Weaning from the ventilator in patients with respiratory failure

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Aan Marian,
aan mijn kinderen

Contents

Chapter 1

General Introduction

1. Introduction

Weaning from the ventilator is the gradual withdrawal of mechanical ventilatory support (1). Mechanical ventilation is well-accepted as rescue therapy in patients with life-threatening respiratory failure. As this treatment is associated with substantial morbidity and mortality, ventilatory support is only considered beneficial when applied during a limited period [2]. In many patients however weaning from the ventilator is a cumbersome process. In this chapter the issues related to the weaning process will be discussed.

Firstly, the cardio-pulmonary diseases present before the acute respiratory failure necessitating ventilatory support, will be reviewed with emphasis on respiratory function before the critical illness. The nutritional status of the patients will be discussed, as this is known to affect the clinical course during ventilatory support and weaning.

Secondly, the conditions leading to the institution of mechanical ventilation will be discussed with emphasis on the pathophysiology of the acute respiratory failure. The effects of mechanical ventilation on respiratory muscle function as well as the effects of critical illness on body composition will be considered.

Finally, factors related to the withdrawal of ventilatory support as respiratory load and neuromuscular function will be elucidated. The term "weaning" is most properly applied to the withdrawal of ventilatory support in those patients in whom recovery from respiratory failure is incomplete. In such patients the effects of nutritional support on the weaning process with respect to respiratory muscle function and metabolism will be considered.

It should be underlined that the definition of weaning excludes the abrupt discontinuation of mechanical ventilation applied in patients in whom the original cause of acute respiratory failure has completely resolved [1, 3]. In these patients spontaneous breathing can be resumed and ventilatory support can be discontinued at once without the risk of respiratory failure.

2. Pre-existing cardio-pulmonary diseases

Difficult weaning from the ventilator is frequently encountered in patients with pre-existing cardio-pulmonary diseases. This applies particularly to patients suffering from severe chronic obstructive pulmonary disease (COPD) or severe congestive heart failure (CHF).

The limited pulmonary reserves of these patients contribute to the acute respiratory insufficiency leading to ventilatory support and subsequently affect the ability to resume spontaneous breathing after a period of mechanical ventilation.

Studies using scoring systems in intensive care patients have revealed that the impact of chronic health problems on the survival of an acute illness is hard to assess [4]. Limited data are available to establish the effects of pre-existing cardio-pulmonary diseases on the process of withdrawal of ventilatory support.

The predictive value of lung function tests has been studied in patients with pulmonary disease. In patients with COPD, lung function tests obtained prior to the acute respiratory failure leading to ventilatory support, were found to predict the clinical course [2]. Both weaning from the ventilator and survival after the period of mechanical ventilation were correlated with the premorbid FEV_1-value [5]. The duration of ventilatory support however did not correlate with the FEV_1-value, but did correlate with the premorbid level of activity.

In patients with severe CHF mechanical ventilation is applied as supportive treatment for cardiogenic pulmonary edema. Although ventilatory support can restore oxygenation in these patients, this treatment can critically disturb the delicate cardio-pulmonary equilibrium. After the patient has been stabilized hemodynamically during the mechanical ventilatory support, weaning attempts can provoke pulmonary edema by a sudden increase in the preload of the left ventricle [6]. As pulmonary congestion causes the lungs to be stiffer, the workload of the respiratory muscles will increase and weaning attempts will lead to muscle fatigue. Variables of cardiac function have been examined to predict the outcome of weaning from the ventilator in patients after cardiac surgery [7]. Preoperative cardiac function tests proved to be poor predictors of respiratory adequacy [7]. A limited number of patients was on long-term ventilatory support after surgery in this study,

which might have affected the results.

3. Nutritional status prior to the start of mechanical ventilation

The nutritional status of patients prior to surgery or severe illness is known to affect clinical outcome. In the classic investigation of Studley, preoperative weight loss was highly predictive of outcome after gastric surgery [8]. In patients operated for chronic peptic ulcer disease, a preoperative weight loss of more than 20 per cent was associated with a postoperative mortality rate of 33 per cent in contrast to a rate of 3.5 per cent among those who had lost less weight.

In patients with COPD the occurrence of acute respiratory failure was found to be related to the nutritional status [9]. Two groups of patients with COPD admitted to the hospital were compared: one group with acute respiratory failure to such a degree that ventilatory support was required and a second group with pulmonary infection without respiratory failure. Significant differences in nutritional status were found between the two groups: malnutrition was mainly present in the patients with acute respiratory failure [9]. In another study examining patients with acute respiratory failure of varying etiology, malnutrition was frequently encountered and malnourished patients requiring ventilatory support had a significantly higher mortality than well-nourished patients requiring mechanical ventilation [10]. Although in these studies a relationship between respiratory failure and malnutrition was established, they did not attempt to dissociate cause from effect.

Malnutrition is known to affect respiratory function in different ways. These effects include altered pulmonary defense mechanisms, decreased ventilatory drive and weakened respiratory muscles. Malnourished childeren were found to have marked reductions in secretory IgA in respiratory fluids, as well as low serum levels of complement [11]. Healthy volunteers were shown to have a substantial reduction in their ventilatory response to hypoxia after a ten days of calorie restriction [12].

The relationship between nutritional status and respiratory muscles has been elegantly elucidated by studies on diaphragms obtained at necropsies. In one investigation diaphragm muscle mass was related to body weight obtained in patients with a variety of disease excluding COPD, obesity and overt

edema [13]. In underweight patients diaphragm muscle mass was significantly lower than in a group of normal weight patients who died suddenly of trauma or poisoning. A highly significant linear relationship was found between diaphragm muscle mass and body weight. In another study, patients with morphometrically graded emphysema had lower body and diaphragm weights compared to patients without emphysema [14]. These data suggest that malnutrition affects diaphragm muscle mass in the same way as it does other skeletal muscle.

In agreement with these results, underweight patients without pulmonary disease were found to have substantially reduced respiratory muscle strength [15]. This muscle weakness was shared almost equally among the inspiratory and expiratory muscles. Consequently, the respiratory muscle capacity to handle increased ventilatory loads in pulmonary disease may well be impaired in malnourished patients.

4. Conditions leading to ventilatory support

Taking into account the wide variety of conditions leading to ventilatory support, it is appropriate to describe the causes of acute respiratory failure according to the underlying pathophysiological mechanisms. This approach is preferable as the withdrawal of ventilatory support can be considered as an exercise requiring reversal of the factors that led to the respiratory failure. Two types of acute respiratory failure can be distinguished [2]:

1) Acute hypoxemic respiratory failure

   This type of respiratory failure results from airspace filling or collapse leading to hypoxemia as venous blood traverses non-ventilated units and mixes with flow traversing well-ventilated alveoli. Major causes for hypoxemic respiratory failure are pulmonary edema, pneumonia, atelectasis and pulmonary hemorrhage.

2) Alveolar hypoventilation

   This type of respiratory failure results from the inability of the respiratory system to maintain alveolar ventilation sufficiently to eliminate the carbon dioxide produced by the tissues. Hypoxemia develops as alveolar P,O_2 falls in accordance with a rising alveolar P,CO_2. The pathophysiological mechanisms leading to alveolar

hypoventilation are diminished ventilatory drive, neuromuscular weakness and increased ventilatory load leading to respiratory muscle fatigue.

A third type of respiratory failure has been described, referred to as "perioperative" respiratory failure. This type of respiratory failure is a multifactorial form of respiratory insufficiency. Atelectasis due to collapse of airways when the end-expiratory lung volume decreases below the closing volume, increased mechanical load imposed by pulmonary and abdominal pathology and neuromuscular weakness synergize to produce hypoxemia and alveolar hypoventilation. This type of respiratory failure is frequently encountered in elderly postoperative patients, especially after abdominal surgery.

Although hypoxemia is a prerequisite for the diagnosis of respiratory failure, hypoxemia per se does not constitute an indication for mechanical ventilation; even severe hypoxemia can in most cases be reversed by oxygen therapy. Mechanical ventilation is indicated in life-threatening respiratory failure, when hypoxemia is associated with alveolar hypoventilation. In conditions as pulmonary edema and pneumonia a decreased lung compliance is found, leading to an increase in the elastic work load. In the "perioperative" respiratory failure an increased work of breathing is also found, associated with the collapse of the dependent airways during expiration. When after a period of full ventilatory support, discontinuation of mechanical ventilation is attempted, the initial respiratory failure is of paramount importance. The persistence of an increased mechanical work load coupled with a reduced respiratory muscle strength precludes early withdrawal of ventilatory support in many patients. Although the abnormalities in gas exchange and lung mechanics can be corrected during the period of ventilatory support, no supportive treatment is available to improve respiratory muscle function. The effects of mechanical ventilation on respiratory muscle function have not been elucidated, but it has been suggested that these effects are comparable to the changes in limb muscles due to detraining [16]. The time course of changes in skeletal muscle succinate dehydrogenase (SDH) and cytochrome oxidase has been studied in healthy volunteers during detraining after an 8 weeks period of endurance

training [17]. In these subjects who had not been engaged in any regular physical training during the preceding year, the activity of the oxidative enzymes increased significantly during the training period. During detraining the cytochrome oxidase activity returned to pre-training levels within 2 weeks; the SDH activity decreased to pre-training levels at 6 weeks. These data indicate a high turnover rate of oxidative enzymes in the tricarboxylic acid cycle as well as the respiratory chain and are considered to have wide implications on respiratory muscle function during ventilatory support [18].

5. Catabolic illness during ventilatory support

Patients ventilated for acute respiratory failure as part of a critical illness are frequently catabolic, associated with a variety of clinical events. These alterations include hypermetabolism, immunosuppression characterized by an increase in the frequency of nosocomial infections and protein breakdown leading to a loss of muscle mass and a decrease in wound healing [19]. In such patients other factors such as prolonged bed rest and the use of curarization may contribute to the body protein loss. The catabolism of skeletal muscle protein has been ascribed to the actions of endogeneously produced mediators [20, 21]. Up till now, no treatment is available to prevent this protein breakdown. It has been demonstrated with sophisticated techniques, such as body composition measurements, that aggressive nutritional support does not prevent substantial losses of body protein in critically ill patients [22].

The effects of critical illness on respiratory muscle function in the short-term have been studied in animal models. Pneumococcal sepsis induced in rats impaired diaphragmatic contractility within 3 days without affecting muscle mass [23]. The effects of endotoxic shock have been studied in a dog model. In spontaneously breathing endotoxemic dogs respiratory muscle blood flow was found to increase to nearly 9% of cardiac output, compared to 2% in mechanically ventilated animals [24]. This increased respiratory muscle blood flow was associated with a threefold increase in diaphragmatic oxygen consumption, which was out of proportion to the increase in ventilatory load of the respiratory muscles.

6. Withdrawal of ventilatory support: respiratory muscle load and function

Although withdrawal of mechanical ventilatory support can fail for a variety of reasons, the most common cause is an imbalance between the level of ventilation needed by the patient and the ability of the patient's respiratory system to respond [18]. The level of ventilation required is related to the CO_2-production of the tissues, the central respiratory drive and the measure of "dead space" ventilation. Elevated CO_2-production leads to an increase in minute ventilation and respiratory rate by ventilatory control mechanisms. The CO_2-production is known to rise due to an increase in metabolic rate as can be found in fever or in psychosis with agitation. Nutritional therapy is another means of modulating CO_2-production [25].

The work required of the respiratory muscles for ventilation is determined by the impedance of the respiratory system. The respiratory muscles work against two main forces:

1. elastic forces resulting from the distension of the tissues of the lung and chest wall, when a volume change occurs
2. flow-resistive forces offered by the airways to the flow of gas and viscous energy dissipation in the tissues [26].

Since expiration is usually passive, no muscle forces are needed during quiet breathing and only the inspiratory work is considered. Inertial forces which are small in comparison to the elastic and flow-resistive forces, are usually neglected.

The energy required for ventilation is determined by the ratio of the work performed by the respiratory muscles (W) and the mechanical efficiency of these muscles (E): W/E [27]. The energy required for ventilation can be estimated by measuring the oxygen cost of breathing ($V'O_2$,resp) as a substitute. The $V'O_2$,resp can be obtained by measuring the oxygen uptake during a period of mechanical ventilation and a subsequent period of spontaneous breathing: the difference in oxygen uptake is considered to be the $V'O_2$,resp [28]. An increase in work rate or a decrease in efficiency of the respiratory muscles will increase the $V'O_2$,resp. This was studied thirty years ago in spontaneously breathing subjects, in whom the extra oxygen consumption associated with an added respiratory work load was measured [29]. The increase in oxygen uptake per unit added respiratory work load

was found to be considerably greater in patients with emphysema than in normal subjects. Consequently the calculated efficiency of the respiratory muscles was higher in normal subjects when compared with patients with emphysema: the efficiency amounted to 8% in normal subjects against 2% in patients with emphysema.

Respiratory muscle fatigue, defined as the inability to generate the pressure required for an adequate alveolar ventilation, can also be described in terms of energy expenditure, work and efficiency [27]. Respiratory muscle fatigue can occur when the rate of oxygen consumption of the muscle is limited by the oxygen supplied by the muscle blood flow. Respiratory muscle fatigue will develop when the ratio of work to the efficiency of respiratory muscle exceeds the energy available by oxygen supply. All three variables can reduce endurance time: increased work of breathing, low rate of oxygen supply or low energy stores and low efficiency of the respiratory muscles. The endurance time is the time a subject can sustain an adequate alveolar ventilation before respiratory muscle fatigue develops.

Useful information on respiratory muscle fatigue has been obtained when, during resistive breathing, transdiaphragmatic pressures were compared to the maximum transdiaphragmatic pressure that could be generated [30]. The critical transdiaphragmatic pressure measured at the functional residual capacity, above which the diaphragm became fatigued, was about 40% of the maximum. Although respiratory muscle fatigue has predominantly been studied in healthy subjects during resistive breathing, the application of this concept seems attractive in patients weaning from the ventilator. Failure to wean from mechanical ventilation can be expected, when the ratio between the transdiaphragmatic pressures during spontaneous breathing and the maximum transdiaphragmatic pressure generated against an occlusion exceeds 0.4.

7. Respiratory measurements in patients weaning from the ventilator

In order to study the various aspects of respiration in patients in whom weaning is attempted, several methods are described. The most important are the measurements of ventilatory drive, work of breathing, oxygen cost of breathing and respiratory muscle strength.

1. Ventilatory drive

Several methods to estimate ventilatory drive in spontaneously breathing subjects have been described in the past. These methods include the mean inspiratory flow rate and the ventilatory response to carbon dioxide [31]. These methods are however unable to differentiate between patients who do not respond adequately because of central or neuromuscular inadequacy and patients who cannot respond because of mechanical abnormalities as airway obstruction or decreased compliance of the respiratory system [32]. Therefore these techniques are of limited value when applied in patients weaning from the ventilator.

The pressure developed at 0.1 second after an occluded inspiration has been introduced as simple technique to estimate inspiratory neuromuscular drive [32]. It is assumed that this pressure represents the force generated by the inspiratory muscles in a more or less isometric contraction under the same respiratory neural stimulus as an unobstructed breath. Hence, the P 0.1 is considered to be a useful index that corresponds to the neuronal drive and the effectiveness of inspiratory muscle contraction without being affected by flow resistance or compliance of the respiratory system. This pressure is however affected by the lung volume because of the changing geometry of the respiratory system and the force-length relationship of the inspiratory muscles. Although this technique can only differentiate patients with an increased neuromuscular drive from those with a "normal" drive, P 0.1 is considered an important prognostic sign of weaning outcome in ventilated patients [33, 34].

2. Work of breathing

The work required by the respiratory muscles to inflate the whole respiratory system can be estimated by using the Campbell approach [35]. In a diagram the change in esophageal pressure is plotted against the change in volume. The change in esophageal pressure in relation to atmospheric pressure is used in order to obtain changes in transthoracic wall pressure. In the pressure-volume diagram a line is drawn between the values of the esophageal pressure at end-

inspiration and end-expiration; the slope of this line represents the dynamic lung compliance (CL, dyn). A second line is drawn in the diagram representing the pressure-volume relationship of the chest wall. The two lines intersect at functional residual capacity. According to the Campbell approach the total inspiratory work is estimated by measuring the area enclosed between the pressure-volume loop during inspiration and the relaxation curve of the chest wall [35].

Considering this approach, it should be established whether expiration really ends at functional residual capacity. It is well-established that frequently in patients with COPD the expiration ends at a lung volume exceeding the functional residual capacity due to the elevated expiratory airway resistance. This condition leads to the presence of a positive alveolar pressure at end-expiration, a pressure known as intrinsic positive end-expiratory pressure or intrinsic PEEP [36].

Firstly, intrinsic PEEP was described in ventilated patients with COPD when the expiration time set by the ventilator was too short to expire to the level of the functional residual capacity [36]. Subsequently the presence of intrinsic PEEP was also established in spontaneously breathing patients with COPD [37, 38].

When expiration ends at a lung volume above the functional residual capacity, the line representing chest wall compliance does not intersect in the pressure-volume diagram the line representing lung compliance at end-expiration. Therefore this condition should be considered in the estimation of work of breathing: intrinsic PEEP acts as an inspiratory threshold during spontaneous breathing [37].

3. Oxygen cost of breathing

The energy required for ventilation can be estimated by measuring the oxygen uptake ($V'O_2$) during mechanical ventilation and a subsequent period of spontaneous breathing: the difference in $V'O_2$ is called oxygen cost of breathing or $V'O_2$,resp [28]. Considering this approach, it is assumed that the respiratory muscles are completely at rest during mechanical ventilation and their activity during spontaneous breathing causes for the most part the increase in $V'O_2$. Both assumptions have been challenged. After discontinuation of ventilatory support, heart

rate and cardiac output rise in most cases. This is associated with an increase in oxygen uptake of the cardiac muscle. Stress and agitation are also frequently encountered during weaning, leading to a rise in oxygen uptake of the other skeletal muscles.

Consequently, the determination of $V'O_2$,resp in patients weaning from the ventilator has only limited value and is not suitable for the purpose of predicting weaning outcome [39, 40].

4. Respiratory muscle strength

Respiratory muscle strength can be assessed by measuring maximum inspiratory and expiratory pressures against an occlusion [15]. In order to obtain the maximum pressures, these measurements should be performed at residual volume (RV) for the inspiratory and at total lung capacity (TLC) for the expiratory pressure. As in patients weaning from the ventilator these conditions cannot be fulfilled, in these patients measurements are usually done at end-expiration and end-inspiration respectively. The maximum inspiratory pressure against an occluded airway (Pimax) has primarily been studied. In patients with acute respiratory failure due to COPD, low levels of Pimax are commonly encountered. The reduced inspiratory muscle strength in these patients should partially be explained by the elevated lung volumes at end-expiration. This hyperinflation results in mechanical dysfunction of the inspiratory muscles [41]. In those patients the clinical value of Pimax is limited as lung volumes cannot be assessed during the measurements of inspiratory muscle strength. It is also well-known that the value of Pimax to predict weaning outcome is rather limited [42]. This can be explained by the fact that Pimax is a measure of strength and not of endurance. Strength is defined as the ability to develop force against resistance in a single contraction against endurance as the ability to exercise for long periods before the onset of fatigue [43]. It is clear that a measure of strength as Pimax has only limited value in predicting the onset of fatigue during a long period of spontaneous breathing.

8. Nutritional support and weaning from the ventilator

In patients weaning from the ventilator nutritional therapy should strongly be considered as supportive treatment. Patients with acute respiratory failure leading to ventilatory support are often initially malnourished or become malnourished secondary to the critical illness, resulting in a prolonged period of mechanical ventilation. Malnutrition present at the start of the weaning attempts may affect weaning outcome due to its adverse effects on lung function.

There is ample evidence that nutritional support can improve respiratory function in malnourished patients. These effects of nutrition have been studied primarily in patients who were malnourished, but had no signs of pulmonary disease. In these patients malnutrition was associated with reduced respiratory muscle strength and endurance [15, 44]. Institution of nutritional therapy improved respiratory muscle strength and increased body cell mass [44].

The role of nutritional support in patients weaning from the ventilator with respect to the improvement of the respiratory muscle function, has not been well-established. It is clear that respiratory muscle function can improve by the weaning process itself. There is also evidence that nutritional support can facilitate this weaning process. In one study weaning outcome has been related to the nutritional support applied. Successful weaning was encountered in a significantly higher percentage of patients who received nutritional support compared to the group of patients who received no feeding during the weaning period [45]. In that study the effect of the nutritional support on respiratory muscle function has however not been assessed.

Nutritional support can affect weaning attempts in various ways. Nutrition increases O_2-consumption ($V'O_2$) and CO_2-production ($V'CO_2$) compared to values in the postabsorptive state. In patients receiving total parenteral nutrition, overfeeding with high carbohydrate loads was found to precipitate respiratory distress secondary to elevated $V'CO_2$ [46, 47]. In a case report was demonstrated that a depleted patient who received a carbohydrate load in excess of energy needs, responded with lipogenesis associated with a large increase in $V'CO_2$ and a respiratory quotient above 1.0 [46]. In normal

subjects elevation of $V'CO_2$ leads to increases in minute ventilation and respiratory rate by ventilatory control mechanisms. Patients with impaired pulmonary function and limited ventilatory reserves may however be unable to increase ventilation and hypercapnia may result [47, 48]. As the use of fat emulsions is associated with smaller increases in $V'CO_2$ than isocaloric amounts of glucose, a combination of fat and glucose is commonly applied in parenteral nutrition [49].

A relationship between nutrition and ventilatory drive has been established. In normal man a decrease in the ventilatory response to hypoxia and hypercapnia was found after a 10-day period of semi-starvation [12]. In normal subjects who received a hypocaloric intake of 480 kcal per 24 h of glucose intravenously for 7 days, a decrease of the mean inspiratory flow, as indicator of neuromuscular drive was found, which was reversed by an infusion of aminoacids within 4 hours [50]. In depleted patients who had no signs of pulmonary disease, infusion of aminoacids reduced the resting arterial P,CO_2 and enhanced the ventilatory response to carbon dioxide [51]. In surgical patients weaning from mechanical ventilation, high protein intake did however not affect arterial P,CO_2 and ventilatory response to hypercapnia [52]. In these patients hypocapnia and an increased responsiveness to CO_2 was found during standard protein intake, which was unaltered during high protein intake. The effect of protein intake on ventilatory drive is not mediated by changes in pH, but seems to be mediated through a decreased synthesis of serotonin in the brain [53].

9. Outline of thesis

In this thesis various aspects of metabolism and respiratory mechanics related to the process of weaning from the ventilator in patients with respiratory failure are described.

In chapter 2 the role of nutrition was studied in patients in whom a prolonged period of weaning from mechanical ventilation was encountered. In this patient group the effects of nutritional support on respiratory muscle function and nutritional status were assessed.

In chapter 3 a system for continuous long-term determination of $V'O_2$ and $V'CO_2$ during mechanical ventilation and weaning from the ventilator is

described. This system has been used in the clinical studies described in the chapters 4, 5 and 6.

In chapter 4 the effects of enteral nutrition were investigated in patients who were on long-term mechanical ventilation. High calorie feeding was compared to moderate calorie feeding with respect to their effects on $V'O_2$ and $V'CO_2$. In a subgroup of these patients the effects of the two feeding regimens were also studied during periods of spontaneous breathing.

In chapter 5 the effects of enteral feeding with a high protein content on measures of ventilatory drive was investigated in ventilated patients. In this study nutritional support with a high protein content was compared to feeding with a moderate protein content. In order to estimate ventilatory drive, determinations of $V'O_2$ and $V'CO_2$ and measurements of arterial blood-gases were obtained both during periods of ventilatory support and periods of spontaneous breathing.

In chapter 6 the effect of high fat, low carbohydrate enteral nutrition on $V'CO_2$ was compared to a standard feeding regimen in mechanically ventilated patients. The objective of the study was to determine whether high fat, low carbohydrate feeding could reduce $V'CO_2$ in ventilated patients and by doing so could facilitate the weaning process.

In chapter 7 respiratory measurements applied in patients with COPD during ventilatory support and weaning attempts are described. An outline of the techniques to determine intrinsic PEEP, functional residual capacity and work of breathing is given. Both the various methods applied in the literature and the techniques applied in the chapters 8 and 9 of this thesis are described.

In chapter 8 the effect of positive end-expiratory pressure (PEEP) applied by the ventilator was studied in ventilated patients with COPD. Mechanical ventilation with PEEP was compared to ventilatory support without PEEP with respect to determinations of airway pressures, relaxed expiratory flow-volume curves and end-expiratory lung volumes.

In chapter 9 the effects of continuous positive airway pressure (CPAP) applied as weaning mode, were investigated in patients with COPD, who were mechanically ventilated for acute respiratory failure. In those patients CPAP was compared to spontaneous breathing without positive pressure. The effects of CPAP on estimations of work of breathing and flow-volume

relationships were studied in relation to the level of intrinsic PEEP present during spontaneous breathing without positive pressure.
In chapter 10 the summary of the thesis is described.

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Chapter 2

Nutritional support and weaning from the ventilator

B. van den Berg. Presented in part as invited paper at the International Symposium on Intensive Care and Emergency Medicine, Brussels, 1992.

Abstract

The effect of nutritional intake on respiratory muscle function and weaning outcome was studied in relation to the effect on nutritional status in ventilator-dependent patients in whom attempts to wean from the ventilator lasted for at least 30 days.

19 consecutive patients were studied retrospectively: 10 were long-term survivors, 9 patients died. Substantial weight loss was found in the whole patient group: the % ideal body weight amounted to 97 ± 6 and 84 ± 5 for the start and at the end of the weaning period respectively (means ± SE, $p < .001$). Neither weight loss nor nutritional intake was found to affect survival. A negative correlation was established between weight loss and calorie intake ($r = -.78$ $p < .005$). At the end of the weaning period a significant difference was found in serum-albumin levels: the levels amounted to 33 ± 1 and 28 ± 2 $g.l^{-1}$ for survivors and non-survivors respectively (means ± SE, $p < .05$). The maximum inspiratory pressure against an occlusion (Pimax) in all patients during the weaning period: a positive correlation was found between the improvement in Pimax and calorie intake ($r = .83$ $p < .01$).

In this study nutritional support was not found to affect survival in ventilator-dependent patients. Nutritional support could however reduce weight loss and was associated with increases of Pimax in these patients.

1. Introduction

Ventilated patients in whom repeated attempts to wean from mechanical ventilation are unsuccessful, are considered a heavy burden on intensive care resources [1]. This applies in particular to patients who have to stay for weeks in the intensive care unit in order to be weaned from the ventilator. In most cases, elderly patients with limited pulmonary reserves are involved. The withdrawal of the ventilatory support fails in these patients for a variety of reasons. Parenchymal lung damage altering pulmonary mechanics and gas-exchange, and respiratory muscle dysfunction leading to muscle weakness, seem to be major causes of ventilator dependence [2]. The metabolic response to injury associated with protein breakdown and impairment of respiratory function is considered as one of the underlying mechanisms in this condition. The provision of optimal nutrition has always been considered as the mainstay in the supportive treatment of ventilator-dependent patients [2]. Several studies have suggested that nutritional support could enhance weaning from the ventilator [3, 4]. Although the effect of nutritional support on weaning attempts was found to be related to the course of serum-albumin levels in these patients, the effects of feeding on other measures of nutritional status as body weight have not been assessed [4].

In order to assess the clinical relevance of nutritional support in ventilator-dependent patients, we studied retrospectively patients from our department in whom a prolonged period of weaning from the ventilator was encountered. In these patients data on respiratory muscle function, nutritional status and feeding regimens were collected during the period of weaning attempts. The effect of nutritional support on respiratory muscle function and weaning outcome was studied in relation to the effect on nutritional status.

2. Patients and Methods

2.1. Patients

For the study all patient files from our department from 1989 till 1992 were examined. In order to assess long-term effects of feeding on nutritional status, only patients were included in whom weaning from the ventilator lasted for at least 30 days. Using this criterion 19 patients were identified. Patient data including pre-existing cardio-pulmonary diseases, immediate causes for institution of mechanical ventilation and complicating illness associated with prolonged ventilatory support are shown in table 1. 12 Male patients against 7 female patients were identified. The age of the patients at the start of ventilatory support varied from 55 to 79 years with a mean of 69 years.

Considering the pre-existing diseases only 2 patients were found to have no impairment with respect to respiratory or cardiac function. Chronic obstructive pulmonary disease (COPD) was found in 10 patients; the values of VC and FEV_1, expressed as a percentage of the reference value are shown in table 1 (5). Congestive heart failure (CHF) was found in 5 patients.

With respect to the conditions leading to the institution of mechanical ventilation, in 5 patients an acute exacerbation of COPD was found; in 12 patients surgery proved to be the immediate cause for ventilatory support: cardiac surgery in 5 patients, pulmonary surgery in 4 and abdominal surgery in 3 patients. In 11 patients a complicating illness associated with prolonged ventilatory support could be identified, 6 of which were severe infections.

The duration of ventilatory support varied from 38 to 154 days with a median of 70 days; the number of days applied for weaning varied from 30 to 90 days with a mean of 46 days.

