ($p<0.01$), general health perceptions ($p=0.04$) and vitality ($p=0.04$). All differences showed medium effect size.

Behavioural/emotional problems

Data was available on 17 arterial switch patients and is presented in Table 4. Overall, behavioural/emotional functioning was good. There was no significant difference between the arterial switch patients and the normative data from the Dutch general population on any of the ASR scales (data not shown). Arterial switch patients had significantly less somatic complaints than the Mustard patients ($p=0.04$).

DISCUSSION

This study describes the outcome of a small cohort of arterial switch patients. However, this group represent a good sample of the whole surgical cohort and was studied extensively, including MRI and psychological outcome. This study offers the possibility of a historical comparison with outcome after Mustard operation, because a large cohort of Mustard patients was studied with the same follow-up protocol after a comparable period of time in our institution before.

Twenty-two years after ASO, excellent survival, low morbidity and favorable quality of life was found and outcomes are significantly better than after Mustard correction. Lessons from the past taught us that one should be careful with early optimism: where first results of the Mustard operation were reported to be good, major problems became apparent in adult life, of which most significant the failing capacity of the right ventricle to sustain the systemic circulation.[2,19] Until now, few studies have been published on the outcome after ASO in adulthood. And until now results are favourable.[5-8] Therefore, optimism about the outcome after ASOs seems justified.

Our results show that both survival and event-free survival of TGA patients have dramatically improved with the introduction of ASO, as was expected and hoped for. In this study we compared the outcome of the two surgical techniques used in patients with TGA, as both cohorts are based on the planned follow-up of consecutive operated patients and not random patients seen at an outpatient clinic. Furthermore, both groups are studied in a similar designed long-term follow-up study using the same instruments for a medical and psychological assessment.

In our cohort of arterial switch patients there was a relatively high percentage of complex TGA. Survival was clearly better than after the Mustard procedure and comparable with other studies after ASO with a lower percentage of complex TGA.[4,5,6] However, in complex arterial switch patients the event rate per patient year was considerably higher than in the simple patients. Pulmonary artery stenosis was especially common in these patients.

Clinical condition and ventricular function

Arterial switch patients were in good clinical condition 22 years after surgery, whereas only 24% of the Mustard patients were in NYHA class I. The inferior condition of the Mustard patients may be caused by the impaired systemic (right) ventricular function.

At long-term follow-up 93% of arterial switch patients in our study had normal systemic (left) ventricular function. The feared deterioration of the ventricular function late after arterial switch operation, related to coronary artery abnormalities, was not observed. However, in one patient, a diminished LV function was found (ejection fraction 41% using MRI) without a good explanation. Also, diastolic function parameters were found to be normal in this small sample of patients.

Surprisingly, we found a reduced exercise capacity in arterial switch patients compared to the normal Dutch population (although better than Mustard patients).[19] This reduced exercise capacity was not exclusively found in patients with diminished LV function or significant right ventricular outflow tract obstruction. The reduced levels of physical activity may be caused by overprotection of parents during childhood. In addition, lack of training or self-esteem has been described in literature, as cause for this diminished exercise capacity.[20] Ischemia was also suggested, and in our study three patients showed ST segment changes; however, additional evaluation excluded coronary pathology. Giardini et al. described reduced exercise capacity in young patients after ASO, but none showed ischemic electrocardiographic changes during exercise.[21] Finally, chronotrope incompetence may play a role.[22]

The development of arrhythmias was rare and sinus rhythm with normal conduction is maintained long-term after ASO, while after Mustard procedure there is a high incidence of supraventricular arrhythmias and sinus node dysfunction. Only one arterial switch patient with complex TGA and moderate LV function underwent ICD implantation for

ventricular tachycardia; he also had a mildly elevated NT-proBNP. This was also seen in two other patients, who did not have a diminished LV function. More data on biomarkers as a predictor of adverse outcome are warranted.[23]

Valvular abnormalities

From other studies, we know that neo-aortic regurgitation may become a problem later in life.[24] Our results confirm the presence of mild to moderate neo-aortic regurgitation in 21% of the patients, and none of them has yet required reintervention and none showed severe regurgitation.

Some degree of neo-aortic root dilatation is almost universal and several studies have shown serial increases in neo-aortic root diameter.[24] We found in 44% of the ASO patients a neo-aortic root of more than 40 mm. Early data suggest that neo-aortic dilatation may stabilize in adulthood, but follow-up is too short to be certain.

The main indication for reintervention in ASO patients was pulmonary artery stenosis, as was the case in the study by Oda et al.[7] In our study, nearly half of the arterial switch patients had a residual gradient across the pulmonary artery or pulmonary valve, and some may need additional reinterventions in the future, warranting further close monitoring.

Health-related quality of life and behavioral/emotional problems

Self-reported physical functioning and vitality were better in arterial switch patients compared with normative data.[17] This is remarkable, as exercise capacity was reduced. Overestimation of physical functioning compared with actual exercise test results has also been found by Gratz et al. [25]

Of noteworthy is that behavioral/emotional functioning was as good as in the normal population.[18]

Compared with the Mustard group,[26] arterial switch patients scored more favorably on physical functioning, general health, and vitality, which confirms the results of Muller et al.[8] In addition, they had less self-reported somatic complaints.[27] These findings are of utmost importance as subjective well-being influences costs of medical and also other care.

STUDY LIMITATIONS

As with many studies on congenital heart disease, patient numbers are small in this study. Furthermore, we realize that a direct comparison between the results of Mustard and arterial switch patients in the same era would be the best possible study design. However, this is not feasible as nowadays all our TGA patients undergo an ASO. The study

design, using the same tests after a comparable follow-up period and at the same age, seems the second best option. The two groups differ in several aspects: not only have surgical treatment feasibilities and age at repair changed, but anesthetic techniques and neonatal care have also improved. Both groups were the first cohort of patients using that specific surgery; therefore, results of more recent patients may be slightly different. Although patients were lost to follow-up due to foreign citizenship, the cohort described represents all arterial switch patients still under regular follow-up.

CONCLUSION

Long-term follow-up after ASO shows excellent survival, low morbidity, and favorable quality of life, and is clearly better when compared with the outcome after Mustard operation. Good cardiac function is the norm after ASO. However, results indicated lower-than-expected exercise capacity, the ongoing risk of developing important neo-aortic root dilatation with neo-aortic regurgitation. Reinterventions for pulmonary artery problems did occur. Careful systematic clinical follow-up is warranted to monitor these patients further.

ACKNOWLEDGEMENTS

We would like to thank Denise van der Linde and Petra Opić for their help with statistical analyses, and Professor Hall for his support in the English grammar.

REFERENCES

1. van der Linde D, Konings EE, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *JACC* 2011;58:2241-7.
2. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, et al. Decline in ventricular function and clinical condition after Mustard repair for transposition of the great arteries (a prospective study of 22-29 years). *Eur heart J* 2004;25:1264-70.
3. Jatene AD, Fontes VF, Paulista PP, et al. Anatomic correction of transposition of the great vessels. *J Thorac Cardiovasc Surg*.1976;72:364-70.
4. Losay J, Touchot A, Serraf A, et al. Late outcome after arterial switch operation for transposition of the great arteries. *Circulation* 2001;104:I121-6.
5. Lalezari S, Bruggemans EF, Blom NA, et al. Thirty-year experience with the arterial switch operation. *Ann Thorac Surg.* 2011;92:973-9.
6. Tobler D, Williams WG, Jegatheeswaran A, et al. Cardiac outcomes in young adult survivors of the arterial switch operation for transposition of the great arteries. *JACC* 2010;56:58-64.
7. Oda S, Nakano T, Sugiura J, et al. Twenty-eight years' experience of arterial switch operation for transposition of the great arteries in a single institution. *Eur J Cardiothorac Surg.* 2012;Oct;42(4):674-9.
8. Muller J, Hess J, Horer J, et al. Persistent superior exercise performance and quality of life long-term after arterial switch operation compared to that after atrial redirection. *Int J Cardiol*. 2013 Jun 20;166(2):381-4 Published online First: 18 November 2011.
9. Y Yamazaki A, Yamamoto N, Sakamoto T, et al. Long-term outcomes and social independence level after arterial switch operation. *Eur J Cardiothorac Surg.* 2008;33:239-43.
10. Vandekerckhove KD, Blom NA, Lalezari S, et al. Long-term follow-up of arterial switch operation with an emphasis on function and dimensions of left ventricle and aorta. *Eur J Cardiothorac Surg.* 2009;35:582-7.
11. Meijboom F, Szatmari A, Deckers JW, et al. Long-term follow-up (10 to 17 years) after Mustard repair for transposition of the great arteries. *J Thorac Cardiovasc Surg.* 1996;111:1158-68.
12. Vahanian A, Baumgartner H, Bax J, et al. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur heart J* 2007;28:230-68.
13. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr.* 2003;16:777-802.
14. Roman MJ, Devereux RB, Kramer-Fox R, et al. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. *Am J Cardiol.* 1989;64:507-12.
15. Luijnenburg SE, Robbers-Visser D, Moelker A, et al. Intra-observer and interobserver variability of biventricular function, volumes and mass in patients with congenital heart disease measured by CMR imaging. *Int J Cardiovasc Imaging* 2010;26:57-64.
16. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.

17. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol.* 1998;51:1055-68.

18. Vanheusden K, van der Ende J, Mulder CL, et al. Beliefs about mental health problems and help-seeking behavior in Dutch young adults. *Soc Psychiatry Psychiatr Epidemiol*. 2009;44:239-46.

19. Budts W, Scheurwegs C, Stevens A, et al. The future of adult patients after Mustard or Senning repair for transposition of the great arteries. *Int J Cardiol.* 2006;113:209-14.

20. Massin MM, Hovels-Gurich HH, Gerard P, et al. Physical activity patterns of children after neonatal arterial switch operation. *Ann Thorac Surg.* 2006;81:665-70.

21. Giardini A, Khambadkone S, Rizzo N, et al. Determinants of exercise capacity after arterial switch operation for transposition of the great arteries. *Am J Cardiol.* 2009;104:1007-12.

22. de Koning WB, van Osch-Gevers M, Ten Harkel AD, et al. Follow-up outcomes 10 years after arterial switch operation for transposition of the great arteries: comparison of cardiological health status and health-related quality of life to those of the a normal reference population. *Eur J Pediatrics* 2008;167:995-1004.

23. Eindhoven JA , van den Bosch AE, Jansen PR, Boersma E, Roos-Hesselink JW, The usefulness of Brain Natriuretic Peptide in Complex Congenital Heart Disease, *JACC* 2012 in press.

24. Schwartz ML, Gauvreau K, del Nido P, et al. Long-term predictors of aortic root dilation and aortic regurgitation after arterial switch operation. *Circulation* 2004;110:II128-32.

25. van Rijen EH, Utens EM, Roos-Hesselink JW, et al. Current subjective state of health, and longitudinal psychological well-being over a period of 10 years, in a cohort of adults with congenital cardiac disease. *Cardiol Young* 2005;15:168-75.

26. van Rijen EH, Utens EM, Roos-Hesselink JW, et al. Longitudinal development of psychopathology in an adult congenital heart disease cohort. *Int J Cardiol.* 2005;99:315-23.

PART 3

Summary and discussion

11

Summary

SUMMARY

The major improvement in survival of patients with congenital heart disease since the introduction of surgical repair in the 1950s has led to an increasing focus on late complications and quality of life.

This thesis focusses on the outcome beyond 30 years of follow-up in five patient groups with common congenital heart defects: atrial septal defect, ventricular septal defect, pulmonary stenosis, tetralogy of Fallot and transposition of the great arteries. These groups have been followed prospectively for several decades and are seen in the hospital every ten years. As follow-up is now approximating 40 years, we made a first effort to determine predictors for outcome.

In chapter 2, the results after surgical closure of an atrial septal defect are described. Survival is very good (91% after 40 years) and the reintervention rate is very low, but still, two patients died suddenly in their fourth decade, possibly due to arrhythmia. Although there were no signs of pulmonary hypertension, no increase in sinus node dysfunction and a low incidence of atrial arrhythmias, we unexpectedly found a decrease in right ventricular function in 1/3 of our patients and in left ventricular function in 1/5. Although none of our patients developed heart failure, this underscores the need for life-long follow-up even in these patients who are considered to have had a benign congenital heart defect.

In chapter 3, we describe the outcome after surgical repair of a ventricular septal defect. Here, survival is significantly less than in the general population (78% after 40 years). This is mainly due to perioperative mortality, probably reflecting the early era of congenital heart surgery with less experience and less sophisticated equipment than nowadays, as perioperative mortality is much lower in the current era. Nevertheless, also patients who survived their operation have a slightly lower survival than the general population (86% after 40 years). Mortality is due to sudden death, reoperations for concomitant lesions and heart failure. Morbidity is substantial, with 28% of the patients experiencing an adverse event by 40 years of follow-up. There is a 13% incidence of arrhythmia and 12% of reinterventions. Although patients are very satisfied with their quality of life and physical capacities, half of them have a diminished exercise capacity. Left ventricular function did not decrease significantly over time, but there was a significant decrease in RV function. Ventricular-ventricular interaction may play a role. Moreover, there was a significant increase in aortic regurgitation. Although overt heart failure developed in only 4% yet, the decline in ventricular function and increase in aortic regurgitation warrants lifelong careful follow-up in these patients as well.

Chapter 4 is a review on pulmonary stenosis (PS), which can be valvular, subvalvular or supravalvular. Initially, all significant pulmonary stenoses were repaired surgically. Nowadays, the first choice treatment for valvular PS is percutaneous balloon valvuloplasty. While the diagnosis of severe PS was established by cardiac catheterisation in the past, this can nowadays be done by echocardiography and/or cardiac MRI. Inevitably, follow-up after surgical repair is longer than after percutaneous treatment, but for both treatment modalities survival is reported to be good. Both treatment options can lead to pulmonary regurgitation, which is tolerated well for many years, but may eventually lead to right ventricular dilatation and dysfunction. Therefore, patients with pulmonary regurgitation after PS repair should remain under regular follow-up and may need a new intervention as is well-known in Fallot patients.

Chapter 5 describes the long-term outcome in patients who underwent surgical repair of pulmonary stenosis in childhood. In them, survival is comparable to the general population (93% after 40 years), but the need for reinterventions is substantial: one quarter of patients needed a reintervention during 40 years of follow-up. Reinterventions were necessary for residual PS in the early decades, and for severe pulmonary regurgitation from the 2nd decade after repair onwards. The incidence of atrial arrhythmias is limited, and no ventricular arrhythmias were observed. Subjective health status is good and patients rate their own physical functioning at least as good as the general population. However, also in this patient group, there was a decline in both left and right ventricular function, and diminished left ventricular function was related to observed diminished exercise capacity.

Chapter 6 describes the outcome in patients after surgical repair of tetralogy of Fallot. Cumulative survival in this group is clearly diminished, with only 72% alive after 40 years of follow-up. Although perioperative mortality was high in this early era of congenital heart surgery, late mortality cannot be neglected. Late attrition is due to heart failure and ventricular arrhythmias. Morbidity is high, with 44% of patients needing a reintervention, 17% having symptomatic arrhythmias and 3% developing heart failure. There is a gradual decline in both right and left ventricular function, and also LV diastolic function is impaired in many patients. Progressive aortic root dilatation, however, does not seem to be a major problem.

The decline in left as well as right ventricular function appears to be the effect of ventricular-ventricular interaction, as RV and LV dysfunction were clearly related in our study. There are also signs of diminished contractile reserve, for during dobutamine stress, on cardiac MRI both RV and LV function increased only at low dose dobutamine, but failed to increase at high dose dobutamine infusion. However, exercise capacity is relatively good (89% of the norm) and did not deteriorate in the last 10 years.

Chapter 7 reveals the outcome in our group patients who received a Mustard repair for transposition of the great arteries. In this group, survival was known to be the least favorable of all 5 groups (68% after 40 years) and within decades after operation the function of the systemic right ventricle was observed to decline. The expectation of further decline in systemic ventricular function was confirmed by our study, but the survival was not as bad as was expected. Although late mortality was mainly due to heart failure in the previous decade, in this last decade patients died due to ventricular arrhythmias. Reinterventions were necessary mainly for either baffle stenosis or leakage, and most of them were performed in the first 2 decades after Mustard repair. Thus, baffle problems seem to have been addressed effectively in the past and new stenoses were rarely encountered. An increase in tricuspid regurgitation was observed, in line with further deterioration of systemic RV function. Cardiac magnetic resonance imaging (CMR) findings seem to confirm the decline in systemic RV function, although it is difficult to judge the function by CMR as normal values for these ventricles do not exist. The incidence of supraventricular arrhythmias doubled over the last decade and this is worrisome, as SVTs are associated with sudden cardiac death. No increase in VT on Holter monitoring was observed, although five patients clinically experienced VT and two even died of it. Indications for ICD are not well established. There is concern about inappropriate shocks and lead complications in these relatively young patients, with substantial psychological impact. Pacemakers, on the other hand, are often needed and implanted in Mustard patients, mainly for sinus node disease. Although signs of sinus node disease are found increasingly in many of our patients, there were a few additional pacemaker implantations over the last decade. Despite all problems described above, exercise capacity remained remarkably stable since last follow-up and also subjective health-related quality of life was reported to be good.

In chapter 8 and 9, we describe two important aspects of quality of life in adult congenital patients that have been somewhat or even totally neglected in the past: sports participation and sexual functioning. Patients with congenital heart disease are known to have lower educational levels, lower occupational levels and lower income compared to the general population. Also, there is more psychopathology in young adulthood, but this problem appears to dissolve with increasing age. Having survived into middle adulthood, are there also more problems with sports participation and in sexual functioning compared to the general population?

In chapter 8, we investigated sports participation and its clinical consequences in our surgically repaired ASD, VSD, PS, Fallot and Mustard patients. Historically, patients with congenital heart disease were discouraged from participating in any sports because it was thought to be dangerous. Fear still exists that strenuous physical exercise may induce arrhythmia or other adverse events, even sudden death. On the other hand,

even in heart failure patients, nowadays exercise training is thought to be beneficial: it improves condition and quality of life. In our study, no association was found between sports participation and (sudden) death. Almost half of our patients were engaged in sports. This is less than in the normal population. Probably obviously, patients with complex congenital heart disease were found to practice the fewest hours of sports and engage more often in less intensive sports. The patients that were engaged in sports had a better exercise tolerance, a healthier life style and in those with moderate/complex congenital heart disease even a better subjective physical function than patients who did not. Moreover, indications were found that ventricular function remained stable more often in patients who perform sports. In regard of the observed deterioration of ventricular function found over time in all diagnosis groups, this is an important notion. However, more research is mandatory to give better insight in the effects of sports and provide optimal advice to our patients.

In Chapter 9, we describe sexual functioning in congenital heart disease patients. The majority of the patients was married and sexually active. Compared to the general population, both females and males scored worse on sexual functioning scales: women reported a wide range of problems, including less sexual desire, less arousal and more pain during intercourse. However, the amount of really pathologic sexual dysfunction was equal to that in the general female population. Men reported more erectile dysfunction, which was significantly more frequent than in the general male population, more orgasmic dysfunction and less intercourse satisfaction.

Questioned about pregnancy and heredity, female patients appeared to have more anxiety concerning infertility due to their heart defect and recurrence risk of their heart defect. Especially patients with moderate or complex congenital heart disease were concerned that their heart disease would have a negative effect on the outcome of their child. With regard to pregnancy itself, female patients were concerned that a pregnancy and delivery would have a negative effect on their cardiac condition and overall clinical condition. This concern was most frequently observed in women with moderate/complex congenital heart disease. Virtually all patients would have wished to have had more information on these matters, as well as on safety and potential side effects of contraception methods. As their anxieties may be exaggerated or unjustified or, contrarily, insufficient, more information should be given to patients on sexuality, pregnancy and heredity. This information should be given timely, preferably at young age, before sexuality and pregnancy become an issue in daily life.

Chapter 10 describes the long-term outcome of the current treatment strategy for transposition of the great arteries: the arterial switch operation (ASO). A historical comparison with the Mustard patients is made. The major advantage of ASO is that the left

ventricle is sustaining the systemic circulation, like in the normal heart. Survival up to 25 years after ASO is obviously better than after Mustard operation (97% versus 77%), and in 93% LV function remained preserved (versus 6% normal systemic ventricular function in the Mustard group). This was also reflected by a much better exercise capacity in ASO patients (85% versus 72% of the norm), although the exercise capacity in ASO patients was not normal. Although several ASO patients needed a reintervention for pulmonary artery stenosis due to the Lecompte manoeuvre, and one ASO patient suffered from ventricular tachycardia, the event-free survival in the ASO group was significantly better than in the Mustard group (77% versus 44%).

12

General discussion

DISCUSSION

The milestone successes since the early years of surgical congenital heart defect repair have led to dramatic improvements in the prognosis of patients with congenital heart disease. Most patients now survive well into their adult years and focus has shifted from mere survival to late complications and quality of life. Many patients do suffer from residual problems. This is still creating new challenges, both in diagnosing and treating these patients, but also in organizing the care for them. Congenital cardiology has become an established subspecialty in cardiology, and the growing population in congenital heart disease patients needs to be met by a sufficient number of specialized cardiologist and trained nurses. Even in a country as small as the Netherlands, this implies that academic, tertiary, centers for congenital heart disease should stratify the specific care in cooperation with non-academic centers. In this regard, permission for surgical and interventional treatment is limited to a few tertiary centers only. The non-academic hospitals will increasingly participate in the outpatient care for patients with congenital heart disease. To facilitate the organization of care, we need to learn which patients are at increased risk of developing serious adverse events and should be taken care of in tertiary centers and which patients are at lower risk and therefore can be managed in a secondary or even primary care center. This is not an easy goal to accomplish, because the ongoing innovation of surgical repair for congenital heart defects, as well as new insights and developments in medical care have resulted in many changes and adaptations in surgical techniques, resulting in an actual present day variety of patients. In addition, many forms of congenital heart disease can be treated percutaneously nowadays. Therefore, outcome in patients that were treated in the earliest era of congenital heart surgery cannot thoughtlessly be extrapolated to patients that are treated later on. Nevertheless, prospectively studying the long-term outcome of patients that were operated in earlier eras remains the only way to improve our knowledge and will provide important information and feedback for both patients and their treating physicians on what may be expected in different diagnoses groups.

Survival

In general, survival is decreased in all forms of congenital heart disease, whether simple or complex.[1] However, in our study we see a clear difference between simple lesions such as ASD, VSD and PS on the one hand, tetralogy of Fallot in the middle and more complex lesions such as TGA corrected with a Mustard repair on the other (Figure 1).

The substantial perioperative mortality in the early years of congenital heart surgery will have contributed to the idea of decreased life expectancy. In our cohort, there were clear differences in perioperative mortality between the groups. It was substantial in Mustard,

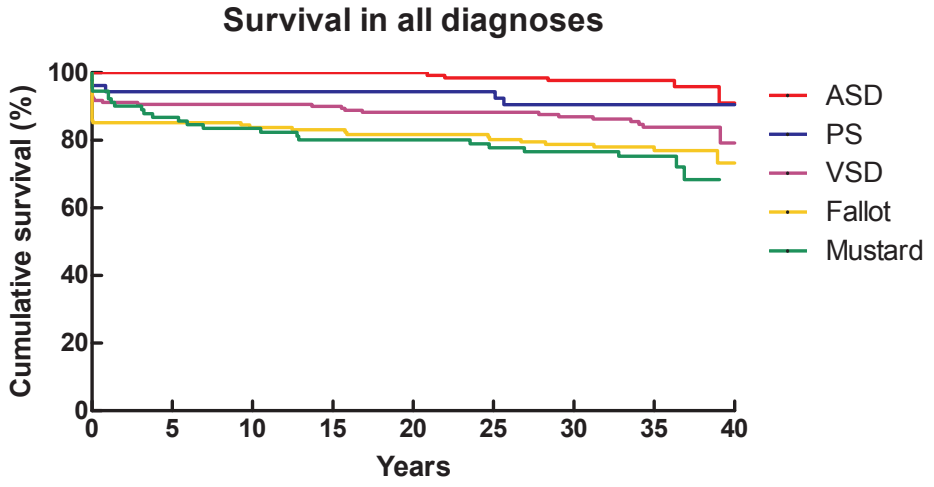


Figure 1. Kaplan-Meier curves for survival in all diagnoses studied.

VSD and Fallot repair (Table 1). Nowadays, perioperative mortality is much lower, surely in the congenital heart defects that were studied in this thesis. Perioperative mortality after Fallot repair nowadays is close to zero even in neonates.[2, 3] We found that in ASD and pulmonary stenosis, survival is as good as in the normal population. As we are now observing their life expectancy to be near normal, societal limitations should be re-assessed. Since life expectancy can be considered normal in selected diagnoses, no generalized limitations can be applied anymore. The cardiac anomaly in itself is not necessarily a reason anymore for these patients to be withheld from a mortgage or affordable life and disability insurance. Still, many insurance companies demand higher

Table 1. Cumulative survival and incidence of events.

	ASD	PS	VSD	Fallot	Mustard
Perioperative mortality	0%	2%	10%	16%	5%
Cumulative survival*	91%	93%	76%	72%	68%
Survival excluding postoperative mortality*	91%	95%	86%	86%	72%
Event-free survival*	60%	67%	62%	26%	19%
Reinterventions	2%	25%	13%	44%	46%
SVT	16%	9%	10%	13%	28%
VT	0%	0%	0%	6%	6%
Pacemaker	6%	12%	6%	10%	33%
ICD	0%	0%	0%	5%	6%
Heart failure	0%	0%	3%	3%	23%
Endocarditis	0%	0%	4%	<1%	<1%

* survival after 40 years of follow-up

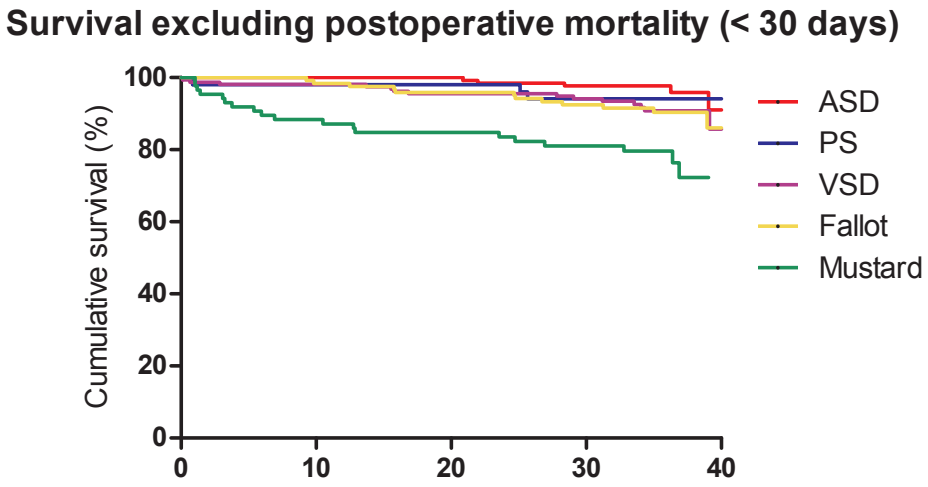


Figure 2. Kaplan-Meier curves for survival excluding perioperative mortality (< 30 days postoperative).

insurance premiums because of supposed decreased longevity and higher mortality and disability in patients with any form of congenital heart disease. This appears to be unjust in patients after successful ASD of PS repair. After the initial perioperative mortality the survival curve is exactly the same is in the normal Dutch population (Figure 2).

Once patients have survived the perioperative period, survival after VSD repair is also very good, but slightly less than in the normal population. Although in our cohort, mortality did not differ significantly between isolated and non-isolated VSD, the cardiac morbidity that occurred seems to be related to additional cardiac lesions that developed or were detected during follow-up and do not appear to be related to the congenital defect itself. In tetralogy of Fallot, perioperative mortality was substantial, reflecting the early surgical era with less sophisticated perioperative care techniques. For example, in the early years, deep hypothermia was used to limit the necessity of cardiopulmonary bypass, which was at that time associated with a higher risk of complications when used in neonates and small children.[4] Later on, the use of deep hypothermia was limited because of concerns regarding inadequate neurologic protection and negative effects on postoperative inflammatory response.[5, 6] However, the patients that survived repair showed a very acceptable survival, only mildly decreased in comparison with the general population. Mortality was mostly due to heart failure and arrhythmia, which is in concordance with the literature,[7, 8] but worrisome nevertheless. The worst survival was expected, and found, in the patients after Mustard repair. Although, even in those early days, perioperative mortality was rather low (5%) in comparison with Fallot and VSD repair, their survival curve clearly deviates from that of the general population.

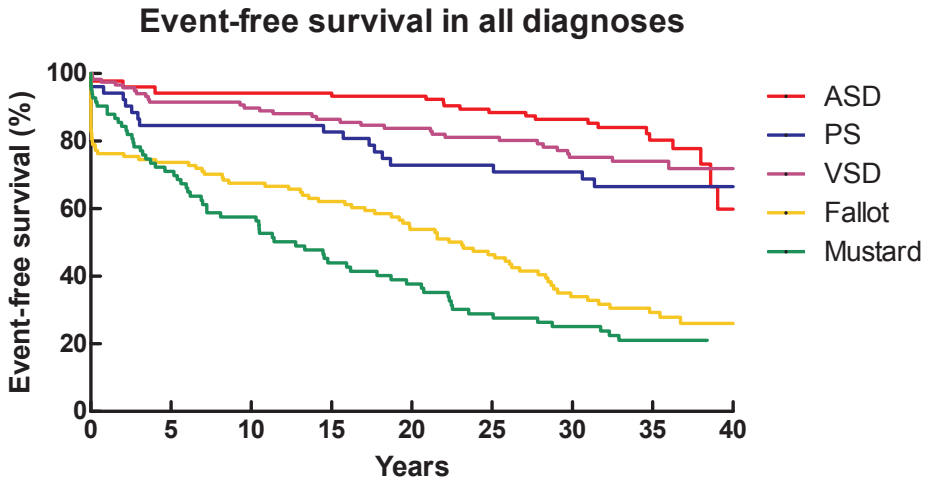


Figure 3. Kaplan-Meier curves for survival free from cardiac reintervention, symptomatic arrhythmia, PM/ICD implantation, heart failure, endocarditis or stroke.

Mustard patients were already known to show marked decrease of their systemic right ventricular function and are at risk of arrhythmia. In the previous decade, mortality in Mustard patients was due to heart failure. In the last decade, however, their mortality was due to ventricular arrhythmias. This is alarming, although in congenital heart disease sudden death is among the common modes of death, especially in the cyanotic lesions.[9, 10] Our finding stresses the need for better identification of patients at risk for these arrhythmias. So far, the association between reduced systemic ventricular function and arrhythmia and sudden death is understandable and has indeed been described in patients after atrial switch repair.[11-13] However, considering the fact that all atrial switch patients will eventually develop progressive systemic RV dysfunction, we need more reliable predictors to further identify which patients are at the highest risk of arrhythmic death and who need ICD implantation for primary prevention. Whether ICD therapy for these ventricular arrhythmias will indeed improve life expectancy, will have to be determined in future studies. Heart failure due to progressive systemic RV dysfunction may eventually be a more important determinant of life expectancy.

Event-free survival is not equal to the pattern of survival: here even in some of the groups with good survival, the event rate was substantial (Figure 3).

Reinterventions

Reinterventions were necessary at least in some patients in all of the studied diagnoses (Table 1). Only in the ASD group, the reintervention rate was very low.

In patients after VSD repair, reinterventions were mainly necessary for concomitant cardiac lesions which could not or did not have to be repaired during the initial opera-

tion. In several cases reintervention was necessary for aortic valve abnormalities that developed later on. A relation between these aortic valve abnormalties and the VSD cannot be excluded. Considering the increase in aortic regurgitation that was found, more reinterventions for aortic valve disease may be expected in the future. This necessitates continuation of close follow-up in patients after VSD repair, to allow timely aortic valve intervention. If aortic regurgitation is discovered in time, aortic valve repair may be performed instead of aortic valve replacement. In patients with an unrepaired small VSD located in close proximity of the aortic valve, close vigilance for any deterioration of valve function is warranted, to prevent the development of aortic regurgitation by the hemodynamic effects of the high-velocity VSD jet (Venturi effect).[14]

Pulmonary regurgitation after repair of tetralogy of Fallot, is a well-recognized problem. It is known to be associated with the often liberal use of a transannular patch to resolve right ventricular outflow obstruction in the early days of Fallot repair. Our results show that more and more patients need reintervention for severe pulmonary regurgitation with longer follow-up, even in our center, where a rather conservative approach towards pulmonary valve replacement is still advocated.

Because of this high prevalence of pulmonary regurgitation in patients operated upon in the early surgical era, during the subsequent eras the surgical strategy has shifted towards avoiding prior palliative shunt placement and transannular patching whenever possible. There still is debate on which is the optimal timing and policy for primary Fallot repair, especially concerning repair in neonates.[15, 16] In them, often the right ventricular outflow tract is too narrow for repair without the use of a transannular patch. However, even in the neonatal period, Fallot repair is performed with low mortality and morbidity nowadays.[3] The group of Ichikawa studied the outcome after repair of tetralogy of Fallot with preservation of the pulmonary annulus.[17] They found a good survival (96% after 20 years) and freedom from moderate or worse pulmonary regurgitation of 35% after 20 years. So even after using annulus sparing surgical techniques, the amount of pulmonary regurgitation is substantial. More recently, new pulmonary valve sparing techniques have been developed and used, including balloon dilatation of the PV annulus and reconstruction of the valve cusps, with good short-term results.[18-20] However, even with the use of these techniques, early pulmonary regurgitation does still occur. Whether this will lead to the same rate of reinterventions after very long follow-up needs to be established, but the hope is that it will be less of a problem than in our cohort. Based on the results of all different strategies so far, and knowing that there will always be a trade-off between relief of the outflow tract obstruction and the avoidance of valve incompetence, we believe that early Fallot repair should be advocated, with the use of a valve sparing technique and avoidance of transannular patching whenever possible, to minimize the risk of development of substantial regurgitation. Unless cyanotic spells

preclude postponement of repair, it is a good strategy to wait for some months and operate at the age of 3-6 months, to avoid the potential negative effects of extracorporeal circulation which are more outspoken in neonates, and are a cause of increased perioperative morbidity and mortality in them.[16, 21, 22] Postponing repair until after the early neonatal period will also allow growth of both child and right ventricular outflow tract, so that the need for a transannular patch can be critically assessed.

Reintervention for pulmonary regurgitation was also necessary in many patients after PS repair, albeit to a lesser extent than in Fallot patients. This may be related to the fact that transannular patching was used more often in the Fallot group that in the PS group. Also in the PS group, the presence of PR was related to the use of a transannular patch. Additionally, pulmonary regurgitation may be tolerated less well in Fallot patients due to a worse RV function compared to PS patients with the same amount and duration of PR as described by Puranik et al,[23] making reintervention necessary earlier. Recurrent pulmonary stenosis does occur after surgical repair of PS in a minority of patients. This does not seem to imply that the result of the primary valvulotomy of the dysplastic pulmonary valve was suboptimal, for even in the earliest era of surgical repair the immediate results of valvulotomy were good, despite the sometimes limited time available in cardiac arrest by inflow occlusion. When a reoperation for recurrent stenosis has become necessary, the surgeon often finds newly fused cusps of the dysplastic valve. This phenomenon is apparently also seen in tetralogy of Fallot, where sometimes a recurrent stenosis of the right ventricular outflow tract develops. When this occurs, it does so in the first years after repair. As ventricular pressure overload may be tolerated less well than volume overload, reinterventions for recurrent stenosis may be necessary earlier in the follow-up.