All patients were ventilated in the volume-controlled mode before attempts to wean were started. The mode of weaning consisted of short periods of low levels of CPAP (Continuous Positive Airway Pressure) or inspiratory pressure support alternated by full ventilatory support in

no:	sex	age	pre-existing cardio-pulmonary ilness	condition leading to mechanical ventilation	complicating ilness associated with prolonged ventilatory support	VC %-predicted	FEV1 %predicted	survival-death
1	f	64	COPD	exacerbation of COPD	syndrome of Ogilvie	65	20	S
2	f	63	COPD	exacerbation of COPD		86	29	S
3	m	62	COPD	surgery for gastric ca				S
4	f	59	CHF, COPD	mitral-valve replacement	paravalvular leakage	86	37	S
5	m	72	COPD, TBC	exacerbation of COPD		40	23	S
6	m	55	COPD	bilobectomy for ca	thoracic empyema	78	45	S
7	m	69	CHF	mitral-valve replacement		64	45	S
8	f	59	CHF	mitral-valve replacement	endocarditis			S
9	m	71	none	pneumonectomy for ca	empyema, polyneuropathy	91	55	S
10	m	68	pneumonectomy, TBC	surgery for cholecystitis	peritonitis			S
11	m	69	COPD	bullectomy for pneumothorax	pleural empyema	58	23	D
12	m	78	COPD	exacerbation of COPD		56	22	D
13	m	75	COPD	pleural empyema		78	39	D
14	f	65	COPD, CHF	exacerbation of COPD		58	34	D
15	f	71	CHF	mitral-valve replacement	pleura-adhesions			D
16	m	68	coronary heart disease	CABG	vasculitis, renal failure	94	95	D
17	m	79	myositis	surgery for diverticulitis	aspiration-pneumonia	67		D
18	m	66	none	bilobectomy for ca	thoracic empyema	107	86	D
19	f	75	kyphoscoliosis	epilepsy				D

VC = vital capacity, measured before start mechanical ventilation; FEV1 = forced expiratory volume in 1 s, measured before start mechanical ventilation; COPD = chronic obstructive pulmonary disease; CHF = congestive heart failure; ca = carcinoma; TBC = tuberculosis; CABG = coronary artery bypass graft.

order to rest the respiratory muscles. Subsequently the periods of weaning were extended in day-time while ventilatory support was applied overnight. At last the nocturnal ventilatory support was gradually discontinued. Weaning was considered successful if a patient could be liberated from the ventilator and survived for at least one month afterwards. Weaning was considered unsuccessful if attempts to discontinue ventilatory support had failed or the patient died of respiratory failure within one month after disconnection of the ventilator.

2.2. Methods

In order to estimate the nutritional status before the start of the mechanical ventilation, the heights and weights of the patients at that time were obtained. These weights were expressed as percentage of ideal body weight (%IBW) for the individual patients. The ideal body weight for each patient's height was calculated using standard tables [6]. Malnutrition was defined as % IBW less than 90. The changes in body weight during the period of ventilatory support and the weaning period were assessed. The weights of the patients at the start and at the end of the weaning period were obtained and a mean weight loss per week during that period was calculated for each patient. Serum-albumin levels were collected at the start and at the end of the weaning period.

The data on the nutritional support of the patients were collected from the patient files. The type of nutrition i.e. parenteral or enteral nutrition or hospital diet was assessed. A mean calorie intake was calculated from all the consecutive days on which weaning procedures were encountered. This mean calorie intake was related to the basal metabolic rate calculated from the Harris-Benedict equations on the basis of the patients' weights measured at the start of the weaning period [7].

As measure of respiratory strength the maximum negative pressure (Pimax) which the patients could generate against an occluded airway

at end-expiration, was obtained. In order to establish the effect of the weaning attempts on respiratory muscle strength, the values of Pimax measured at the start and at the end of the weaning period were compared. The changes in Pimax observed in the patients during the weaning period were related to their nutritional intakes.
The clinical outcome of the patients was assessed in relation to the measures of nutritional status and respiratory muscle strength.

2.3. Statistical analysis

For statistical analysis Student-T-tests for both independent and correlated samples were used. Differences with a p-value less than .05 were considered statistically significant. Correlations were calculated using the Pearson correlation coefficient. Results are described as means and standard errors unless otherwise indicated.

3. Results

With respect to the clinical outcome of the patient group, 10 patients were long-term survivors and 9 patients died. No correlations could be established between clinical outcome and pre-existing diseases, conditions leading to the start of mechanical ventilation or complicating illness. Neither correlations could be established between clinical outcome and the duration of ventilatory support or the duration of the weaning attempts.
The data with respect to number of weaning days, days with enteral and parenteral nutrition, body weights, nutritional intakes and respiratory muscle strength are shown in table 2. In 15 patients a body weight could be obtained before the start of mechanical ventilation. Expressed as percentage of ideal body weight (%IBW) the weights varied from 64 to 138 with a mean of 101. 7 Of these patients were considered to be malnourished. At the start of the weaning attempts values of body weight were available in 17 patients: the %IBW varied from 63 to 141

TABLE 2
Patient data

no:	no. of ventilator days	no. of weaning days	no. of days TPN-+EN	%IBW start mech vent	%IBW start weaning	%IBW end weaning	Feed/BMR	PImax in cm H_2O during weaning early	late	survival/death
1	66	39	39	0.87	0.87	0.73	1.41	-32	NA	S
2	40	36	36	1.24	1.27	1.10	1.15	-26	-40	S
3	68	55	55	NA	0.63	0.58	1.14	-27	NA	S
4	64	40	40	0.82	0.74	0.70	1.43	NA	NA	S
5	61	54	17	1.38	1.38	1.12	0.89	-38	NA	S
6	154	43	0	NA	0.94	0.94	NA	-42	-64	S
7	68	46	46	1.15	1.14	0.92	0.96	-30	-46	S
8	38	36	31	0.87	0.87	0.78	1.14	NA	-24	S
9	84	55	28	1.35	1.41	1.10	0.99	-31	-55	S
10	83	28	0	NA	1.07	1.00	NA	-33	-37	S
11	46	37	37	NA	0.91	0.72	0.93	NA	-33	D
12	72	65	65	0.64	0.67	0.56	1.19	-30	-39	D
13	47	30	30	0.89	0.78	NA	1.31	-22	NA	D
14	73	31	0	1.19	0.89	0.92	NA	-39	-44	D
15	68	66	20	0.78	NA	NA	1.57	-43	NA	D
16	61	46	46	1.01	0.96	0.71	1.29	-30	-49	D
17	78	33	10	0.81	0.75	0.67	1.20	-55	-71	D
18	105	90	90	1.10	0.98	0.87	1.38	-44	-60	D
19	61	37	29	1.01	NA	NA	0.99	NA	-43	D

TPN + EN = total parenteral and enteral nutrition: %IBW = percentage ideal body weight; FEED/BMH = calorie intake expressed as percentage of basal metabolic rate; PImax = maximal inspiratory pressure against occluded airway; NA = not assessed.

with a mean of 96. In 13 patients both weights at the start of mechanical ventilation and at the start of the weaning attempts could be obtained.
In these patients the ventilatory support had lasted for an average of 19 days before the weaning attempts started. Comparison of these weights did not reveal a significant difference: the %IBW amounted to 102 ± 6 and 98 ± 7 for the weights at the start of the ventilatory support and at the start of the weaning attempts respectively.
For the nutritional support applied during the weaning period predominantly enteral feeding was used. Of the total of 867 weaning days studied, enteral feeding was applied in 547 days (63%), parenteral nutrition in 59 days (7%) and hospital diet in 261 days (30%). Parenteral nutrition was used for short periods in 7 patients and was replaced by enteral nutrition during weaning attempts. In a total of 16 patients enteral feeding was applied during extended periods of time: in 8 of these patients enteral feeding was replaced by hospital diet during the weaning period. 3 Patients were able to eat the hospital diet during the full weaning period: in these patients the calorie intake has not been assessed. In the remaining 16 patients a mean calorie intake per day was calculated for the days they received enteral and/or parenteral nutrition. The average calorie intake varied from 1208 to 1955 kcal/day with a mean of 1538 kcal/day. This calorie intake was related to the basal metabolic rate calculated from the Harris-Benedict equations. The ratios between the mean calorie intakes and the basal metabolic rates varied from .89 to 1.43 with a mean of 1.18. Considering the clinical outcome of the patients, no difference could be established between the nutritional intakes of the survivors and non-survivors.
At the end of the weaning period the body weight of 16 patients could be obtained. Expressed as %IBW the values ranged from 56 to 138 with a mean of 84. Compared to the values of %IBW at the start of the weaning period, a significant weight loss was found at the end of weaning (figure 1). In the 3 patients who received hospital diet during the full weaning period, only minor changes in body weight were

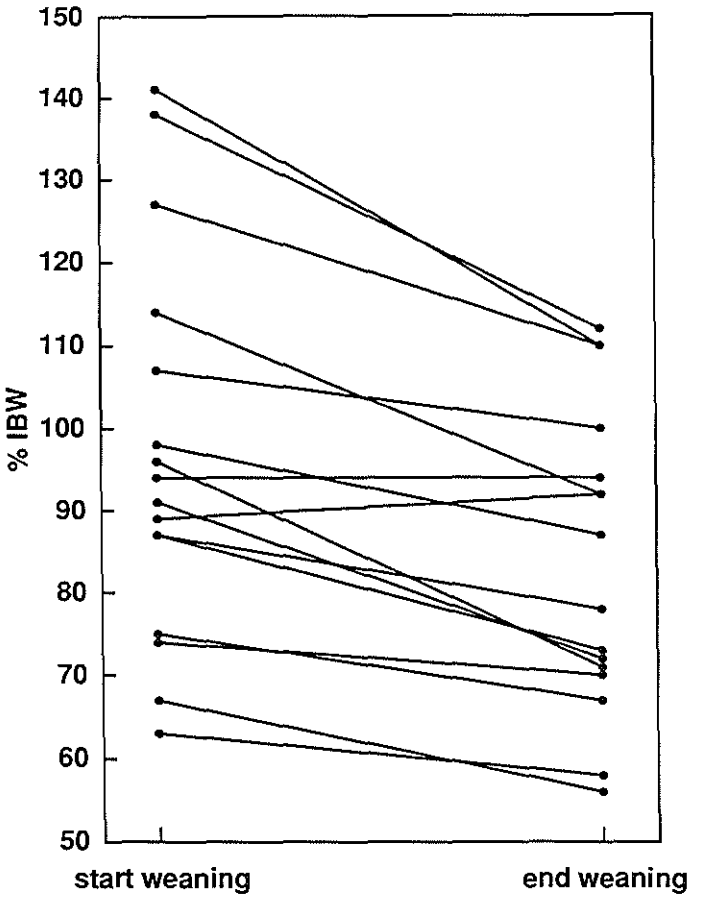

Figure 1. The values of body weight expressed as percentage ideal body weight of the individual patients at the start and at the end of the weaning period.

established. For the whole patient group the mean values of %IBW amounted to 97 ± 6 and 84 ± 5 for the start and the end of the weaning period respectively ($p < .001$). In table 3 these values of %IBW are shown for the survivors and non-survivors. Comparisons of

%IBW at the start and at the end of the weaning periods revealed significant differences for both survivors and non-survivors. When the data of the survivors were compared to those of the non-survivors, the values of %IBW did not differ significantly.

For 13 patients, the weight loss observed during the weaning period was related to the nutritional support. The weight loss calculated per week was related to the nutritional support expressed as the ratio of calorie intake to basal metabolic rate. A negative correlation was found between weight loss and calorie intake ($r = -.78$ $p < .005$, figure 2).

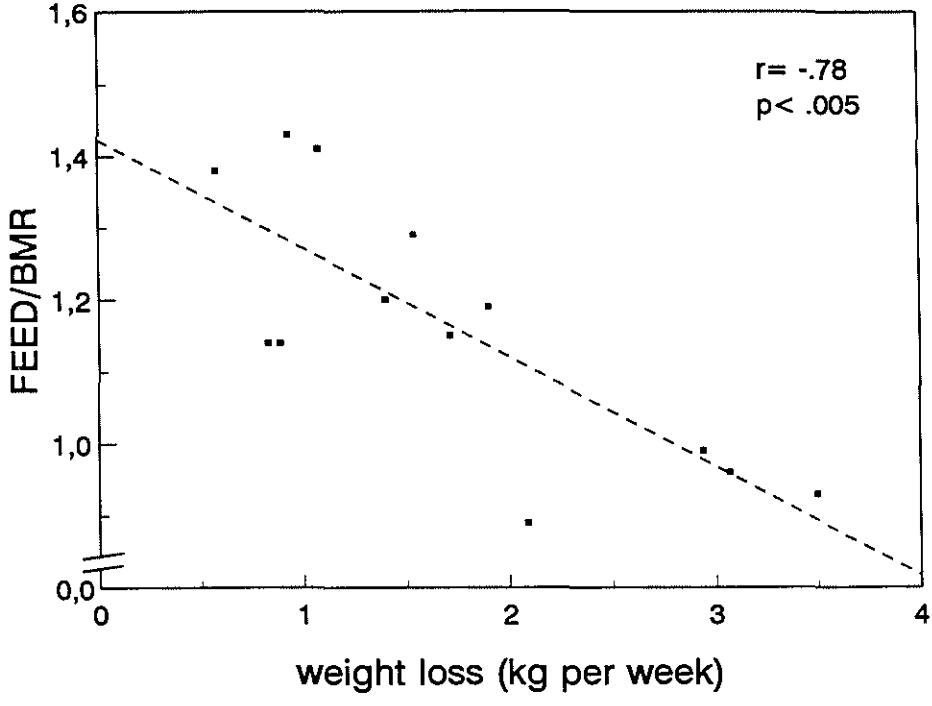

Figure 2. Relationship between the weight loss and the calorie intake of the individual patients during the period of weaning. The weight loss is expressed in kg per week; the nutritional intake is expressed as the ratio between actual calorie intake and basal metabolic rate calculated for each patient. The regression line is also shown.

Serum-albumin levels were available at the start and at the end of the weaning period in all patients. Significant differences in serum-albumin levels were found comparing survivors and non-survivors. At the start of the weaning procedures the levels of serum-albumin did not differ between the patient groups: the values amounted to 29 ± 2 and 27 ± 2 $g.l^{-1}$ for survivors and non-survivors respectively. At the end of the weaning period a significant higher serum-albumin level was found in the survivors: for the survivors the serum-albumin levels amounted to 33 ± 1 against 28 ± 2 $g.l^{-1}$ for the non-survivors ($p < .05$). No correlation could be established between nutritional intakes and serum-albumin levels of the patients obtained at the end of the weaning period.

Pimax was measured in 18 patients on at least one occasion. At the start of the weaning programmes Pimax was measured in 15 patients: the values ranged from -22 to -55 cmH_2O with a mean of -35 cmH_2O. In 10 patients Pimax values were available both early during the weaning programme and at the end of that period. In all patients a more negative Pimax was found at the end of the weaning period compared to the values obtained earlier (figure 3). At the start of the weaning period the mean Pimax amounted to -36 ± 3 cmH_2O against -50 ± 4 cmH_2O at the end of that period ($p < .001$). Analyzing these results for survivors and non-survivors separately, revealed in both groups significantly more negative Pimax values at the end of the weaning period (table 3). No differences in Pimax values were found when survivors were compared to non-survivors. For 7 patients the improvement in Pimax was related to the nutritional support. The improvement in Pimax calculated per week was related to the nutritional support expressed as the ratio of calorie intake to basal metabolic rate. A positive correlation was found between improvement in Pimax and calorie intake ($r = .84$ $p < .05$).

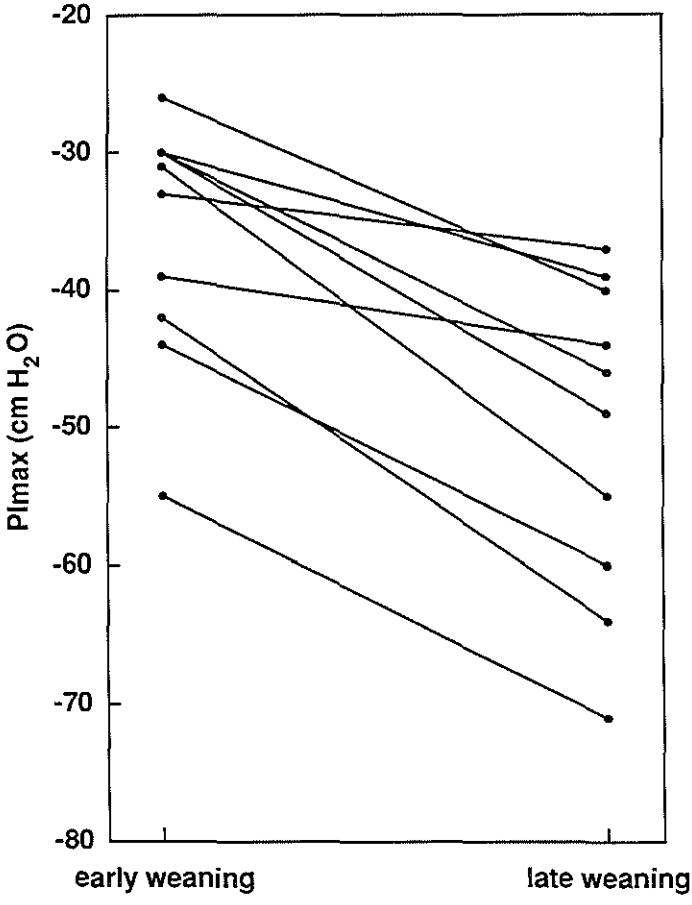

Figure 3. The values of the maximum inspiratory pressure (Pimax) of the individual patients obtained early and late during the weaning period.

4. Discussion

In this study the clinical course of ventilator-dependent patients during the period of weaning from the ventilator was investigated with respect to nutrition and respiratory muscle function. In these patients a substantial weight loss was found during the weaning period, unrelated however to the weaning outcome.

TABLE 3
Nutritional indices and respiratory muscle strength

	%IBW start weaning (mean ± SE)	%IBW end weaning (mean ± SE)
survivors n = 10	103 ± 8	90 ± 6**
non-survivors n = 6	86 ± 5	74 ± 5*
total n = 16	97 ± 6	84 ± 5**

	PImax cm H_2O start weaning (mean ± SE)	Pimax cm H_2O end weaning (mean ± SE)
survivors n = 5	-32 ± 3	-48 ± 5*
non-survivors n = 5	-40 ± 5	-53 ± 6**
total n = 10	-36 ± 3	-50 ± 4**

%IBW = percentage ideal body weight; PImax = maximum inspiratory pressure against occluded airway.
Paired T-tests: * = $p < .05$; ** = $p < .01$.

In the majority of the patients pre-existing cardiopulmonary diseases associated with limited respiratory reserves were found. It is well-known that the effect of chronic health problems on survival of an acute illness is difficult to establish [8]. The predictive value of lung function tests have been studied extensively in patients with pulmonary diseases. It has been shown that in patients with COPD lung function tests obtained prior to the acute respiratory failure leading to ventilatory support are predictive of the clinical course [9]. Both weaning from the ventilator and survival after the period of mechanical ventilation were correlated with the premorbid level of FEV_1 [9]. No such correlation could however be established in this study. This should be explained by the small number of patients in this study in whom data of lung function tests were available.

For this study %IBW was used for nutritional assessment as this measure was considered the most useful screening tool in patients with chronic lung disease [10]. Before the start of mechanical ventilation

malnutrition defined as a weight less than 90% IBW was found in almost half of the patients. In a previous study malnutrition was established in the same degree in patients with COPD and acute respiratory failure [11]. At the start of the weaning attempts, the weights of the patients in this study were found to be unaltered compared to the period before the start of ventilatory support. This finding should be interpreted with caution. It is well-established that in patients with critical illness total body water is increased [12]. Consequently in those patients losses of lean body mass and fat stores can be underestimated if body weight is used to define malnutrition. The depletion observed during the weaning period could very well have started not at the beginning of that period, but much earlier during the period of mechanical ventilation.

Comparing the weights at the start of the weaning attempts to those at the end of the weaning period a substantial weight loss was encountered in the patient group. This weight loss was found to be related to the type of patients studied: only minor changes in weight were found in the 3 patients who received hospital diet during the full weaning period. This finding suggests that these 3 patients differed from the patients receiving enteral or parenteral feeding with respect to energy needs and catabolism. With respect to the patients who received predominantly enteral nutrition, 9 of 13 patients were considered malnourished at the end of the weaning period. The weight loss established in these patients should in part be ascribed to inadequate calorie intake. A negative correlation was established between the degree of weight loss and the nutritional intake: this suggests that in these patients weight loss could be reduced by high calorie intakes. There is ample evidence that in critical care patients nutritional support by the enteral route is cumbersome due to frequent interruptions and that the daily goal calorie intake can not often be reached [13, 14]. Also in this study enteral feeding had to be withheld in the patients for various reasons as vomiting, ileus or surgical procedures.

The weight loss should also be related to the immobilization of the patients. All patients were bedridden during the weaning period except

for the 3 patients who could eat hospital diet and have their meals sitting in a chair at the bedside. In all patients daytime was used for attempts to wean from the ventilator and no physical training of limb muscles was pursued during the weaning period.

In this study no relation was established between weight loss and weaning outcome. Neither difference was found between survivors and non-survivors with respect to nutritional intake during the weaning period. In previous studies it has been suggested that nutritional support could enhance weaning from the ventilator [3, 4]. In one investigation patients receiving protein-free, energy-deficient routine i.v. diet were compared to patients receiving nutritional support of 2000-3000 kcal/day [3]. The number of patients who could be weaned from the ventilator, was significantly higher in the latter group. No data were however provided on the weight loss of the patients during the weaning period. In another study all patients received an average calorie intake of 2600 kcal/day [4]. It was suggested that successfull weaning was more likely in those patients who responded to nutritional support with an increase in protein synthesis i.e. increases in the levels of serum-albumin and serum-transferrin [4]. Although in our study the average calorie intake only amounted to 1500 kcal/day, similar results were obtained with respect to the course of serum-albumin levels during the weaning period. Significantly higher serum-albumin levels were found in the patients who were successfully weaned from the ventilator. It has however been suggested that the serum-albumin level represents rather a biologic marker of severity of illness instead of a nutritional marker [15]. Consequently the higher albumin-levels found in the successfully weaned patients are suggestive of a decreased metabolic stress instead of a better nutritional status.

For this study Pimax was used as estimation of respiratory muscle strength. It has been established that Pimax can be considered as measure for the nutritional status of patients who do not suffer from pulmonary diseases [15]. It is obvious that in patients with respiratory failure the relationship between respiratory muscle strength and nutritional status no longer exists. In this study an improvement in Pimax

values of the patients was encountered during the weaning period, whereas a substantial weight loss was assessed at the same time. It could be suggested that the Pimax improved in these patients due to training of the respiratory muscles while the weight loss was related to the immobilization during the weaning period. Nutritional support was found to exert a beneficial effect on respiratory muscle strength as a positive correlation was established between the improvement in Pimax and the average calorie intake. The Pimax proved however to be unrelated to the weaning outcome in this study. This is in agreement with previous studies, indicating the limited value of Pimax to predict weaning outcome [17]. Pimax as estimation of respiratory muscle strength should be related to the work load of these muscles in order to predict outcome of weaning attempts.

In this study the beneficial effect of nutritional support on weaning outcome in ventilator-dependent patients could not be established. Substantial weight loss was encountered during the weaning period, unrelated to the clinical outcome of the patients. It was however suggested that high calorie intake could reduce weight loss and was associated with improvements of respiratory muscle strength in this patient group.

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Chapter 3

A simple and accurate automated system for continuous long-term metabolic studies during artificial ventilation

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Abstract

Energy expenditure and the amount of metabolized carbohydrate, protein and lipid can be calculated from the O_2 consumption, CO_2 production and nitrogen excretion using indirect calorimetry. A low-cost automatic system has been developed suitable for short- and long-term measurements during artificial ventilation, in which the gas analyzers were calibrated automatically every 10 min and in which the desired variables were calculated and printed every 5 min. O_2 and CO_2 concentrations of mixed expired and inspiratory gas, the expired minute volume V'_E and patient's rectal temperature, were sampled at regular time intervals and a simple programmable calculator with printer was used for the on-line data analysis. Tests on accuracy, stability, reproducibility and feasibility showed this system to be suitable for clinical application.

1. Introduction

Measurement of respiratory gas exchange in patients on artificial ventilation has proven to be important for the assessment of nutritional needs and the metabolic effects of nutritional support. Energy expenditure, carbohydrate, protein and lipid metabolism can be estimated from O_2 consumption ($V'O_2$), CO_2 production ($V'CO_2$) and nitrogen excretion.

For balance studies $V'O_2$ and $V'CO_2$ should be measured (semi-)continuously for long periods (one or more days) instead of several hours, in order to eliminate effects of incidental changes in metabolic activities [1 - 7].

The commercial equipment generally used for these long-term studies in an intensive care situation is expensive. Moreover, systematic and random errors in $V'O_2$ and $V'CO_2$ up to 13% have been reported [8, 9, 10]. This paper presents the description and testing of an inexpensive, simple and accurate automated unit for the semi-continuous monitoring of variables for metabolic studies, to be connected to any ventilator equipped with an expiratory flow transducer. The unit is composed of:

(i) a valve system for selection of respiratory and calibration gases with

an automatic control of valve setting;

(ii) relatively inexpensive analyzers for oxygen and carbon dioxide respectively;

(iii) a 12-bit analog-to-digital converter; and

(iv) a programmable pocket calculator and printer for data acquisition.

2. Metabolic unit and ventilator

The metabolic unit was developed in combination with a servo-ventilator, Siemens 900B or C (figure 1). Expired minute volume V'E was measured by means of the flow transducer of the ventilator. For monitoring respiratory

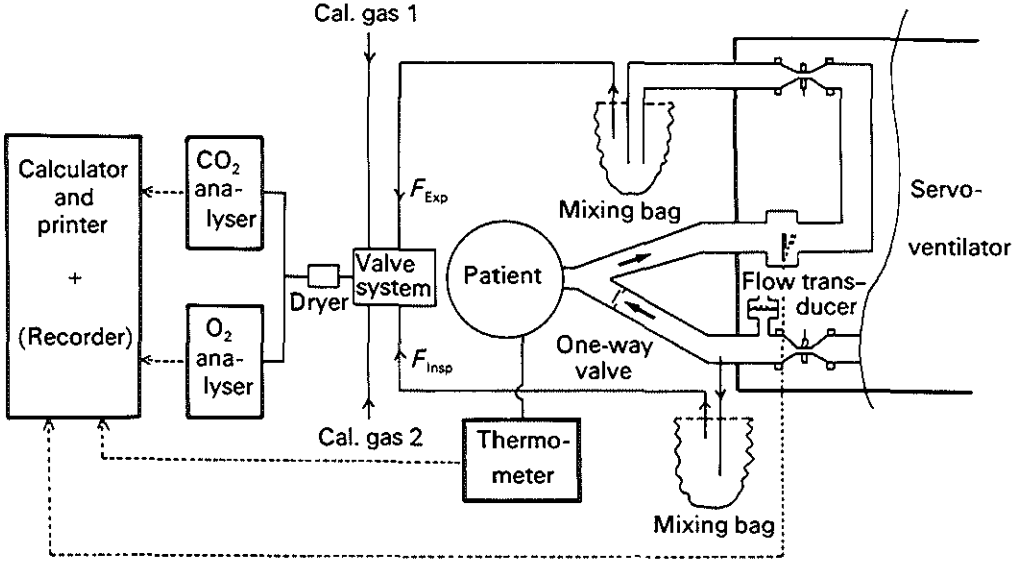

Figure 1. Apparatus for continuous measurements of O_2 consumption, CO_2 production, metabolic variables and rectal temperature in ventilated patients. The dashed line indicates signal flow and the arrows the direction of airflow.
Samples of cal.gas 1, cal.gas 2, inspiratory air (Finsp) and expiratory air (Fexp) were selected by the valve system. For further explanation see text.

gases an infrared type CO_2 analyzer (Siemens, type Ultramat M) and a paramagnetic O_2 analyzer (Mijnhardt, Type Oxylyzer) were used. The signals from the gas analyzers and flow transducer were transmitted via a 12-bit analog-to-digital converter to a programmable HP-41 CX calculator for on-line data acquisition. These calculators can be programmed without the help of computer specialists, in contrast to systems described in the literature [11]. Moreover, V'_E, O_2 and CO_2 signals were recorded on a four-channel recorder (Goertz, type SE 460). This recorder is not an obligatory part of the unit, but was used for trouble shooting during the period of system development. For unidirectional gas flow a one-way valve was placed in the Y-piece near the patient. To avoid pressure variations influencing the gas analysis, respiratory gases were sampled via mixing bags. To get a flow-weighted mean of the inspiratory gas fraction an artificial leak, discharging into a mixing bag, was made in the inspiration line of the ventilator.

All gases were dried before analysis. Calibration of V'_E with a wet spirometer before and after a 24 h observation period was satisfactory. A patient's V'_E was automatically corrected to BTPS conditions, using room temperature, barometric pressure and the saturated vapour pressure at room temperature. An observation period of any given length consisted of a sequence of cyclic periods of 10 min for analysis. Each analysis cycle (figure 2) was subdivided in six periods: two for calibration with O_2 and CO_2 concentrations, chosen close to the inspiratory and mixed expiratory fractions, and four for alternately measuring twice inspiratory and mixed expiratory gas fractions (F_I,O_2, F_E,O_2 and F_E,CO_2). Sampling either calibration gases or ventilatory air was set automatically by means of the valve system. Valve setting was controlled by an electromechanical cam timer (C.d.c., type Mini flex 6006). The cam timer allowed variation in time of analysis periods and number and length of subdivisions. In this study the cam timer was set for all observations as described above.