Nowadays, the first choice treatment for isolated pulmonary valve replacement is balloon valvuloplasty. Periprocedural and long-term survival are very good, but follow-up is inevitably shorter than after surgical PS repair. Reintervention after pulmonary balloon valvuloplasty is reported to be necessary in up to 30% of patients after 10 year of FU, and almost exclusively for residual or recurrent stenosis so far.[24]

Timing of reintervention for PR also remains difficult. Guidelines are based on expert opinion because of lack of consistent literature.[25] Pulmonary valve replacement should be considered for many reasons, and although many papers and guidelines were published on the topic, there is no consensus on clear-cut thresholds for when to intervene. When a patient with severe pulmonary regurgitation becomes symptomatic, the need for intervention will be obvious. However, a patient may only become symptomatic after severe deterioration of right ventricular function, which may not be reversible after valve replacement or, in severe cases, may even preclude surgery. In patients after Fallot repair, there are reports that advocate a threshold for right ventricular volume, for example 160 ml/m2 or 170 ml/m2,because once the right ventricle has dilated beyond

that threshold, irreversible RV deterioration may occur.[26, 27] In our opinion, however, it is difficult to explain the need for intervention in a completely asymptomatic patient if RV volume is the only criterion. In addition echocardiographic and MRI measurements both have their limitations in providing consistent and precise information. In our center, we apply a more selective approach, valuing longitudinal developments over static figures.[28] We take into account changes in ventricular size and function as well as objective measurement of exercise capacity to unmask unapparent functional deterioration and development of arrhythmias or ventricular extrasystoles. Based on our results, this seems a reasonable strategy: we did not see a high incidence of heart failure or a steep rise in mortality.

When the indication for pulmonary valve replacement is established, the choice of valve substitute may be difficult. Historically, there is a preference for the use of a homograft, because of fear of valve thrombosis in mechanical valve prosthesis. The risk of valve thrombosis used to be regarded as considerable.[29, 30] Results after PVR with a biological valve are good and still considered the gold standard.[31] The limited durability of biological valves is still a problem, though, and need for reintervention for biological valve deterioration is the rule. Because of this, the use of mechanical valves is reconsidered in selected cases. Fairly recently, reports by Frehling and Dehaki show reasonably good results after mechanical pulmonary valve replacement, with freedom of valve thrombosis in 91% of their patients after 10 years. The patients in their group that did experience valve thrombosis could often be treated with thrombolysis and 98% remained free from reintervention after 10 years.[32, 33] In general, however, most often a non-mechanical valve is chosen. So once the pulmonary valve is replaced, the countdown is started towards repeated reinterventions. In our center, the freedom from valve-related re-operation after placement of a pulmonary allograft is reported to be 81% at 15 years.[34] A recent study by Sabate Rotes et al showed 75% freedom from reintervention 15 years after PVR using a homograft in patients with tetralogy of Fallot.[35] Also after the Ross procedure (in which the aortic valve is replaced by the patients' own pulmonary valve and a homograft is placed between the RVOT and pulmonary artery), the durability of the homografts is quite good.[36] Since the introduction of percutaneous pulmonary valve implantation, the outlook for patients after homograft valve replacement has improved. They now can often be treated by percutaneous valve implantation when their biological valve becomes dysfunctional. How long exactly a percutaneous PVR will delay the next surgical reintervention remains to be established, because follow-up on these valves is still somewhat limited. Durability so far is good, with over 90% of the patients surviving free from reintervention after 5 years of follow-up.[37] However, there is concern about endocarditis in these percutaneous valves, which is reported in up to 6% after a mean follow-up of 2 years[38] , and more often than after surgical pulmonary valve replacement (8.5 vs 6%) in a direct comparison made by the group of Boudjemline.[39] Percutaneous

pulmonary valve endocarditis (PPVE) may run a very aggressive course and mortality rates are high. Because vegetations may be difficult to detect and antibiotic therapy is prescribed easily when a patient has fever without a clear diagnosis, PPVE may easily be missed initially. Both doctors and patients should be aware of the risk and remain vigilant for possible signs. Taking blood cultures before starting antibiotics should be advocated. Currently, percutaneous techniques to implant pulmonary valves have extended towards use in native pulmonary valves in selected cases.[40]

In patients after Mustard repair, reinterventions were mainly necessary for baffle-related problems. These problems apparently become manifest in the first decades after Mustard repair, and don't seem to be a problem during late follow-up. Baffle leakage will be present directly after surgery, but may take a while to become a significant problem. Baffle stenosis may become a problem due to relatively limited growth: one can imagine that baffles that are constructed in the first year of life will become relatively too small during childhood growth. Our result show that, once resolved, these baffle problems do not often return. In the last decade of our study no interventions for baffle problems were necessary.

So far, only two of our Mustard patients underwent heart transplantation, which may be regarded as the ultimate reintervention for a failing systemic right ventricle. Observing the gradual decline in ventricular function in this group, an increasing number of these patients may be expected to require a transplant in the (near) future. This is not an easy treatment option, because a heart transplantation after Mustard repair may be technically challenging and there is an increased risk of perioperative complications compared to heart transplantation in required heart disease. [41] Furthermore, there is a very strict screening traject before a patient can be accepted for transplantation and a shortage in donor organs. Additionally, a donor suitability may be further hampered by mismatches in HLA-compatibility, which occur more often in congenital patients who have had prior interventions and blood transfusions. Moreover, development of pulmonary hypertension due to longstanding systemic RV dysfunction may preclude suitability for transplantation of the heart only. These patients may require a heart-lung transplantation, but donor organ shortage and unsatisfactory results have made this an illusionary treatment option in the Netherlands. Whereas implantation of ventricular assist devices (VADs) as a bridge to transplantation, or even as destination therapy, is customary in end-stage failure of systemic left ventricular failure nowadays,[42] this is not a widely performed strategy in patients with systemic right ventricular failure yet. However, VADs are used even in this group of patients. Although implantation of such a device will be more complicated in a heavily trabeculated systemic right ventricle or in a patient who had extensive prior heart surgery, successful implantations are being reported increasingly.[43-45] There is even a case report of a patient in whom a ventricular

assist device was implanted to achieve reversal of pulmonary hypertension to enable subsequent heart transplantation.[46]

Arrhythmia and sudden cardiac death

Arrhythmias were encountered in all patient groups that were studied, but the incidence in the patients with simple congenital heart defects was low. Atrial arrhythmias and pacemaker implantations were encountered in all diagnosis groups, but ventricular arrhythmias and ICD-implantations were only observed in Fallot and Mustard patients.

Atrial tachyarrhythmias may be caused by increased wall stress due to atrial volume overload, leading to fibrosis of the atrial wall. Also, the presence of an atrial scar may lead to reentrant tachycardia. In patients after ASD closure and Mustard repair the presence of an atrial scar is obvious. In the other diagnoses, this may not be the case. For example, repair of pulmonary stenosis using circulatory arrest by inflow occlusion may have been performed through an incision in the pulmonary artery. Unfortunately, in the surgical reports from several decades ago, the locations of incision and cannulation are not always indicated clearly. Probably they were considered to be so obvious that describing them in all details was considered superfluous.

As in ASD patients the incidence of atrial arrhythmias was low, early closure of an ASD appears to prevent atrial arrhythmias. They are much more frequent, occurring in up to 50%, in unrepaired ASD.[47] This supports the issue of increased wall stress due to longstanding atrial volume overload. The presence of an atrial scar does not seem to induce atrial reentrant tachycardia on a large scale in our group. Moreover, the presence of any form of atrial arrhythmia on Holter recording does not predict clinically relevant arrhythmias. In patients undergoing ASD closure at adult age, atrial arrhythmias are more frequent before closure and they typically do not disappear after surgical closure. It was thought that the surgical scar might play a role, but because we did not find these arrhythmias often after surgical repair in childhood, it seems that this is not the major factor. In a study by Silversides et al,[48] a previous history of atrial arrhythmia and age > 55 years were risk factors for (recurrent) arrhythmia after percutaneous ASD closure in adults, but the incidence of new onset atrial arrhythmia was low. Whether device ASD closure will also prevent the occurrence of SVTs in the long term or will make patients prone to arrhythmias by direct stretching of the atrial septum or circular scar formation around the device remains to be established. So far, the occurrence of new onset atrial arrhythmias after device closure appears to be low.[49 50]

The finding that in our patients after VSD repair, the incidence of atrial arrhythmia was also low, and lower than in patients after VSD closure at adult age ,[51] may indicate that these arrhythmias are indeed caused by the mechanism of atrial volume overload. Patients after PS repair did suffer from arrhythmias the least, and only atrial arrhythmias occurred.

Although ventricular arrhythmias were not observed in patients after ASD, VSD or PS repair, some patients did die suddenly in these groups. An arrhythmic cause of death cannot be excluded in these cases and in some even seemed likely.

In the patients with more complex forms of congenital heart defects, i.e. the Fallot and Mustard patients, late occurrence of arrhythmia and sudden death is a much bigger problem. In both groups, the atrial scars made during the repair may predispose to re-entrant atrial tachycardias, and there is concern about ventricular arrhythmias. Though, overall, the incidence of arrhythmia in patients after Fallot repair was not very high, and lower than described by others,[52] both atrial and ventricular arrhythmias were found in our cohort. The prevalence of arrhythmias on Holter-recording did not predict outcome, and this prevalence did not increase over time either. To our opinion, the routine performance of Holter-recordings in asymptomatic patients is of limited value. Increase of QRS-duration over time and a QRS-duration over 180 ms have been associated with ventricular tachyarrhythmia and sudden death.[53, 54] Although in our cohort QRS-duration indeed increased significantly over time, and several patients have a QRS-duration > 180 ms, we were not able to confirm this predictive value. This may of course be due to the relatively small size of our group and the relatively low incidence of arrhythmic events. However, ventricular arrhythmias and arrhythmic death was encountered in our Fallot group and some patients did receive an ICD for secondary prevention.

In the group of Mustard patients, the cumulative incidence of atrial arrhythmias was high and several patients experienced ventricular arrhythmias. The incidence of atrial arrhythmias has doubled over the last decade. This is worrisome, as they are known to predict sudden cardiac death in this patient group.[11] Obviously, the presence of extensive atrial scar tissue will play a major role in the pathophysiology of these atrial arrhythmias. Indeed, atrial macro-reentrant tachycardia is often encountered in patients after atrial switch operations,[55, 56] and atrial arrhythmias occur much less frequently in patients with congenitally corrected transposition of the great arteries, who also have a systemic right ventricle, but without the atrial scarring.[57] Apart from the atrial scars, increase of atrial pressures over time, caused by decline in ventricular function and consequent increase in end-diastolic ventricular pressures and systemic AV-valve regurgitation, may also play a role in the development of atrial arrhythmias, especially atrial fibrillation, in Mustard patients. More than atrial reentry tachycardias, the occurrence of atrial fibrillation may be an indicator of hemodynamic decline. The incidence of ventricular arrhythmias appears to increase over time, and several patients died of them. Risk stratification and decision making on whom to provide with an intracardiac defibrillator (ICD) remain difficult. Obviously, patients with severe or progressive failure of their systemic RV will be at higher risk of ventricular arrhythmias and sudden cardiac death. So far, however, implantation of ICDs as a primary preventive strategy is not widely used. As many patients suffer from supraventricular tachycardias as well, they will be at a higher risk of

receiving inappropriate ICD shocks. Furthermore, lead complications and device infections pose a serious threat to these still relatively young patients, who may probably need their ICDs for a long time. This will all have impact on the quality of life.[58] The arguments pro and con the use of an ICD for primary prevention in these patients have to be carefully considered and tailored to every individual patient. In my opinion, ventricular dysfunction in itself must not be the only criterion to decide towards ICD implantation. There has to be an additional criterion, for example an increase in premature ventricular beats or non-sustained ventricular tachycardias on Holter recording. When a Mustard patient needs a device because of conduction disease, adding the ICD function seems wise in the setting of a severely decreased systemic RV function, even when there is no evidence of non-sustained VTs yet. Hopefully, the development of better discrimination algorithms and better leads will diminish the negative impact of an ICD on quality of life in the future.

Bradyarrhythmias were also encountered in all diagnosis groups. This may be the result of the lesion itself. Of course they can be also due to peri-operative damage to the conduction system. Certainly in the earliest era of cardiac surgery, the anatomic knowledge of the major conductive pathways was not as precise as it is today. Nowadays, well-trained surgeons know exactly how to avoid damage to the conduction tissue. Later on, progression of fibrosis of the conduction system may develop due to advancing age or hemodynamic sequellae of the repaired cardiac defect leading to increased wall stress. Furthermore, the use of anti-arrhythmic drugs to treat tachyarrhytmias may compromise conduction. Drug-induced bradycardia may indeed also be an indication for pacemaker implantation.

In ASD patients, most pacemakers were implanted during early follow-up, and 2/3 of the patients who received a pacemaker had bradycardia in the early postoperative period. This is compatible with peri-operative damage to the conduction system. However, although no significant increase in signs of sinus node disease or AV-conduction delay was found on Holter-recordings, some patients needed a pacemaker late after surgery for AV-block.

Despite the early era, the incidence of postoperative conduction problems after VSD repair was very limited, and the rate of late pacemaker implantation is low. Very few patients had complete heart block, although damage to the conduction system has been reported after surgical VSD closure.[59]

Peri-operative damage to the conduction system was not a problem after PS repair, as in this group the first pacemaker was implanted after 17 years of follow-up. In the Fallot group, there were a few patients requiring a pacemaker early after surgery, and the rate of late pacemaker implantation is low.

Sinus node disease is the main reason for pacemaker implantation in patients after Mustard repair. Although signs of sinus node disease were observed on Holter-record-

ings in more than half of our patients, only very few pacemakers were implanted for this indication during late follow-up.

Overall, late conduction disorders were not a major problem in any group, but still did occur in some of the patients. This underscores the need for continuation of follow-up. As the benefit of Holter monitoring in the absence of complaints appears to be very limited, this is not a good diagnostic tool. Perhaps implantation of a very small continuous loop recorder would be a better way of detecting arrhythmias and conduction disorders. It will be interesting to study the utility of this relatively new diagnostic method. For now, we inform our patients about the symptoms to be aware of, and to seek medical attention in case of such symptoms.

Heart failure and ventricular function.

Although heart failure was absent in the groups after ASD and PS repair, we observed at least some deterioration of ventricular function in all diagnosis groups.

The further decline in systemic RV function that was observed in our Mustard population is no surprise, and this declined function is now confirmed by CMR in our study. Although normal values are not available for these systemic RVs in CMR, on visual assessment they are clearly abnormal. Many different theories exist on why the RV fails as a systemic ventricle. It is thought to be due to a combination of many factors, among which pre-repair hypoxic damage; differences in myocardial fiber orientation between the right and left ventricle, making the RV contraction more like a bellow than like the wringing motion of he left ventricle; presumed mismatch between blood supply and demand in the systemic RV that is usually provided with a single coronary artery instead of two for a left ventricle and impaired inflow through the non-compliant atrial baffles, compromising ventricular filling.[60] Others have shown increased fibrosis (indicated by late gadolinium enhancement on CMR) in systemic RVs. [61, 62] The presence and extent of fibrosis are related to higher levels of NT-proBNP and lesser exercise capacity parameters[61] , as well as ventricular function and adverse clinical outcome.[62] In patients after Fontan repair, myocardial fibrosis is associated with adverse ventricular mechanics and ventricular arrhythmias.[63] Whether this also holds for Mustard patients has to be determined.

The eventual failure of the systemic right ventricle is a major problem, because until today there is no successful strategy to avoid it, apart from changing the type of surgical repair: the atrial switch has been replaced by the arterial switch operation. In dysfunctional systemic left ventricles, ACE-inhibitors and beta-blockers have been proven to be able to support the ventricle and prevent or delay deterioration, often even leading to improvement of left ventricular function. Treatment strategies for failing left ventricles are well established. On the contrary, although several aspects of heart failure in systemic right ventricles are alike, some aspects are clearly different and no medication

has shown any real benefit in delaying or preventing heart failure in failing systemic RVs. So far, for Mustard patients with heart failure, heart transplantation, and maybe a ventricular assist device are the only ultimate therapeutic options.

In patients after Fallot repair, late deterioration of not only right, but also left ventricular function has been a concern for some time.[64-66] Indeed this deterioration was confirmed in our study, and observed to be progressive. The decrease in RV and LV function was again confirmed by CMR, by which we also showed decreased contractile reserve. In contrast, this lack in contractile reserve was not found after Fallot repair in children.[67] This may be due to shorter follow-up or due to better surgical techniques and perioperative care in these children that were operated in a more recent era.

Several factors can be thought to be involved in this RV dysfunction: prior to surgical repair, the right ventricular myocardium may be damaged by hypoxia and pressure overload; during repair, there may be ischemic damage due embolic micro infarction or lesions to aberrant coronaries, as well as due to ventricular incision. Post repair, the right ventricle may be further challenged by residual obstruction of the right ventricular outflow tract and pulmonary regurgitation, and the presence of a patch in the RVOT may have negative effects RV myocardial contraction.[23] Arguments for pre-repair damage to the ventricular myocardium are found in CMR studies, which have showed that late gadolinium enhancement (LGE), a sign of myocardial fibrosis, was present in the right ventricles of patients after Fallot repair and that the amount of LGE is was higher in patients operated at an older age.[68] LGE has also been demonstrated in children and young adults with (unoperated) aortic stenosis, and this was related to diastolic dysfunction in these patients.[69] An argument for perioperative damage to right ventricular function may be that the fibrosis is often located at the sites of surgical resections and incisions.[68] The presence and amount of fibrosis is related to exercise tolerance and neurohormonal activation, as well as arrhythmia.[68]

The deterioration of LV function in Fallot appears to be mostly due to ventricular-ventricular interaction.[70] There is increasing evidence for the presence of subclinical diastolic dysfunction of the left ventricle in Fallot patients. Dragulescu et al demonstrated by strain imaging studies that abnormal LV mechanics are present in children and adolescents after Fallot repair even in the absence of systolic LV dysfunction.[71] In their study, the volumes and function of the patients LVs, tested by CMR, were similar to those of healthy controls. The LV longitudinal, radial and circumferential strain and twist patterns, however, were clearly lower in Fallots than in controls. The study by Ahmad et al, also showed diastolic dysfunction of the LV in Fallot patients: LV filling was disturbed by RV dilatation.[72] In our own center, LV twist patterns were clearly abnormal in our Fallot cohort[73]

Myocardial fibrosis is also found in the left ventricles of patients after Fallot repair.[68] This may reflect perioperative ischemic damage, but there are signs that ventricular-

ventricular interaction may cause fibrosis as well: a study of the effects of pulmonary artery banding on ventricular fibrosis in rabbits showed development of fibrosis in both right and left ventricle and this appeared to be related to an increase of profibrotic signaling pathways, especially TGF-β1.[74] These effects may play a role in Fallot as well.

Probably the causes of deterioration in ventricular function in PS patients are similar, at least to a certain degree, to those in Fallot.

Although the original effect of an ASD is volume overload of the right ventricle, this appears to be much better tolerated than the volume overload by PR in Fallot. In ASD, the volume overload rarely causes the RV to fail and therefore ASD can go undetected well into adult life.[75] This is absolutely not the case in Fallot patients with PR. This difference in response to volume overload between (unoperated) ASD patients and (operated) Fallot patients was confirmed by an echocardiographic deformation imaging study by Dragulescu et al.[76] In our cohort of operated ASD patients, the presence of RV dilatation was evident already, but we now observed systolic RV dysfunction for the first time. Deterioration of left ventricular function was observed in some patients as well. This has not been described before and is not easy to explain. Maybe also in these patients, the answer lies in ventricular-ventricular interaction, but we were not able to show a relation between RV ad LV dysfunction in our study. Whether the systolic functional deterioration was preceded by diastolic function, which may be an argument to underscore the role of ventricular-ventricular interaction is not known, for diastolic function was not assessed before.

Finally, in the VSD-group, LV-dysfunction was observed during the previous studies in our cohort. It did not increase over time however, but was confirmed by the up-to-date echocardiography techniques. In contrast, right ventricular dysfunction was not observed during the earlier studies, but was now found in 17% of the VSD patients. Whereas LV-function may not have completely recovered from the volume load caused by the VSD prior to repair, the reason for right ventricular dysfunction must be sought elsewhere. We did not find a relation between RV dysfunction and right ventriculotomy or the use of a VSD patch, although these were applied very frequently in our cohort. There was a relation between RV dysfunction and the presence of elevated pulmonary pressure and with having a pacemaker, which may compromise ventricular function by increased afterload and altered activation patterns respectively. We assume that ventricular-ventricular interaction must pay a role too, for when a left ventricle becomes more spherical, this changes the orientation of the septal myocardial fibers, affecting RV systolic contraction. More recently, RV dysfunction was demonstrated in children after VSD repair using tissue Doppler techniques.[77] One may question whether subtle signs of systolic RV dysfunction were indeed present before in our patients, but simply not detected by lack of these newer echo techniques.

Endocarditis

In none of the groups studied, endocarditis was a frequent problem. In the patients with repaired ASD and PS, no endocarditis was observed at all, and the incidence in Fallot and Mustard patients was very low (<1%). The highest incidence of endocarditis was found in VSD patients, but during the latest follow-up, the one case of endocarditis that occurred may also have been associated with the presence of a pacemaker instead of the repaired VSD. Historically, VSD is indeed regarded as one of the congenital heart defects with a higher risk of developing endocarditis,[78] and in a Dutch risk stratification model it was found to be associated with a higher endocarditis risk.[79] However, a recent report from Rushani et al did not identify VSD as a risk factor for IE in children.[80] The incidence of endocarditis in congenital heart disease is still substantial, but due to better diagnostics and treatment strategies the mortality has declined remarkably.[81] Whether the incidence of endocarditis is going to increase after the adjustment of the guidelines for prevention of bacterial endocarditis in 2009, remains to be awaited.

Determinants of outcome

Early postoperative arrhythmias

In our study, in all diagnosis group but pulmonary stenosis (in which the occurrence of postoperative arrhythmias was least well documented), the occurrence of arrhythmias, both tachy- and bradyarrhythmias, in the early postoperative period were related to outcome. The relation between early and late arrhythmias and pacemaker implantation, as found in the ASD group, is imaginable, for surgical damage to the conduction system may not always recover and postoperative scars and fibrosis may become a substrate for arrhythmias.

The relation with heart failure in the Mustard group was unexpected and is harder to explain. We postulated that postoperative AV-block and subsequent pacemaker implantation could contribute to decrease in ventricular function through the longstanding abnormal ventricular activation. This has been described by others, both in congenital and acquired heart disease.[82, 83] Biventricular pacemaker implantation for bradycardia indications is reported to prevent LV dysfunction in the long run,[83] but implantation of such a biventricular device is often not easy and sometimes even impossible in patients with congenital heart disease.[84, 85] Besides that, many of the patients in our cohort requiring a pacemaker did so before biventricular pacing was even invented yet.

In case of persisting postoperative arrhythmias, the use of antiarrhythmic medications may compromise ventricular function through negative inotropic effects.

Another possible explanation for the association of postoperative arrhythmias with heart failure may be that the occurrence of these arrhythmias itself is an indicator of worse hemodynamic status after surgery. The incidence of and risk factors for arrhyth-

mia in the direct postoperative period have been studied by others.[86] These arrhythmias do indeed seem to be related to greater case complexity and prolonged CPB time. Moreover, postoperative arrhythmias have been associated with higher postoperative rise in troponin levels, reflecting greater peri-operative myocardial damage.

In patients after repair of Fallot, early postoperative arrhythmias were even predictive of (late) mortality. As mentioned above, postoperative arrhythmias may be related to higher complexity of congenital heart defects and myocardial damage. When they occur, they may also prolong ventilator time and postoperative intensive care stay, which are associated with increased postoperative mortality.[86] Late mortality may be mediated through late arrhythmias, which were found to be predicted by the same early postoperative arrhythmias in this group. It is widely known that mortality late after Fallot repair is often arrhytmogenic.[9] Also in our group, the presence of SVT on the ECG in 1990 or 2001 appeared to predict mortality. More attention for (early) arrhythmias seems warranted and the predictive role and underlying mechanism of these arrhythmias should be focus for further research.

Use of palliative shunts and transannular patches.

In both Fallot and PS patients, the use of a transannular patch (TAP) was associated with adverse outcome: in both groups TAP use predicted pulmonary valve replacement. This is hardly surprising, as pulmonary regurgitation is an inevitable consequence of TAP use, and has been reported elaborately before. In The Fallot group, TAP use also predicted late arrhythmias, potentially also facilitated by volume overload of the right heart due to pulmonary regurgitation. It did not predict mortality, though.

The use of a palliative shunt before complete repair resulted in more events in the PS group and higher mortality in the Fallot group. As in our study the use of prior palliation was mainly related to the era of surgery, this cannot be explained by mere disease complexity. This finding underscores the benefit of early primary repair, which has been common practice for years now.

Other predictors for outcome

In the VSD group, the number of events was too low to test separate outcomes. Non-isolated VSD and longer aortic cross-clamp time were associated with a higher risk of late events. Both may be explained by more complex heart disease, which may take longer to repair and, as mentioned before, by the concomitant lesions which needed intervention later on.

We were a little surprised by our finding that older age at repair was related to a lower risk for events in the PS group. Maybe this is due to natural selection: possibly the patients with less severe disease survived until surgical treatment of their PS became

available, while patients with more severe disease did not survive until surgical treatment became available.

Quality of Life and social functioning

Subjective health status, social and emotional function and overall quality of life were reported to be good in all of the patient groups we studied. Even subjective physical functioning was reported to be good, except by the patients after Mustard repair. These result are similar to those of 20 and 10 years ago[87, 88], and also in line with other literature.[89, 90] Other studies report impaired quality of life on the domains of physical functioning.[91] The absence of impairment in psychosocial functioning may be due to several factors. The awareness of being born with a heart defect may cause patients to adjust their expectations in life and redefine their internal standards and values. This response shift may make them more appreciative of the things that they are able to do instead of regretting things they cannot. One study reported quality of life to be worse in younger patients with congenital heart disease compared to older patients.[92] This may indeed reflect a readjustment of expectations with increasing age. On the other hand, lack of knowledge of their heart condition may give rise to unrealistic expectations towards physical capabilities in patients with congenital heart disease. This may cause the subjective impairment in physical functioning described by others.[91]

Sports participation

There are clear controversies about sports participation in patients with congenital heart disease. In the past many patients were advised against physical exercise because of fear for unsafety, especially the occurrence of sudden cardiac death. Both parents and doctors were rather overprotective.[93] Recently, however, concerns changed in the direction of the negative effects of a sedentary life style. In both healthy individuals and patients with acquired heart disease, engaging in sports and physical exercise have been shown to be beneficial.[94, 95] Sports participation is reported to be associated with better exercise capacity and quality of life in adults with congenital heart disease.[96, 97] Recently, there are reports that these beneficial effects are seen in children and adolescents with congenital heart disease as well.[98, 99] Recommendations on sports participation in patients with congenital heart disease have become less strict over time.[100, 101] Nevertheless, our study shows that sports participation is still lower in these patients than in the general population. Although many patients in our cohort now have young families and busy jobs, which they may report to be the reason for not doing regular exercise, this cannot be the sole explanation, because these factors are present in the general population as well.

Although medical insights on sports participation have evolved, patients and maybe also doctors may still have a wrong idea or feel unsure about what level of exercise they

can safely perform. Patients who have heard their whole life that participation in sports will be unsafe for them, will need some time to adjust to these new insights. However, Moons already reported in 2005 that patients knowledge about what exercise they were allowed to perform was good in over 2/3 of them.[102] So, are there other factors involved? Maybe some patients unnecessarily use their heart disease as an excuse not to perform physical exercise. Their heart defect may give them some secondary disease profit. Also, their environment may still be too careful and simply not allow them to participate. Laws of liability may also have a negative influence on sports participation in sports clubs. Patients (as well as their environment) should be made more aware of the beneficial effects of physical exercise and - after individual risk assessment- encouraged more to engage in it.

The most feared negative effect of sports participation still is sudden cardiac death. When sudden death occurs during exercise or sports, it obviously has a great impact. On the other hand, patients with congenital heart disease should not be withheld from the beneficial effects of exercise and sports participation. We did not find an increased risk of adverse events like sudden death or arrhythmias in patients who did engage in sports, both in simple and more complex disease. However, our findings should be interpreted with care, because there were some cases of sudden death during exercise in our group and whether our patients were advised on sports participation was not studied. Moreover, our study used self-reported sports participation and exercise capacity, which is not always in line with reality.

Literature on the safety of sports participation in congenital heart disease is sparse. Studies that report on the incidence of cardiovascular events during sports participation have been focusing on sudden cardiac death in athletes mostly.[103] From these studies we know that SCD in athletes is mostly due to hypertrophic cardiomyopathy and coronary anomalies. Whether, and especially which congenital heart defects are at risk of SCD induced by exercise is not to be learned from these reports, as hardly any congenital heart disease was included in these studies. From the studies reporting on SCD in athletes, it is learned that most SCD happens in individuals of which the presence of heart disease was unknown. In this aspect, our patients with congenital heart disease are in advantage: at least we know how their heart functions and we can make an individual exercise recommendation.

It is important to realize that sports participation does not imply competitive sports participation necessarily. Historically, competitive sports were discouraged in almost all patients with congenital heart disease in fear of these patients pushing themselves too far due to pear pressure.[104] In the general population, however, the incidence of sudden cardiac death is equal in non-competitive and competitive sports.[105] Clearly more prospective studies are necessary in this field. For now, we feel that sports participation should not be discouraged, but individual advice is crucial.

Sexual functioning

In our study we found that patients with congenital heart disease become sexually active at a significantly older age than the general Dutch population, and both women and men scored lower on sexual functioning scales.[106] This is different from what was reported by Moons et al,[107] who reported a similar frequency of sexual problems in patients with congenital heart disease and healthy controls. Nevertheless, in that study, patients reported to be more distressed by these problems than the healthy controls. In our group, there was no relation between diminished sexual functioning and ventricular function or socio-economic status. In males, the increased erectile and orgasmic dysfunction was not related to the use of medication, for instance beta blocking agents, which we would have expected. Physical sexual development does not seem to be delayed, as the age of menarche was not different from the general population in our female patients. The difference in age of losing virginity becomes even more notable considering the fact that educational levels in our patients were lower than in the general population.[87] A lower educational level is usually associated with losing virginity at a younger age.[106] Perhaps growing up in a more protected - or even overprotected - environment may cause this difference,[108] or anxiety and feelings of insecurity and shame regarding the thoracotomy scar. Insecurity about their scar was noted especially in young female patients in our cohort previously,[109] but appears to have diminished now that the patients are older. Furthermore, anxiety about not being able to perform sexual activities due to their cardiac disease may make patients more hesitative to engage in a sexual relationship. At least, our patients with more complex heart disease reported concerns on not being able to endure pregnancy or to be able to raise children. These anxieties may have contributed to avoiding sexual relationships.

Conclusions, clinical implications and future perspectives

This thesis provides insight in the very long term survival and morbidity in patients that underwent repair of a congenital heart defect (ASD, VSD, PS, Fallot or TGA) in childhood, now up to over 40 years ago. Survival in patients after ASD or PS repair is normal. In patients who survived their VSD of Fallot repair, survival is also good. As expected based on previous reports, survival after Mustard repair of TGA is clearly decreased and we must prepare for an ongoing and possibly accelerating decline.

Most patients with repaired congenital heart defects are leading satisfactory and fairly normal lives, fully participating in society: they have a job, get married, have children and do everything that healthy people do. Sports participation, however, is reduced in comparison with the general population. Because sports participation is related to better exercise tolerance in daily life, as well as better quality of life, we should provide our patients with better information on the safety and benefits of sports participation, and keep stimulating them to implement regular exercise in their daily routine. Specialized

training programs addressing specific patient groups may help to overcome any anxiety towards sports participation and help sustain a good exercise routine and level. In addition, providing more information on specific sexual issues and impact of pregnancy is important for patients and should be implemented in standard care.

Despite the good survival and quality of life, late morbidity is substantial. Additionally, we found deterioration of ventricular function over time in patients in all diagnosis groups. This implies that all patients, even those who had only mild congenital heart defects and are asymptomatic, must remain under follow-up in the outpatient clinic. On top of the growth of our patient population due to the improved survival, this will add to the need for specialist care providers and centers to expand. These care providers must be adequately trained in congenital heart disease, and be aware of any late problems that may occur, even in patients who apparently are doing fine. Unfortunately, sudden (cardiac) death occurred in all groups we studied, and also in patients in whom that was not expected at all. Despite our finding new and confirming known predictors of adverse outcome, individual risk stratification remains difficult. Furthermore, it is impossible to extrapolate our results, observed in patients operated in the first era of congenital heart surgery, to patients operated for the same diagnosis in later eras. The latter underwent different surgeries and nowadays an increasing number of patients is treated percutaneously. We therefore must continue to study the outcome in all different groups of congenital heart disease, after all different ways of repair and treatment.

Despite this interpretation of "old" results and attempting to apply them to the moving target that congenital heart disease still is today, it is fascinating to see that things that we learn from these old cohorts of patients do provide new insights that may be useful today. For example, we probably did not notice subclinical signs of ventricular failure in the past, because we did not have the diagnostic techniques to unmask them yet. In this aspect, biomarkers like NT-proBNP may be useful. Early signs of ventricular decline are being discovered increasingly by new diagnostic tools. There is increasing evidence that systolic ventricular failure is preceded by diastolic ventricular dysfunction. This diastolic dysfunction should and probably can be detected earlier. Tissue Doppler and speckle tracking deformation imaging and evaluation of diastolic ventricular function are upcoming and should be implemented in routine care. However, normal values of diastolic dysfunction in acquired heart disease do not necessarily apply to congenital heart disease. Defect-specific criteria should be developed. Meanwhile, follow-up of changes in the already available criteria should prompt therapeutic action sooner. This too is easier said than done, especially in patients after Mustard repair, in whom effective (medical) treatment strategies currently still do not exist. None of the studies assessing the use of (conventional) medical therapy that were performed so far managed to show any benefit. In all studies, the negative results are feared to be - at least in part - due to small sample sizes. It is always very difficult to collect enough patients to participate.

And maybe we have been addressing the wrong target: possibly failure of a systemic RV is not mainly due to increased afterload. Preload limitations (the inability to increase preload during exercise because of the incompliant atrial baffle tissue) may play an important role as well, or the inevitable development of tricuspid regurgitation. Therefore, we need larger, international, multicenter studies with longer follow-up, in which the changes in diastolic and systolic ventricular function are assessed by state-of the art echocardiography and CMR to adequately assess the effects of afterload reduction and beta-blockers. With regard to determination of diastolic function in congenital heart disease, we need studies relating echocardiographic parameters to invasive measurements, for example pressure-volume loop recordings or invasive end-diastolic pressure measurements. Possibly gadolinium late enhancement CMR may help us to explain why the conventional parameters like E' don't work: we may prove that these measurements are done in patch or scar tissue (for example the VSD patch in Fallot) instead of myocardial tissue.