Each analysis cycle $V'O_2$ and $V'CO_2$ in $ml.min^{-1}$ (STPD), the respiratory exchange ratio RQ, the ventilation equivalent (V'_E) for O_2 in $l.mmol^{-1}$ and the resting energy expenditure (REE) in kJ per 24 h were derived twice. Using the reference values according to Harris and Benedict [12] and Elwyn et al

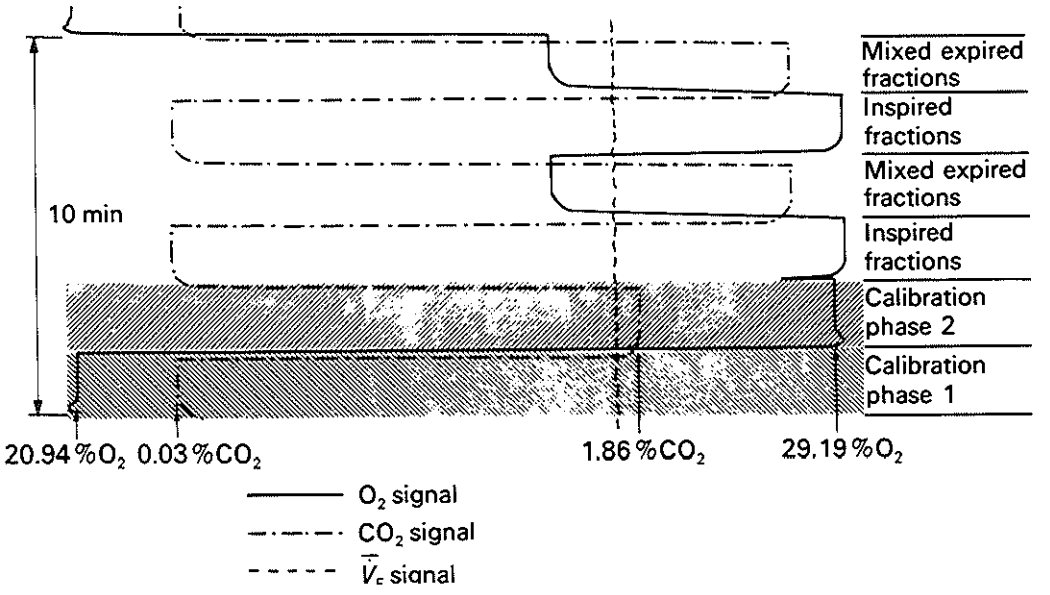

Figure 2. Analog recorder output of an analysis cycle. Cycle time 10 min; subdivisions 1'40''.

[13] REE was also expressed as a percentage. Using the Haldane correction for $V'O_2$ calculations inspired minute volume was calculated from the expired minute volume assuming neither production nor consumption of nitrogen. Then the inspired amount of N_2 is equal to the expired amount under steady state conditions, so that according to the standard equation [14]:

$$V'O_2 = V'E \left(\frac{1 - FE,O_2 - FE,CO_2}{1 - FI,O_2} .FI,O_2 - FE,O_2 \right)$$

When during an observation F_I,O_2 was changed erroneous results were usually obtained in one 10 min analysis cycle, because the change of F_I,O_2 occurred faster than that of F_E,O_2, due to wash-in or wash-out of N_2. The Haldane correction is then not valid. In the next 10 min cycle the results were stable again. Bronchial lavage caused wrong results. However the calculator recognized and rejected these errors, because during suction the V'_E signal was zero.

In addition to the ventilatory and metabolic data, we measured simultaneously rectal temperature with an 'Ellab' temperature measuring system (Type Du 35), which was electrically calibrated at 0°C and 40°C. Additional devices to the HP 41 CX calculator were an HP 82143A printer, an HP-IL converter kit (type 82166 A), an HP-41 interface module (type 82160 A) and an extended I/O-module (type 82183 A). For data storage and plotting purposes a computer interface unit (HP, 82164 A) could be applied for communication with other systems, as for example a central computer and tape recorder.

3. System evaluation

3.1. Flow transducer

The analog V'_E output of the flow transducer (type Silverman) of the ventilator was calibrated with a wet spirometer in series with the ventilator. Calibration was performed within a V'_E range of 0-18 $l.min^{-1}$. In all flow transducers of nine different ventilators a proportional relationship between the voltage output (ΔE) and V'_E was found, where ΔE is the difference between the voltage measured at V'_E and at zero flow. An offset in voltage at zero flow was set to avoid sampling problems by the pocket calculator at a zero level. The coefficients of determination (r^2) for all proportional relationships $\Delta E = \alpha V'_E$ were 0.999.

The calibration factor α ($= \Delta E/V'_E$) in Vl^{-1} min was determined either before and after an observation period or every 24 h when the observation period was of a longer duration. Calibration factors were very stable even for weeks and continuous use, as also reported by Henderson et al [15, 16]. Servo-ventilators have the additional advantage of a negligible effect of zero-drift in the flow signal, because the equipment re-sets itself to zero during each

ventilatory cycle when the expiratory valve is closed.
The sensitivity of the expiratory V' transducer for changing concentrations of O_2 was checked in a lung model with a V'_E of 7.5 $l.min^{-1}$ and varying F_I,O_2. Although a maximum difference of only 1.3% was found between the flow signals, when using ambient air and an F_I,O_2 of 0.98 respectively, V'_E calibration was performed using an O_2 concentration equal to that in the expiratory air.

3.2. Accuracy of the gas analyzers

For gas calibration purposes a mixing pump (Wösthoff, type M 300) was used. The linearity of the infrared CO_2 analyzer (Siemens, Ultramat M) was checked in the range 0-7% CO_2. The relationship between the percentage of CO_2 and the voltage output (E) of the analyzer was linear between 0 and 7%. The regression equation was $E = 1.347\ (\%CO_2) - 0.033$, with a coefficient of determination $r^2 = 0.999$.
The linearity of the paramagnetic O_2 analyzer (Mijnhardt, Oxylyzer) was checked with various O_2-N_2 mixtures. The relationship between the voltage output (E) of the analyzer and the O_2 percentage was linear between 0% and 100% O_2; $E = 0.009\ (\%O_2) + 0.004$, with a coefficient of determination $r^2 = 0.999$.
Although no special stability requirements for long-term drift of both analyzers were necessary because of the frequent two-points calibration during every analysis cycle, we nevertheless checked the stability of both analyzers by studying all calibrations ($n = 144$) during a 24 h observation period in a patient. We used ambient air (20.94% O_2; 0.03% CO_2) and a mixture of 29.19% O_2, 1.86% CO_2 in N_2 respectively. The analog recordings of CO_2 and O_2 showed in both cases a variation coefficient of 0.10%.

3.3. Temperature measuring system

The linearity of the Ellab temperature measuring system (type Du 3s) was checked by comparing the analog voltage output with a calibrated mercury thermometer. Temperature and analog voltage output (E) was linearly related between 0 and 40°C; $E = 0.041\ (°C) - 0.005$, with a coefficient of determination $r^2 = 0.999$. The electrical values for 0 and 40°C calibration

coincided within 0.1 °C with the experimentally measured values and were stable for months. The electrical two points calibration was performed before and after each 24 h observation period.

3.4 Total system

To evaluate the total system of ventilator and gas analyzers we compared measured $V'O_2$, $V'CO_2$ and RQ with predicted values. Predicted values were obtained from a lung model according to Damask [9] ventilated with the Siemens Servo-ventilator, while ethanol was burned. Observations in the model were performed as for patients, i.e. a sequence of analysis cycles during the observation.

Damask, Henderson et al and Lepape et al simulated $V'O_2$ and $V'CO_2$ by introducing known amounts of N_2 and CO_2 respectively into the model [9, 16, 17]. In these studies burning of ethanol in the model was only used for simulation of an RQ equal to 0.67. Complete combustion of ethanol occurs when a colourless flame is observed so in that case not only RQ but also predictable values of $V'O_2$ and $V'CO_2$ can be achieved. Assuming the ethanol is burning at a constant rate, we predicted the mean $V'O_2$ and $V'CO_2$ from total weight loss of ethanol and total burning time (70 min, i.e. seven analysis cycles). To prevent weight loss by evaporation ethanol was cooled with ice.

The model was ventilated with a minute volume of 7.5 l min^{-1} at a rate of 20 cycles per minute. The observations were performed either with an F_I,O_2 = 0.2094 or an F_I,O_2 = 0.2938. Comparing the estimated $V'O_2$ and $V'CO_2$ respectively with the predicted values we found a maximum relative deviation of 2% in both $V'O_2$ and $V'CO_2$, while the maximum variation coefficients were 3% (table 1). For the RQ the maximum relative deviation was 1.5% and the maximum variation coefficient 1.5%. We assumed the random variations were due to a combined effect of fluctuations in the burning rate of ethanol, applied minute volume and gas analyzers during the seven analysis cycles.

TABLE 1

Comparison of estimated $V'O_2$, $V'CO_2$ and RQ with a predicted $V'O_2$, $V'CO_2$ and RQ, when ethanol burns at various O_2 pressures.

		$V'O_2$ (l min^{-1}) STPD			$V'CO_2$ (l min^{-1}) STPD			RQ			
		Measured			Measured			Measured			
Organic Compound	FI,O_2	Predicted	Mean	SD	Predicted	Mean	SD	Predicted	Mean	SD	n
Ethanol	0.209	.100	.098	.002	.067	.067	.002	0.67	0.68	0.01	14
Ethanol	0.294	.168	.170	.003	.112	.114	.003	0.67	0.67	0.005	14

The system was only tested by burning ethanol in F_I,O_2 = 0.2094 and 0.2938 respectively. At higher F_I,O_2 ethanol was burning so fast and giving off so much heat that ethanol evaporation was inevitable. Oxygen consumption and carbon dioxide production were then different from that predicted. We intended to evaluate the functioning of the whole system. Problems might arise at higher F_I,O_2, however, not primarily dependent on the apparatus, but due to inaccuracy in the Haldane correction. Such problems are involved in all types of equipment using this correction. In the literature Ultman and Bursztein [18] described the influence of F_I,O_2 on the accuracy of metabolic variables, when using the Haldane correction. However, mistakes due to the Haldane correction will influence only $V'O_2$ and not $V'CO_2$, so causing unexpected RQ values. Indirect proof of the validity of our system working with a F_I,O_2 value up to 0.50 is the fact that a lot of patients had an expected RQ of about 0.7 under fasting conditions.

4. Application

In patients on long-term mechanical ventilation we try to supply adequate calories to avoid undernourishment, resulting in weight loss and finally tissue depletion. Increasing caloric and protein intake could be a possible way of curtailing these losses. However, hyperalimentation might cause an increased $V'CO_2$ resulting in failure to wean the patient from the ventilator [2, 4]. To minimize such metabolic consequences accurate long-term balance studies of energy requirements are necessary, prior to initiating therapy and regularly during hyperalimentation. In balance studies lasting 24 h or longer, a continuous observation period is often replaced by a greater number of shorter observations spread over the total observation period to estimate mean energy expenditure. Arising from irregular changes in activity of the patient considerable errors might be possible: we therefore developed an automated semi-continuous system.

Figure 3 is an illustration of a 32 h observation period in one patient. For the first hour of this observation the patient was in a fasting state with a mean RQ of 0.82. After this first hour a high caloric nutrition scheme of 5.24 MJ per 24 h lipid, 6.98 MJ per 24 h carbohydrate and 2.33 MJ per 24 h protein

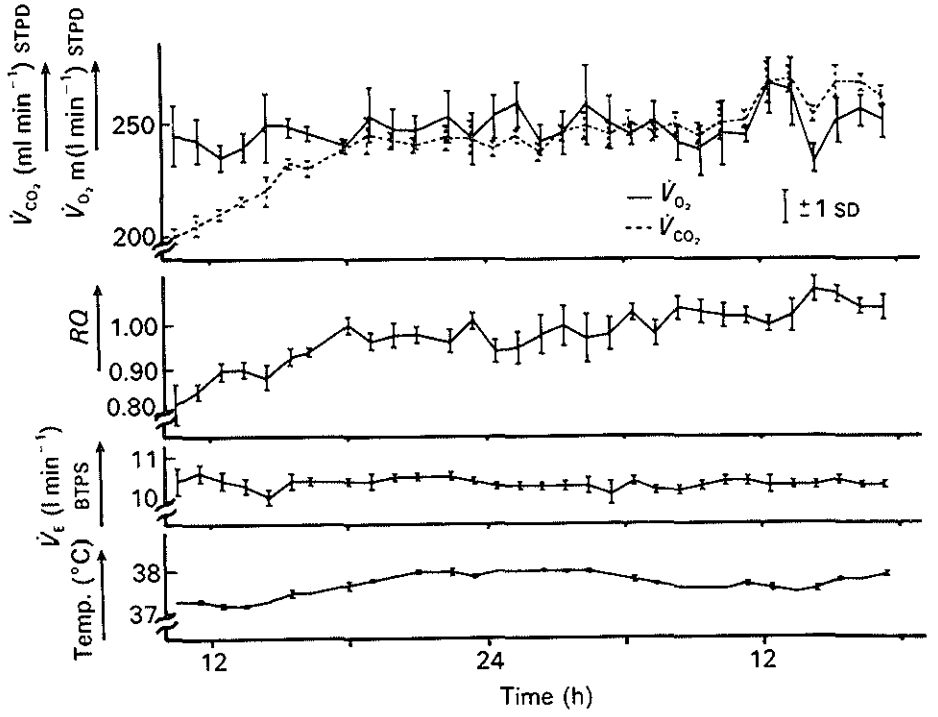

Figure 3. Recording of a 32 h observation period in one patient with a mean $F_I O_2$ = 0.4000. For the first hour of this observation the patient was in a fasting state with a mean RQ = 0.82. After this a high caloric nutrition scheme of 5.24 MJ per 24 hour lipid, 6.98 MJ per 24 hour carbohydrate and 2.33 MJ per 24 hour protein was started. After a 20 h period the RQ rises significantly above 1.00, presumable because of lipid synthesis.

regime was started. After a 20 h period the RQ increased significantly above 1.00. This was presumably caused by lipid synthesis, because a 32 h observation period with a moderate caloric intake did not result in a $V'CO_2$, exceeding $V'O_2$.

The high caloric nutrition caused such an increase in $V'CO_2$, that respiratory distress was induced during weaning from the ventilator, due to the patient's limited pulmonary reserves. Mean values and the standard deviations were calculated every hour from six observation cycles giving 12 data. The standard deviations of the $V'O_2$, $V'CO_2$ and V'E determinations in this non-sedated patient were comparable with the results of Roberts et al [19] and Westenskow et al [10] in sedated patients. The standard deviations were

dependent on both the accuracy of the various measuring devices and the changes in patient activity within the one-hour periods. After sedation and muscle relaxation smaller standard deviations were observed (figure 4), most probably resulting from a more stable ventilation and metabolic rate. A larger

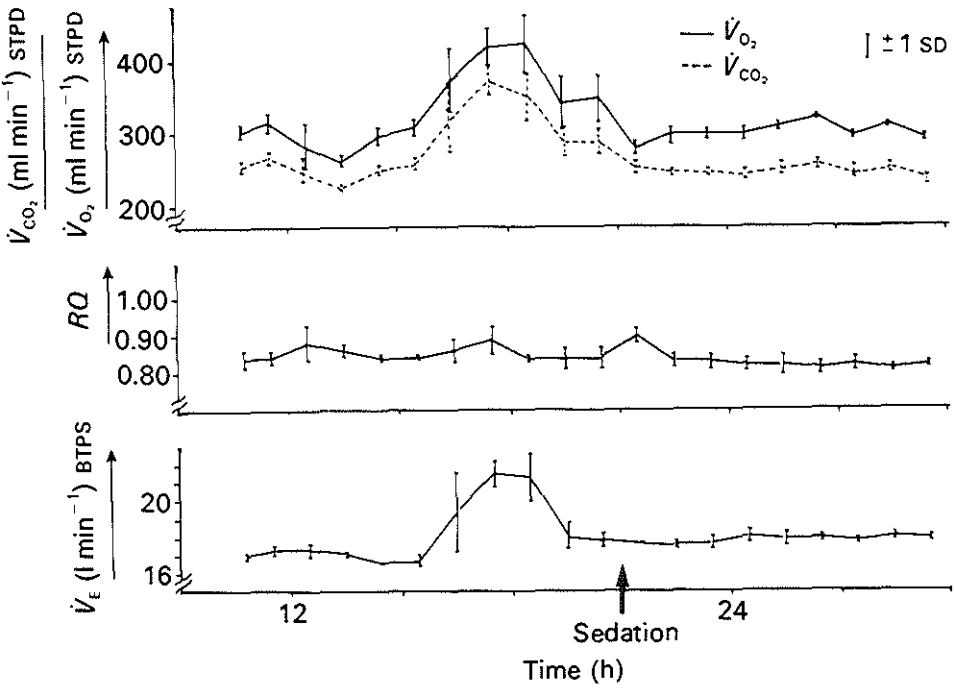

Figure 4. Effect of sedation on the standard deviation in the $V'O_2$, $V'CO_2$, RQ and V'_E measurement in one patient. The arrow marks the instant of sedation (Diazepam) and muscle relaxation (Pancuronium). F_I,O_2 = 0.4000.

fluctuation in minute ventilation (V'_E) in the patient without sedation was caused by triggering of the ventilator due to spontaneous breathing activity. Corresponding changes in $V'O_2$ and $V'CO_2$ are illustrative of the patient's restlessness.

The standard deviation of $V'O_2$ appeared to be higher than that of $V'CO_2$. A reason for this difference might be that $V'O_2$ is calculated from four measured variables F_I,O_2, F_E,O_2, F_E,CO_2 and V'_E, compared with two variables for $V'CO_2$, being F_E,CO_2 and V'_E. Less accumulation of random fluctuations will occur when the number of basic variables is smaller [18].

5. Conclusion

A simple and inexpensive system for accurate semi-continuous long-term measurements of respiratory gas exchange during mechanical ventilation has been presented. Frequent automatic calibration diminished the dependence on stability demands of the gas analyzers without losing accuracy. A programmable pocket calculator having data sampling functions was satisfactory for long-term on-line observations and data analysis. Besides the financial aspects our equipment has the following advantages:

1. Flexibility, i.e. the possibility of coupling it to more and various types of ventilators, instead of dedication to one ventilator.
2. Flexibility in software: programs can be modified easily. In most commercially available equipment modifications can be made only with difficulty.
3. This system is less bulky than systems based on a mass spectrometer or Douglas bag method.
4. Most gas analyzers are sensitive to pressure changes, therefore we measured all gas fractions at atmospheric conditions by using sampling bags with a small overflow opening.
5. The machine samples a volume-weighted F_I,O_2.
6. Most commercially available equipment is calibrated every few hours, mostly with one calibration gas and sometimes even not automatically. Our apparatus calibrates itself automatically by a two-point calibration every 10 min.

The advantage of this frequent calibration was illustrated in figure 3. When gas analyzers are only calibrated every few hours the increase in $V'CO_2$ above $V'O_2$ could also be explicable by drift of the device. Because of the frequent calibration, drift could be rejected as an explanation. These changes were thus of biological origin.

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Chapter 4

Metabolic and respiratory effects of enteral nutrition in patients during mechanical ventilation

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Abstract

The effect of enteral feeding on O_2-consumption ($V'O_2$) and CO_2-production ($V'CO_2$) was studied in 9 ventilator-dependent patients, who were in a stable condition without signs of hypermetabolism. Resting energy expenditure (REE) in postabsorptive state was assessed and enteral feeding was started by continuous drip (480 kcal carbohydrate, 360 kcal vegetable fat and 160 kcal milkprotein: 6.4 g Nitrogen/1000 ml). Patients were given a moderate and a high caloric intake: 1.5 and 2.0 times REE. $V'O_2$ and $V'CO_2$ were determined for a 24 h period, beginning 7 h after the start of the dietary intake. Significantly greater increases in $V'O_2$ and $V'CO_2$ and RQ were found during high caloric intake compared with the moderate caloric intake. $V'O_2$, $V'CO_2$ and arterial blood-gases were obtained in 4 patients during weaning from the ventilator. The increase in $V'CO_2$ induced by the high caloric feeding resulted in a rise in arterial CO_2 tension (Pa,CO_2) and respiratory distress. High caloric enteral nutrition can cause a significant increase in $V'CO_2$ inducing respiratory distress during weaning from the ventilator in patients with limited pulmonary reserves. Moderate caloric nutrition will be preferable to these patients in order to facilitate the weaning.

1. Introduction

Nutritional support is associated with increases in O_2-consumption ($V'O_2$) and CO_2-production ($V'CO_2$) compared with values in the postabsorptive state [1, 2, 3]. The magnitude of changes in $V'O_2$ and $V'CO_2$ during total parenteral nutrition using glucose as nonprotein energy source appears to depend on the metabolic state of the patient [1]. The use of fat emulsions as a source of nonprotein calories in total parenteral nutrition is associated with smaller increases in $V'CO_2$ than occurs with isocaloric amounts of glucose [4, 5]. Elevation of $V'CO_2$ leads to an increase in minute ventilation and respiratory rate by ventilatory control mechanisms [6]. However, in patients with impaired pulmonary function and limited ventilatory reserves an increase in

$V'CO_2$ can induce respiratory distress [7,8]. Hypercapnia during mechanical ventilation has been described in such patients within hours after total parenteral nutrition was started [8]. Increased $V'CO_2$ leading to hypercapnia during weaning from the ventilator has also been described in patients recovering from the adult respiratory distress syndrome [9].
We studied the effect of enteral nutrition on $V'O_2$ and $V'CO_2$ in patients on long-term mechanical ventilation. The effect of nutritional support on $V'O_2$, $V'CO_2$ and arterial blood-gases was also studied during spontaneous breathing after discontinuation of ventilatory support.

2. Patients and methods

2.1. Patients

From November 1983 to January 1986, 9 patients, 6 males and 3 females, aged from 38 to 72 years (mean 57.5) were studied. The patients were on ventilatory support for neurological or chronical pulmonary disease for 12 to 38 days before the study (Table 1). All patients were in a stable condition

TABLE 1
Patient data

Patient No	Age yrs	Sex m/f	BSA m^2	Primary diagnosis	Serum Alb. $g.l^{-1}$	CHI %
1	38	m	2.02	Guillain-Barré Syndrome	30	50
2	39	f	1.60	Guillain-Barré Syndrome	33	57
3	57	m	1.65	Guillain-Barré Syndrome	24	70
4	51	m	2.21	Guillain Barré Syndrome	32	68
5	58	f	1.37	Chronic polyneuropathy	28	52
6	72	f	1.75	Tetanus	30	76
7	66	m	2.00	Polyneuropathy-carcinoma	25	41
8	65	m	2.00	Polyneuropathy-carcinoma	18	55
9	72	m	1.92	COPD history of TBC	26	62
Mean	58					
SD	13					

BSA = body surface area; Alb. = albumin; CHI = creatinine height index; SD = standard deviation; COPD = chronic obstructive pulmonary disease; TBC = tuberculosis.

without hepatic, renal or circulatory failure; none were febrile. For nutritional assessment the serum albumin levels and the creatinine height index were obtained according to standard techniques [10]. The patients were on controlled ventilation through a cuffed tracheostomy tube with a volume-cycled ventilator (Siemens Servo-ventilator 900 B or 900 C, Siemens-Elema AB, Sweden) and enteral nutrition was given through a nasogastric tube. Except for the patient with tetanus, they were not sedated or paralyzed. Four patients could breath spontaneously for short periods during the study period. The patients were breathing through a modified T-piece system separating inspiratory and expiratory gasflows in 2 patients and with the help of the continuous positive airway pressure (CPAP) system of the Siemens Servo-ventilator 900 C in the other 2 patients.

2.2. Indirect calorimetry

Oxygen uptake ($V'O_2$), carbon dioxide production ($V'CO_2$) and respiratory quotient (RQ) were determined using an indirect calorimetric technique [11]. The system used was suitable for both long-term (> 2 days) and frequent metabolic monitoring during mechanical ventilation and periods of weaning from the ventilator. Basic variables for the metabolic measurements were expiratory minute ventilation ($V'_{E,ATPS}$), F_I,O_2 (fractional O_2-concentration in inspiratory gas), F_E,O_2 and F_E,CO_2 (mixed expired fractional concentrations of O_2 and CO_2 respectively).

The V'_E was measured using the Silverman flowtransducer from the Siemens Servoventilator, calibrated before and after the measurement with a Bear Ultrasonic spirometer. The F_I,O_2 and F_E,O_2 were measured using a paramagnetic oxygen-analyzer (Mijnhardt Bunnik, Holland). The F_E,CO_2 was measured using an infrared carbon dioxide-analyzer (Siemens type Ultramat M). The analyzers were calibrated with calibration-gases, covering the gas-concentration range expected in the patients.

The equations from which the metabolic variables were calculated including the Haldane correction for the RQ dependent difference in inspiratory and expiratory volume, are the same as those used in similar systems [12, 13].

Our system differs in that we use low cost components such as a HP 41 CX pocket calculator for sampling, processing and automatic calibrations at 10 min intervals, and a HP 82143 A printer. The accuracy of the gas exchange variables was tested by an approach, comparable with that described by Damask et al. [14], based on the controlled burning of organic fuels. Comparing the estimated $V'O_2$ and $V'CO_2$ respectively with the predicted values we found a maximum relative deviation of 2% in both $V'O_2$ and $V'CO_2$, while the maximum variation coefficients were 3%. For the RQ the maximum relative deviation was 1.5% and the maximum variation coefficient 1.5%.

2.3. Nutrition

Enteral nutrition was given through the nasogastric tube by continuous flow using an IVAC-pump (IVAC corporation San Diego CA.).

Nutrison^R (Nutricia, Zoetermeer, Holland) was used consisting of 480 kcal carbohydrates, 360 kcal vegetable fat and 160 kcal milkprotein: 6.4 g Nitrogen/1000 ml. The composition of the enteral nutrition is in agreement with published recommendations [15]. The amount of vitamins and minerals are the recommended daily allowances of the WHO.

The amounts of each constituent were calculated from the composition obtained from the manufacturer's specifications. Energy contents of the diet were calculated from published values. The energy content of the protein was included in the total energy content of the diet. Exact intake was measured by difference in weights of full and emptied containers.

2.4. Study protocol

The study protocol is presented schematically in Figure 1. After an overnight fast the hourly mean of $V'O_2$ and $V'CO_2$ was obtained during 1 h to establish actual resting energy expenditure (REE). The actual resting energy expenditure was compared with the predicted value according to the Harris and Benedict equations. The actual REE was used to calculate the dietary intake. Two enteral diets, with the same composition, but with moderate and

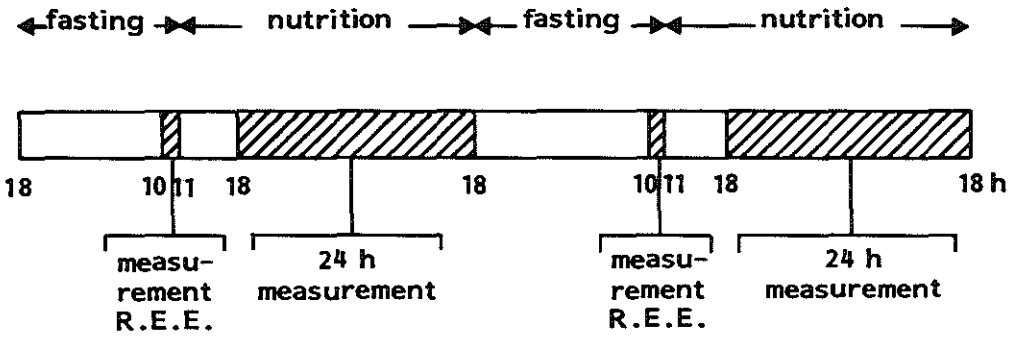

Figure 1. Schematic presentation of the study protocol. The two 24 h measurements of metabolic variables are respectively for caloric intakes of 1.5 and 2.0 times the resting energy expenditure (REE).

high caloric intake were administered. The moderate caloric intake per 24 h was set as 1.5 times the REE and the high caloric intake as 2.0 times the REE.

After the measurements in fasting state, the moderate caloric intake was started. Seven hours after starting the dietary intake a 24 h balance study was performed, determining intake, $V'O_2$, $V'CO_2$ and urine nitrogen output. After the 24 h balance study enteral nutrition was stopped and the patient fasted 16 h to obtain a second REE. Then the high caloric intake was started. A second 24 h balance study started 7 h later.

The mean $V'O_2$, $V'CO_2$, RQ and REE over the 24 h was calculated. The values obtained in the postabsorptive state were compared with mean values obtained during a stable 2 h period at the end of the balance study. The 24 h nitrogen intake was compared with the urinary nitrogen output.