Regarding the issue of timing of PVR in Fallot patients, we need to add (LV) diastolic function assessment and (RV) contractile reserve measurement to the decision making. With these parameters of ventricular function we should be able to identify those patients who would benefit from PVR before they start to show systolic ventricular dysfunction. The current availability to perform repeat pulmonary valve interventions may facilitate the decision towards earlier PVR, but the concerns on endocarditis after percutaneous pulmonary valve implantation preclude a "one size fits all" guideline.

The problem of inevitable heart failure in Mustard patients remains to be a major issue. Few patients will qualify for interventions on tricuspid regurgitation, for in many the precarious state of their systemic ventricle will increase the perioperative risk unacceptably. In selected patients, pulmonary artery banding may cause a useful shift of the interventricular septum to improve the systemic RV function, but we doubt that this will be an option for many patients. So in the end, we have to screen them for heart transplantation. The timing of when to start this screening is also extremely difficult, as many patients are functioning very well with their poorly contracting systemic RV. Also more attention should be paid to the specific needs of ventricular assist device therapy in patients with congenital heart disease. These patients are often young and may indeed benefit from these new techniques, but anatomic and technical hurdles should be overcome.

Finally, involving patients and patient-organizations in the design and implementation of future research seems logic and important.

REFERENCES

1. Tennant PW, Pearce MS, Bythell M, Rankin J. 20-year survival of children born with congenital anomalies: a population-based study. *Lancet*. 2010;375:649-656.
2. Kirsch RE, Glatz AC, Gaynor JW, Nicolson SC, Spray TL, Wernovsky G, Bird GL. Results of elective repair at 6 months or younger in 277 patients with tetralogy of Fallot: a 14-year experience at a single center. *J Thorac Cardiovasc Surg*. 2014;147:713-717.
3. Tamesberger MI, Lechner E, Mair R, Hofer A, Sames-Dolzer E, Tulzer G. Early primary repair of tetralogy of fallot in neonates and infants less than four months of age. *Ann Thorac Surg*. 2008;86:1928-1935.
4. Barratt-Boyes BG. Cardiac surgery in neonates and infants. *Circulation*. 1971;44:924-925.
5. Jonas RA. Deep hypothermic circulatory arrest: current status and indications. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2002;5:76-88.
6. Birdi I, Caputo M, Underwood M, Bryan AJ, Angelini GD. The effects of cardiopulmonary bypass temperature on inflammatory response following cardiopulmonary bypass. *Eur J Cardiothorac Surg*. 1999;16:540-545.
7. Nollert G, Fischlein T, Bouterwek S, Bohmer C, Klinner W, Reichart B. Long-term survival in patients with repair of tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. *J Am Coll Cardiol*. 1997;30:1374-1383.
8. Norgaard MA, Lauridsen P, Helvind M, Pettersson G. Twenty-to-thirty-seven-year follow-up after repair for Tetralogy of Fallot. *Eur J Cardiothorac Surg*. 1999;16:125-130.
9. Oechslin EN, Harrison DA, Connelly MS, Webb GD, Siu SC. Mode of death in adults with congenital heart disease. *Am J Cardiol*. 2000;86:1111-1116.
10. Pillutla P, Shetty KD, Foster E. Mortality associated with adult congenital heart disease: Trends in the US population from 1979 to 2005. *Am Heart J*. 2009;158:874-879.
11. Kammeraad JA, van Deurzen CH, Sreeram N, Bink-Boelkens MT, Ottenkamp J, Helbing WA, Lam J, Sobotka-Plojhar MA, Daniels O, Balaji S. Predictors of sudden cardiac death after Mustard or Senning repair for transposition of the great arteries. *J Am Coll Cardiol*. 2004;44:1095-1102.
12. Schwerzmann M, Salehian O, Harris L, Siu SC, Williams WG, Webb GD, Colman JM, Redington A, Silversides CK. Ventricular arrhythmias and sudden death in adults after a Mustard operation for transposition of the great arteries. *Eur Heart J*. 2009;30:1873-1879.
13. Puley G, Siu S, Connelly M, Harrison D, Webb G, Williams WG, Harris L. Arrhythmia and survival in patients >18 years of age after the mustard procedure for complete transposition of the great arteries. *Am J Cardiol*. 1999;83:1080-1084.
14. Tweddell JS, Pelech AN, Frommelt PC. Ventricular septal defect and aortic valve regurgitation: pathophysiology and indications for surgery. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu*. 2006:147-152.
15. Pozzi M, Trivedi DB, Kitchiner D, Arnold RA. Tetralogy of Fallot: what operation, at which age. *Eur J Cardiothorac Surg*. 2000;17:631-636.
16. Donmez A, Yurdakok O. Cardiopulmonary bypass in infants. *J Cardiothorac Vasc Anesth*. 2014;28:778-788.

17. Hoashi T, Kagisaki K, Meng Y, Sakaguchi H, Kurosaki K, Shiraishi I, Yagihara T, Ichikawa H. Long-term outcomes after definitive repair for tetralogy of Fallot with preservation of the pulmonary valve annulus. *J Thorac Cardiovasc Surg.* 2014;148:802-808; discussion 808-809.

18. Vida VL, Guariento A, Castaldi B, Sambugaro M, Padalino MA, Milanesi O, Stellin G. Evolving strategies for preserving the pulmonary valve during early repair of tetralogy of Fallot: mid-term results. *J Thorac Cardiovasc Surg.* 2014;147:687-694; discussion 694-686.

19. Mavroudis CD, Frost J, Mavroudis C. Pulmonary valve preservation and restoration strategies for repair of tetralogy of Fallot. *Cardiol Young.* 2014;24:1088-1094.

20. Vida VL, Angelini A, Guariento A, Frescura C, Fedrigo M, Padalino M, Sanders SP, Thiene G, Stellin G. Preserving the pulmonary valve during early repair of tetralogy of Fallot: Anatomic substrates and surgical strategies. *J Thorac Cardiovasc Surg.* 2015;149:1358-1363 e1351.

21. Van Arsdell GS, Maharaj GS, Tom J, Rao VK, Coles JG, Freedom RM, Williams WG, McCrindle BW. What is the optimal age for repair of tetralogy of Fallot? *Circulation.* 2000;102:III123-129.

22. Bakhtiary F, Dahnert I, Leontyev S, Schroter T, Hambsch J, Mohr FW, Kostelka M. Outcome and incidence of re-intervention after surgical repair of tetralogy of fallot. *J Card Surg.* 2013;28:59-63.

23. Puranik R, Tsang V, Lurz P, Muthurangu V, Offen S, Frigiola A, Norman W, Walker F, Bonhoeffer P, Taylor AM. Long-term importance of right ventricular outflow tract patch function in patients with pulmonary regurgitation. *J Thorac Cardiovasc Surg.* 2012;143:1103-1107.

24. Cuypers JA, Witsenburg M, van der Linde D, Roos-Hesselink JW. Pulmonary stenosis: update on diagnosis and therapeutic options. *Heart.* 2013;99:339-347.

25. Baumgartner H, Bonhoeffer P, De Groot NM, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJ, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E, Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of C, Association for European Paediatric C, Guidelines ESCCfP. ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). *Eur Heart J.* 2010;31:2915-2957.

26. Oosterhof T, van Straten A, Vliegen HW, Meijboom FJ, van Dijk AP, Spijkerboer AM, Bouma BJ, Zwinderman AH, Hazekamp MG, de Roos A, Mulder BJ. Preoperative thresholds for pulmonary valve replacement in patients with corrected tetralogy of Fallot using cardiovascular magnetic resonance. *Circulation.* 2007;116:545-551.

27. Therrien J, Provost Y, Merchant N, Williams W, Colman J, Webb G. Optimal timing for pulmonary valve replacement in adults after tetralogy of Fallot repair. *Am J Cardiol.* 2005;95:779-782.

28. Meijboom FJ, Roos-Hesselink JW, McGhie JS, Spitaels SE, van Domburg RT, Utens LM, Simoons ML, Bogers AJ. Consequences of a selective approach toward pulmonary valve replacement in adult patients with tetralogy of Fallot and pulmonary regurgitation. *J Thorac Cardiovasc Surg.* 2008;135:50-55.

29. Miyamura H, Kanazawa H, Hayashi J, Eguchi S. Thrombosed St. Jude Medical valve prosthesis in the right side of the heart in patients with tetralogy of Fallot. *J Thorac Cardiovasc Surg.* 1987;94:148-150.

30. Horer J, Vogt M, Stierle U, Cleuziou J, Prodan Z, Schreiber C, Lange R. A comparative study of mechanical and homograft prostheses in the pulmonary position. *Ann Thorac Surg.* 2009;88:1534-1539.

31. Kogon BE, Rosenblum JM, Mori M. Current Readings: Issues Surrounding Pulmonary Valve Replacement in Repaired Tetralogy of Fallot. *Semin Thorac Cardiovasc Surg.* 2015;27:57-64.

32. Freling HG, van Slooten YJ, van Melle JP, Ebels T, Hoendermis ES, Berger RM, Hillege HL, Waterbolk TW, van Veldhuisen DJ, Willems TP, Pieper PG. Pulmonary valve replacement: twenty-six years of experience with mechanical valvar prostheses. *Ann Thorac Surg.* 2015;99:905-910.

33. Dehaki MG, Ghavidel AA, Omrani G, Javadikasgari H. Long-Term Outcome of Mechanical Pulmonary Valve Replacement in 121 Patients with Congenital Heart Disease. *Thorac Cardiovasc Surg.* 2015;63:367-372.

34. Mokhles MM, van de Woestijne PC, de Jong PL, Witsenburg M, Roos-Hesselink JW, Takkenberg JJ, Bogers AJ. Clinical outcome and health-related quality of life after right-ventricular-outflow-tract reconstruction with an allograft conduit. *Eur J Cardiothorac Surg.* 2011;40:571-578.

35. Sabate Rotes A, Eidem BW, Connolly HM, Bonnichsen CR, Rosedahl JK, Schaff HV, Dearani JA, Burkhart HM. Long-term follow-up after pulmonary valve replacement in repaired tetralogy of Fallot. *Am J Cardiol.* 2014;114:901-908.

36. Mokhles MM, Charitos EI, Stierle U, Rajeswaran J, Blackstone EH, Bogers AJ, Takkenberg JJ, Sievers HH. The fate of pulmonary conduits after the Ross procedure: longitudinal analysis of the German-Dutch Ross registry experience. *Heart.* 2013;99:1857-1866.

37. Fraisse A, Aldebert P, Malekzadeh-Milani S, Thambo JB, Piechaud JF, Aucoururier P, Chatelier G, Bonnet D, Iserin L, Bonello B, Assaidi A, Kammache I, Boudjemline Y. Melody (R) transcatheter pulmonary valve implantation: results from a French registry. *Arch Cardiovasc Dis.* 2014;107:607-614.

38. Malekzadeh-Milani S, Ladouceur M, Patel M, Boughenou FM, Iserin L, Bonnet D, Boudjemline Y. Incidence and predictors of Melody(R) valve endocarditis: a prospective study. *Arch Cardiovasc Dis.* 2015;108:97-106.

39. Patel M, Malekzadeh-Milani S, Ladouceur M, Iserin L, Boudjemline Y. Percutaneous pulmonary valve endocarditis: incidence, prevention and management. *Arch Cardiovasc Dis.* 2014;107:615-624.

40. Boudjemline Y, Brugada G, Van-Aerschot I, Patel M, Basquin A, Bonnet C, Legendre A, Bonnet D, Iserin L. Outcomes and safety of transcatheter pulmonary valve replacement in patients with large patched right ventricular outflow tracts. *Arch Cardiovasc Dis.* 2012;105:404-413.

41. Goldberg SW, Fisher SA, Wehman B, Mehra MR. Adults with congenital heart disease and heart transplantation: optimizing outcomes. *J Heart Lung Transplant.* 2014;33:873-877.

42. Patel CB, Cowger JA, Zuckermann A. A contemporary review of mechanical circulatory support. *J Heart Lung Transplant.* 2014;33:667-674.

43. George RS, Birks EJ, Radley-Smith RC, Khaghani A, Yacoub M. Bridge to transplantation with a left ventricular assist device for systemic ventricular failure after Mustard procedure. *Ann Thorac Surg.* 2007;83:306-308.

44. Maly J, Netuka I, Besik J, Dorazilova Z, Pirk J, Szarszoi O. Bridge to transplantation with long-term mechanical assist device in adults after the Mustard procedure. *J Heart Lung Transplant.* 2015;34:1177-1181.

45. Neely RC, Davis RP, Stephens EH, Takayama H, Khalpey Z, Ginns J, Lee SH, Chen J. Ventricular assist device for failing systemic ventricle in an adult with prior mustard procedure. *Ann Thorac Surg.* 2013;96:691-693.

46. Arendt K, Doll S, Mohr FW. Failing Mustard circulation with secondary pulmonary hypertension: mechanical assist device to achieve reverse pulmonary vascular remodelling for subsequent heart transplantation. *Heart.* 2010;96:1164.

47. Shah D, Azhar M, Oakley CM, Cleland JG, Nihoyannopoulos P. Natural history of secundum atrial septal defect in adults after medical or surgical treatment: a historical prospective study. *Br Heart J.* 1994;71:224-227; discussion 228.

48. Silversides CK, Siu SC, McLaughlin PR, Haberer KL, Webb GD, Benson L, Harris L. Symptomatic atrial arrhythmias and transcatheter closure of atrial septal defects in adult patients. *Heart.* 2004;90:1194-1198.

49. Wilson NJ, Smith J, Prommete B, O'Donnell C, Gentles TL, Ruygrok PN. Transcatheter closure of secundum atrial septal defects with the Amplatzer septal occluder in adults and children-follow-up closure rates, degree of mitral regurgitation and evolution of arrhythmias. *Heart Lung Circ.* 2008;17:318-324.

50. Kaya MG, Baykan A, Dogan A, Inanc T, Gunebakmaz O, Dogdu O, Uzum K, Eryol NK, Narin N. Intermediate-term effects of transcatheter secundum atrial septal defect closure on cardiac remodeling in children and adults. *Pediatr Cardiol.* 2010;31:474-482.

51. Mongeon FP, Burkhart HM, Ammash NM, Dearani JA, Li Z, Warnes CA, Connolly HM. Indications and outcomes of surgical closure of ventricular septal defect in adults. *JACC Cardiovasc Interv.* 2010;3:290-297.

52. Khairy P, Aboulhosn J, Gurvitz MZ, Opotowsky AR, Mongeon FP, Kay J, Valente AM, Earing MG, Lui G, Gersony DR, Cook S, Ting JG, Nickolaus MJ, Webb G, Landzberg MJ, Broberg CS, Alliance for Adult Research in Congenital C. Arrhythmia burden in adults with surgically repaired tetralogy of Fallot: a multi-institutional study. *Circulation.* 2010;122:868-875.

53. Gatzoulis MA, Till JA, Somerville J, Redington AN. Mechanoelectrical interaction in tetralogy of Fallot. QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. *Circulation.* 1995;92:231-237.

54. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosenthal M, Nakazawa M, Moller JH, Gillette PC, Webb GD, Redington AN. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet.* 2000;356:975-981.

55. Hayes CJ, Gersony WM. Arrhythmias after the Mustard operation for transposition of the great arteries: a long-term study. *J Am Coll Cardiol.* 1986;7:133-137.

56. Kanter RJ, Papagiannis J, Carboni MP, Ungerleider RM, Sanders WE, Wharton JM. Radiofrequency catheter ablation of supraventricular tachycardia substrates after mustard and senning operations for d-transposition of the great arteries. *J Am Coll Cardiol.* 2000;35:428-441.

57. Dobson R, Danton M, Nicola W, Hamish W. The natural and unnatural history of the systemic right ventricle in adult survivors. *J Thorac Cardiovasc Surg.* 2013;145:1493-1501; discussion 1501-1493.

58. Opic P, Utens EM, Moons P, Theuns DA, van Dijk AP, Hoendermis ES, Vliegen HW, de Groot NM, Witsenburg M, Schalij M, Roos-Hesselink JW. Psychosocial impact of implantable cardioverter defibrillators (ICD) in young adults with Tetralogy of Fallot. *Clin Res Cardiol.* 2012;101:509-519.

59. Siehr SL, Hanley FL, Reddy VM, Miyake CY, Dubin AM. Incidence and risk factors of complete atrioventricular block after operative ventricular septal defect repair. *Congenit Heart Dis.* 2014;9:211-215.

60. Winter MM, Bouma BJ, Groenink M, Konings TC, Tijssen JG, van Veldhuisen DJ, Mulder BJ. Latest insights in therapeutic options for systemic right ventricular failure: a comparison with left ventricular failure. *Heart.* 2009;95:960-963.

61. Plymen CM, Sado DM, Taylor AM, Bolger AP, Lambiase PD, Hughes M, Moon JC. Diffuse myocardial fibrosis in the systemic right ventricle of patients late after Mustard or Senning surgery: an equilibrium contrast cardiovascular magnetic resonance study. *Eur Heart J Cardiovasc Imaging.* 2013;14:963-968.

62. Babu-Narayan SV, Goktekin O, Moon JC, Broberg CS, Pantely GA, Pennell DJ, Gatzoulis MA, Kilner PJ. Late gadolinium enhancement cardiovascular magnetic resonance of the systemic right ventricle in adults with previous atrial redirection surgery for transposition of the great arteries. *Circulation.* 2005;111:2091-2098.

63. Rathod RH, Prakash A, Powell AJ, Geva T. Myocardial fibrosis identified by cardiac magnetic resonance late gadolinium enhancement is associated with adverse ventricular mechanics and ventricular tachycardia late after Fontan operation. *J Am Coll Cardiol.* 2010;55:1721-1728.