Statistical analysis was performed on the increase of $V'O_2$, $V'CO_2$ and RQ comparing the differences between moderate caloric intake and postabsorptive state with the differences between high caloric intake and postabsorptive state.
Weaning studies were performed in the postabsorptive state and during the balance studies. Immediately after measuring in fasting state during controlled ventilation the patient was breathing spontaneously for a period of 30 min - 1 h. During this period V'_E, respiratory rate, $V'O_2$, and $V'CO_2$ were obtained. Arterial blood-gases were obtained at the end of the weaning period. The next day the weaning procedure was repeated during the dietary intake.
The results obtained during spontaneous breathing in the postabsorptive state were compared with those obtained during weaning in the balance studies. For statistical analysis a Student T-test for paired observations was used.

3. Results

The mean REE of the 9 patients in the postabsorptive state was 1695 kcal/day, which was 113% of predicted (Table 2).
In Figure 2 the means and SD of $V'O_2$, $V'CO_2$ and RQ of the 9 patients are shown in postabsorptive state and during the 24 h balance studies of the two feeding regimens with 6 h intervals. During the last 6 h of the balance studies $V'O_2$, $V'CO_2$ and RQ did not change significantly, suggesting that a steady state had been reached. Table 2 presents the individual changes in $V'O_2$, $V'CO_2$ and RQ together with their means and SD as caused by the two feeding regimens. The values in the postabsorptive state are compared with the values obtained during a stable 2 h period at the end of the 24 h balance studies. High caloric intake appears to increase significantly $V'O_2$, $V'CO_2$ and RQ with respect to moderate caloric intake ($p = 0.04$, $p = 0.009$, $p = 0.03$ respectively). Four patients (patients no. 1, 2, 5 and 9) showed only a small

TABLE 2

The data of REE, $V'O_2$, $V'CO_2$ and RQ in postabsorptive state and during the two nutritional intakes of the individual patients with the means and SD.

Pat No.:	Postabsorptive state REE kcal/24 h			Postabsorptive state			Moderate cal. nutrition			Postabsorptive state			High cal. nutrition		
	pred.	meas.	% pred.	$V'O_2$ l/min/ m^2 STPD	$V'CO_2$ l/min/ m^2 STPD	RQ	$V'O_2$ l/min/ m^2 STPD	$V'CO_2$ l/min/ m^2 STPD	RQ	$V'O_2$ l/min/ m^2 STPD	$V'CO_2$ l/min/ m^2 STPD	RQ	$V'O_2$ l/min/ m^2 STPD	$V'CO_2$ l/min/ m^2 STPD	RQ
1	1595	1584	99	.111	.096	0.86	.121	.112	0.92	.121	.099	0.82	.123	.130	1.06
2	1320	1440	109	.129	.105	0.81	.144	.137	0.96	.141	.117	0.84	.156	.156	1.00
3	1402	1961	140	.173	.131	0.76	.176	.154	0.87	.173	.131	0.76	.217	.183	0.84
4	1909	2145	112	.143	.102	0.71	.156	.131	0.83	.143	.102	0.71	.173	.147	0.85
5	1147	1123	98	.117	.098	0.84	.128	.127	0.99	.116	.097	0.84	.135	.142	1.05
6	1312	1393	106	.115	.089	0.77	.136	.125	0.92	.119	.086	0.72	.142	.139	0.98
7	1632	1949	119	.147	.107	0.73	.168	.130	0.77	.144	.101	0.70	.173	.147	0.85
8	1632	1967	121	.142	.113	0.80	.153	.140	0.91	.142	.113	0.80	.169	.160	0.95
9	1525	687	111	.125	.106	0.85	.130	.114	0.88	.134	.102	0.76	.153	.162	1.06
AVG	1497	1695	113	.133	.105	0.79	.146	.129	0.89	.137	.105	0.77	.160	.152	0.96
SD	227	337	13	.019	.012	0.05	.019	.013	0.07	.017	.013	0.05	.027	.015	0.09

REE = resting energy expenditure; pred. = predicted; meas. = measured; STPD = standard temperature, pressure dry; AVG = mean; SD = standard deviation.

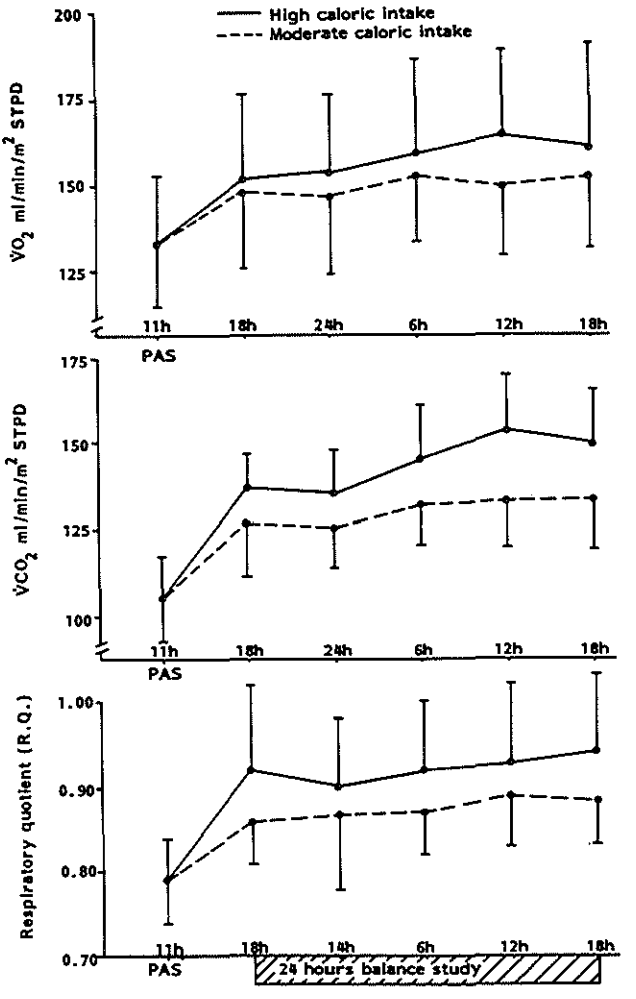

Figure 2. The means and SD of $V'O_2$, $V'CO_2$ and RQ of the 9 patients in postabsorptive state and during the two nutritional intakes. PAS = postabsorptive state.

increase in $V'O_2$ compared with the increase in $V'CO_2$ during high caloric intake. In these patients a RQ $\geq$ 1.00 was found. The mean REE in the postabsorptive state of these 4 patients was 104% of predicted as compared with 119% of predicted in the remaining 5 patients.

A significantly positive correlation was found between the increase in $V'O_2$ due to the high caloric intake and the REE in the postabsorptive state expressed as percentage of predicted ($p < 0.05$).

Table 3 shows the energy intake and expenditure and the nitrogen intake and output obtained from the 24 h balance study for the two nutritional intakes. Comparing the moderate and high caloric intake on the average, only a small increase in energy expenditure was found. During the moderate caloric intake the urinary nitrogen balance was only slightly positive.

TABLE 3

Energy intake and expenditure and nitrogen intake and output, measured during the two different nutritional intakes.

	Moderate caloric intake	High caloric intake
Energy intake kcal/24 h ± SD	2555 ± 553	3710 ± 600
Nitrogen intake gN/24h ± SD	15.7 ± 3.5	22.8 ± 3.4
Energy expenditure kcal/24 h ± SD	1906 ± 366	2070 ± 402
Nitrogen output gN/24h ± SD	13.2 ± 6.7	13.9 ± 5.7

Table 4 shows physiological measurements obtained during weaning from the ventilator in 4 patients in the postabsorptive state and during the two different nutritional regimens. Compared with the postabsorptive state nutritional support caused increases in minute ventilation, respiratory rate, $V'O_2$ and $V'CO_2$. During the moderate caloric intake, the different variables increased significantly, with exception of the arterial CO_2 tension (Pa,CO_2), indicating that the patients by increasing their minute ventilation were able to maintain their Pa,CO_2 at the same level as during the postabsorptive state. The high caloric intake caused greater increases in the different variables, compared with the postabsorptive state. A comparable increase in minute ventilation was found during both moderate and high caloric intake, however, during the high caloric intake a significant increase in Pa,CO_2 was found.

4. Discussion

The aim of the study was to investigate the effects of enteral nutrition on metabolic variables in ventilator-dependent patients and the consequences of these changes for weaning from the ventilator.

We had previously found that patients with respiratory insufficiency caused by the Guillain-Barré syndrome were in negative nitrogen balance for weeks when a nutritional intake of 2000 kcal and 12.8 g Nitrogen (80 g protein) per 24 h was provided (unpublished observations). In these patients a fall in serum albumin and creatinine excretion was found. Increasing caloric and protein intake was suggested as a possible means of curtailing these losses. In this study we investigated the effects of a moderate and high caloric intake using different infusions rates of the same, commonly used, standard diet. The carbohydrate-fat ratio of the diet was 55 : 45. In 9 patients we studied the effects of a moderate and high caloric intake on $V'O_2$, $V'CO_2$ and RQ during mechanical ventilation; in 4 of the 9 patients the nutritional effects could also be studied during periods of weaning from the ventilator. Eight patients in this study were on long-term mechanical ventilation for respiratory failure due to muscle weakness caused by neurological illness; 1 patient was ventilated for respiratory failure due to previous extensive tuberculosis. These patients had no further organ failure apart from respiratory insufficiency. They were all on enteral nutrition before the study period and they had, according to the serum albumin levels and creatinine/height index, signs suggestive of malnutrition.

The mean actual REE in the postabsorptive state was 13.2% above the predicted value, a percentage to be expected in non-hypermetabolic patients [7]. Patient 3 had an unexpected large difference between actual and predicted REE, presumably due to autonomic dysfunction caused by the Guillain-Barré syndrome [16].

The study consisted of two 24 h measurements separated by another 24 h (Fig. 1). The 24 h balance study was initiated 7 h after the start of the enteral nutrition; the greater part of the increases in $V'O_2$ and $V'CO_2$ occurred in these 7 h (Fig. 2). The periods of weaning during the 24 h balance study were assumed to have a minor influence on the metabolic

TABLE 4

Physiological measurements during weaning from the ventilator in 4 patients in postabsorptive state and during nutritional support.

	Postabsorptive state	Moderate caloric intake	p-value	Postabsorptive state	High caloric intake	p-value
MV l/min BTPS ± SD	7.8 ± 1.9	9.5 ± 3.0	p = 0.006	8.1 ± 2.2	9.9 ± 3.2	ns
Resp rate/min ± SD	30 ± 11	34 ± 13	p = 0.01	29 ± 11	36 ± 12	p = 0.03
$V'O_2$ l/min/m^2 STPD ± SD	.145 ± .022	.158 ± .027	p = 0.001	.141 ± .026	.170 ± .032	p = 0.002
$V'CO_2$ l/min/m^2 STPD ± SD	.098 ± .008	.116 ± .016	p = 0.0002	.098 ± .011	.136 ± .028	p = 0.0006
Pa,CO_2 kPa ± SD	6.0 ± 1.4	6.0 ± 1.3	ns	5.6 ± 1.3	6.7 ± 1.2	p = 0.007

MV = minute ventilation; BTPS = body temperature, pressure saturated; STPD = standard temperature, pressure dry; ns = not significant.

variables, because gas exchange was only disturbed for a relatively short time.

The results of our study showed significantly larger increases in $V'O_2$, $V'CO_2$ and RQ for the high caloric than the moderate caloric intake. Large differences were found in the increases of $V'O_2$ during the high caloric intake. These differences are known to be related to the metabolic state of the patients [1]. According to the results of studies with total parenteral nutrition the patients in our study with a low ratio between actual and predicted REE had the smallest increase in $V'O_2$ [1].

In contrast to many studies of the effects of total parenteral nutrition on metabolic variables, the number of investigations of enteral nutrition is small [3, 17, 18]. Our results are comparable with investigations of parenteral and enteral nutrition [3, 4, 17]. Our study differs from the other investigations of enteral nutrition in the long-term metabolic measurements of ventilator-dependent patients and the measurements during weaning from the ventilator.

Investigations of the effects of an elevated $V'CO_2$ on weaning were published on 2 patients who recovered from the adult respiratory distress syndrome and on postabsorptive patients during mandatory minute ventilation [9, 17]. In both studies different caloric intakes were used and an elevated $V'CO_2$ leading to hypercapnia during weaning was found [9, 17]. We found that the moderate caloric intake caused an increase in $V'CO_2$, which was tolerated by the 4 patients studied during periods of weaning, as evidenced by unchanged arterial CO_2 tensions. During the high caloric intake, because of limited reserves in minute ventilation, patients were unable to increase CO_2 excretion sufficiently during weaning, resulting in a rise in arterial CO_2 tension.

The nutritional support of patients on long-term mechanical ventilation due to chronic respiratory insufficiency must be adapted to the actual resting energy expenditure in the postabsorptive state. High caloric intake will cause a massive increase in CO_2 production leading to respiratory distress during spontaneous breathing in patients with respiratory muscle weakness, moderate caloric nutrition is preferable in these patients for purpose of weaning.

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Chapter 5

Effects of dietary protein content on weaning from the ventilator

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Abstract

The effect of enteral nutrition with different protein contents on metabolic and ventilatory variables during weaning from the ventilator was studied in 10 mechanically ventilated patients as indication of the effect of protein on the ventilatory drive. Resting energy expenditure (REE) was assessed in the postabsorptive state and 2 enteral regimens both with a fat and carbohydrate content 1.25 times REE but with a moderate (190 mg N/kg/24 h) and high (260 mgN/kg/24 h) protein content were given to the patients in random order. Minute ventilation (V'E), CO_2-production ($V'CO_2$), O_2-consumption ($V'O_2$) and arterial blood-gases were obtained during mechanical ventilation and weaning. Compared with postabsorptive state, both intakes gave significant increases in $V'CO_2$ during mechanical ventilation; the $V'CO_2$-values were equal for both regimens before the start of the weaning procedures. High protein intake was associated with significantly higher $V'CO_2$ during weaning and smaller increases in Pa,CO_2 from mechanical ventilation to the end of the weaning period, compared with the moderate protein intake. This result is in agreement with studies in which an infusion of amino-acids in spontaneously breathing healthy volunteers increased ventilatory drive. For mechanically ventilated patients high protein nutrition may be beneficial in enhancing weaning from the ventilator.

1. Introduction

Nutritional support affects ventilation in different ways. Nutrition increases O_2-production ($V'O_2$) and CO_2-production ($V'CO_2$) compared with values in the postabsorptive state [1, 2, 3]. Elevation of $V'CO_2$ leads to an increase in minute ventilation and respiratory rate by ventilatory control mechanisms [4]. This increase in $V'CO_2$ can induce respiratory distress in patients with impaired pulmonary function and limited ventilatory reserves [5, 6]. A relationship between nutrition and ventilatory drive has been described. In healthy volunteers protein has been found to increase ventilatory drive during rebreathing of CO_2 [7]. This effect of protein on the ventilatory drive appears to be centrally mediated through a decreased synthesis of serotonin in the

brain [8].

To study the effect of protein on ventilation we administered 2 enteral regimens with different protein contents to patients on long-term mechanical ventilation. Metabolic measurements were performed in these patients during mechanical ventilation and weaning from the ventilator. The effect of protein on ventilation was evaluated by determining minute ventilation (V'_E), $V'O_2$, $V'CO_2$ and arterial blood-gases during weaning.

2. Patients and methods

2.1. Patients

From August 1986 till August 1987, 10 patients, 5 males and 5 females, aged 53 to 81 years were studied. The patients were suffering from neurological or cardio-pulmonary diseases and were mechanically ventilated between 13 and 34 days before the study (Table 1). The mechanical ventilation had to be continued in these patients, because attempts to wean from the ventilator had failed. During the studyperiod the patients were haemodynamically stable, and showed no signs of hepatic or renal failure. Except for patient no. 4, the patients showed no signs of peripheral edema. None were febrile. Serum albumin levels and creatinine height index were used as measures of nutritional status [9, 10].

The patients were on controlled ventilation through a cuffed tracheostomy tube with a volume-cycled ventilator (Siemens Servo-ventilator 900C, Siemens-Elema, Sweden) and they were not sedated or paralyzed. Mechanical ventilation was adjusted to normocapnia and to a Pa,O_2-value above 10 kPa. The patients were weaned using the continuous positive airway pressure (CPAP) system of the Siemens Servo-ventilator. Due to the limited ventilatory reserves of the patients the periods of weaning lasted 30 to 60 min and were ended when the patients were too short of breath or tired to continue. The aim of the study and the sequence of the studyprotocol were explained to the patients and their relatives and informed consent was obtained.

TABLE 1
Patient data

Patient No	Age yrs	Sex m/f	Primary diagnosis	Serum Alb. $g.l^{-1}$	CHI %
1	81	f	COPD, congestive heart failure	26	72
2	55	m	Congestive heart failure, lung carcinoma	21	29
3	71	f	Amyotrophic Lateral Sclerosis	29	91
4	74	f	Congestive heart failure	18	74
5	70	m	COPD, chest trauma	25	87
6	68	m	COPD, pulmonary emboli	24	88
7	72	m	COPD, pneumonia	23	44
8	59	f	Myotonic Dystrophy	28	60
9	53	f	Polyneuropathy	28	51
10	69	m	COPD, stenosis of the trachea	29	43
Normal values				36 - 48	>80

Alb = albumin
COPD = chronic obstructive pulmonary disease
CHI = creatinine height index

2.2. Nutrition

Enteral nutrition was given through a nasogastric tube by continuous flow using an IVAC-pump (IVAC Corporation, San Diego, CA., USA). Two enteral diets, differing in protein content, were administered. As moderate protein nutrition, Nutrison^{R} (Nutricia, Zoetermeer, Holland) was used, consisting of 480 kcal carbohydrates, 360 kcal vegetable fat and 160 kcal milk protein: 6.4 gr N per 1000 ml, with a nitrogen: nonprotein kcal ratio 1 : 131.

To increase the protein content of the enteral nutrition. 14 gr Proteine 88^{R} (Wander, Uden, Holland), consisting of 12.3 gr protein, was added to 1000 ml Nutrison^{R}. The protein-rich solution consisted of 480 kcal carbohydrates, 360 kcal fat and 210 kcal protein: 8.4 N per 1000 ml. The nitrogen: nonprotein kcal ratio was 1 : 100.

The amounts of each constituent were calculated from the composition obtained from the manufacturer's specifications. The energy contents of the diet were calculated from published values. Exact intake was measured by difference in weights of full and emptied containers.

2.3. Indirect calorimetry

Oxygen uptake ($V'O_2$), carbon dioxide production ($V'CO_2$) and respiratory quotient (RQ) were determined using an indirect calorimetric technique, described in a previous paper [11]. The system is suitable for both long-term and frequent metabolic monitoring during mechanical ventilation and weaning with the CPAP-system. Basic variables from the metabolic measurements were expiratory minute ventilation (V'_E, ATPS), F_I,O_2 (fractional O_2-concentration in inspiratory gas), F_E,O_2 and F_E,CO_2 (mixed expired fractional concentrations of O_2 and CO_2 respectively).

The V'_E was measured using the Silverman flow transducer from the Siemens Servo-ventilator, calibrated before and after the measurement with a wet spirometer. The F_I,O_2 and F_E,O_2 were measured using a paramagnetic oxygen-analyzer (Mijnhardt type Oxylyzer, Mijnhardt Bunnik, Holland). The F_E,CO_2 was measured using an infrared carbon dioxide-analyzer (Siemens type Ultramat M). The analyzers were calibrated with calibration-gases covering the gas-concentration range in the patients.

The equations, from which the metabolic variables were calculated, including the Haldane correction for the RQ dependent difference in inspiratory and expiratory volume, are the same as those used in similar systems [12, 13].

2.4. Laboratory measurements

Nitrogen output was determined by measuring nitrogen in 24 h urine using the Dumas technique. Arterial pH, P,CO_2, P,O_2 and bicarbonate levels were obtained using the ABL3 (Radiometer Copenhagen). Total blood CO_2 content was calculated using the standard formula [14].

2.5. Study protocol

The study protocol is presented schematically in Figure 1. After an overnight fast V'_E and $V'O_2$ were determined for 1 h during mechanical ventilation, followed by a period of weaning. Before and at the end of the weaning procedure, arterial blood-gases were obtained. The hourly mean of $V'O_2$ and $V'CO_2$ during mechanical ventilation was used to establish actual resting energy expenditure (REE). The actual resting energy expenditure was compared with the predicted value according to the Harris and Benedict

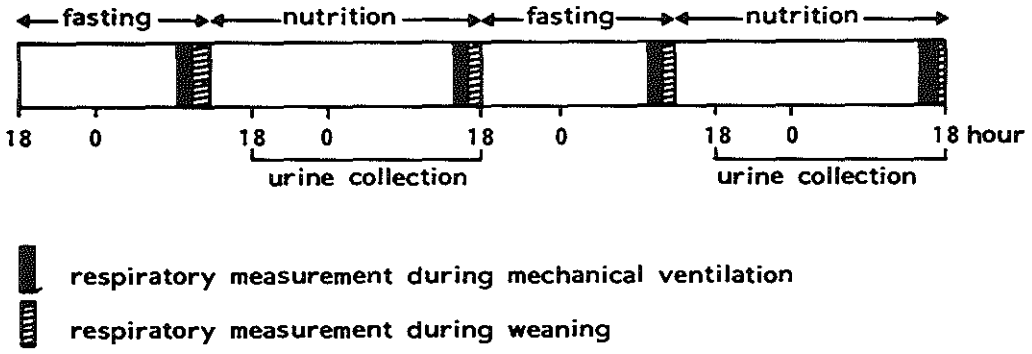

Figure 1. Study protocol

equations. The actual REE was used to calculate dietary intake.

After the measurements in postabsorptive state, enteral nutrition was started. The carbohydrate and fat intake per 24 h was set at 1.25 times the REE. The patients were randomized to receive either the moderate or the high protein regimen first. The nutrition was administered for 30 h. Approximately 27 h after the start of the enteral nutrition $V'O_2$ and $V'CO_2$ were measured during 1 h of mechanical ventilation, followed by a period of weaning. Before and at the end of the weaning period, arterial blood-gases were obtained. During the last 24 h of the nutritional intake, urine was collected to measure the nitrogen output. After stopping the enteral feed, the patients fasted for 16 h to obtain a second REE. The second nutritional intake was then started and the measurements were repeated.

Mean $V'O_2$, $V'CO_2$ and RQ, obtained during mechanical ventilation in the postabsorptive state, were compared with the values after 27 h of enteral nutrition, to evaluate the effect of the intakes on the metabolism of the patients. The nitrogen output in the urine was compared for both nutritional

regimens.
During weaning V'_E, $V'O_2$, $V'CO_2$, RQ and arterial blood-gases were obtained. Because one patient was unable to wean for longer than 30 min during both nutritional intakes, and a second patient could only wean for 30 min during the high protein intake, the measurements at 30 min after the start of weaning, which were available for all patients, were analyzed. The values obtained during moderate protein intake were compared with those obtained during high protein intake. To evaluate the influence of the $V'CO_2$ and blood-gases during mechanical ventilation on the values during weaning, the differences in $V'CO_2$ and Pa,CO_2 between weaning and mechanical ventilation were compared for both nutritional intakes. Blood-gases during mechanical ventilation were compared with values during weaning.
For statistical analysis Student-T-tests were used, appropriate for cross-over clinical trials [15]. Using these tests, time-trends (period effects) between the first and the second study period were investigated. Carry-over effects (residual effects) in the second period, from treatment applied in the first period, were also analyzed. Differences with a p-value less than 0.05 were considered statistically significant.

3. Results

There were no significant differences in $V'O_2$, $V'CO_2$, REE and arterial blood-gases, during mechanical ventilation and weaning, between the 2 measurements in the postabsorptive state. The actual REE in the postabsorptive state was between 1.00 and 1.03 times the predicted values, suggesting that the patients were not hypermetabolic.
The energy intakes for the moderate and high protein nutritional regimens amounted to 1691 ± 325 and 1745 ± 376 nonprotein kcal per 24 h (means and standard deviations) respectively; the difference was not significant. The nitrogen intakes were 12.88 ± 2.48 and 17.44 ± 3.76 g N per 24 h, corresponding to 192 mg and 261 mg N/kgBW/24 h. The urinary nitrogen output increased from 9.80 ± 2.14 g N, in the moderate protein regimen, to 11.64 ± 4.49 g N per 24 h in the high protein intake; this

TABLE 2
Effects of enteral nutrition on metabolic variables during mechanical ventilation

	Postabsorptive state (mean ± SD)	Moderate protein intake (mean ± SD)
$V'CO_2$ l/min/m² STPD	.095 ± .008	.113 ± .010**
$V'O_2$ l/min/m² STPD	.111 ± .012	.119 ± .014*
R.Q.	0.86 ± 0.04	0.96 ± 0.06**
	Postabsorptive state (mean ± SD)	High protein intake (mean ± SD)
$V'CO_2$ l/min/m² STPD	.096 ± .010	.116 ± .015**
$V'O_2$ l/min/m² STPD	.115 ± .011	.120 ± .015
R.Q.	0.83 ± 0.03	0.97 ± 0.05**

STPD = Standard Temperature Pressure Dry
Difference between nutrition and postabsorptive state:
* = significant difference ($p < 0.05$)
** = significant difference ($p < 0.01$).

difference is not significant. The effects of the enteral nutrition on the metabolic measurements of the patients are shown in Table 2. Comparison of the variables in the postabsorptive state during mechanical ventilation, with the values obtained the next day, during both nutritional intakes, revealed significant increases in $V'CO_2$ and RQ for both regimens. Although the $V'O_2$ increased during both intakes, only the values obtained during the moderate protein regimen were significantly higher than the values in the postabsorptive state.

The effects of both nutritional regimens on the respiratory variables during mechanical ventilation and weaning, are shown in Table 3. During mechanical ventilation, the measurements showed no significant differences, except that the mean Pa,CO_2 during the high protein nutrition was significantly higher than the value during moderate protein intake. During weaning, the high protein intake was associated with a higher V'_E and $V'CO_2$ than the moderate protein intake; the difference in $V'CO_2$ between both intakes was statistically significant. Comparison of increases in $V'CO_2$ from mechanical ventilation to the end of the weaning for both intakes also revealed a significant difference. Although the Pa,CO_2 at the end of the

TABLE 3

Effects of enteral nutrition on respiratory variables during mechanical ventilation and spontaneous breathing

	1 Moderate Protein Intake (mean ± SD)	2 High Protein Intake mean ± SD)	Difference (1-2) (mean ± SEM)
Mechanical Ventilation			
$V'CO_2$ l/min/m² STPD	.113 ± .010	.116 ± .015	-.003 ± .003
$V'O_2$ l/min/m² STPD	.119 ± .014	.120 ± .015	-.001 ± .003
R.Q.	0.96 ± 0.06	0.97 ± 0.05	-0.01 ± 0.02
Pa,CO_2 kPa	4.2 ± 0.45	4.5 ± 0.45	-0.3* ± 0.1
Spontaneous breathing			
V'_E l/min BTPS	8.0 ± 2.1	8.5 ± 2.3	-0.5 ± 0.3
$V'CO_2$ l/min/m² STPD	.108 ± .017	.117 ± .015	-.009* ± .003
$V'O_2$ l/min/m² STPD	.135 ± .025	.143 ± .031	-.008 ± .006
R.Q.	0.82 ± 0.09	0.84 ± 0.11	-0.02 ± 0.02
Pa,CO_2 kPa	5.7 ± 0.7	5.5 ± 1.0	+0.2 ± 0.2
$\Delta V'CO_2$ l/min/m² STPD	-.005 ± .016	+.002 ± .014	-.007* ± .003
$\Delta Pa,CO_2$ kPa	+1.5 ± 0.8	+1.0 ± 1.1	+0.5* ± 0.2

STPD = standard temperature, pressure dry.
BTPS = body temperature, pressure saturated.
$\Delta V'CO_2$ = $V'CO_2$ spontaneous breathing-$V'CO_2$ mechanical ventilation.
$\Delta Pa,CO_2$ = Pa,CO_2 spontaneous breathing-Pa,CO_2 mechanical ventilation.
SD = standard deviation; SEM = standard error of the mean.
Difference between moderate and high protein intake:
* = significant difference ($p = < 0.05$)

weaning was lower during high protein intake, the difference between both intakes failed to reach statistical significance. However, during high protein intake there was a significantly smaller increase in Pa,CO_2 from mechanical ventilation to the end of weaning. The arterial pH, P,CO_2, P,O_2, bicarbonate-levels and total CO_2 contents during mechanical ventilation are compared with the values during weaning in Table 4. Significant changes are found in arterial pH and Pa,CO_2 for both nutritional intakes and in the bicarbonate-levels and total CO_2 contents only during the moderate protein intake.
No carry-over effects from treatment or any time-trends were demonstrable for any of the parameters studied.

TABLE 4

Effects of enteral nutrition on arterial blood-gases and acid-base relationship during mechanical ventilation and spontaneous breathing

	Mechanical Ventilation (mean ± SD)	Spontaneous breathing (mean ± SD)
Moderate Protein Intake:		
pH	7.48 ± 0.03	7.39 ± 0.05**
Pa,CO_2 kPa	4.2 ± 0.4	5.7 ± 0.7**
Pa,O_2 kPa	14.1 ± 3.5	13.4 ± 2.1
Bicarbonate mmol/l	23.3 ± 2.7	25.4 ± 2.7*
Total CO_2 content mmol/l	24.3 ± 2.7	26.7 ± 2.7*
High Protein Intake:		
pH	7.45 ± 0.05	7.38 ± 0.06**
Pa,CO_2 kPa	4.5 ± 0.4	5.5 ± 1.0**
Pa,O_2 kPa	13.6 ± 2.9	14.2 ± 2.8
Bicarbonate mmol/l	23.3 ± 2.1	23.3 ± 3.0
Total CO_2 content mmol/l	24.3 ± 2.1	24.6 ± 3.0

SD = Standard Deviation
Difference between spontaneous breathing and mechanical ventilation:
* = significant difference ($p < 0.05$).
** = significant difference ($p < 0.01$).