64. Ghai A, Silversides C, Harris L, Webb GD, Siu SC, Therrien J. Left ventricular dysfunction is a risk factor for sudden cardiac death in adults late after repair of tetralogy of Fallot. *J Am Coll Cardiol.* 2002;40:1675-1680.

65. Broberg CS, Aboulhosn J, Mongeon FP, Kay J, Valente AM, Khairy P, Earing MG, Opotowsky AR, Lui G, Gersony DR, Cook S, Ting JG, Webb G, Gurvitz MZ, Alliance for Adult Research in Congenital C. Prevalence of left ventricular systolic dysfunction in adults with repaired tetralogy of fallot. *Am J Cardiol.* 2011;107:1215-1220.

66. Diller GP, Kempny A, Liodakis E, Alonso-Gonzalez R, Inuzuka R, Uebing A, Orwat S, Dimopoulos K, Swan L, Li W, Gatzoulis MA, Baumgartner H. Left ventricular longitudinal function predicts life-threatening ventricular arrhythmia and death in adults with repaired tetralogy of fallot. *Circulation.* 2012;125:2440-2446.

67. Luijnenburg SE, Mekic S, van den Berg J, van der Geest RJ, Moelker A, Roos-Hesselink JW, Bogers AJ, de Rijke YB, Strengers JL, Mulder BJ, Vliegen HW, Helbing WA. Ventricular response to dobutamine stress relates to the change in peak oxygen uptake during the 5-year follow-up in young patients with repaired tetralogy of Fallot. *Eur Heart J Cardiovasc Imaging.* 2014;15:189-194.

68. Babu-Narayan SV, Kilner PJ, Li W, Moon JC, Goktekin O, Davlouros PA, Khan M, Ho SY, Pennell DJ, Gatzoulis MA. Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of fallot and its relationship to adverse markers of clinical outcome. *Circulation.* 2006;113:405-413.

69. Dusenbery SM, Jerosch-Herold M, Rickers C, Colan SD, Geva T, Newburger JW, Powell AJ. Myocardial extracellular remodeling is associated with ventricular diastolic dysfunction in children and young adults with congenital aortic stenosis. *J Am Coll Cardiol.* 2014;63:1778-1785.

70. Kempny A, Diller GP, Orwat S, Kaleschke G, Kerckhoff G, Bunck A, Maintz D, Baumgartner H. Right ventricular-left ventricular interaction in adults with Tetralogy of Fallot: a combined cardiac magnetic resonance and echocardiographic speckle tracking study. *Int J Cardiol.* 2012;154:259-264.

71. Dragulescu A, Friedberg MK, Grosse-Wortmann L, Redington A, Mertens L. Effect of chronic right ventricular volume overload on ventricular interaction in patients after tetralogy of Fallot repair. *J Am Soc Echocardiogr.* 2014;27:896-902.

72. Ahmad N, Kantor PF, Grosse-Wortmann L, Seller N, Jaeggi ET, Friedberg MK, Mertens L. Influence of RV restrictive physiology on LV diastolic function in children after tetralogy of Fallot repair. *J Am Soc Echocardiogr.* 2012;25:866-873.

73. Menting ME, Eindhoven JA, van den Bosch AE, Cuypers JA, Ruys TP, van Dalen BM, McGhie JS, Witsenburg M, Helbing WA, Geleijnse ML, Roos-Hesselink JW. Abnormal left ventricular rotation and twist in adult patients with corrected tetralogy of Fallot. *Eur Heart J Cardiovasc Imaging.* 2014;15:566-574.

74. Friedberg MK, Cho MY, Li J, Assad RS, Sun M, Rohailla S, Honjo O, Apitz C, Redington AN. Adverse biventricular remodeling in isolated right ventricular hypertension is mediated by increased transforming growth factor-beta1 signaling and is abrogated by angiotensin receptor blockade. *Am J Respir Cell Mol Biol.* 2013;49:1019-1028.

75. Craig RJ, Selzer A. Natural history and prognosis of atrial septal defect. *Circulation.* 1968;37:805-815.

76. Dragulescu A, Grosse-Wortmann L, Redington A, Friedberg MK, Mertens L. Differential effect of right ventricular dilatation on myocardial deformation in patients with atrial septal defects and patients after tetralogy of Fallot repair. *Int J Cardiol.* 2013;168:803-810.

77. Klitsie LM, Kuipers IM, Roest AA, Van der Hulst AE, Stijnen T, Hazekamp MG, Blom NA, Ten Harkel AD. Disparity in right vs left ventricular recovery during follow-up after ventricular septal defect correction in children. *Eur J Cardiothorac Surg.* 2013;44:269-274.

78. Gersony WM, Hayes CJ, Driscoll DJ, Keane JF, Kidd L, O'Fallon WM, Pieroni DR, Wolfe RR, Weidman WH. Bacterial endocarditis in patients with aortic stenosis, pulmonary stenosis, or ventricular septal defect. *Circulation.* 1993;87:I121-126.

79. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, Veen G, Stappers JL, Grobbee DE, Mulder BJ. Turning 18 with congenital heart disease: prediction of infective endocarditis based on a large population. *Eur Heart J.* 2011;32:1926-1934.

80. Rushani D, Kaufman JS, Ionescu-Ittu R, Mackie AS, Pilote L, Therrien J, Marelli AJ. Infective endocarditis in children with congenital heart disease: cumulative incidence and predictors. *Circulation.* 2013;128:1412-1419.

81. Knirsch W, Nadal D. Infective endocarditis in congenital heart disease. *Eur J Pediatr.* 2011;170:1111-1127.

82. Nothroff J, Norozi K, Alpers V, Arnhold JO, Wessel A, Ruschewski W, Buchhorn R. Pacemaker implantation as a risk factor for heart failure in young adults with congenital heart disease. *Pacing Clin Electrophysiol.* 2006;29:386-392.

83. De Sisti A, Marquez MF, Tonet J, Bonny A, Frank R, Hidden-Lucet F. Adverse effects of long-term right ventricular apical pacing and identification of patients at risk of atrial fibrillation and heart failure. *Pacing Clin Electrophysiol.* 2012;35:1035-1043.

84. Janousek J. Cardiac resynchronisation in congenital heart disease. *Heart.* 2009;95:940-947.

85. Motonaga KS, Dubin AM. Cardiac resynchronization therapy for pediatric patients with heart failure and congenital heart disease: a reappraisal of results. *Circulation.* 2014;129:1879-1891.

86. Rekawek J, Kansy A, Miszczak-Knecht M, Manowska M, Bieganowska K, Brzezinska-Paszke M, Szymaniak E, Turska-Kmiec A, Maruszewski P, Burczynski P, Kawalec W. Risk factors for cardiac arrhythmias in children with congenital heart disease after surgical intervention in the early postoperative period. *J Thorac Cardiovasc Surg.* 2007;133:900-904.

87. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Psychosocial functioning of the adult with congenital heart disease: a 20-33 years follow-up. *Eur Heart J.* 2003;24:673-683.

88. Opic P, Roos-Hesselink JW, Cuypers JA, Witsenburg M, van den Bosch A, van Domburg RT, Bogers AJ, Utens EM. Psychosocial functioning of adults with congenital heart disease: outcomes of a 30-43 year longitudinal follow-up. *Clin Res Cardiol.* 2015;104:388-400.

89. Kamphuis M, Ottenkamp J, Vliegen HW, Vogels T, Zwinderman KH, Kamphuis RP, Verloove-Vanhorick SP. Health related quality of life and health status in adult survivors with previously operated complex congenital heart disease. *Heart.* 2002;87:356-362.

90. Moons P, De Bleser L, Budts W, Sluysmans T, De Wolf D, Massin M, Gewillig M, Pasquet A, Suys B, Vliers A. Health status, functional abilities, and quality of life after the Mustard or Senning operation. *Ann Thorac Surg.* 2004;77:1359-1365; discussion 1365.

91. Fteropoulli T, Stygall J, Cullen S, Deanfield J, Newman SP. Quality of life of adult congenital heart disease patients: a systematic review of the literature. *Cardiol Young.* 2013;23:473-485.

92. Bruto VC, Harrison DA, Fedak PW, Rockert W, Siu SC. Determinants of health-related quality of life in adults with congenital heart disease. *Congenit Heart Dis.* 2007;2:301-313.

93. Reybrouck T, Mertens L. Physical performance and physical activity in grown-up congenital heart disease. *Eur J Cardiovasc Prev Rehabil.* 2005;12:498-502.

94. Miller TD, Balady GJ, Fletcher GF. Exercise and its role in the prevention and rehabilitation of cardiovascular disease. *Ann Behav Med.* 1997;19:220-229.

95. Fleg JL, Cooper LS, Borlaug BA, Haykowsky MJ, Kraus WE, Levine BD, Pfeffer MA, Pina IL, Poole DC, Reeves GR, Whellan DJ, Kitzman DW, National Heart L, Blood Institute Working G. Exercise training as therapy for heart failure: current status and future directions. *Circ Heart Fail.* 2015;8:209-220.

96. Dean PN, Gillespie CW, Greene EA, Pearson GD, Robb AS, Berul CI, Kaltman JR. Sports participation and quality of life in adolescents and young adults with congenital heart disease. *Congenit Heart Dis.* 2015;10:169-179.

97. van der Bom T, Winter MM, Knaake JL, Cervi E, de Vries LS, Balducci A, Meregalli PG, Pieper PG, van Dijk AP, Bonvicini M, Mulder BJ, Bouma BJ. Long-term benefits of exercise training in patients with a systemic right ventricle. *Int J Cardiol.* 2015;179:105-111.

98. Dulfer K, Duppen N, Kuipers IM, Schokking M, van Domburg RT, Verhulst FC, Helbing WA, Utens EM. Aerobic exercise influences quality of life of children and youngsters with congenital heart disease: a randomized controlled trial. *J Adolesc Health.* 2014;55:65-72.

99. Duppen N, Takken T, Hopman MT, ten Harkel AD, Dulfer K, Utens EM, Helbing WA. Systematic review of the effects of physical exercise training programmes in children and young adults with congenital heart disease. *Int J Cardiol.* 2013;168:1779-1787.

100. Hirth A, Reybrouck T, Bjarnason-Wehrens B, Lawrenz W, Hoffmann A. Recommendations for participation in competitive and leisure sports in patients with congenital heart disease: a consensus document. *Eur J Cardiovasc Prev Rehabil.* 2006;13:293-299.

101. Budts W, Borjesson M, Chessa M, van Buuren F, Trigo Trindade P, Corrado D, Heidbuchel H, Webb G, Holm J, Papadakis M. Physical activity in adolescents and adults with congenital heart defects: individualized exercise prescription. *Eur Heart J.* 2013;34:3669-3674.

102. Moons P, De Volder E, Budts W, De Geest S, Elen J, Waeytens K, Gewillig M. What do adult patients with congenital heart disease know about their disease, treatment, and prevention of complications? A call for structured patient education. *Heart.* 2001;86:74-80.

103. Vaseghi M, Ackerman MJ, Mandapati R. Restricting sports for athletes with heart disease: are we saving lives, avoiding lawsuits, or just promoting obesity and sedentary living? *Pediatr Cardiol.* 2012;33:407-416.

104. Maron BJ, Zipes DP. Introduction: eligibility recommendations for competitive athletes with cardiovascular abnormalities-general considerations. *J Am Coll Cardiol.* 2005;45:1318-1321.

105. Risgaard B, Winkel BG, Jabbari R, Glinge C, Ingemann-Hansen O, Thomsen JL, Ottesen GL, Haunso S, Holst AG, Tfelt-Hansen J. Sports-related sudden cardiac death in a competitive and a noncompetitive athlete population aged 12 to 49 years: data from an unselected nationwide study in Denmark. *Heart Rhythm.* 2014;11:1673-1681.

106. Bakker F, Vanwesenbeeck I. Sexuele gezondheid in Nederland 2006. Rutgers Nisso Groep. Delft: Eburon; 2006.

107. Moons P, Van Deyk K, Marquet K, De Bleser L, Budts W, De Geest S. Sexual functioning and congenital heart disease: Something to worry about? *Int J Cardiol.* 2007;121:30-35.

108. Ong L, Nolan RP, Irvine J, Kovacs AH. Parental overprotection and heart-focused anxiety in adults with congenital heart disease. *Int J Behav Med.* 2011;18:260-267.

109. van Rijen EH, Utens EM, Roos-Hesselink JW, Meijboom FJ, van Domburg RT, Roelandt JR, Bogers AJ, Verhulst FC. Medical predictors for psychopathology in adults with operated congenital heart disease. *Eur Heart J.* 2004;25:1605-1613.

PART 4

Epilogue

List of publications

1. Schwagten B, Cuypers J, Szili-Torok T. The magnetic navigation system allows avoidance of puncturing a baffle during ablation of a postincisional macroreentrant tachycardia. *Cardiol Young*. 2009 Apr;19(2):216-9.

2. Moltzer E, Roos-Hesselink JW, Yap SC, Cuypers JA, Bogers AJ, de Jaegere PP, Witsenburg M. Endovascular stenting for aortic (re)coarctation in adults. *Neth Heart J*. 2010 Sep;18(9):430-6.

3. Altındag T, Roos-Hesselink JW, Cuypers JA, van Domburg R, de Jaegere PP, Meijboom FJ, Witsenburg M. Transcatheter device closure of atrial septal defects in patients aged 40 years and older. *Neth Heart J*. 2010 Nov;18(11):537-42.

4. van der Linde D, Yap SC, van Dijk AP, Budts W, Pieper PG, van der Burgh PH, Mulder BJ, Witsenburg M, Cuypers JA, Lindemans J, Takkenberg JJ, Roos-Hesselink JW. Effects of rosuvastatin on progression of stenosis in adult patients with congenital aortic stenosis (PROCAS Trial). *Am J Cardiol*. 2011 Jul 15;108(2):265-71.

5. Akca F, Bauernfeind T, Witsenburg M, Dabiri Abkenari L, Cuypers JA, Roos-Hesselink JW, de Groot NM, Jordaens L, Szili-Torok T. Acute and long-term outcomes of catheter ablation using remote magnetic navigation in patients with congenital heart disease. *Am J Cardiol*. 2012 Aug 1;110(3):409-14

6. Cuypers JA, Witsenburg M, van der Linde D, Roos-Hesselink JW. Pulmonary stenosis: update on diagnosis and therapeutic options. *Heart*. 2013 Mar;99(5):339-47.

7. Rossi A, van der Linde D, Yap SC, Lapinskas T, Kirschbaum S, Springeling T, Witsenburg M, Cuypers J, Moelker A, Krestin GP, van Dijk A, Johnson M, van Geuns RJ, Roos-Hesselink JW. Ascending aorta dilatation in patients with bicuspid aortic valve stenosis: a prospective CMR study. *Eur Radiol*. 2013 Mar;23(3):642-9.

8. Ruys TP, van der Bosch AE, Cuypers JA, Witsenburg M, Helbing WA, Bogers AJ, van Domburg R, McGhie JS, Geleijnse ML, Henrichs J, Utens E, Van der Zwaan HB, Takkenberg JJ, Roos-Hesselink JW. Long-term outcome and quality of life after arterial switch operation: a prospective study with a historical comparison. *Congenit Heart Dis*. 2013 May-Jun;8(3):203-10.

9. Opić P, Roos-Hesselink JW, Cuypers JA, Witsenburg M, van den Bosch A, van Domburg RT, Bogers AJ, Utens EM. Sexual functioning is impaired in adults with congenital heart disease. *Int J Cardiol*. 2013 Oct 9;168(4):3872-7.

10. Cuypers JA, Opić P, Menting ME, Utens EM, Witsenburg M, Helbing WA, van den Bosch AE, Ouhlous M, van Domburg RT, Meijboom FJ, Bogers AJ, Roos-Hesselink JW. The unnatural history of an atrial septal defect: longitudinal 35 year follow up after surgical closure at young age. *Heart*. 2013 Sep;99(18):1346-52.

11. Eindhoven JA, van den Bosch AE, Ruys TP, Opić P, Cuypers JA, McGhie JS, Witsenburg M, Boersma E, Roos-Hesselink JW. N-terminal pro-B-type natriuretic peptide and its relationship with cardiac function in adults with congenital heart disease. *J Am Coll Cardiol*. 2013 Sep 24;62(13):1203-12.

12. Menting ME, Eindhoven JA, van den Bosch AE, Cuypers JA, Ruys TP, van Dalen BM, McGhie JS, Witsenburg M, Helbing WA, Geleijnse ML, Roos-Hesselink JW. Abnormal left ventricular rotation and twist in adult patients with corrected tetralogy of Fallot. *Eur Heart J Cardiovasc Imaging*. 2014 May;15(5):566-74.

13. Younge JO, Eindhoven JA, Utens EW, Opić P, Cuypers JA, van den Bosch AE, Witsenburg M, van Domburg RT, Hunink MG, Roos-Hesselink JW. Association between N-terminal pro-brain natriuretic peptide and quality of life in adult patients with congenital heart disease. *Cardiol Young*. 2015 Feb;25(2):288-94

14. Cuypers JA, Eindhoven JA, Slager MA, Opić P, Utens EM, Helbing WA, Witsenburg M, van den Bosch AE, Ouhlous M, van Domburg RT, Rizopoulos D, Meijboom FJ, Bogers AJ, Roos-Hesselink JW. The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years. *Eur Heart J*. 2014 Jul 1;35(25):1666-74.

15. Eindhoven JA, Menting ME, van den Bosch AE, Cuypers JA, Ruys TP, Witsenburg M, McGhie JS, Boersma E, Roos-Hesselink JW. Associations between N-terminal pro-B-type natriuretic peptide and cardiac function in adults with corrected tetralogy of Fallot. *Int J Cardiol*. 2014 Jul 1;174(3):550-6.