The relationship between the values of $V'CO_2$ of the individual patients during weaning at the moderate and high protein intakes is shown in Figure 2. The $V'CO_2$ at the moderate protein intake was found to correlate with the values at the high protein intakes ($r = 0.81$ $p < 0.005$). Similar correlations were found for all other variables studied during weaning.

4. Discussion

The aim of the study was to investigate the effect of enterally administered protein on metabolic and ventilatory variables in ventilator-dependent patients. The effect of protein-intake, on weaning from the ventilator, was

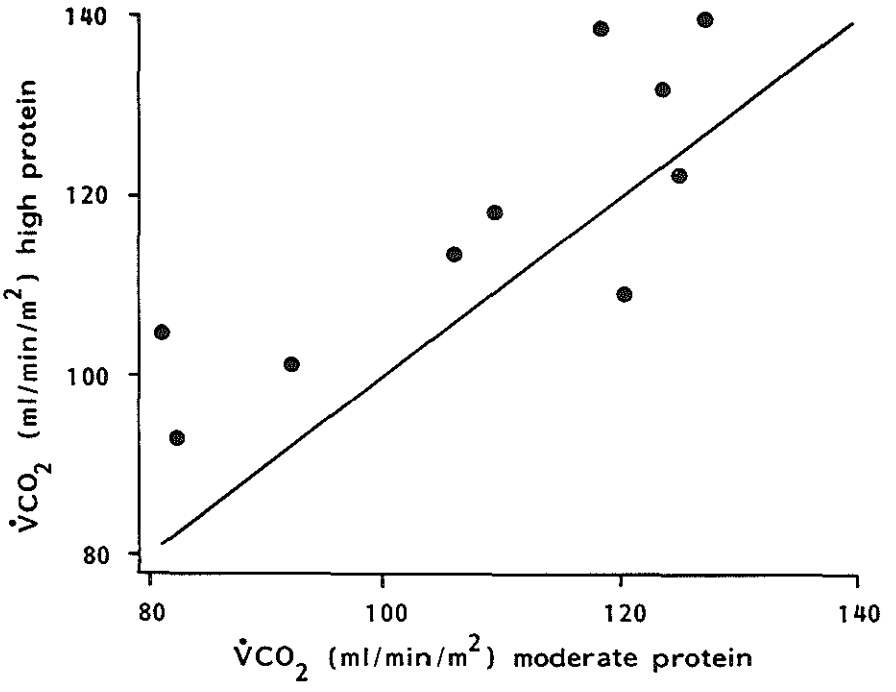

Figure 2. Relationship between the values of $V'CO_2$ of the individual patients during weaning at the moderate and the high protein nutrition. Correlation of both measurements: $r = .83$ ($p < 0.005$). The drawn line represents the line of identity.

studied as an indication of the effect of protein on the ventilatory drive. The effect of protein on ventilatory drive has been studied extensively in healthy volunteers and in undernourished patients without impaired pulmonary function [7, 8, 16]. Intravenous infusion of amino-acids was associated with increases in V'_E and $V'CO_2$ and decreases in Pa,CO_2 in both groups. The relationship between V'_E and Pa,CO_2, observed during inhalation of CO_2, showed a marked leftward shift during amino-acid infusion, indicating an increased ventilatory drive. The change in ventilatory drive was found to be correlated with changes in the plasma ratio of the neutral amino-acids to tryptophan. The enhanced ventilatory drive appeared to result, in part, from increased plasma concentrations of the branched chain amino-acids, which inhibit tryptophan uptake and serotonin synthesis in the brain [8]. The question remains to be solved whether the increased ventilatory drive associated with amino-acid infusions found in healthy

volunteers, is also demonstrable in patients with impaired pulmonary function. Especially in patients with chronic obstructive pulmonary disease (COPD) or neuromuscular illness, respiratory failure is related to decreased respiratory muscle strength, which can preclude increases in V'_E related to administration of protein [17, 18].

In this study the effect of protein on V'_E, $V'CO_2$ and blood-gases was studied during weaning from the ventilator in patients with respiratory failure due to COPD or neuromuscular illness. In all patients mechanical ventilation has been started for acute respiratory failure, and attempts to wean from the ventilator had been unsuccessful before the study was started. All patients showed low serum-albumin levels and creatinine height indices, suggesting malnourishment; however, low values of these parameters can be found, unrelated to malnourishment, in intensive care patients. The patients were not hypermetabolic, comparing actual REE in fasting state with the predicted values.

V'_E, $V'CO_2$ and Pa,CO_2 during weaning are related to the ventilatory drive of the patient and the $V'CO_2$ during the period of mechanical ventilation before weaning. The ventilatory drive during weaning is also related to the acid-base status. Pre-existing metabolic alkalosis leads to hypoventilation and hypercapnia during weaning. In the same way metabolic acidosis leads to hyperventilation and hypocapnia.

In a previous study we found that, during weaning at high energy intakes, ventilator-dependent patients were unable to increase CO_2-excretion sufficiently, resulting in a rise in Pa,CO_2 [19]. In the present study 2 enteral regimens with moderate and high protein, but with similar energy content were compared. The energy content was equal in both regimens, in order to provide an equal $V'CO_2$ during the period of mechanical ventilation before weaning. The study consisted of 2 periods of 30 h of enteral nutrition, preceded and separated by 16 h of fasting. Both nutritional intakes increased $V'CO_2$ and RQ significantly during mechanical ventilation, compared with the postabsorptive state. At the moderate protein intake the Pa,CO_2 was significantly lower, compared with the value at the high protein intake; however, the bicarbonate-levels and total CO_2 contents were equal at both intakes.

During weaning the high protein intake was associated with a higher V'_E, a higher $V'CO_2$ and a lower Pa,CO_2 compared with the moderate protein intake. Significant differences between both regimens were found in $V'CO_2$ and in the changes in $V'CO_2$ and Pa,CO_2 during the period from mechanical ventilation to weaning. The arterial bicarbonate-levels and total CO_2 contents increased significantly during weaning, compared with the values during mechanical ventilation at the moderate protein intake. During the high protein intake, no increase in arterial bicarbonate was found. These results suggest an increase in ventilatory drive, induced by the high protein intake. The small differences in both variables during weaning might be related either to the relatively small increase in protein from the moderate to the high protein intake, or to the limited ventilatory reserves of the patients. In studies using parenteral nutrition, high amino-acid intakes have been found to be associated with a significant increase in $V'CO_2$ between the moderate and high protein regimens [8].

There was no significant difference in the nitrogen output in the urine during the two study periods. Calculation of nitrogen balances in these patients has no value considering the duration of the study.

We conclude that nutritional support with a high protein intake and a moderate energy content may be beneficial in ventilator-dependent patients. A moderate energy intake, consisting of fat and carbohydrates equal to 1.25 times actual REE in the postabsorptive state, was found to be adequate, according to $V'CO_2$ and RQ values. High protein content may enhance weaning, in patients mechanically ventilated for respiratory failure, by increasing the CO_2-excretion. This result is in agreement with studies on the effect of amino-acids on the ventilatory drive in healthy volunteers.

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Chapter 6

High fat, low carbohydrate, enteral feeding in patients weaning from the ventilator

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Abstract

Objective: To study whether high fat, low carbohydrate enteral nutrition could reduce $V'CO_2$ in patients during ventilatory support and weaning from the ventilator in order to facilitate the weaning process.
Design: prospective, randomized controlled study.
Setting: Medical ICU of a university hospital.
Patients: 32 ventilator-dependent patients with a prospect of weaning from mechanical ventilaton.
Interventions: high fat feeding administered to 15 patients and standard isocaloric feeding administered to 17 patients, both in a dosage of 1.5 times basal metabolic rate.
Measurements and results: Respiratory and metabolic measurements were obtained both during mechanical ventilation and weaning procedures. High fat feeding was associated with significantly lower RQ values compared with standard feeding: the mean (± SEM) RQ values during mechanical ventilation amounted to .91 ± .01 and 1.00 ± .02 and during weaning to .72 ± .02 and .86 ± .02 for high fat and standard nutrition respectively (both p-values $< .001$). High fat feeding reduced the CO_2-excretion both during mechanical ventilation and weaning, but only the decrease during weaning proved to be significant: the mean (± SEM) CO_2-excretion amounted to .177 ± .010 and .231 ± .011 l/min STPD for the high fat and standard feeding respectively ($p < 0.01$). No significant differences were found in the Pa,CO_2 during weaning between the two feeding groups. Neither difference was found when the time spent on mechanical ventilation was compared between the two patient groups.
Conclusion: High fat, low carbohydrate enteral feeding significantly reduced the RQ values in ventilated patients with decreases in $V'CO_2$, but in this study failed to reduce the time required to wean from the ventilator.

1. Introduction

In the last decade the importance of nutritional support in mechanically ventilated patients has been underlined [1]. In patients who at first failed to wean from mechanical ventilation, the response to nutritional support was considered a prognostic sign of success in weaning [2]. However, nutritional support affects ventilation in different ways. Nutrition increases oxygen consumption ($V'O_2$) and carbon dioxide production ($V'CO_2$) due to the thermic effects of the nutrients. In patients with limited ventilatory reserves, high calorie diets in excess of energy requirements were found to precipitate respiratory distress due to increased $V'CO_2$ [3]. In particular parenteral nutrition with high carbohydrate loads resulted in markedly increased $V'CO_2$, with a respiratory quotient rising to values above 1.0 [4]. A shift from predominantly carbohydrate diets to diets with a high fat content has been suggested, to reduce respiratory quotient and $V'CO_2$ [5]. Consequently high fat, low carbohydrate nutrition would appear to be beneficial to patients with limited ventilatory reserves [6]. However, in patients with chronic obstructive pulmonary disease (COPD) conflicting results have been published about the effects of high fat, low carbohydrate feed on Pa,CO_2 [5, 7].
We studied the effects of a high fat, low carbohydrate enteral feed compared with a standard enteral nutrition in ventilator-dependent patients. Minute ventilation, $V'O_2$, $V'CO_2$ and arterial blood-gases were obtained during mechanical ventilation and periods of weaning from the ventilator.

2. Patients and Methods

2.1. Patients

32 adult patients suffering from chronic obstructive pulmonary disease (COPD), neurological illness or pneumonia in the absence of COPD, requiring mechanical ventilation and who could be enterally fed, were entered into the study. Patients were excluded from the study if they had evidence of diabetes mellitus, renal or hepatic failure, or respiratory failure without a prospect of weaning from the ventilator.

Body height and weight, percentage ideal body weight, triceps skinfold (TSF), arm muscle circumference (AMC) and serum albumin levels were obtained as measures of nutritional status. The ideal body weight for each patient's height was calculated using standard tables [8]. Arm muscle circumference was calculated according to the methods of Blackburn et al. [8]. Apache II-scores were obtained at entry of the study to assess severity of illness [9]. All patients with COPD were maintained on a stable broncho-dilator regimen including theophylline and inhaled beta-stimulating drugs. The investigative protocol was approved by the institutional ethics committee, and informed consent was obtained from the patient or family in all cases.

2.2. Mechanical ventilation.

The patients were on controlled ventilation through a cuffed endotracheal tube with a time-cycled ventilator (Siemens Servo-ventilator 900C, Siemens-Elema, Sweden). Mechanical ventilation using the volume-controlled mode, was adjusted to normocapnia and a Pa,O_2-value above 10 kPa. Mean minute ventilation was 10.8 l/min (SD 2.1), mean respiratory frequency was 16/min (SD 4).

2.3. Weaning

Weaning was performed using the continuous positive airway pressure (CPAP) mode of the Siemens Servo-ventilator. Weaning was started as soon as the patients fulfilled the following conditions:

1. mechanical ventilation with FI,O_2 less than 50% and a PEEP level less than 10 cm H_2O;

2. mechanical ventilation without sedation or relaxation;
3. absence of high fever or circulatory failure;
4. serum bicarbonate level less than 28 mmol/l.

2.4. Nutrition

Patients received either a high fat, low carbohydrate feed or a standard enteral feed. The dosage prescribed was 1.5 times basal metabolic rate calculated from the tables of Harris and Benedict and was kept constant during the study.

The enteral nutrition was given through a nasogastric tube by continuous flow for 24 h per day using a Flexiflo II enteral feeding pump. As high fat, low carbohydrate enteral feed, Pulmocare ® (Abbott Laboratories, Amstelveen, Holland), consisting of 16.7% protein, 55.2% fat and 28.1% carbohydrates, was used. As standard enteral nutrition, Ensure Plus ® (Abbott Laboratories, Amstelveen, Holland), consisting of 16.7% protein, 30% fat and 53.3% carbohydrates, was used.

2.5. Respiratory and Metabolic measurements

Respiratory minute volume (V'_E), oxygen uptake ($V'O_2$), carbon dioxide production ($V'CO_2$) and respiratory quotient (RQ) were determined using an indirect calorimetric technique, described in a previous paper [10]. For these measurements the V'_E was obtained using the flow transducer (type Silverman) from the ventilator calibrated with a wet spirometer in series with the ventilator. For monitoring of the respiratory gases an infrared type CO_2-analyzer (Siemens, type Ultramat M) and a paramagnetic O_2-analyzer (Mijnhardt, type Oxylyzer), were used.

Alternately inspiratory and mixed expiratory gas fractions were measured using two mixing bags to avoid pressure variations influencing the gas analysis. For $V'O_2$ calculation the Haldane-correction was used [11]. Considering the influence of the F_IO_2 on the accuracy of the metabolic variables, measurements were only obtained at F_IO_2-values less than 45% [12]. In order to measure F_IO_2 accurately, a flow-weighted mean of the inspiratory gas fraction was obtained using a continuous leak in the inspiratory line of the ventilator discharging into a mixing bag. The inspiratory

gas was sampled intermittently from this mixing bag for gas analysis. During mechanical ventilation peak airway pressures were obtained in all patients using the pressure transducer from the ventilator.

2.6. Study Protocol

15 Patients were randomly allocated to the high fat, low carbohydrate feeding, the remaining 17 patients to the standard nutrition. Stratification was done on basis of the nature of their underlying diseases: COPD versus neurological illness and pneumonia in the absence of COPD. 12-24 Hours after the start of the nutritional support respiratory and metabolic measurements were obtained during mechanical ventilation and weaning if the patient fulfilled the criteria to start spontaneous breathing. In order to assess the ability of the respiratory muscles to cope with the respiratory workload during weaning, the maximum static inspiratory pressure (Pimax) was measured. If the patients did not fulfill the criteria to start weaning, the measurements were done only during mechanical ventilation and were repeated two times a week.

V'_E, $V'O_2$, $V'CO_2$ and RQ were obtained for 1 hour during mechanical ventilation. At the end of this period arterial blood-gases were measured. Subsequently weaning was started during which the respiratory and metabolic measurements were continued. The weaning trial was ended when the patient was too short of breath or tired to continue. During weaning arterial blood-gases were obtained according to a fixed time-schedule: at 30 minutes and, as long as the patient sustained spontaneous breathing, at 1 hour, 2 hours and 3 hours after the start of the trial. If the patient was unable to wean for 30 minutes, no blood-gases were obtained and the results of the weaning trial were discarded. After the weaning trial mechanical ventilation was resumed in order to rest the respiratory muscles. Subsequently after a period of rest varying from 4 to 6 hours, the weaning trial was repeated. During the night the patients were ventilated and weaning was not attempted. The ability of the patient to breath spontaneously for 3 hours was used as endpoint of the study. If the patient was unable to fulfill this condition, the study was terminated on the 15th day after the start of the nutritional support.

In order to compare the effects of the nutritional regimens, the measurements obtained in the two patient groups on the third day of the study were used.
The mean $V'O_2$, $V'CO_2$ and RQ obtained during mechanical ventilation for the two patient groups were compared to evaluate the effect of the nutritional regimens on the patients' metabolism.
The measurements obtained during the first half hour of weaning were used to evaluate the effects of nutrition on respiration, because only a limited number of the patients could sustain spontaneous breathing for periods of time longer than 30 minutes on the third day of the study. The values of V'_E, $V'O_2$, $V'CO_2$ and RQ obtained during the first 30 minutes of weaning and the Pa,CO_2 measured at the end of that period were compared to evaluate the effects of the two nutritional regimens on respiration.
In order to establish the clinical relevance of the measurements obtained during the first half hour of weaning, correlations were calculated between measurements at the first half hour and the third hour of weaning. For this purpose the measurements of all patients who could wean for 3 hours were used, irrespectively of the day of the study.
The median time in days, from the start of the study until the patient could breath spontaneously for 3 hours during a weaning trial, was compared between the patient groups in order to evaluate the effect of nutrition on the time required to wean the patients from the ventilator.

2.7. Statistical methods

In order to compare differences in the respiratory measurements and the time required for weaning from the ventilator between the feeding groups the Mann-Whitney test was used. Two-way analysis of variance (ANOVA) was used to evaluate simultaneously differences between feeding groups and differences between patient groups according to the nature of the respiratory failure [13]. To allow for the multiple comparisons, statistical significance was tested at $p = 0.01$ instead of the conventional $p = 0.05$ [14]. For calculation of the correlations the Pearson correlation coefficient was used. Data given are means ($\pm$ SEM), or indicated otherwise.

3. Results

Considering the results of the study, we found an imbalance between the two patient groups. Although the number of patients with COPD did not differ between the two feeding groups, an imbalance was present between the number of patients ventilated for acute-on-chronic respiratory failure due to COPD, against patients with COPD ventilated for other causes of respiratory insufficiency such as cerebral hemorrhage, cardiac failure or abdominal surgery.
In the high fat, low carbohydrate feeding group 10 out of 11 patients with COPD were ventilated for acute-on-chronic respiratory failure due to COPD, against only 5 out of 13 patients in the standard feeding group. In contrast to the patients with COPD ventilated for other causes of respiratory failure, the patients with acute-on-chronic respiratory failure were intubated and ventilated for severe hypercapnia. In the latter group hypercapnia was also present during the weaning procedures. As this imbalance substantially affected the results, two-way analysis of variance was used in order to evaluate whether the results obtained at the two nutritional regimens were related to the nature of the respiratory failure.
The patient group receiving high fat, low carbohydrate feeding and ventilated for "other causes" consisted of 5 patients: one patient with COPD, three patients with pneumonia and one patient with neurological illness. The patient group receiving standard feeding and ventilated for "other causes" consisted of 12 patients: 8 patients with COPD, 3 patients with pneumonia and one patient with neurological illness. The patient data on admission are shown in table 1. Considering the two patient groups according to the nutritional intakes, no significant differences were found.
Neither significant difference was found in the calorie intake: 1943 ± 306 kcal per 24h in the high fat, low carbohydrate and 2003 ± 277 kcal per 24h in the standard feeding group (means and SD).

3.1. Measurements during mechanical ventilation

The results of the measurements obtained during mechanical ventilation at the third day of the study were compared. Measurements of 14 patients in

TABLE 1
Patient characteristics at entry into the study.
Data given are number of patients or means ± SD.

	High fat, low carbohydrate feed	Standard feed
No of patients	15	17
Male/female	10/5	13/4
Underlying conditions:		
Patients with COPD	11	13
(Patients with ARF-on-CRF due to COPD)	(10)	(5)
Patients with neurological illness	1	1
Patients with pneumonia	3	3
% Ideal Body Weight	95 ± 24	115 ± 27
Triceps skin fold mm	11.9 ± 6.9	13.4 ± 7.7
Arm muscle circumference cm	22.0 ± 3.5	24.1 ± 4.2
Serum-albumin g/l	28.6 ± 4.7	28.0 ± 5.9
Apache II score	15 ± 4	14 ± 4

ARF-on-CRF = acute-on-chronic respiratory failure.

the high fat, low carbohydrate feeding group were available, subdivided in 10 patients with acute-on-chronic respiratory failure and 4 patients ventilated for other causes of respiratory failure. In the standard feeding group measurements of 16 patients were available consisting of 5 patients with acute-on-chronic respiratory failure and 11 patients ventilated for other causes. With regard to the ventilator-settings, no differences were found comparing the FI,O_2-values applied during the ventilatory support: the values amounted to .35 ± .01 and .36 ± .01 for the high fat, low carbohydrate and standard feeding groups respectively. The results of the respiratory and metabolic measurements are shown in Table 2. Concerning the two feeding groups a significant difference was found in RQ; the difference in $V'CO_2$ failed to reach significance (p-values < .001 and .08 respectively). The

TABLE 2
Respiratory and metabolic measurements during mechanical ventilation, obtained on the 3rd day of the study
Data given are means ± SEM

Mechanical ventilation	Min. Vent. l/minBTPS	$V'O_2$ l/minSTPD	$V'CO_2$ l/minSTPD	R.Q.	Pa,CO_2 kPa
High fat, low carbohydrate feed total no = 14	9.9 ± .6	.218 ± .013	.199 ± .011	.91 ± .01*	5.1 ± .3
Standard feed total no = 16	11.0 ± .7	.225 ± .007	.225 ± .008	1.00 ± .02*	5.0 ± .2

Min. Vent. = minute ventilation; BTPS = body temperature pressure saturated; STPD = standard temperature pressure dry (* = $p < 0.001$).

effects of the nutritional regimens on RQ and $V'CO_2$ proved to be independent of the nature of the respiratory failure. No differences were found in minute ventilation, $V'O_2$ or Pa,CO_2. Neither differences were found comparing the peak airway pressures measured during mechanical ventilation: the peak airway pressures amounted to 27 ± 2 and 30 ± 3 cm H_2O for the high fat, low carbohydrate and standard feeding group respectively. The ANOVA revealed a significant difference in Pa,CO_2 between the patients with acute-on-chronic respiratory failure to those ventilated for other causes. This difference proved to be independent of the type of nutrition used. The Pa,CO_2 amounted to 5.5 ± .2 and 4.5 ± .2 kPa for the patients ventilated for acute-on-chronic respiratory failure and for other causes respectively ($p < .001$).

3.2. Measurements during weaning procedures

Measurements obtained during weaning on the third day of the study were compared. Data of 12 patients in the high fat, low carbohydrate feeding group were available against those of 14 patients in the standard nutrition group. 8 of the 12 patients in the high fat, low carbohydrate feeding group were ventilated for acute-on-chronic respiratory failure due to COPD against 5 of the 14 patients in the standard feeding group.

Comparing the two feeding groups no significant differences were found in the values of Plmax obtained at the start of the weaning procedures: the

TABLE 3

Respiratory and metabolic measurements during weaning from the ventilator, obtained on the 3rd day of the study.
Data given are means ± SEM.

Weaning	Min. Vent. l/minBTPS	$V'O_2$ l/minSTPD	$V'CO_2$ l/minSTPD	R.Q.	Pa,CO_2 kPa
High fat, low carbohydrate feed total = 12	8.8 ± .9	.244 ± .010	.177 ± .010*	.72 ± .02**	6.4 ± .4
Standard feed total = 14	10.5 ± .8	.271 ± .013	.231 ± .011*	.86 ± .02**	5.9 ± .3

Min. Vent. = minute ventilation; BTPS = body temperature pressure saturated; STPD = standard temperature pressure dry. (* = $p < 0.01$; ** = $p < 0.001$).

values amounted to -32 ± 2 and -34 ± 3 cmH_2O for the high fat, low carbohydrate feeding and standard feeding groups respectively. Neither differences were found comparing the Pimax values of the patient groups according to the nature of the respiratory failure.

The data of the respiratory and metabolic measurements during weaning are shown in Table 3 and Figure 1-3. Significant differences between the two feeding groups were found in mean CO_2-excretion and mean RQ (p-values < .01 and .001 respectively). The differences in minute ventilation, $V'O_2$ and Pa,CO_2 were not significant. The ANOVA further revealed that no significant differences in CO_2-excretion or RQ were present when the patients with acute-on-chronic respiratory failure were compared to those ventilated for other causes. The effects of the nutritional intakes with respect to RQ and CO_2-excretion proved to be independent of the nature of the respiratory failure.

Significant differences however were found in minute ventilation and Pa,CO_2 comparing the patient groups according to the cause of the respiratory failure. These differences proved to be independent of the type of nutrition used. The mean minute ventilation amounted to 7.9 ± .5 against 11.5 ± .9 l/min BTPS and the mean Pa,CO_2 to 7.0 ± .5 against 5.3 ± .2 kPa in the acute-on-chronic respiratory failure group against the patient group ventilated for other causes (p-values < .01 and .001 respectively).

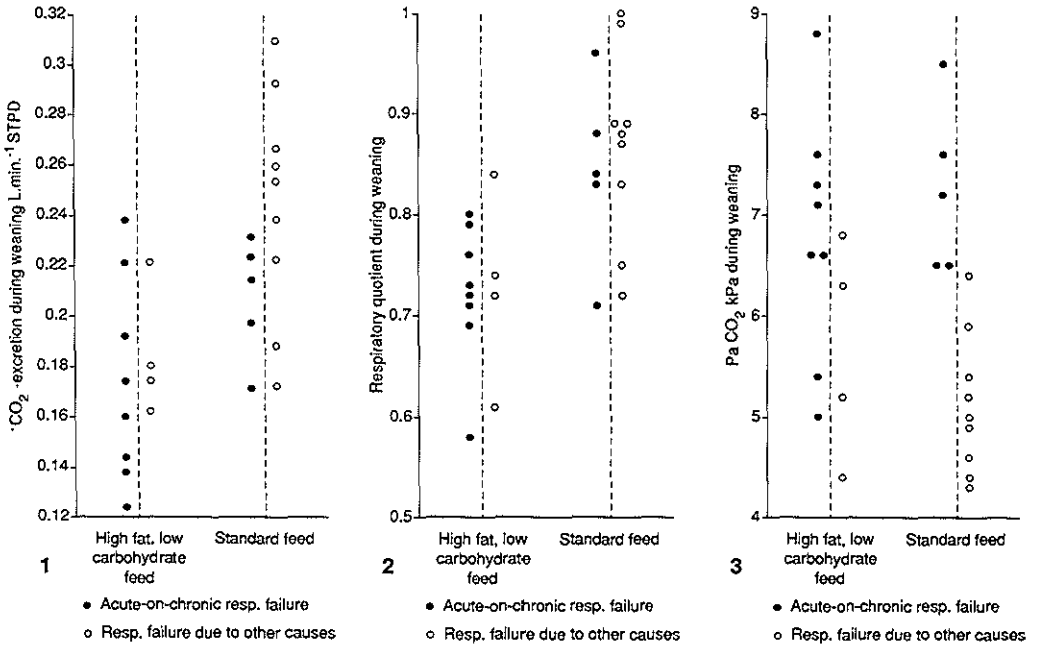

Figure 1, 2, 3. The values of CO_2-excretion, RQ and Pa,CO_2 of the individual patients during weaning from the ventilator. The values are shown according to the nutritional regimen and to the nature of the respiratory failure.

Correlations between the first half hour and the third hour of weaning were obtained in 25 patients: 11 patients in the high fat, low carbohydrate feeding group and 14 patients in the standard feeding group. Significant correlations were found in both groups for CO_2-excretion and RQ. As to the CO_2-excretion the correlation coefficients amounted to .83 and .87 ($p < .01$ and

$p < .001$ respectively) for the two feeding groups. For the RQ the correlation coefficients amounted to .72 and .78 ($p = .01$ and $p < .01$ respectively).

3.3. Time required to wean from the ventilator

In two patients the endpoint of the study could not be reached: the enteral feeding had to be ended because of gastric retention in one patient in the high fat, low carbohydrate feed group and in one patient in the standard nutrition group after 3 and 7 days respectively. Both patients were ventilated for "other causes" of respiratory failure.

Five patients failed to breath spontaneously for 3 hours within 15 days from the start of the study: two patients in the high fat, low carbohydrate feeding group, as against three patients in the standard nutrition group. Of these patients one patient in the high fat, low carbohydrate feeding group against two patients in the standard feeding group were ventilated for acute-on-chronic respiratory failure. The median time of the study amounted to 4 days in the high fat, low carbohydrate feeding group against 6 days in the standard nutrition group: a difference which failed to reach significance.

4. Discussion

This study was designed to investigate the effects of a high fat, low carbohydrate enteral feeding on gas-exchange in patients during mechanical ventilation and weaning from the ventilator.

Although the stratification resulted in a comparable number of patients with COPD in both feeding groups, subdivision into different causes of respiratory failure in the patients with COPD revealed an imbalance between the two feeding groups. Analysis of the results revealed that patients with acute-on-chronic respiratory failure due to COPD were predominantly found in the high fat, low carbohydrate enteral feeding group. It was clear that in particular in these patients hypercapnia was found during weaning from the ventilator. Consequently this imbalance had to be taken into account at the analysis of the results.

Therefore two-way analysis of variance was used in order to evaluate differences between the patient groups defined by the nutritional regimens and the nature of the respiratory failure simultaneously.