16. Eindhoven JA, Menting ME, van den Bosch AE, McGhie JS, Witsenburg M, Cuypers JA, Boersma E, Roos-Hesselink JW. Quantitative assessment of systolic right ventricular function using myocardial deformation in patients with a systemic right ventricle. *Eur Heart J Cardiovasc Imaging*. 2015 Apr;16(4):380-8.

17. Cuypers JA, Menting ME, Konings EE, Opić P, Utens EM, Helbing WA, Witsenburg M, van den Bosch AE, Ouhlous M, van Domburg RT, Rizopoulos D, Meijboom FJ, Boersma E, Bogers AJ, Roos-Hesselink JW. Unnatural history of tetralogy of Fallot: prospective follow-up of 40 years after surgical correction. *Circulation*. 2014 Nov 25;130(22):1944-53.

18. Menting ME, van den Bosch AE, McGhie JS, Cuypers JA, Witsenburg M, Geleijnse ML, Helbing WA, Roos-Hesselink JW. Ventricular myocardial deformation in adults after early surgical repair of atrial septal defect. *Eur Heart J Cardiovasc Imaging*. 2015 May;16(5):549-57.

19. Opić P, Roos-Hesselink JW, Cuypers JA, Witsenburg M, van den Bosch A, van Domburg RT, Bogers AJ, Utens EM. Psychosocial functioning of adults with congenital heart disease: outcomes of a 30-43 year longitudinal follow-up. *Clin Res Cardiol*. 2015 May;104(5):388-400.

20. Eindhoven JA, Roos-Hesselink JW, van den Bosch AE, Kardys I, Cheng JM, Veenis JF, Cuypers JA, Witsenburg M, van Schaik RH, Boersma E. High-sensitive troponin-T in adult congenital heart disease. *Int J Cardiol.* 2015 Apr 1;184:405-11.

21. Brugts JJ, Cuypers JA, Polak P, Ouhlous M, van de Woestijne P, Wessels M, Roos-Hesselink J. Quadricuspid aortic valve and anomalous systemic venous connection in a patient with cat-eye syndrome. *Circulation*. 2015 Mar 31;131(13):1225-7.

22. Opić P, Utens EM, Cuypers JA, Witsenburg M, van den Bosch A, van Domburg R, Bogers AJ, Boersma E, Pelliccia A, Roos-Hesselink JW. Sports participation in adults with congenital heart disease. *Int J Cardiol*. 2015 May 6;187:175-82.

23. Menting ME, Cuypers JA, Opić P, Utens EM, Witsenburg M, van den Bosch AE, van Domburg RT, Meijboom FJ, Boersma E, Bogers AJ, Roos-Hesselink JW. The unnatural history of the ventricular septal defect: outcome up to 40 years after surgical closure. *J Am Coll Cardiol*. 2015 May 12;65(18):1941-51.

24. Opić P, Roos-Hesselink JW, Cuypers JA, Witsenburg M, van den Bosch A, van Domburg RT, Bogers AJ, Utens EM. Longitudinal development of psychopathology and subjective health status in

CHD adults: a 30- to 43-year follow-up in a unique cohort. *Cardiol Young*. 2015 Jun 16:1-9. [Epub ahead of print]

25. Menting ME, van den Bosch AE, McGhie JS, Eindhoven JA, Cuypers JA, Witsenburg M, Geleijnse ML, Helbing WA, Roos-Hesselink JW. Assessment of ventricular function in adults with repaired Tetralogy of Fallot using myocardial deformation imaging. *Eur Heart J Cardiovasc Imaging*. 2015 Jul 29.[Epub ahead of print]

26. Eindhoven JA, van den Bosch AE, Oemrawsingh RM, Baggen VJ, Kardys I, Cuypers JA, Witsenburg M, van Schaik RH, Roos-Hesselink JW, Boersma E. Release of growth-differentiation factor 15 and associations with cardiac function in adult patients with congenital heart disease. *Int J Cardiol*. 2015 Sep 14;202:246-251.

Nederlandse samenvatting

Aangeboren hartafwijkingen zijn de meest voorkomende aangeboren afwijkingen. Ze komen voor bij ongeveer 8 per duizend levendgeborenen. Ongeveer de helft van deze kinderen heeft een milde afwijking waarvoor geen onmiddellijke behandeling nodig is. De andere helft heeft wel op jonge leeftijd een operatie nodig. Voordat hartchirurgie voor aangeboren hartafwijkingen mogelijk werd, overleed het merendeel van deze kinderen op jonge leeftijd, vaak al in het eerste levensjaar. Slechts zo'n 15% haalde de volwassenleeftijd. Dankzij de introductie van hartchirurgie in de vijftiger jaren is de overleving van deze patiënten spectaculair verbeterd. Van de kinderen die tegenwoordig met een hartafwijking geboren worden, bereikt 95% de volwassen leeftijd. Dit heeft geleid tot een sterke groei van het aantal patiënten met een(geopereerde) aangeboren hartafwijking, en deze patiënten worden gelukkig ook steeds ouder. Hierdoor is de nadruk in de zorg voor deze patiënten verschoven van overleven naar kwaliteit van leven. Het wordt steeds belangrijker om te weten met welke late complicaties en problemen ze te maken zouden kunnen krijgen en hoe ze een optimaal leven kunnen leiden.

Dit proefschrift behandelt de lange termijn resultaten na operatie van een aangeboren hartafwijking opgedeeld in vijf verschillende patiëntengroepen, te weten:

- **atriumseptumdefect**: een gat in het tussenschot van de boezems van het hart,
- **ventrikelseptumdefect**: een gat in het tussenschot van de kamers,
- **pulmonaalstenose**: vernauwing van de longslagaderklep,
- **tetralogie van Fallot**: een meer complexe hartafwijking, waarbij er een combinatie is van onder andere ventrikelseptumdefect en pulmonaalstenose, en
- **transpositie van de grote vaten**, waarbij de aorta en longslagader uit de verkeerde hartkamer komen en er dus zuurstofarm in plaats van zuurstofrijk bloed in de lichaamscirculatie terecht komt.

Deze patiënten werden allemaal op jonge leeftijd (<15 jaar) in Rotterdam geopereerd tussen 1968 en 1980 en worden elke tien jaar gevolgd. In het huidige onderzoek hebben we voor het eerst ook geprobeerd om voorspellers voor uitkomsten te identificeren, aangezien de follow-up duur nu de veertig jaar nadert.

In hoofdstuk 2 worden de lange termijn uitkomsten beschreven bij patiënten die werden geopereerd aan een **atriumseptumdefect** (ASD). Het is bekend dat als zo'n ASD niet gesloten wordt, op de lange termijn vaak boezemritmestoornissen en pulmonale hypertensie (hoge bloeddruk in de longbloedvaten) ontstaan. Uit ons onderzoek blijkt dat de patiënten die op kinderleeftijd chirurgische sluiting van hun ASD ondergingen een zo goed als normale overleving hebben (91% na 40 jaar follow-up). Zij hebben weinig nieuwe ingrepen nodig en boezemritmestoornissen komen bij deze patiënten

veel minder vaak voor dan bij patiënten waar het ASD niet is gesloten. Ook pulmonale hypertensie blijkt te worden voorkomen door sluiting van het ASD op kinderleeftijd. Ondanks deze gunstige resultaten zijn er wel twee van de 131 patiënten uit onze groep plots overleden, mogelijk aan een ritmestoornis. Daarnaast heeft een derde van de patiënten een verminderde rechter kamerfunctie en een vijfde een licht verminderde linker kamerfunctie na 40 jaar follow-up. Hoewel geen van de patiënten hartfalen heeft ontwikkeld, blijft het wel belangrijk om deze patiënten, met wie het over het algemeen dus heel goed gaat, levenslang te controleren.

Hoofdstuk 3 beschrijft de lange termijn resultaten bij patiënten die werden geopereerd aan een **ventrikelseptumdefect** (VSD). Ook bij een ongecorrigeerd VSD is er grote kans op ontwikkeling van pulmonale hypertensie en achteruitgang van de pompfunctie van het hart op de lange termijn. De overleving in ons cohort is met 78% na 40 jaar significant minder goed dan in de algemene bevolking. Dit komt vooral doordat de sterfte rondom de operatie aanzienlijk was, waarschijnlijk ten gevolge van het vroege chirurgische tijdperk waarin deze patiënten werden geopereerd: destijds was er aanzienlijk minder ervaring met dit soort operaties en waren de medische apparaten die erbij gebruikt werden veel minder ontwikkeld dan nu. Tegenwoordig is de perioperatieve sterfte veel lager. Desalniettemin hebben ook de patiënten die de operatie overleefden geen helemaal normale overleving (86% na 40 jaar). Doodsoorzaken zijn plotse dood, reoperaties voor bijkomende hartafwijkingen en hartfalen. Een aanzienlijk deel van de patiënten (28%) heeft na 40 jaar follow-up een complicatie gehad. Zo kreeg 13% een ritmestoornis en 12% had een nieuwe ingreep nodig. Hoewel de patiënten zeer tevreden zijn met hun dagelijks leven en fysieke prestaties, heeft toch de helft een verminderd inspanningsvermogen. De linker kamerfunctie nam niet af over de tijd, maar de rechter kamerfunctie verslechterde wel. Hierbij kan interactie tussen de twee hartkamers een rol spelen. Daarnaast was er een toename in aortakleplekkage. Hoewel tot nu toe slechts 4% van de patiënten werkelijk hartfalen kreeg, maken de achteruitgang in kamerfunctie en de toename van aortakleplekkage ook in deze patiënten levenslange follow-up noodzakelijk.

Hoofdstuk 4 is een review over **pulmonaalstenose** (PS). Zo'n PS kan zich bevinden op, onder of boven het niveau van de klep. Aanvankelijk was de behandeling van alle belangrijke pulmonaalstenosen een operatie, maar tegenwoordig worden vernauwingen op klepniveau bij voorkeur behandeld met een ballondilatatie. Voorheen moest de diagnose ernstige PS worden gesteld met een hartcatheterisatie, maar tegenwoordig kan dat met een echo of MRI van het hart. De resultaten op de lange termijn van zowel klepoperatie als ballondilatatie zijn goed, maar niet helemaal te vergelijken, want de follow-up van klepoperaties is langer, omdat deze ingreep al langer gedaan wordt. Beide

behandelmogelijkheden kunnen echter in de loop van de tijd leiden tot pulmonaalkleplekkage. Deze lekkage wordt heel lang goed verdragen, maar kan uiteindelijk wel leiden tot overbelasting van de rechter kamer waardoor de kamerfunctie kan verslechteren. Daarom moeten ook patiënten met pulmonaalkleplekkage na eerdere correctie van hun pulmonaalklepstenose onder controle blijven op de polikliniek. Zij hebben mogelijk in de toekomst een nieuwe klepingreep nodig, zoals bij Fallotpatiënten, een andere hartafwijking met ook lekkage van de pulmonaalklep al uitgebreid bekend is.

In hoofdstuk 5 beschrijven we de lange-termijn uitkomsten van de patiënten die op kinderleeftijd chirurgische correctie ondergingen van een **pulmonaalklepstenose**. Zij hebben een overleving die vergelijkbaar is met de algemenen bevolking (93% na 40 jaar). Na 40 jaar heeft echter wel een kwart van hen een nieuwe ingreep nodig gehad. In de eerste decennia na de operatie was dat vooral vanwege een nieuwe klepvernauwing, maar vanaf de 2^{e} decade was dat vooral vanwege ernstige kleplekkage. Deze patiënten hebben niet vaak boezemritmestoornissen en tot nu toe helemaal geen kamerritmestoornissen. Ze hebben, vinden ze zelf, een goede kwaliteit van leven en kunnen zich net zo goed inspannen als een ander. Ook in deze groep vonden we echter achteruitgang in zowel linker als rechter kamerfunctie, en verminderde linker kamerfunctie bleek gerelateerd aan een verminderd inspanningsvermogen.

In hoofdstuk 6 worden de resultaten 40 jaar na chirurgische correctie van de **tetralogie van Fallot** beschreven. De overleving van deze patiënten is duidelijk minder dan in de algemene bevolking (72% na 40 jaar). Ook in deze groep was de perioperatieve sterfte destijds behoorlijk, maar de overleving van patiënten die hun operatie goed hebben doorstaan is vrij goed (86% na 40 jaar). We kunnen echter niet ontkennen dat ook bij hen de overleving niet helemaal normaal is. Late sterfte is het gevolg van hartfalen en kamerritmestoornissen. Ook hebben veel patiënten restproblemen: 44% had een nieuwe ingreep nodig, 17% had last van ritmestoornissen en 3% ontwikkelde hartfalen. Er is een geleidelijke achteruitgang in zowel rechter als linker systolische kamerfunctie en ook de diastolische linker kamerfunctie is bij veel patiënten inmiddels afgenomen. Progressieve dilatatie van de aorta werd gevreesd maar blijkt in de praktijk geen groot probleem. De verslechtering in functie van linker en rechter kamer kan, in ieder geval gedeeltelijk, verklaard worden door interactie tussen deze twee kamers. Er zijn ook aanwijzingen dat de "contractiele reserve" van de hartkamers verminderd is: bij deze patiënten hebben we met dobutamine stress MRI daarnaar gekeken en hoewel de systolische functie van beide kamers verbeterde na toediening van een lage dosis dobutamine, trad geen verdere verbetering op na toediening van een hoge dosis dobutamine. Desondanks is het inspanningsvermogen van de Fallotpatiënten relatief goed (89% van de norm) en is dat stabiel gebleven over de afgelopen tien jaar.

Hoofdstuk 7 beschrijft de bevindingen in onze patiënten die een **Mustard operatie** hebben ondergaan ter behandeling van **transpositie van de grote** vaten. In deze groep was de overleving duidelijk minder dan normaal: 68% is na 40 jaar nog in leven. Dit kwam niet als een grote verrassing. Het was reeds bekend dat de functie van de rechter kamer, die bij deze patiënten (ten gevolge van hun atriale ompoling) als systeemkamer moet functioneren, vaak al achteruit is gegaan tegen de tijd dat deze patiënten de volwassen leeftijd hebben bereikt. De verwachting was dat deze verslechtering van systeemkamerfunctie zou doorzetten, en onze studie bevestigt dat inderdaad. De overleving was echter toch minder slecht dan werd gevreesd. In de voorgaande decade was sterfte met name het gevolg van hartfalen, maar in de afgelopen tien jaar overleden patiënten met name door kamerritmestoornissen. Nieuwe ingrepen waren met name nodig voor vernauwingen of lekken in de "baffles", de constructie die door de chirurg werd gemaakt om het bloed op boezemniveau naar de andere kamer te leiden. Deze nieuwe ingrepen waren met name nodig in de eerste 2 decennia na Mustardoperatie, en zijn nadien geen groot probleem meer. Wel is er een geleidelijke toename in tricuspidaliskleplekkage (lekkage van de hartklep tussen de boezem en de rechter kamer), die gelijk op gaat met verdere afname van de systeem rechter kamerfunctie. Onze bevindingen bij MRI lijken deze afgenomen functie van de systeem rechter kamerfunctie te bevestigen, hoewel het lastig is om precieze uitspraken te doen omdat er eigenlijk geen normaalwaarden bekend zijn voor een rechter ventrikel die als systeemkamer functioneert. We zagen verder een verdubbeling in het optreden van boezemritmestoornissen in de laatste tien jaar. Dat baart zorgen, omdat ook deze - normaliter milde - ritmestoornissen wel geassocieerd zijn met plotse hartdood in deze patiënten. We vonden geen toename van kamerritmestoornissen op Holter-registraties, maar er waren wel 5 patiënten die daar last van kregen en twee zijn er zelfs aan overleden. Er zijn geen duidelijke criteria voor handen voor preventieve implantatie van een intracardiale defibrillator (ICD) ter bescherming. Deze patiënten zijn relatief jong en hebben vaak ook boezemritmestoornissen waardoor ze meer kans hebben op onterechte ICD-shocks, wat psychisch heel belastend kan zijn. Ook is er zorg om eventuele leadcomplicaties. Pacemakers zijn daarentegen wel vaker nodig in Mustardpatiënten, vooral vanwege sinusknoopdysfunctie. In toenemende mate tonen de patiënten in onze studie wel tekenen van sinusknoopdysfunctie, maar het afgelopen decennium leidde dat niet tot implantatie van veel meer pacemakers. Ondanks alle hierboven beschreven late problemen is de inspanningstolerantie van de patiënten de laatste 10 jaar opvallend stabiel gebleven en vinden ze zelf hun eigen kwaliteit van leven heel goed.

In hoofdstuk 8 en 9 komen twee belangrijke aspecten van kwaliteit van leven aan bod die tot nu toe bij patiënten met aangeboren hartafwijkingen sterk onderbelicht zijn

gebleven, namelijk sporten en seksueel functioneren. Het is bekend dat patiënten met een aangeboren hartafwijking gemiddeld een lager opleidingsniveau, een baan op een lager niveau en een lager inkomen hebben dan de algemene bevolking. Zij hebben ook meer psychologische problemen op jonge leeftijd, maar deze problemen lijken zich op te lossen met het stijgen van de leeftijd. Zijn er, nu de patiënten dertigers en veertigers zijn, ook meer problemen bij sporten en/of in seksueel functioneren dan in de algemene bevolking?