Nutritional assessment of the patients obtained at the start of the study revealed that severe malnourishment was not prominent in this study in contrast to the study of Driver et al. who found a high prevalence of malnutrition in patients with acute respiratory failure and COPD [15].

In this study the calculated basal energy expenditure according to Harris and Benedict was used in order to determine the calorie intake for each patient. Previous experience had tought us that in the disturbing environment of an intensive care unit reproducible measurements of resting energy expenditure in post-absorptive state are hard to obtain in ventilator-dependent patients who are not sedated.

Considering the metabolic measurements obtained during mechanical ventilation it must be stressed that the mode of mechanical ventilation was aimed to reduce the work of breathing of the patients to a minimum. Consequently the $V'O_2$ of the patients has also been affected by the mode of mechanical ventilation. This explains why in our study, during nutritional support, lower values of $V'O_2$ were found compared with data previously reported of spontaneously breathing patients with COPD receiving equivalent amounts of high fat, low carbohydrate and standard enteral diets [5]. Marked higher RQ values were also found in our study compared with studies of equivalent nutritional support in ambulatory spontaneously breathing patients with COPD [5, 7].

Compared with an isocaloric moderate fat diet, the high fat, low carbohydrate feeding was associated with a lower $V'CO_2$ and RQ during mechanical ventilation. This indicates that the patients receiving the high fat, low carbohydrate feeding oxidized more fat than the patients receiving the standard feeding. Only the difference in RQ however proved to be significant. Despite the difference in fat content between the two nutritional intakes, the difference in $V'CO_2$ between the two feeding groups failed to reach significance. If the difference in mean $V'CO_2$ between the two patient groups was expressed as percentage of the mean $V'CO_2$ of the standard feeding group, a reduction in $V'CO_2$ of 12% was found. In another study

using equivalent nutritional support in patients with COPD a significant difference in $V'CO_2$ was found comparing high fat, low carbohydrate and standard feeding groups: the reduction in mean $V'CO_2$ was however 10% [5]. In contrast to our investigation, in that study a cross-over design was used, comparing the nutritional regimens in the same patient group.

No differences were found in minute ventilation or Pa,CO_2 during mechanical ventilation comparing the two feeding groups. In agreement with these results no difference was found in the peak airway pressures measured during the mechanical ventilation. The ANOVA revealed a significantly higher Pa,CO_2-value during mechanical ventilation in the patient group with acute-on-chronic respiratory failure compared to those ventilated for other causes. These higher Pa,CO_2-values should be explained in terms of a lower minute ventilation and a higher dead space ventilation in the patients with acute-on-chronic respiratory failure.

During the weaning trial a significantly lower CO_2-excretion and RQ were found in the high fat, low carbohydrate feeding group. For both variables the difference between the feeding groups was similar for the patients with acute-on-chronic respiratory failure and the patients ventilated for other causes. Comparing the patients with acute-on-chronic respiratory failure to those ventilated for other causes, a significantly higher Pa,CO_2-value and lower minute ventilation was found during weaning in the former group. These differences were unrelated to the nutritional regimen applied. For both CO_2-excretion and RQ significant correlations were found between the first half hour and the third hour of weaning, indicating the predictive value of the measurements at the first half hour of weaning. It is however clear, that these correlations could only be obtained in the group of patients who could sustain weaning for three hours.

It should be discussed what value can be attached to these results in view of the short period of time studied. Clearly, the start of weaning implied considerable changes in the gas exchange of the patients. Comparing the weaning trial to mechanical ventilation an increase in $V'O_2$ was observed in all patients; a decrease in CO_2-excretion was found in the high fat, low carbohydrate feeding group against a slight increase in the standard feeding group. As a result, the RQ values decreased in all patients. The increase in

$V'O_2$ is determined predominantly by the energy expenditure of the respiratory muscles of the patients. The changes in the CO_2-excretion should be elucidated in view of the increased metabolic rate and alterations in the body CO_2-pool during the weaning period. Assuming that with respect to oxidation the ratio between carbohydrate and fat did not alter during the weaning trial, the changes in the CO_2-excretion can then only be explained by an increase in the body CO_2-pool. This suggests that the CO_2-excretion did not equal the CO_2-production of the body and no steady state was present during the half hour's weaning trial. Under these circumstances, because of the unaltered diet, a relationship between the type of nutritional support and the CO_2-excretion and RQ values is however assumed comparable to that during mechanical ventilation. Consequently, the values of CO_2-excretion and RQ may provide valuable information with respect to the effects of feeding on spontaneous breathing.

A previous study reported by Al-Saady, suggested significant reductions in Pa,CO_2 and minute ventilation in patients with high fat, low carbohydrate feeding compared with patients with standard enteral nutrition [6]. This study used enteral nutrition identical to our investigation. However, $V'O_2$ and $V'CO_2$ were not measured during this study and an improvement of pulmonary function with a decrease in dead space ventilation could not be excluded. In contrast to our investigation this study also reported a significant reduction in time spent on mechanical ventilation in the patient group on high fat, low carbohydrate enteral feeding [6]. A marked difference was however present in underlying diseases of the patients between both studies. In our study 15 out of 32 patients were ventilated for acute-on-chronic respiratory failure due to COPD against 1 of 20 patients in the study of Al-Saady [6]. In the latter study successful weaning was defined as 24 hours spontaneous breathing without hypercapnia against only 3 hours spontaneous breathing disregard the level of Pa,CO_2 in our study.

In conclusion high fat, low carbohydrate feeding compared with standard nutrition decreased RQ but failed to reduce $V'CO_2$ significantly in mechanically ventilated patients in this study. Comparing the two nutritional regimens, no difference could be demonstrated in the Pa,CO_2-values during weaning from the ventilator. Although during weaning both CO_2-excretion

and RQ proved to be lower in the high fat, low carbohydrate feeding group, this type of nutrition was unable to shorten the time spent on mechanical ventilation before successful weaning was accomplished.

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Chapter 7

Respiratory measurements in intubated patients with COPD

Introduction

Respiratory insufficiency is a major organ failure encountered in the intensive care unit and mechanical ventilation can be considered as the mainstay in the supportive treatment of such critically ill patients. Research on respiratory mechanics in artificially ventilated patients has recently made considerable progress and has greatly improved patient care [1]. In this chapter the respiratory measurements applied in the chapters 8 and 9 are described. The outline of the techniques is given with respect to the different methods described in the literature. In this chapter successively the techniques to determine intrinsic PEEP, functional residual capacity and work of breathing are described.

1. Intrinsic PEEP

1.1. Introduction

In 1982 Pepe and Marini described 3 mechanically ventilated patients in whom they found a "hidden" positive end-expiratory pressure (PEEP) during intermittent positive pressure ventilation (IPPV) [2]. This pressure was named intrinsic PEEP by the authors in contrast to the positive end-expiratory pressure (PEEP) applied by the ventilator. They showed that in these patients the expiration was terminated by the next inspiration before functional residual capacity, i.e. the relaxed static equilibrium of the respiratory system had been obtained. This phenomenon, known as dynamic hyperinflation, is associated with a lung volume at the end of expiration which exceeds functional residual capacity. Pepe and Marini described that this condition also leaded to the presence of a positive elastic recoil pressure of the total

respiratory system (Pel,rs) at end-expiration: the intrinsic PEEP.
Initially intrinsic PEEP, was demonstrated in patients artificially ventilated for acute respiratory failure due to chronic obstructive pulmonary disease (COPD). In these patients the rate of lung emptying is decreased due to severe airflow obstruction. In the absence of respiratory muscle activity, the rate of lung emptying depends on the balance between the Pel,rs built up during the preceeding lung inflation and the opposing total flow-resistance offered by the respiratory system. In patients with COPD a low elastic recoil pressure of the lungs (Pel,l) will decrease the rate of lung emptying, while an increased flow-resistance will further impede the rate of lung deflation. Accordingly, in these patients dynamic hyperinflation is almost invariably present, because the time-course of passive expiration is prolonged by either a decreased Pel,l or an increased respiratory resistance. As a rule, the magnitude of dynamic hyperinflation will be positively related to the tidal volume and to the mechanical time constant of the respiratory system (i.e. the product of total respiratory resistance and compliance) and inversely related to the expiratory duration [1].
Although the presence of intrinsic PEEP was at first demonstrated in mechanically ventilated patients with COPD, this phenomenon was soon described in patients in various conditions. Low levels of intrinsic PEEP have been found in patients who were ventilated for the adult respiratory distress syndrome [3]. In intubated patients with COPD and acute respiratory failure who were breathing spontaneously through the endotracheal tube, intrinsic PEEP could be detected using different methods [4, 5]. Even in spontaneously breathing patients with COPD in stable condition low levels of intrinsic PEEP have been demonstrated by several authors [6, 7].
In artificially ventilated patients intrinsic PEEP has been described as "hidden", as this pressure cannot be determined by the pressure manometer of the ventilator during the passive expiration. During the expiratory phase the pressure manometer of the ventilator indicates a rapid decrease in airway pressure and does not reveal the presence of a gradient between the alveolar and mouth pressure at end-expiration.
Therefore, several different methods have been suggested to detect intrinsic PEEP. The presence of intrinsic PEEP should be suspected if in ventilated

patients the expiratory flow continues until interrupted by the next inspiration initiated by the ventilator. When the flow signal obtained from the ventilator is recorded in time during the ventilatory cycle, the presence of a positive flow at end-expiration can be easily identified. In the next section the various methods to determine intrinsic PEEP will be described.

1.2. Methods to determine intrinsic PEEP

Several techniques to determine intrinsic PEEP have been described both in patients during mechanical ventilation and in spontaneously breathing patients. These methods can be subdivided in direct and indirect measurements, i.e. intrinsic PEEP can be determined directly using an occlusion technique or indirectly by measuring the pressure needed to counterbalance the intrinsic PEEP level at the start of an inspiration.

1.2.1 Methods to determine intrinsic PEEP in mechanically ventilated patients

Direct measurements.

Originally Pepe and Marini described the occlusion technique in artificially ventilated patients [2]. For this technique the patient is ventilated in the volume-controlled mode and the ventilation is adjusted in order to suppress the inspiratory efforts of the patient during the procedure. Intrinsic PEEP is determined at the end of the expiration by occluding the airway. For that purpose the expiratory line of the ventilator is occluded at the end of the expiration and the next ventilator breath is postponed. When the expiratory line is blocked, the pressure at the endotracheal tube will equilibrate with the alveolar pressure, allowing this pressure to be registered by the pressure manometer of the ventilator. During the procedure the pressure will rapidly reach a plateau which remains unaltered as long as the occlusion continues (Figure 1). It should be emphasized that the pressure measured by the pressure manometer is lower than the true alveolar pressure due to decompression of alveolar gas in the compliant parts of the ventilator tubings. This decompression can be reduced by occluding the airway at the endotracheal tube with an interrupter and measuring the pressure between the tube and the interrupter [8].

Several drawbacks have been described with respect to this technique. At

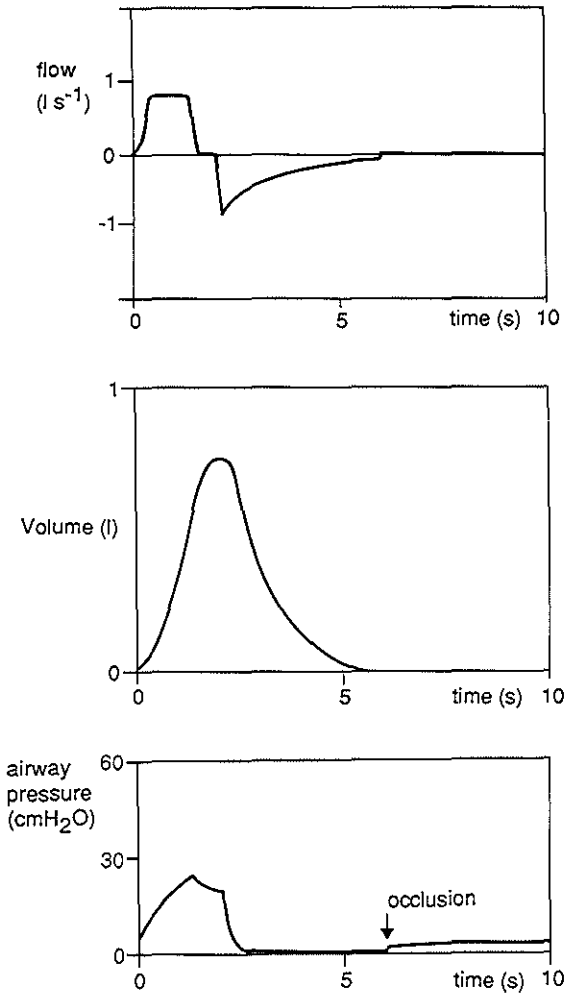

Figure 1. Determination of intrinsic PEEP in ventilated patients. Occlusion applied at end-expiration.

first, the patient should be relaxed during the procedure. It is clear that no plateau in the pressure reading can be obtained, if the patient makes an inspiratory effort during the occlusion. Secondly, most ventilators are not equipped with the facilities to postpone an inspiration and to occlude the valves in the inspiratory and expiratory line simultaneously at end-expiration. If the airway is occluded by an interrupter and the procedure is controlled manually, the occlusion can easily be initiated before the true end-expiratory pressure is obtained, leading to an over-estimation of the level of intrinsic

PEEP.
In order to avoid the technical problems during the occlusion manoeuvre a modification in the technique has recently been described [9]. For this method a three-way manual valve is placed in the inspiratory line of the ventilator circuit. By rotation of this valve the inspiratory volume delivered by the ventilator can be directed to the patient's lungs or to atmosphere. In the last mode the inspiratory line is occluded between the valve and the endotracheal tube. For determination of intrinsic PEEP the valve is rotated during expiration in order to occlude the inspiratory line. Subsequently, at end-expiration the expiratory line is occluded by the valve within the ventilator. The following inspiration is then directed to atmosphere and during that inspiratory time the ventilator circuit is occluded both in the inspiratory and expiratory lines and intrinsic PEEP can be determined.
Finally, it should be stated that several types of ventilators most recently have been equipped with facilities to determine intrinsic PEEP. End-expiratory occlusions can be obtained by using an end-expiratory hold function. When activated, the valves in the inspiratory and expiratory lines within the ventilator are closed at end-expiration and the following inspiration is postponed: intrinsic PEEP can be determined by the pressure manometer of the ventilator.

Indirect approach.
A technique to estimate intrinsic PEEP indirectly has been described by Rossi et al [8]. This method requires a simultaneous and accurate recording of the onset of inspiratory flow and airway pressure in time during a ventilator breath. When intrinsic PEEP is present during the preceeding expiration, the inspiratory flow will not start synchronously with the onset of the applied pressure. In that case, a positive pressure can be observed before the inspiratory flow starts. This positive pressure is required to counterbalance the Pel,rs that was present at end-expiration, i.e. the intrinsic PEEP-level (Figure 2). This approach to estimate intrinsic PEEP does not interfere with the mechanical ventilation, but is only valid when the patient does not make any inspiratory effort during the measurements.

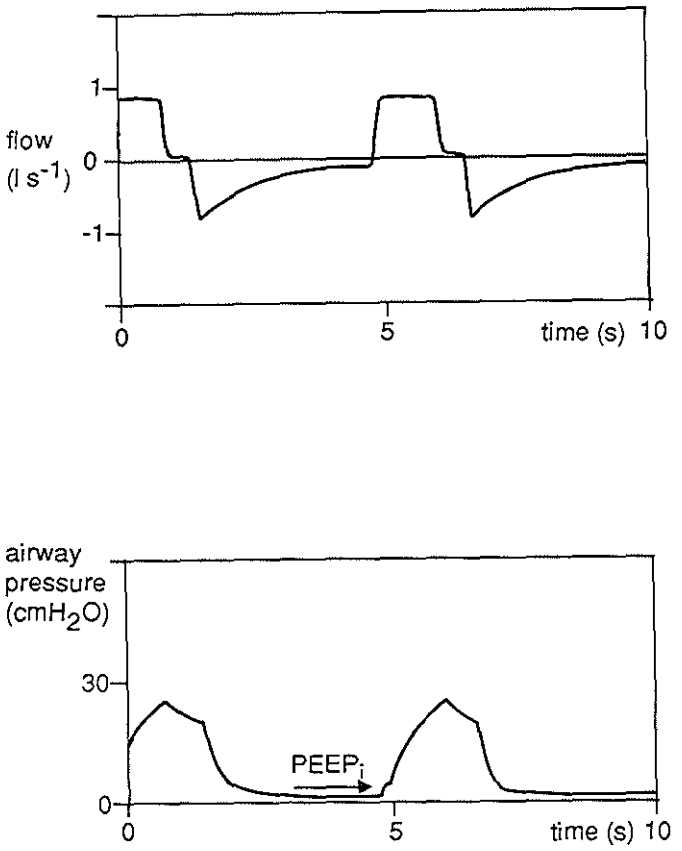

Figure 2. Determination of intrinsic PEEP in ventilated patients. Simultaneous recording of inspiratory flow and pressure.

1.2.2. Methods to determine intrinsic PEEP in spontaneously breathing patients

Direct approach.

Direct measurements of intrinsic PEEP have only been described in spon-

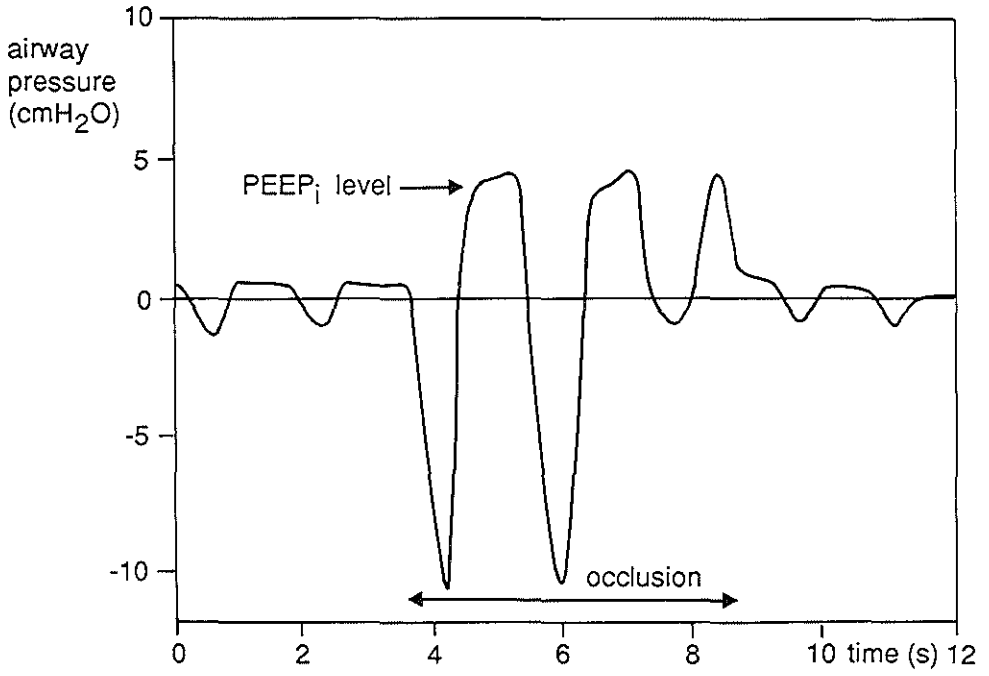

Figure 3. Determination of intrinsic PEEP in intubated spontaneously breathing patients.
Occlusion method using a two-way valve at the endotracheal tube

taneously breathing patients who were intubated with an endotracheal tube [5]. In these patients a technique is used to occlude the airway at end-expiration. For this purpose the patient's endotracheal tube is connected to a two-way valve with the facility to occlude the inspiratory and expiratory line separately. During expiration the inspiratory line is occluded and subsequently during the first inspiratory effort the expiratory line is also obstructed. During the occlusion the airway pressure is measured by a pressure transducer connected to the endotracheal tube. As the patient makes inspiratory efforts against the occluded airway, pressure drops will be recorded. Between these pressure drops a plateau in the pressure recording can be observed (Figure 3). When expiratory muscle activity is absent, this

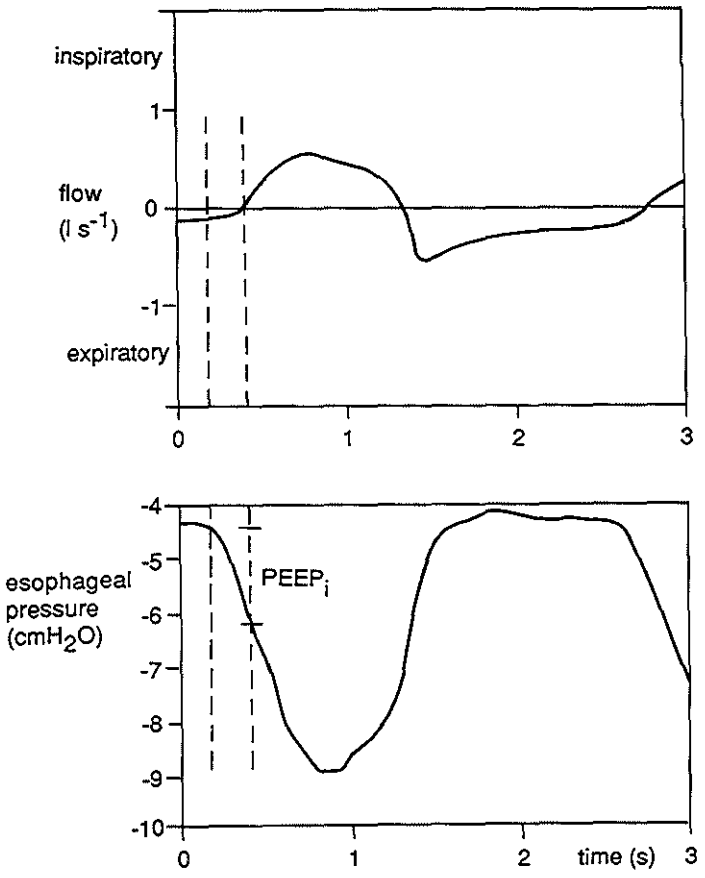

Figure 4. Determination of intrinsic PEEP in spontaneously breathing patients. Simultaneous recording of airflow and esophageal pressure.

plateau corresponds to Pel,rs at end-expiration, that is intrinsic PEEP. In order to measure intrinsic PEEP correctly during this procedure, the activity of the abdominal muscles should be monitored by recording the gastric pressure. In that case the absence of expiratory muscle activity can be verified.

Indirect approach

Indirect estimations of intrinsic PEEP have been described both in patients with stable COPD and in patients in whom the trachea has been intubated for treatment of acute respiratory failure [6, 7, 8]. This approach requires the simultaneous recording in time of the esophageal pressure relative to atmospheric pressure and the flow during quiet breathing. When intrinsic PEEP is present, a decrease in esophageal pressure can be observed before the inspiratory flow starts. It is assumed that this negative deflection in esophageal pressure represents the inspiratory muscle force required to counterbalance the opposing level of the Pel,rs present at end-expiration (intrinsic PEEP). When recorded rapidly, a plateau in the esophageal pressure can be observed during expiration: the start of the inspiratory effort is indicated by the negative deflection in the esophageal pressure. The level of intrinsic PEEP is determined by the change in esophageal pressure from the start of the inspiratory effort to the onset of the inspiratory flow (Figure 4).

1.2.3. Determinations of intrinsic PEEP applied in our investigations

In our investigations described in chapter 8 and 9 occlusion methods have been used both in mechanically ventilated patients and in patients who were breathing spontaneously through an endotracheal tube. In the ventilated patients the occlusion technique was applied using the end-expiratory hold function incorporated in the Siemens Servo ventilators (section 1.2.1.). In spontaneously breathing patients the airway was occluded, using a two-way valve connected to the endotracheal tube (section 1.2.2.) In both procedures the airway pressure was measured at the endotracheal tube by a Validyne pressure transducer (Validyne MP45, Validyne Corp., Northridge, CA) and recorded on a Servogor recorder type 460, (Brown Boveri Company, Rotterdam, Holland). The outlines of the set-up applied for both procedures are depicted in Figure 5 and 6.

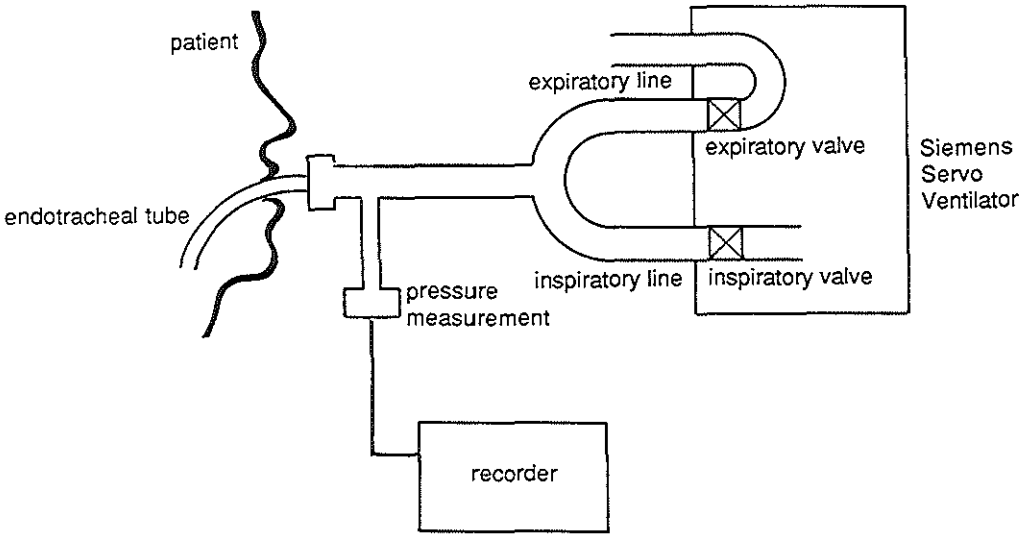

Figure 5. Determination of intrinsic PEEP in a ventilated patient. At end-expiration the inspiratory and expiratory valves within the ventilator are closed: intrinsic PEEP is determined at the endotracheal tube by a pressure transducer.

2. Functional Residual Capacity

2.1. Introduction

The functional residual capacity (FRC) is defined as the relaxed equilibrium volume of the lungs at the end of expiration. A relaxed equilibrium is attained when the elastic recoil pressure of the lungs is balanced by the elastic recoil pressure of the thoracic cage [10]. As the elastic recoil of the lungs and the chest wall exert their forces in opposite directions, they produce at FRC a subatmospheric pressure in the intra-pleural space.

Changes in posture are known to affect FRC in healthy individuals. A reduction in FRC of about 30% is found comparing the supine position to the

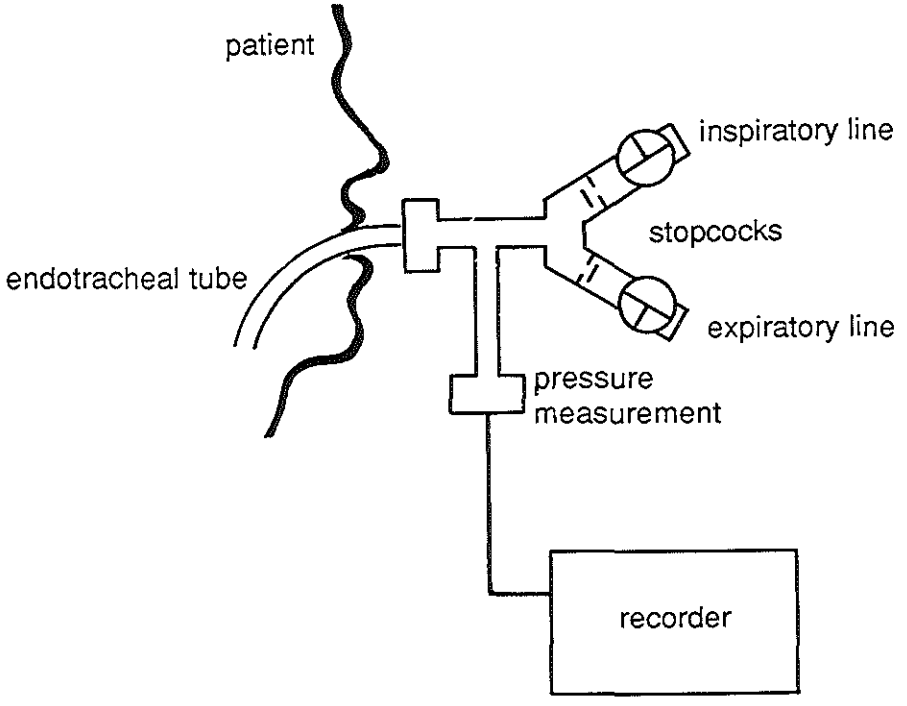

Figure 6. Determination of intrinsic PEEP in intubated patients.
Occlusion method: Two-way valve with stopcocks attached to the endotracheal tube.

upright position: the former position being associated with a shift of the diaphragm into the thorax by the weight of the viscera [10]. In normal subjects factors as body size and age are also known to affect FRC [11]. Due to pathological changes in the elastic recoil of lungs or chest wall, FRC may be reduced or increased. FRC will be reduced due to an increased elastic recoil of lungs, increased stiffness of the chest wall or both, as in pulmonary fibrosis or kyphoscoliosis. Paralysis of the respiratory muscles by muscle relaxants as applied in mechanically ventilated patients also leads to a reduced FRC by a decrease in the tonic activity of the diaphragm [10]. The elastic recoil is diminished in patients with chronic obstructive pulmonary disease (COPD), leading to an increased FRC.