In hoofdstuk 8 hebben we **sportparticipatie** en de klinische gevolgen daarvan onderzocht in onze patiënten met chirurgisch gecorrigeerd ASD, VSD, pulmonaalstenose, tetralogie van Fallot en na Mustardoperatie voor transpositie van de grote vaten. Voorheen werd deze patiënten vaak ontraden om te sporten, omdat gevreesd werd dat dat gevaarlijk voor hen zou kunnen zijn. Er is nog steeds vrees dat zware fysieke inspanning bij deze patiënten kan leiden tot ritmestoornissen of andere complicaties, zelfs plotse dood. Anderzijds is tegenwoordig zelfs bij patiënten met hartfalen aangetoond dat lichaamsbeweging en training gezond is: het verbetert ook bij hen de conditie en kwaliteit van leven. In onze studie hebben we geen verband gevonden tussen deelname aan sport en (plotse) dood. Bijna de helft van de patiënt deed aan sport. Dit is minder dan in de normale bevolking. Zoals we eigenlijk al verwachtten deden de patiënten met meer complexe hartafwijkingen het minst aan sport, en als ze aan sport deden dan was dat op een minder intensief niveau dan de anderen. De patiënten die wel aan sport deden hadden een beter uithoudingsvermogen, een gezondere leefstijl en, bij degenen met een meer complexe hartafwijking zelfs een beter fysiek functioneren dan zij die niet aan sport deden. Er waren daarnaast ook aanwijzingen dat de kamerfunctie vaker stabiel bleef bij patiënten die sporten. Dit is een belangrijke bevinding, aangezien in alle diagnosen een geleidelijke achteruitgang in kamerfunctie is beschreven. Om deze potentieel gunstige effecten van sporten beter te doorgronden en onze patiënten beter te kunnen adviseren, is meer onderzoek naar het effect en de veiligheid van sporten bij patiënten met een aangeboren hartafwijking hard nodig.

In hoofdstuk 9 beschrijven we het **seksuele functioneren** bij patiënte met een aangeboren hartafwijking. De meerderheid van de patiënten is getrouwd en seksueel actief. Vergeleken met de algemene bevolking scoorden zowel de vrouwelijke als de mannelijke patiënten slechter in de vragenlijsten naar seksueel functioneren: vrouwelijke patiënten rapporteerden een scala aan problemen, waaronder verminderde behoefte aan seks, minder makkelijk opgewonden raken en meer pijn bij het vrijen. Echt pathologische seksuele dysfunctie kwam echter bij de vrouwelijke patiënten even vaak voor als bij vrouwen in de algemene bevolking. Mannelijke patiënten rapporteerden meer erectiestoornissen, meer orgasmeproblemen en meer ontevredenheid over ge-

slachtsgemeenschap. Vrouwelijke patiënten hadden vaker last van onzekerheid betreffende zwangerschap en de erfelijkheid van hun aangeboren hartafwijking. Met name de vrouwen met meer complexe hartafwijkingen waren bezorgd dat hun hartafwijking een negatief effect zou kunnen hebben op hun kind. Ten aanzien van de zwangerschap en bevalling zelf waren ze bang dat dat een negatief effect zou kunnen hebben op hun hartfunctie en algemene conditie. Vrijwel alle patiënten gaven aan dat ze graag meer informatie hadden gehad over deze zaken en ook over de veiligheid en eventuele nadelige effecten van de verschillende methoden van anticonceptie. Omdat sommige patiënten overmatig of onterecht bezorgd zijn, en andere zich misschien onvoldoende bewust zijn de risico's van een zwangerschap, moeten onze patiënten betere voorlichting krijgen over seksualiteit, zwangerschap en erfelijkheid. Deze informatie moet tijdig worden gegeven, bij voorkeur al op een jonge leeftijd, voordat seksualiteit en zwangerschap aan de orde zijn in hun dagelijks leven.

Hoofdstuk 10 beschrijft de lange-termijn uitkomsten na de **arteriële switch operatie** (ASO), ofwel de ompoling van de grote vaten zelf. Dit is de nu gangbare behandeling voor patiënten die geboren worden met transpositie van de grote vaten. Er wordt een historische vergelijking gemaakt met de Mustardpatiënten. Het grote voordeel van de ASO is dat de linker kamer de systeemkamer wordt, zoals bij een normaal hart ook het geval is. Overleving tot 25 jaar na ASO is duidelijk beter dan na de Mustardoperatie (97% versus 77%), en bij 93% bleef de linkerkamerfunctie goed (tegenover een goede rechterkamerfunctie bij slechts 6% van de Mustardpatiënten). Dit werd ook weerspiegeld in een veel beter inspanningsvermogen bij de ASO-patiënten vergeleken met de Mustardpatiënten, hoewel ook bij de ASO-patiënten het inspanningsvermogen minder was dan normaal (85% van de norm bij ASO-patiënten versus 72% van de norm bij Mustardpatiënten). Hoewel verscheidene ASO-patiënten een nieuwe ingreep nodig hadden en één van hen kamerritmestoornissen had, was de event-vrije overleving bij de ASO-patiënten duidelijk beter dan in de Mustardgroep (77% versus 44%).

PhD Portfolio

Summary of PhD training and teaching activities

Name PhD student: Judith A.A.E. Cuypers	**PhD period: 2009-2015**
Erasmus MC Department: Cardiology	**Promotors: J.W. Roos-Hesselink, A.J.J.C. Bogers**
Research School: COEUR	**Supervisor: J.W. Deckers**

1. PhD training

	Year	Workload (Hours)
General academic skills		
- BROK course	2015	20
Research skills		
- Short Introductory Course on Statistics & Survival Analysis for MD's	2010	6
In-depth courses		
- COEUR Research seminars	2009-2015	20
- Advanced Life Support	2013	12
Presentations		
- ESC Oral Abstract presentation (2x)	2012-2013	4
- ESC Poster Abstract presentation (2x)	2014-2015	2
- NVVC Voorjaarsvergadering	2015	6
National and International conferences		
- 4th European Echocardiography course on congenital heart disease	2009	20
- European Society of Cardiology	2009, 2011-2015	144
- Cardiac Problems in Pregnancy, Valencia	2010	24
- EuroEcho	2010	19
- NVVC congresses	2010-2015	75
- 10th European Echocardiography course on congenital heart disease	2015	20
Seminars and workshops		
- Harttransplantatie Rotterdam, een donorhart voor de baby en de babyboomer?	2009	6
- Tour d' Horizon	2009, 2014	21
- Ontwikkeling hart	2010	20
- Symposium Acute Coronaire Syndromen	2010	6
- Acute myocardial infarction: the next decade	2010	4
- Cardiology and Vascular Medicine Update and Perspective	2010, 2011	27
- Karel V Symposium (5x)	2010, 2012-2015	30
- Cardiovascular Magnetic resonance Munich, Germany	2011	14
- Mini Symposium Hypertrofische Cardiomyopathie	2011	2
- Thoracale aortapathologie - nieuwe inzichten , actuele behandeling	2011, 2013	10
- 22nd International Symposium on Adult Congenital Heart Disease	2012	30
- Afscheidssymposium Dr. A.H.M.M. Balk	2012	5
- Update hypertrofische cardiomyopathie en contrastecho	2013	4
- Symposium Congenitale Cardiologie	2013	5
- Fifth European meeting on Adult Congenital Heart Disease	2014	22

2. Teaching activities

	Year	Workload (Hours)
Lecturing		
- Lectures affiliated hospitals (4)	2009-2012	4
- RISK/PKV-onderwijs	2009-2015	24
- COEUR congenital heart disease	2009-2015	5
- Minor congenitale cardiologie	2010-2015	4
- Verpleegkundige & hartfunctie congressen	2010-2015	4
- ESMRMB Hands-on MRI course	2011	1
- Advanced Echo Course on Congenital Cardiology	2012, 2014	2
- IC-onderwijs	2012	1
- Summer Med School	2012	1
- Symposium Congenitale Cardiologie	2012	1
- Assistentenonderwijs	2013-2014	2
- Symposium acute cardiologie Dordrecht	2015	0,75

Curriculum vitae

Judith Anne Adriane Ellen Cuypers is geboren op 21 oktober 1973 in Heeze. Na haar eindexamen in 1992 aan het Augustinianum te Eindhoven studeerde zij Geneeskunde aan de Universiteit van Maastricht. Zij behaalde het doctoraal examen in augustus 1998, waarna zij begon als assistent Cardiologie in het Academisch Ziekenhuis Maastricht. In 2000 startte zij daar met de opleiding Cardiologie (Opleider professor dr. H.J.J. Wellens). De interne vooropleiding deed zij in het Rijnland Ziekenhuis te Leiderdorp (Opleider dr. F. Cluitmans), waar zij vervolgens bleef voor het B-jaar Cardiologie. Zij vervolgde haar opleiding tot Cardioloog in het Leids Universitair Medisch Centrum (Opleider professor dr. E. E. van der Wall). Op 1 oktober 2006 werd zij geregistreerd als Cardioloog.

Van oktober 2006 tot juli 2007 werkte zij als Cardioloog bij de Hartrevalidatie van het Bronovo Ziekenhuis in Den Haag. Sinds medio juli 2007 is zij staflid in het Erasmus MC, waar zij zich verder specialiseerde in de aangeboren hartafwijkingen.

Zij is getrouwd met Onno Hendriks en samen hebben zij een zoon: Bram (9 jaar).

Dankwoord

Dan is het boek klaar en denk je dat je er bent. Vervolgens blijkt het laatste – misschien wel meest gelezen- hoofdstuk nog best een klus. Want hoewel promoveren op het laatst voor een groot gedeelte bestaat uit monomaan en eenzaam achter de computer zitten werken, was dit boek er niet gekomen zonder de hulp, op vele fronten, van velen. Hier volgt een poging om hen allemaal te bedanken.

Allereerst wil ik mijn grote waardering uitspreken voor alle patiënten die aan deze studie hebben meegewerkt. Zonder hun bereidheid om al die verschillende onderzoeken te ondergaan en vele vragenlijsten, sommige over heel persoonlijke zaken, in te vullen, was dit proefschrift er überhaupt niet geweest.

Mijn promotoren, professor Jolien Roos-Hesselink en professor Ad Bogers, dank ik voor de gelegenheid dit mooie en klinisch zeer relevante onderzoek te mogen doen. Jolien, als klinisch dokter "pur sang" was promoveren niet altijd al mijn primaire levensdoel, maar toen je mij de gelegenheid bood om dit onderzoek te gaan doen heb ik die kans met beide handen aangegrepen. Jouw gedrevenheid werkt zeer stimulerend, en voor het combineren van research met klinisch werk, gezin en ook nog een sociaal leven heb je mij het goede voorbeeld gegeven. Daarnaast maakt jouw grote inzet het team congenitale cardiologie tot een productieve en toch zeer gezellige en collegiale groep. Ad, jij straalt altijd rust en vertrouwen uit en wist ondanks je drukke agenda steeds genoeg tijd te maken om mij met weinig maar weloverwogen woorden weer een stap verder te helpen. Van zaken zoals het samen napluizen van historische en soms slecht leesbare operatieverslagen heb ik dingen geleerd die in geen enkel leerboek te vinden zijn. Jolien en Ad, dank voor jullie vertrouwen in mij en de geweldige samenwerking bij het verwezenlijken van dit mooie doel.

De leden van de kleine commissie, prof. dr. Werner Budts, prof. dr. Wim Helbing en prof. dr. Felix Zijlstra, dank ik voor het kritisch lezen en beoordelen van mijn proefschrift, en ook prof. dr. Jaap Deckers en prof. dr. Mark Hazekamp dank ik voor hun bereidheid plaats te nemen in de grote commissie.

Mijn meest directe collega's Annemien van den Bosch en Maarten Witsenburg, congenitale sparring partners, werkvrienden, kritische mede-auteurs van mijn manuscripten, dank dat jullie het mij de afgelopen jaren mogelijk hebben gemaakt om tijd vrij te maken om aan het onderzoek te besteden. Mede dankzij jullie bereidheid om klinische zaken over te nemen is me dat gelukt. Sorry dat ik het de laatste maanden over bijna niets anders meer had..

Mijn andere mede-auteurs, Folkert Meijboom, Lisbeth Utens Ron van Domburg, Mohamed Ouhlous, Lisanne Konings, Maarten Slager, Eric Boersma, Dimitris Rizopoulos en Sara Baart, dank ik voor hun zeer gewaardeerde wetenschappelijke input en kritische commentaar. Folkert, zonder jou was de Quality of Life studie er niet geweest. Dank dat je mij – samen met Jolien - naar Rotterdam hebt gehaald! Lisbeth, dankzij jou kijkt onze studie er niet alleen naar de medisch uitkomsten na kinderhartchirurgie, maar ook naar de minstens zo belangrijke uitkomsten op psychosociaal gebied. Jouw toch net wat andere kijk op de zaak werkt verfrissend. Dank voor jouw altijd opbouwende kritiek en vriendelijke suggesties. Ron, het was vaak ver terugzoeken, maar dankzij jouw goede contacten bij het GBA en CBS en niet te vergeten het roemruchte CLINT hebben we toch maar mooi alle oude gegevens weer boven water gekregen. Eric, Dimitris, Sara en hierbij ook niet te vergeten Elena Rosalina Andrinopoulou (Elrozi), met alleen de basiscursus statistiek op zak was ik er nooit gekomen. Dank jullie voor het geduld om samen tot een ook voor verstokte clinici begrijpelijke weergave van de resultaten te komen, terwijl we soms vanuit twee tegengestelde richtingen op dezelfde golflengte moesten zien te raken. Maarten en Lisanne, dank voor het helpen invoeren en analyseren van alle gegevens, jullie hulp aan de basis heeft mij een heel eind op weg geholpen. Mo, het is maar goed dat ik vooraf niet vermoedde dat het tekenen van al die MRI's zo'n enorme klus zou zijn..

Dan mijn kamergenoten van BA-308, van heden en verleden: Titia, Denise, Petra, Jannet, John, Myrthe, Iris, Vivan en Allard en ook de wisselende samenstelling van studenten, jullie houden het ondanks de drukte in ons kippenhok altijd gefocussed en toch gezellig. Myrthe, jij verdient als mijn " number one tweede auteur" de meeste credits, maar jullie allemaal functioneren als helpdesk bij writers block, statistiekperikelen, onbegrijpelijke Word-eigenaardigheden, en zo nodig ook als klaagmuur. Veel van jullie hebben mij links of rechts ingehaald en hebben reeds de doctorstitel. Ik ben blij dat ik dan op gebied van medische zaken jullie hier en daar nog wat kan leren. Nog een speciaal woord van dank voor mijn Quality of Life 3 counterpart Petra Opić: jij hebt ervoor gezorgd dat alle deelnemers aan onze studie vloeiend van het ene naar het andere onderzoek werden geloodst, dat mijn laptop het EMC-systeem aankon, en ondertussen was je al zo'n beetje doctor voordat je dokter was. En nu ga je naar Zwitserland om te worden opgeleid tot intensivist, ik wens jou daar een prachttijd en een geweldige carrière.

Vele anderen hebben bijgedragen aan de uitvoering van mijn studie: mijn dank aan alle echolaboranten, in het bijzonder Jackie McGhie, Marian Blum en Ellen Wiegers, die al die uitgebreide studie-echo's hebben gemaakt; aan alle hartfunctielaboranten en MRI-laboranten voor het vaak doen van extra moeite om alles voor elkaar te krijgen. Nienke en Sjoerd, samen hebben wij ons in alle dobu-stress staande gehouden.

Onze secretaresses Celeste Manley en Tineke van der Kolk, dank voor jullie onmisbare plan- en regelwerk om de studie in goede banen te leiden, en natuurlijk voor jullie moral support! En niet te vergeten René Frowijn voor het maken van al die mooie figuren voor in artikelen, presentaties en dit boek.

Dank aan al mijn collega cardiologen van polikliniek, afdelingen en subspecialisaties, die met teveel zijn om hier stuk voor stuk bij naam te noemen. Het is met jullie allemaal erg prettig samenwerken en naast de serieuze zaken is er gelukkig ook ruimte voor een lach en zelfs – mocht dat nodig zijn - een traan. Dit geldt zeker ook voor mijn collega's van de thoraxchirurgie, kindercardiologie en niet te vergeten de cardiovasculaire radiologen.

Mijn paranimfen, Thomas Wierema en Michelle Michels. Thomas, jou ken ik ondertussen al veel langer wèl dan niet. We gaan terug tot de allereerste onderwijsgroep in Maastricht en ondertussen blijken ook onze gezinnen het uitstekend met elkaar te kunnen vinden. Ik vind het een eer dat je vandaag hier naast me wil staan. Michelle, jij ligt een heel promotietraject op me voor en ik heb veel geleerd van jouw ervaringen. Bijna jaloersmakend hoe georganiseerd jij altijd bent, en dank dat ik daar voor deze dag ook gebruik van mocht maken. Samen naar huis fietsen houdt ons op de hoogte en fit, hoewel.. we moeten nodig weer eens naar de sportschool!

Lieve mam en pap, jullie hebben mij altijd gesteund en gestimuleerd om het beste uit mezelf te halen. Jullie hebben altijd het volste vertrouwen gehad in mij, soms meer dan ikzelf. Altijd zetten jullie alles opzij om hier in Rotterdam bij te springen als dat nodig is. Daarvoor kan ik jullie niet genoeg danken. Maurits en Simone, mijn al lang niet meer zo kleine broer en zus. Jullie zijn er altijd om bij eventuele tegenslagen de boel eens goed te relativeren. Dank voor jullie gezelligheid en afleiding.

Liefste Onno en Bram, jullie houden mij met beide benen op de grond en helpen mij eraan herinneren dat er zoveel meer is dan werken in het leven. Toch zijn jullie voor mijn werk echte Rotterdammers geworden, dat had tevoren niemand kunnen dromen. Hoewel, Feyenoord-fan waren jullie al. Met zijn drietjes zijn wij een sterk team. Onno, je hebt wel eens beweerd dat je wel huisman kon worden "als je vrouw eenmaal een dik cardiologensalaris verdiende…" De afgelopen jaren begon het daar wat betreft de verdeling van de thuistaken wel wat op te lijken. Dank voor je liefde en steun!