2.2. Functional residual capacity in mechanically ventilated patients

In the early days of intensive care medicine respiratory mechanics have been studied mainly in patients with the adult respiratory distress syndrome (ARDS). One of the characteristic features of the ARDS is the reduction of the FRC, associated with interstitial and alveolar edema and consolidation [12]. Application of positive end-expiratory pressure (PEEP) was found to improve oxygenation associated with an increase in end-expiratory lung volume [13]. Due to a positive pressure applied at end-expiration, a new equilibrium will be achieved at a lung volume exceeding FRC. Accordingly, the expiration is terminated at an end-expiratory lung volume that by definition cannot be described as functional residual capacity.

2.3. Functional residual capacity in mechanically ventilated patients with COPD

In the last decade respiratory mechanics have been studied extensively in patients with COPD, who were mechanically ventilated for acute respiratory failure. In these patients dynamic hyperinflation leading to an end-expiratory lung volume exceeding FRC, was almost invariably found.

Dynamic hyperinflation is considered to have adverse effects on the circulation and respiration of these patients. Firstly, this condition leads to the presence of intrinsic PEEP, which exerts the same hemodynamic effects as PEEP applied by the ventilator [2]. Secondly, hyperinflation may affect adversely the respiratory muscle function in patients in whom weaning from the ventilator is pursued. As the diaphragm is flattened at end-expiration due to hyperinflation, its inspiratory muscle function is compromised [14].

2.4. Measurements of end-expiratory lung volume

Two different methods for measuring end-expiratory lung volume (EEV) have been described [15, 16]. As it is impossible to establish by these methods whether the end-expiratory lung volume obtained, corresponds either to FRC or to a lung volume exceeding FRC, in this section the term EEV will be used instead of the term FRC.

The two methods to measure EEV are the open- and closed-circuit indicator

gas dilution techniques. In the first method the EEV is measured by determining the amount of an indicator gas in the lungs after a previous wash-in. The expired indicator gas is determined in a large number of consecutive breaths. The EEV is computed from the inspired and expired gas concentrations, the tidal volumes and the number of breaths [15, 17, 18]. In the closed-circuit method a rebreathing system is used. The EEV is computed from indicator gas concentrations in that system before and at the end of a wash-in-period, when the indicator gas concentration in the lungs equals that in the rebreathing system [16, 19-25].
In patients with dynamic hyperinflation, the end-expiratory lung volume above FRC can be determined during a prolonged expiration time [26]. The procedure can only be applied in mechanically ventilated patients under curarization. By disconnecting the patient of the ventilator during expiration, the patient is allowed to expire completely till FRC is reached. When the expired volume measured during this procedure is compared to the tidal volume determined during the fixed expiratory cycle time applied by the ventilator, the difference between these volumes equals the lung volume above FRC present at the ventilator settings used.

2.5. End-expiratory lung volume in artificially ventilated patients

Both open- and closed-circuit indicator gas dilution methods have been used to determine EEV in mechanically ventilated patients. In these patients, the techniques should fulfill specific demands related to the ventilatory support and the interaction between the ventilator and the respiratory system of the patient.
The EEV should be determined without interfering with the various modes of mechanical ventilation such as ventilation with and without PEEP. This can only be achieved when during the measurements the patient remains connected to the ventilator and the mode of ventilatory support is unchanged despite adaptations required for the technique used. During the measurements variations in F_IO_2 should be avoided as these changes have been found to affect the EEV [20]. It is obvious that absorption of carbon dioxide and oxygen suppletion compensating for oxygen uptake is required in rebreathing systems in case of prolonged equilibrium times in patients with

unequal ventilation.

The tidal volume delivered to the patient's lungs should not be changed during the procedure. Due to the compressible volume of the tubings connecting the ventilator to the endotracheal tube of the patient, the volume delivered to the patient's lungs is slightly smaller than the volume delivered by the ventilator. An increase in compressible volume due to an extension of the ventilator tubings will augment the difference between the tidal volume delivered by the ventilator and that inflating the lungs. This should be considered a major issue when the closed-circuit helium dilution technique is applied. For this technique a rebreathing system is interposed between the ventilator and the patient. In the systems a bag-in-box is used: the inspiratory volume of the ventilator is pushed into the box, emptying the bag into the patient's lungs [21, 22, 23, 25]. It is clear that this technique is inevitably associated with an extension of the ventilator tubings, leading to a reduction of the tidal volume delivered to the patient's lungs. Consequently, tidal volumes should be monitored at the endotracheal tube during the measurement and if necessary increased to equal the volume applied before the procedure [23].

2.6. End-expiratory lung volumes in mechanically ventilated patients with COPD

It is clear that the alterations induced by the closed-circuit indicator gas dilution technique have wide implications, when patients with COPD are studied in whom dynamic hyperinflation is encountered. As stated above, the degree of hyperinflation depends on the compliance and resistance of the respiratory system and on the tidal volume and the expiration time applied by the ventilator. An interruption of the mechanical ventilation such as disconnection of the patient at the start of the measurement, will disturb the equilibrium and alter the EEV. It is also clear that a reduction in tidal volume will lead to a decrease in EEV when the other variables remain unchanged. In contrast, an increase in EEV may be encountered when during the measurement the resistance of the total respiratory system is increased due to the additive resistance of the rebreathing system. As the effects of the reduced tidal volume and of the resistance of the rebreathing system act in

opposite directions with respect to the degree of dynamic hyperinflation, the best approach should be to maintain the level of total PEEP during the measurements of EEV. The total PEEP-level consisting of the levels of PEEP imposed by the measuring device and intrinsic PEEP, can be measured at the endotracheal tube during end-expiratory occlusions. The level of total PEEP should be unaltered comparing the level obtained before the procedure to that obtained during the measurements.

2.7. Measuring device used in our investigations

In our investigations in chapter 8 a closed-circuit indicator gas dilution method is applied, specially constructed for determinations of EEV in mechanically ventilated patients (H. Stam, unpublished investigations). Helium is used as indicator gas. The measuring device is comparable to systems described previously, but differs from these systems in various aspects. The equipment used is depicted in Figure 7.

At first the bag-in-box system and spirometer were replaced by a rolling-seal spirometer. By the rolling-seal the spirometer is divided into two parts: the upper part ventilated by the ventilator and the lower part acting as rebreathing system. By the inflation of the upper part the rolling seal will be pushed downwards, emptying the lower part into the patient's lungs. A displacement transducer in the rolling-seal spirometer is used to monitor volume changes in the rebreathing system. Carbon dioxide absorption is ensured by a cannister with sodalime placed in the rebreathing system. In order to compensate for the oxygen uptake of the patient, oxygen is supplied to the rebreathing system automatically, controlled by the displacement transducer monitoring the volume of the rebreathing system. Consequently, alterations in the inspiratory oxygen concentration which might influence the sensitivity of the helium analyzer, are avoided. In order to produce gas circulation in the rebreathing system a motor blower is built within the circuit. A valve assembly is used to switch from direct ventilation of the patient by the ventilator to ventilation through the rebreathing system.

(Acknowledgement: We wish to thank Mr. H. Stam for allowing us to use the results of his investigations.)

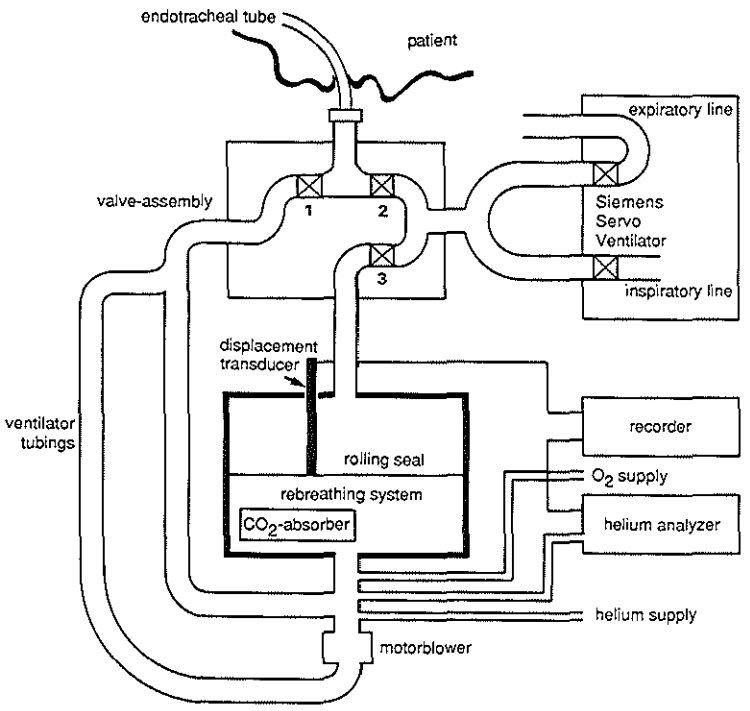

Figure 7. Set up of closed-circuit helium dilution technique using a rolling seal spirometer. The valve-assembly is shown with 3 valves numbered 1-3.
Direct ventilation: ventilator - patient: valve 2 open, valve 1 and 3 closed.
Indirect ventilation: ventilator -rolling seal spirometer - patient: valve 2 closed, valve 1 and 3 open.

In order to test the accuracy of the technique, the resting volume of a mechanical lung model was determined by both the rebreathing system (EEVrb) and a standard helium wash-in procedure in the pulmonary function department (EEVpf). For this purpose, a "Demonstrations-thorax" M20558 (Dräger, Germany) was used that was ventilated by a Siemens Servo ventilator during the rebreathing with the rolling-seal spirometer and ventilated by hand during the standard wash-in procedure. The methods were compared at two different resting volumes of the lung model, adjusted with the use of springs. From a series of 10 consecutive measurements the results for the high resting volume level were: EEVpf = 2.88 l (SD 0.07),

EEVrb = 2.94 l (SD 0.06) and for the low resting volume level: EEVpf = 2.19 l (SD 0.03) and EEVrb = 2.23 l (SD 0.06).
In 5 patients the levels of total PEEP were determined before and during the determination of EEV. All patients were mechanically ventilated in the volume-controlled mode. The level of total PEEP was determined at the endotracheal tube using the interrupter technique at end-expiration. Before the start of the measurement the levels of total PEEP varied from 3.8 to 9.0 cmH_2O; during the procedure the levels varied between 3.2 and 7.0 cmH_2O. The mean values (± SD) amounted to 6.0 ± 1.9 and 5.6 ± 1.4 cmH_2O for respectively the measurements before and during the procedure. Considering these results, it is clear that the lung volumes determined by the rebreathing technique were only slightly affected by the method itself.

3. Work of breathing

3.1. Introduction

In the last decade work of breathing has been studied extensively in intensive care patients. This interest in estimations of respiratory work can be explained in view of the growing number of ventilator-dependent patients and the development of various new modes to wean these patients from the ventilator. Respiratory work has been studied in large groups of ventilator-dependent patients in order to predict weaning outcome [27, 28]. The effects of various weaning modes on the respiratory work of the patients have also been investigated [29, 30]. It is well-established that breathing through ventilator-circuits impose additional work on the respiratory muscles of ventilator-dependent patients, which may hamper the weaning process [29]. Consequently, estimations of respiratory work are considered clinically important in ventilator-dependent patients in whom attempts to wean from the ventilator are pursued.

3.2. Basic principles of estimation of respiratory work.

Mechanical work is described in terms of force and distance. When a force F moves its point of application through a distance L: the work W is given

by W = F x L. Since pressure is force per unit area, force may be replaced by pressure (P) x area (A). Therefore, W = P x A x L and since area x length = volume, work can be described as W = P x V. Consequently, the mechanical work of the respiratory muscles can be described in terms of pressure and volume. In the case of a changing pressure work is described as $\int PdV$. Respiratory work can be estimated from pressure-volume diagrams: the pressures generated by the respiratory muscles against the volume-displacements in and out the lungs [31].

It should be emphasized that respiratory muscle activity is not in all cases associated with the mechanical work represented in pressure-volume diagrams. Only when contraction of respiratory muscles leads to displacement of gas in and out the lungs, mechanical work is represented in the pressure-volume diagram. This work, associated with volume changes, should be more accurately defined as external mechanical work. No external work is performed if respiratory muscles sustain a pressure against a closed airway. In that case, the isothermal compression is associated with energy delivery, which is dissipated as heat over the surface of the lungs.

In accordance with the generally accepted nomenclature in literature, the term 'mechanical work' is used in this section. The respiratory muscles work against three main types of forces [32]:

1. Elastic forces developed in the tissues of lungs and chest wall when a volume change occurs.
2. Flow-resistive forces that depend on the resistance offered by the airways to the flow of gas and on the resistance offered by the non-elastic deformation of tissue.
3. Inertial forces of the tissues.

The effect of gravity is included in the measurements of the elastic forces. Inertial forces are considered negligible, since the associated pressures are extremely small during quiet breathing.

In clinical practice, the best approach to estimate respiratory work during spontaneous breathing is the method involving simultaneous measurement of the changes in lung volume and in intrathoracic pressure. Because esophageal pressure equals intrathoracic pressure, this pressure can be used for convenience' sake. This method can be used to measure elastic work

done on the lungs plus flow-resistive work done on moving gas and lung tissue. The total elastic work can be estimated if in the pressure-volume diagram the compliance of the chest wall is taken into account. It should be underlined that by this method the flow-resistive work done on the thorax cannot be computed. This work to overcome the flow-resistance of the chest wall has been estimated to be in the range of 70% of the flow-resistive work done on the lungs during quiet breathing [33]. Since expiration is usually passive during quiet breathing, expiratory work is as a rule not considered and only the work performed by the inspiratory muscles are taken into account at the computation of work of breathing.

3.3. Estimation of respiratory work in clinical practice

The Campbell diagram

In clinical practice the Campbell diagram is commonly used to compute respiratory work [33]. In this approach all pressures are esophageal pressures relative to atmospheric pressures. In Figure 8 the Campbell diagram is shown: the esophageal pressure on the abscissa is plotted against volume on the ordinate expressed as a percentage of vital capacity. In this representation two lines have been drawn: the line of the static elastic recoil pressure of the lungs and the line of the static elastic recoil pressure of the chest wall. If at various levels lung volume is held constant with the airways unobstructed, the points fall along the curve of the static recoil pressure of the lungs: Pst (L). If the airways are obstructed and the respiratory muscles relaxed, the points representing the various lung volumes fall along the static recoil curve of the chest wall: Pst (W). The two curves intersect at resting end-expiration i.e. functional residual capacity. In the case of an inspiratory volume level with unobstructed airways the inspiratory muscle force is given by the static elastic recoil of the lungs minus that of the thorax.

In Figure 9 a breathing cycle on the Campbell diagram is shown. Two pressure-volume loops are drawn in order to describe one breath. The solid line represents the pressure-volume loop contributed by the lungs in dynamic conditions; the dotted line represents the pressure-volume loop contributed by the chest wall. As stated above, the flow resistive work done on the chest wall cannot be computed. The respiratory work that can be computed,

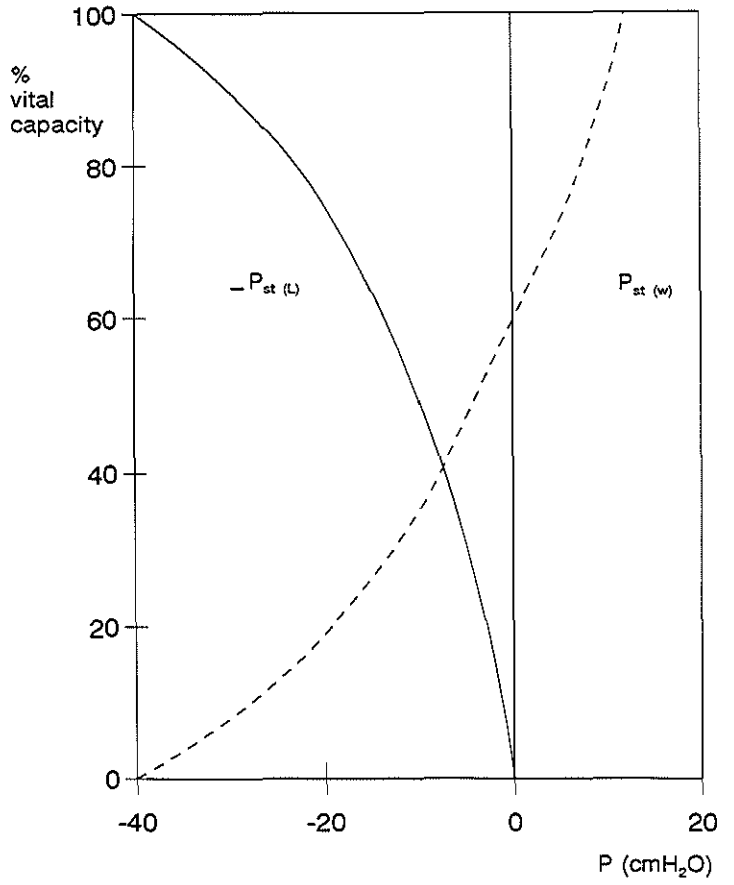

Figure 8. Campbell diagram (see text).

is composed of the respiratory resistive work done on the lungs and the inspiratory elastic work done on lungs and chest wall. The inspiratory resistive work is obtained by integration of the area subtended by the dynamic changes in the esophageal pressure and lung volume during inspiration and the line of the Pst (L). The inspiratory elastic work is obtained by integration of the area subtended by the Pst (L) line, the Pst (W) line and the line drawn between the points on the Pst (L)- and Pst (W) lines at end-inspiration.

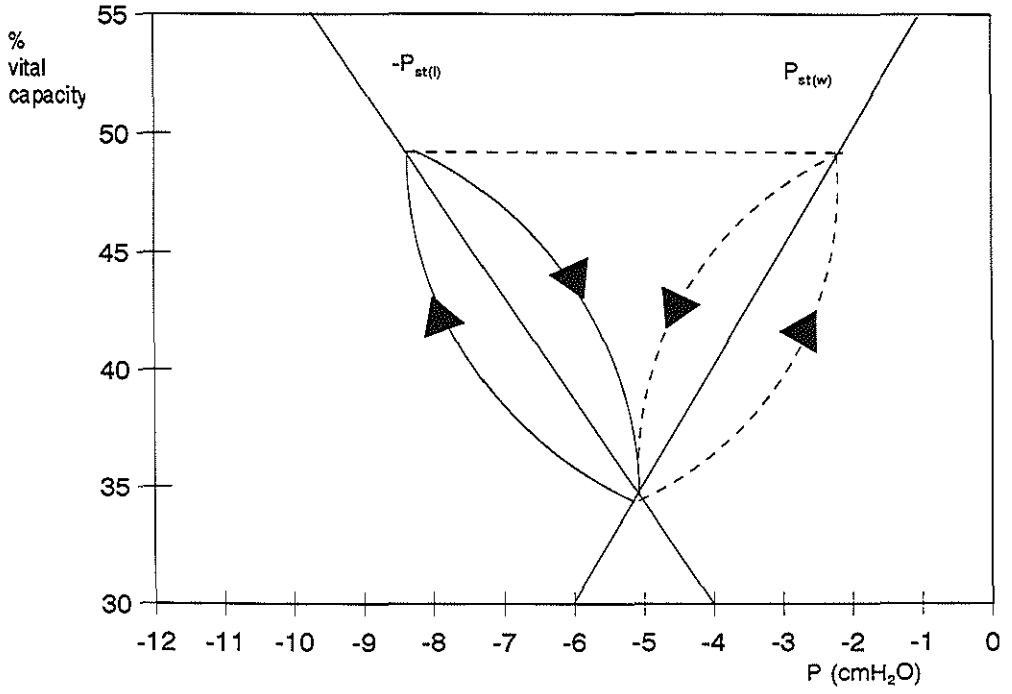

Figure 9. Volume-pressure relationship represented on the Campbell diagram.
Pst (L) = static recoil pressure of the lung
Pst (W) = static recoil of the chest wall

It should be underlined that only the dynamic changes in esophageal pressure and lung volume during the breathing cycle can actually be measured. The line of Pst (L) can be established by drawing a line between the values of the esophageal pressure at the start and the end of inspiration. For the computation of the elastic work the line of Pst (W) has to be fitted on the pressure-volume diagram, taken into account two specific difficulties. At first, the slope of the line of Pst (W) can only be computed if the compliance of the chest wall is actually obtained in a relaxed individual. Because these measurements can only be done in intubated individuals under curarization, standard values are commonly used for the computations. In healthy individuals the compliance of the chest wall is assumed to be 4% of the vital capacity per cmH_2O [34]. Secondly, the Pst (W) line only intersects the Pst (L) line at resting end-expiration. Hence, only if expiration is ended at the

level of functional residual capacity, the Pst (W)line can be fitted intersecting the Pst (L) line at end-expiration.

3.4. Estimation of respiratory work in intubated pations with COPD

In intubated patients with chronic obstructive pulmonary disease (COPD) computations of respiratory work should be considered with respect to specific circumstances as endotracheal intubation and to the pathophysiology of the underlying disease.

The presence of an endotracheal tube is known to increase the resistive component of the respiratory work substantially, dependent on the endotracheal tube size. The flow-resistances of the different endotracheal tubes have been studied extensively; the pressure-flow relationships of the tubes have been expressed over a wide range of flows [35]. Two such relationships are:

$$Pres = k1V' + k2V'^2$$

$$Pres = a.V'^b$$

(Pres = resistive pressure; k1, k2, a and b are constants)

The first expression was introduced by Rohrer [33]; expression no. 2 was introduced by Ainsworth and Eveleigh [33].

The respiratory work imposed by the presence of the endotracheal tube has been estimated in healthy volunteers. Breathing through endotracheal tubes was associated with significant increases in respiratory work, which were magnified at higher minute ventilation through narrow tubes [36]. Beside the additional respiratory work imposed by the endotracheal tubes, breathing through ventilator circuits is also known to increase respiratory work [29, 37]. This additional flow-resistive work can be computed by simultaneous measurement of changes in airway pressure and volume. In order to minimize this additional work, experimental circuits applied for spontaneous breathing in intubated patients should be carefully chosen with respect to the diameter of the tubings and the ventilatory flow.

In order to compute respiratory work in patients with COPD the presence of dynamic hyperinflation should be taken into account [1]. As stated before,

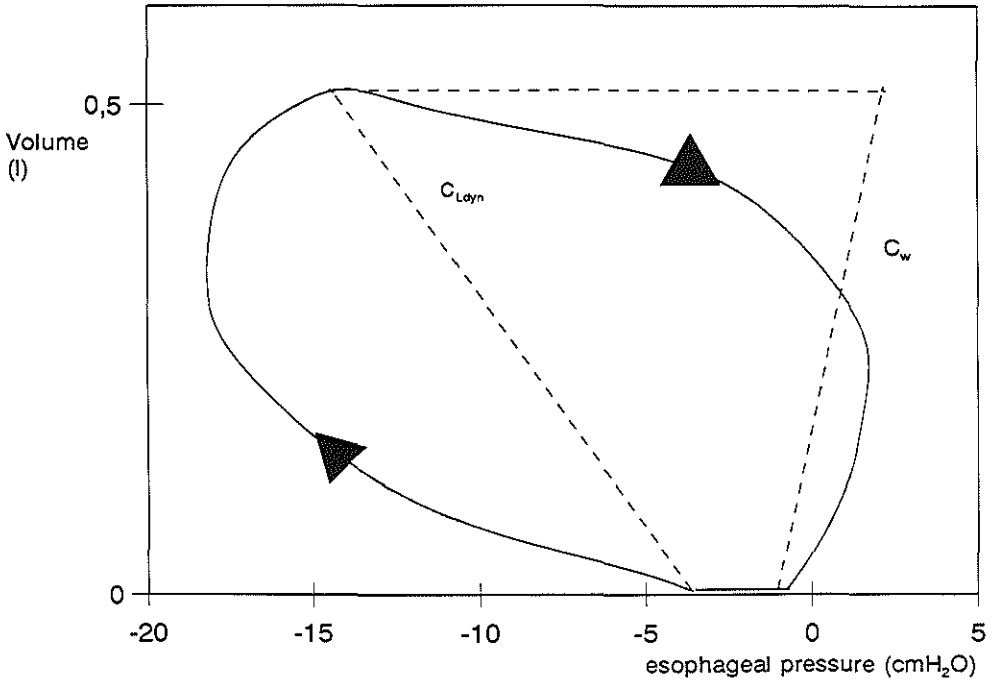

Figure 10. Pressure volume diagram of spontaneously breathing patients with COPD.

dynamic hyperinflation associated with the presence of intrinsic PEEP is almost invariably present in intubated patients with COPD. It is also clear that in these patients the presence of an endotracheal tube leads to an additional flow-resistance during inspiration.

The presence of intrinsic PEEP is known to increase respiratory work, as this condition acts as an inspiratory threshold to the respiratory muscles. Since intrinsic PEEP is present at end-expiration, the patients must generate a negative inspiratory pressure, equivalent in magnitude to intrinsic PEEP-level before the inspiratory flow can start [38]. This phenomenon can be identified in the pressure-volume diagram of these patients. In the pressure-volume loop shown in Figure 10 a decrease in esophageal pressure is noted at the start of inspiration without a change in volume. This decrease in esophageal pressure corresponds with the negative inspiratory pressure counterbalancing

the level of intrinsic PEEP. This estimation of intrinsic PEEP is similar to that described in section I.2.2 under heading: indirect approach.
This phenomenon also affects the computation of the line of the static recoil pressure of the chest wall (Cw line) in the pressure-volume diagram. In the presence of dynamic hyperinflation, the expiration is terminated at a lung volume above functional residual capacity. Consequently, the line of Cw cannot be fitted intersecting the line of the elastic recoil pressure of the lungs ($C_{L, dyn}$). As discussed previously, only at functional residual capacity the lines of $C_{L,dyn}$ and Cw intersected i.e. the elastic recoil pressures of lungs and chest wall are equal. At an end-expiratory lung volume above functional residual capacity the elastic recoil pressure of the chest wall is not equal to the elastic recoil pressure of the lungs.
Two methods have been described to estimate the elastic recoil pressure of the chest wall at end-expiration [38, 4]. For the first method the pressure-volume loop is used. In the pressure-volume loop the recoil pressure of the chest wall at end-expiration is assumed to correspond with the negative deflection that occurs before the beginning of inspiration [38]. Although the observer error may present difficulties, this method can be used in principle in each pressure-volume curve. As hyperinflation can vary from breath to breath, these pressure points will also vary relatively to ambient pressure.
The second method is to estimate the static elastic recoil pressure of the chest wall during tracheal occlusions. In order to measure this static pressure, the patient should breath through a two-way valve with the facility to occlude the inspiratory and expiratory line separately. During expiration the inspiratory line is occluded and subsequently during the inspiratory effort against the occluded airway the expiratory valve is also closed. By measuring the plateau in the esophageal pressure between the inspiratory efforts, the static elastic recoil pressure of the chest wall at end-expiration can be estimated [4]. In Figure 11 a recording of airway and esophageal pressure during tracheal occlusion is shown. The static elastic recoil pressure of the chest wall measured accordingly can be used in the pressure-volume loops to determine the position of the line of Cw at end-expiration. It should be underlined that static pressures can only be measured during tracheal occlusions if no active expiratory effort is present. Besides, this method

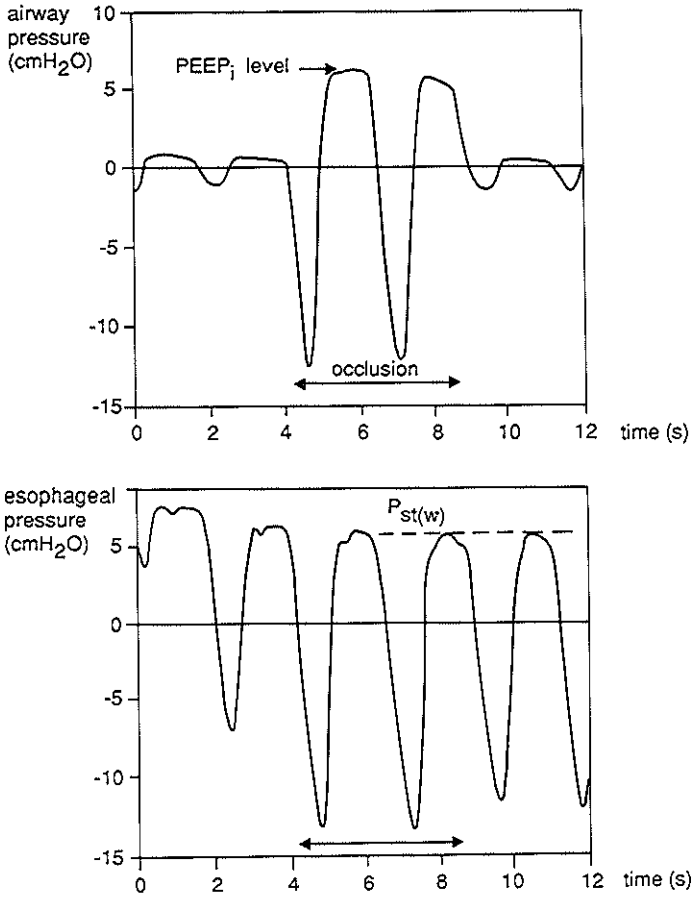

Figure 11. Estimation of the static recoil pressure of the chest wall at end- expiration (Pst (w)). Recording of airway and esophageal pressure in time in an intubated patient with COPD.

provides a mean static elastic recoil pressure of the chest wall at end-expiration: it is clear that this pressure will vary according to the degree of hyperinflation. Despite these objections, the measurements obtained during tracheal occlusions were found to correlate well with the first method of the negative deflection points on the pressure volume loops [5].

It has been established that the compliance of the chest wall in patients with COPD is within normal limits [39]. The compliance of the chest wall is assumed to be 4% of vital capacity per cmH_2O [34]. Predicted normal values of vital capacity have been used in clinical studies of patients with COPD [4, 5].

Taken into account all the previously mentioned conditions, it is assumed that this method yields the best approach to estimate respiratory work in intubated patients with COPD.

3.5. Estimations of respiratory work obtained in patients in this thesis.

The set-up of the measurements applied to estimate respiratory work in patients in chapter 9 is depicted in Figure 12. The esophageal pressure was measured using an esophageal balloon attached to a nasogastric tube (National Catheter Argyle NY). The position of the esophageal balloon was

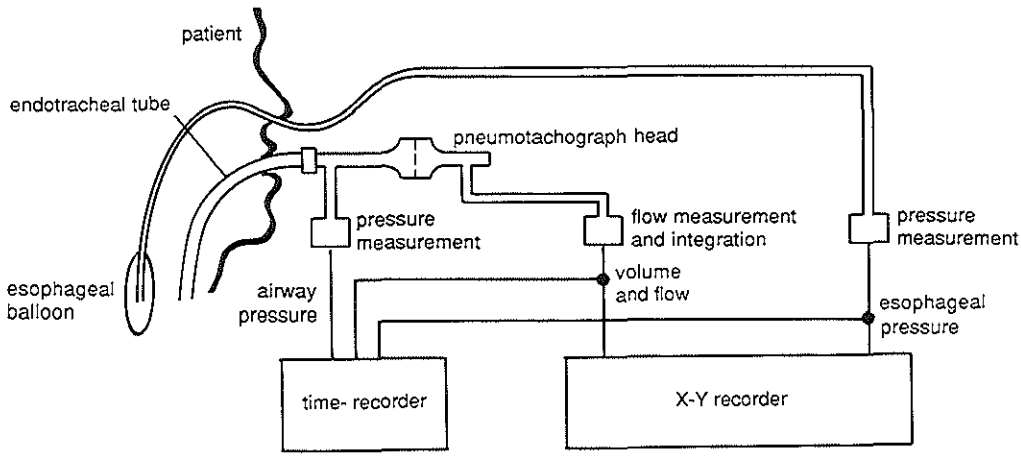

Figure 12. Set up of determination of respiratory work in intubated patients

controlled with the occlusion technique described by Fleury et al [4]. The airway pressure was measured at the endotracheal tube by a Validyne pressure-transducer (Validyne MP45, Validyne Corp. Northridge, CA). The occlusion technique, as described before, was used to estimate the levels of intrinsic PEEP and of the static recoil pressure of the chest wall at end-expiration. Flow was measured by a heated pneumotachograph (Jaeger, Würzburg, Germany) connected to the endotracheal tube. Volume was obtained by integration of the flow. Volume and esophageal pressure were recorded on an X-Y-recorder in order to obtain pressure-volume diagrams. Simultaneously airway pressure, esophageal pressure, volume and flow were recorded on a time-recorder. Respiratory work was computed from the pressure-volume diagram using the Campbell approach. The line of the chest wall compliance was fitted into the pressure-volume diagram, taken into account the abrupt deflection in the pressure-volume loop at end-expiration. A high correlation was found between the static recoil pressure point of the chest wall obtained by estimation in the pressure-volume loop and the one obtained by the occlusion method (Chapter 9).

4. Summary

In this chapter the respiratory measurements applied in the chapters 8 and 9 are described. The various procedures are discussed in view of the techniques described in the literature. As all measurements are performed in intubated patients with COPD both during mechanical ventilation and spontaneous breathing, the specific problems related to this patient group are emphasized. This applies also to the condition of dynamic hyperinflation which was present in all patients studied.

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Chapter 8

Effects of PEEP on respiratory mechanics in patients with COPD on controlled mechanical ventilation

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Abstract

We studied the effects of positive end-expiratory pressure (PEEP) applied by the ventilator on respiratory mechanics in ventilated patients with chronic obstructive pulmonary disease (COPD). Airway pressures, relaxed expiratory flow-volume curves and end-expiratory volumes (EEV) were measured. In all patients investigated without PEEP applied by the ventilator, an intrinsic PEEP-level (PEEPi) and a concavity in the flow-volume curve was present. Ventilator-PEEP caused a significant decrease in PEEPi in all patients ($p < 0.01$). In patients in whom ventilator-PEEP exceeded PEEPi, significant increases occurred in airway pressures and EEV ($p < 0.05$) and moreover the shape of the flow-volume curve was changing. In patients in whom the level of ventilator-PEEP was below the PEEPi-level, no significant changes in airway pressures, EEV of flow-volume curves were found. We conclude: 1) PEEP applied by the ventilator can reduce PEEPi in ventilated patients with COPD without significant changes in airway pressures, EEV or flow-volume curves. 2) Expiratory flow-volume curves can be used to estimate the effects of ventilator-PEEP on EEV.

1. Introduction.

In mechanically ventilated patients with chronic obstructive pulmonary disease (COPD) increased airway resistance and loss of elasticity of lung tissue have profound influences on respiratory mechanics. Considering these factors the expiration time determined by the ventilator is often too short to achieve complete expiration to functional residual capacity (FRC) [1]. Consequently, at end-expiration a lung volume above FRC and a positive alveolar pressure is found [1, 2]. This pressure is called intrinsic Positive End-Expiratory Pressure (PEEPi) in contrast to the (extrinsic) Positive End-Expiratory Pressure applied by the ventilator [1, 3, 4]. Although PEEPi is associated with the same haemodynamic effects as PEEP applied by the ventilator, important differences between both types of PEEP exist, as the increase in patient effort to "trigger" assisted ventilator breaths due to the presence of PEEPi [1].

In order to reduce PEEPi, application of PEEP by the ventilator has been suggested [5]. The clinical benefit of application of ventilator-PEEP has been challenged in view of increases in lung volume and intrathoracic pressure [6]. Other authors stated that the effect of ventilator-PEEP on expiratory lung volume depends upon the level of PEEP applied [1, 5, 7]. However, in these studies only lung volume changes derived from spirometry of plethysmography were reported. Studying the effects of PEEP applied by the ventilator, the end-expiratory lung volume, determining the elastic recoil of the respiratory system, is a key variable.

We studied the effects of PEEP applied by the ventilator on airway pressures, expiratory flow-volume curves and end-expiratory lung volumes in patients with COPD. For this investigation absolute lung volumes were measured. From these measurements the effects of ventilator-PEEP on expiratory flow and lung volume were examined in relation to the level of PEEPi present.

2. Patients and Methods.

2.1. Patients.

Twelve patients with COPD aged 56-75 yrs were studied. Patient data are

TABLE 1
Patient data

Patient no.	Age yrs	Sex m/f	BH m	BW kg	VC l	FEV_1 l	FEV_1 %N	Cause of respiratory failure	Concomitant disease
1	75	f	1.54	48	1.19	0.39	22	exacerb.	
2	75	m	1.73	54	2.35	1.55	53	exacerb.	
3	56	m	1.78	70	4.10	1.03	29	exacerb.	
4	73	m	1.78	82	3.00	0.80	26	exacerb.	
5	72	m	1.80	91	1.50	0.64	24	exacerb.	TBC in past
6	63	f	1.67	78	2.58	0.69	29	exacerb.	
7	71	m	1.77	108	2.20	1.10	36	exacerb.	
8	69	f	1.65	55	2.55	1.02	46	pneumonia	
9	59	m	1.72	105	1.89	0.76	24	exacerb.	
10	72	m	1.60	63	n.d.	n.d.		gastric perforation	
11	71	f	1.60	67	1.32	0.49	25	exacerb.	thoracoplasty
12	64	f	1.58	47	1.66	0.38	19	exacerb.	

BH = body height; BW = body weight; VC = vital capacity; FEV_1 = forced expiratory volume in 1 s.; FEV_1 %N = FEV_1 expressed as percentage of normal value; exacerb. = exacerbation of COPD; TBC = tuberculosis; n.d. = not done.

shown in table 1. Pulmonary function tests, including vital capacity (VC) and forced expiratory volume in 1 s (FEV_1), were obtained shortly before or after the period of mechanical ventilation when the patients were breathing spontaneously without an endotracheal tube. The FEV_1 is also expressed as percentage of predicted [8]. Respiratory failure was caused by acute exacerbations of chronic bronchitis in 10 patients; in the remaining two patients mechanical ventilation had been started because of pneumonia in one patient and surgery for a gastric perforation in the other patient. The 10 patients admitted for acute exacerbation were studied within a week after starting mechanical ventilation; the two patients admitted for other causes were studied after 14 days of ventilatory support when they had recovered from the acute event.

Before the study all patients were alert and haemodynamically stable. They were ventilated through a cuffed endotracheal tube size 7-9 (inner diameter: 7.0-9.0 mm) with the exception of patients no. 10 and 11 who were ventilated through cuffed tracheostomy tubes no. 6 and 8 (inner diameter: 7.0 and 8.5 mm respectively).

The aim of the study was explained to the patients and informed consent was obtained. During the study the patients were sedated with midazolam and paralyzed with pancuronium.

2.2. Methods.

During the study the patients were ventilated in the supine position with a Siemens Servo 900C ventilator (Siemens-Elema, Solna, Sweden). The volume-controlled mode was used with an average tidal volume of .65 l and a respiratory rate of 10-12 min^{-1}. The inspiratory : expiratory ratio was set as follows: the inflation amounted to 25%, the inflation hold 10% and the expiration 65% of the cycle. This mode of ventilation was chosen to ensure an equal time for expiration in all patients. Airway pressures were measured at the endotracheal tube with a Validyne pressure transducer and recorded in time on a Servogor recorder (type 460, Brown Boveri Company, Rotterdam, Holland). To obtain the pressures during airway occlusion the end-inspiratory and end-expiratory hold buttons of the Servo 900C were used. The end-inspiratory pressure was defined as the pressure measured at 1.5 s after occlusion of the airway. End-expiratory pressure was measured using an expiration hold of 4 s. This end-expiratory pressure is called total PEEP (PEEPtot). Extrinsic PEEP (PEEPe), is defined as the pressure at the endotracheal tube during the last second of expiration. The difference between the pressures at the endotracheal tube during the expiration hold and during the last second of expiration is called PEEPi [9]. The compressible volume of the ventilator tubings was not taken into account. For the estimation of the total compliance of the respiratory system, expiratory tidal volume was measured using the Silverman flow-transducer of the Servo 900C ventilator calibrated with a wet spirometer. The total static compliance was calculated by dividing expiratory tidal volume by the driving pressure, the difference between end-inspiratory and end-expiratory pressure (PEEPtot).

The end-expiratory lung volume (EEV) was obtained by using a closed circuit helium-dilution technique comparable with a system described previously [10]. The system used consists of a rolling seal spirometer, the back compartment of which was connected to the ventilator and the front compartment to the patient. In this way a rebreathing system was established operated by the ventilator without changing the ventilatory mode. The CO_2 excreted by the patient was absorbed by sodalime in the spirometer. Moreover the rebreathing volume was kept constant by automatic suppletion of O_2 to compensate for the O_2 uptake by the patient. This O_2 stabilization allows long equilibration times of 8-10 minutes obligatory in patients with severely unequal ventilation.

Relaxed expiratory flow-volume curves were obtained using a heated pneumotachograph (Lilly) at the expiratory port of the ventilator. Volume displacement was obtained by integration of the flow signal (Jaeger, Würzburg, F.R.G.). The flow-volume curve was recorded on an X-Y recorder (X-Y 733, Brown Boveri Company, Rotterdam, Holland).

From the flow-volume curve the peak expiratory flow (V'max ex), the expiratory flows at 50 and 25% of expiration volume (V'50 ex, V'25 ex) and the end-expiratory flow at the moment the valve of the ventilator closed (V'endex) were measured.

The resistance at end-expiration was estimated as the quotient of driving pressure and simultaneous flow. In this case PEEPi was considered as driving pressure. In order to estimate the resistance of the equipment, the pressure-flow relationship of the endotracheal tubes, ventilator tubings and pneumotachograph was obtained [11]. The relationship was curvilinear described by a power function of the form: $P = aV'^{b}$, where a and b were constants. Results for endotracheal tubes of representative sizes are shown in figure 1. For the study, the flow resistance of the equipment was subtracted from the resistance of the total respiratory system.

All measurements were performed in duplicate at two end-expiratory pressures applied by the ventilator: zero end-expiratory pressure and a low PEEP-level. This level of ventilator-PEEP was not adjusted to any criterium but was chosen by chance. Afterwards the level of ventilator-PEEP was defined as the difference between the two PEEPe-levels obtained at both

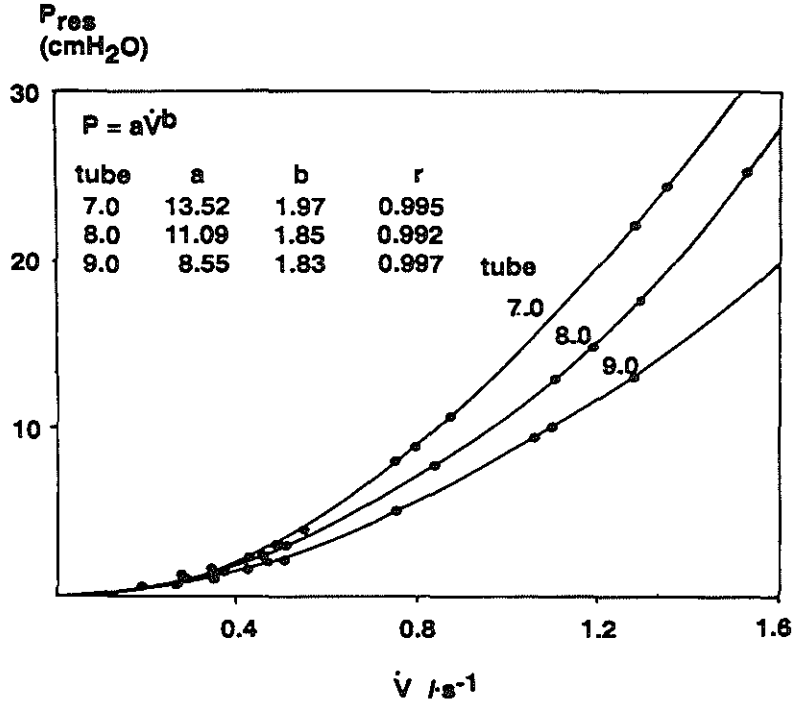

Figure 1. The relationship between resistive pressure (Pres) and airflow (V') for endotracheal tubes and ventilator tubings is shown. Also indicated are the results obtained by fitting measurements to power function of the form Pres = aV'^{b}, where a and b are constants (r = correlation coefficients)

ventilator settings. The level of ventilator-PEEP varied from 3.0 to 9.3 cm H_2O with an average of 5.8 cm H_2O. For reasons of simplicity we will refer to 6 cm H_2O ventilator-PEEP in the following text. The scissor type expiration valve from the Siemens Servo 900C ventilator was used as PEEP valve [12]. No randomization was applied. The measurements at the different ventilator settings were obtained at least five minutes after the ventilator-PEEP level had been changed.

The measurements obtained without ventilator-PEEP was compared with those at the applied ventilator-PEEP. From the flow-volume curves isovolume flows obtained at the two ventilator-PEEP levels were compared. From the curves obtained without ventilator-PEEP the expiratory flow after exhalation of 15% of expiration volume was measured. At the applied ventilator-PEEP level the expiratory flow at the corresponding expiration volume was ob-

tained, taken into account the increase in EEV associated with the PEEP applied by the ventilator. For statistical analysis the Wilcoxon matched pairs test was used. Differences with p-values less than 0.05 were considered statistically significant. Correlations were examined by linear regression analysis [13].

3. Results

The pressure-, volume-related measurements of the individual patients obtained without and with ventilator-PEEP are shown in table 2. The measurements obtained without ventilator-PEEP revealed a PEEPi ranging from 2.0 to 14.1 cm H_2O. Although no PEEP was applied by the ventilator, all patients showed a very low PEEPe varying from 0.4 cm H_2O to 1.3 cm H_2O. The patients were divided into two groups. In the patients no. 1-6 a PEEPi level was obtained below the value of ventilator-PEEP applied in the second part of the study (the low PEEPi group). The PEEPi level of the patients no. 7-12, exceeded the value of ventilator-PEEP used later in the study (the high PEEPi group). PEEPi decreased significantly ($p < 0.05$) in both patient groups comparing the two ventilator settings without and with ventilator-PEEP; however, a significant increase in total PEEP ($P < 0.05$) was only found in the patients with a low PEEPi. Accordingly significant increases in end-inspiratory pressure (P,endinsp) and end-expiratory volume (EEV) ($p < 0.05$) were only found in the patients of the low PEEPi group; in the patients of the high PEEPi group no significant changes were found in P,endinsp, PEEPtot or EEV comparing the measurements obtained without and with ventilator-PEEP. When the change of EEV was compared with the change in PEEPtot for the 12 patients, a positive correlation was found which proved to be significant ($r = 0.76$ $p = 0.004$).

The total compliance did not change at 6 cm H_2O of ventilator-PEEP in either patient group: for the 12 patients the means and standard deviations amounted to 0.073 ± 0.023 l.cm H_2O^{-1} for the values obtained without ventilator-PEEP and 0.072 ± 0.022 l.cm H_2O^{-1} at 6 cm H_2O of ventilator-PEEP.

TABLE 2

Effects of ventilator-PEEP on respiratory mechanics

	Ventilator-PEEP = 0 cmH_2O					Ventilator-PEEP = 5.8 cmH_2O				
Patient No.:	P,endins cmH_2O	PEEPi cmH_2O	PEEPe cmH_2O	PEEPtot cmH_2O	EEV l	P,endins cmH_2O	PEEPi cmH_2O	PEEPe cmH_2O	PEEPtot cmH_2O	EEV l
1	9.9	2.0	0.5	2.5	1.68	15.5	0.7	6.7	7.4	2.05
2	11.0	3.0	0.5	3.5	2.22	14.1	2.0	3.5	5.5	2.56
3	13.3	4.0	0.8	4.8	3.44	16.4	1.4	6.9	8.3	3.98
4	12.1	5.0	0.5	5.5	3.01	16.2	4.7	5.5	10.2	3.41
5	20.6	5.9	0.4	6.3	1.18	23.4	2.6	6.4	9.0	1.53
6	16.8	6.7	1.3	8.0	2.41	20.6	1.2	10.6	11.8	2.96
Mean	14.0	4.4	0.7	5.1	2.32	17.7*	2.1*	6.6	8.7*	2.75*
SD	3.7	1.6	0.3	1.8	0.76	3.2	2.0	5.5	2.0	0.82
7	13.0	6.3	0.5	6.8	2.79	15.4	5.0	4.3	9.3	3.06
8	22.3	9.3	0.4	9.7	2.51	23.7	6.1	5.6	11.7	2.42
9	19.0	9.8	0.6	10.4	1.95	17.3	1.9	8.2	10.1	2.05
10	20.6	11.0	0.5	11.5	3.06	21.2	6.7	5.6	12.3	3.03
11	28.5	12.4	0.7	13.1	1.07	28.5	6.2	7.0	13.2	1.04
12	23.7	14.1	0.8	14.9	4.40	26.2	9.2	6.8	16.0	4.52
Mean	21.2	10.5	0.6	11.1	2.63	22.1	5.9*	6.3	12.1	2.69
SD	4.7	2.5	0.1	2.6	1.02	4.6	2.2	1.2	2.2	1.07

P,endins = end-inspiratory pressure; PEEPi = intrinsic PEEP; PEEPe = extrinsic PEEP; PEEPtot = total PEEP; EEV = end-expiratory volume; SD = standard deviation.

Wilcoxon matched pairs test: significant difference: * = $0.05 > p > 0.01$.

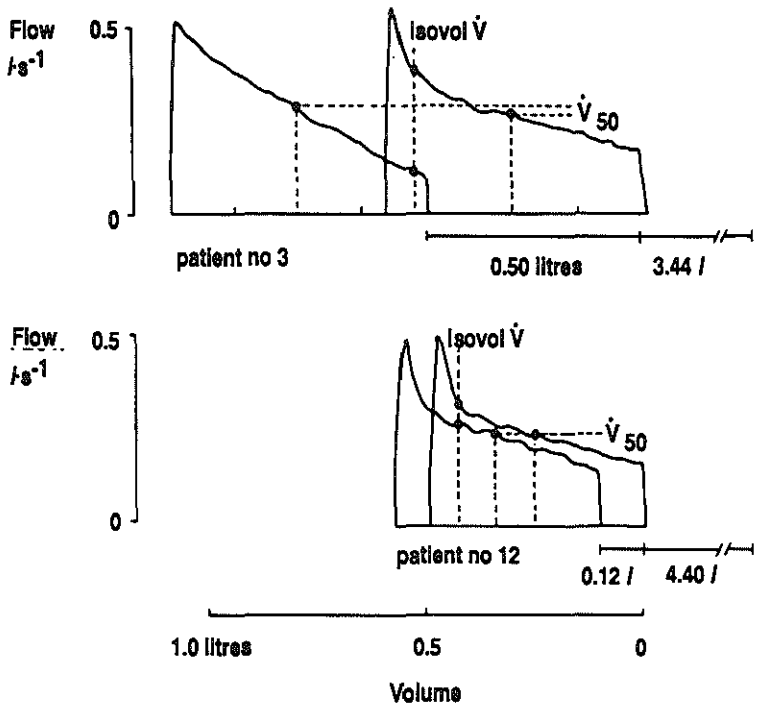

Figure 2. Relaxed expiratory flow-volume curves of patients no. 3 and 12 at ventilator-PEEP levels of 0 and 6.8 cmH_2O. The horizontal scale relates to both changes in EEV and volume changes in the flow-volume curves; V'50 = expiratory flow at 50% of expiration volume; Isovol V' = isovolume flow; EEV = end-expiratory volume.

The effects of ventilator-PEEP on the relaxed expiratory flow-volume relationships of patients no. 3 and 12 are shown in figure 2. The right-sided curves represent the expiratory flow-volume relationships obtained without ventilator-PEEP. A concavity in the flow-volume curves is noted suggesting dynamic airway compression at lower lung volumes. Expiratory flow is still present at the moment the expiration valve of the ventilator closes. At this point an EEV of 3.44 l and 4.40 l respectively is shown on the right side of the curves. The left-sided curves represent the flow-volume relationships at 6 cm H_2O ventilator-PEEP. The shift to the left with respect to the curve obtained without ventilator-PEEP is caused by increases in EEV of 0.50 and 0.12 l respectively for patients no. 3 and 12 associated with the application of ventilator-PEEP. In patient no. 3 application of 6.9 cm H_2O of PEEP by the

ventilator leads to an alteration in the shape of the flow-volume curve: the bi-phasic curve has been altered in a mono-phasic curve. In the flow-volume curves of patient no. 12 no change in the shape of the curve is found comparing zero with 6.8 cm H_2O of ventilator-PEEP. The isovolume expiratory flows are also indicated in the figure. The isovolume expiratory flow of patient no. 3 was reduced from 0.35 $l.s^{-1}$ to 0.13 $l.s^{-1}$ at 6.9 cm H_2O ventilator-PEEP; the isovolume flows of patient no. 12 were 0.28 $l.s^{-1}$ and 0.24 $l.s^{-1}$ at zero and 6.8 cm H_2O ventilator-PEEP.

The expiratory flows measured from the flow-volume curves and the resistances calculated from driving pressure and flow are shown in table 3. In the patient group with low PEEPi significant increases in V'50 ex and V'25 ex were found associated with a significant decrease in V'endex comparing the measurements obtained with and without ventilator-PEEP ($p < 0.05$). In the patient group with high PEEPi no significant changes were found in expiratory flows. The levels of isovolume flows obtained without ventilator-PEEP were not different for the two patient groups; a significant decrease in isovolume flow was only found in the low PEEPi group comparing zero with 6 cm H_2O of ventilator-PEEP. No significant changes were found in V'max ex in either patient group.

However, the resistance at end-expiration was significantly reduced for both patient groups comparing the two ventilator settings.

Significant correlations were found between the changes in EEV and expiratory flows. For the 12 patients the change in EEV was positively correlated with the change in V'50 ex ($r = 0.65$ $p = 0.02$) and negatively correlated with the change in isovolume expiratory flow ($r = -0.81$ $p = 0.002$).

4. Discussion.

The occurrence of PEEPi is frequently encountered in patients with COPD who are mechanically ventilated. However, PEEPi can originate from different pathophysiological mechanisms [14].

In our study the PEEPi found was associated with dynamic airway compres-

sion, considering the patients were paralyzed and the tidal volume and respiratory rate were low, making other types of PEEPi unlikely. However, the presence of expiratory flow limitation was not confirmed in our study. Flow limitation can only be estimated using the interrupter technique during relaxed expiration [7, 11]. The presence of expiratory flow limitation is suggested when application of ventilator-PEEP is associated with an unchanged expiratory flow at the same lung volume [7, 11]. This was also demonstrated in our study in the patients with a PEEPi-level higher than the applied ventilator-PEEP. PEEPi was measured at the endotracheal tube using an airway occlusion at end-expiration. Using this technique we could also demonstrate that during expiration the airway pressure did not fall to zero, although no ventilator-PEEP was applied. This PEEPe was present in all patients, caused by the ventilatory tubings in the presence of an end-expiratory flow.

We investigated the effects of a low ventilator-PEEP on PEEPi, end-expiratory lung volumes and expiratory flow-volume curves. The clinical benefit of application of ventilator-PEEP to mechanically ventilated patients in whom PEEPi is found, remains to be determined [5, 6, 7]. Increase in the pressure downstream of the critical site of flow limitation (the "equal pressure point") is considered not to influence the expiratory flow until the applied ventilator-PEEP exceeds the level of the extramural pressure surrounding the airway [14]. If the ventilator-PEEP exceeds this critical pressure, an increase in end-expiratory lung volume will occur associated with a reduction in expiratory flow at the same lung volume. The hyperinflation causes the elastic recoil to increase and the equal pressure point will be displaced downstream.

Application of ventilator-PEEP in this study caused a significant decrease in PEEPi in all patients. However, the effects of ventilator-PEEP on airway pressures, end-expiratory volumes and flow-volume curves varied among the individual patients. Data-analysis could discern two groups of patients with different responses to the application of ventilator-PEEP. The difference

Legends of Table 3.
V'maxex = peak expiratory flow; V'50ex V'25ex = expiratory flow at 50 and 25% of expiration volume; V'endex = expiratory flow at end-expiration; IsovolV' = isovolume flow; Rendex = transpulmonary resistance calculated from PEEPi and V'endex; SD = standard deviation. Wilcoxon matched pairs test: significant difference: * = $0.05 > p > 0.01$.

TABLE 3

Effects of ventilator-PEEP on respiratory mechanics

	Ventilator-PEEP = 0 cmH_2O						Mean ventilator-PEEP = 5.8 cmH_2O					
Pat. No.:	V'maxex $l.s^{-1}$	V'50ex $l.s^{-1}$	V'25ex $l.s^{-1}$	V'endex $l.s^{-1}$	IsovolV' $l.s^{-1}$	Rendex $cmH_2O.l^{-1}.s$	V'maxex $l.s^{-1}$	V'50ex $l.s^{-1}$	V'25ex $l.s^{-1}$	V'endex $l.s^{-1}$	IsovolV' $l.s^{-1}$	Rendex $cmH_2O.l^{-1}.s$
1	0.47	0.20	0.14	0.08	0.37	26.6	0.59	0.29	0.14	0.04	0.11	13.2
2	0.52	0.17	0.12	0.09	0.31	34.9	0.42	0.19	0.14	0.09	0.18	17.9
3	0.56	0.26	0.20	0.17	0.35	23.2	0.51	0.29	0.20	0.12	0.13	6.4
4	0.46	0.17	0.14	0.12	0.26	42.6	0.38	0.18	0.14	0.12	0.19	35.6
5	0.88	0.29	0.19	0.12	0.59	47.3	0.76	0.32	0.20	0.11	0.25	19.0
6	0.74	0.29	0.20	0.16	0.42	42.0	0.73	0.36	0.24	0.11	0.15	4.5
Mean	0.61	0.23	0.16	0.12	0.38	36.1	0.57	0.27*	0.18*	0.10*	0.17*	16.1*
SD	0.16	0.05	0.03	0.03	0.10	8.7	0.14	0.07	0.04	0.03	0.05	10.2
7	0.53	0.18	0.13	0.11	0.29	59.7	0.41	0.18	0.14	0.11	0.19	42.6
8	0.54	0.18	0.13	0.10	0.36	90.1	0.66	0.18	0.13	0.09	0.38	65.4
9	0.68	0.28	0.20	0.14	0.46	66.5	0.65	0.31	0.21	0.13	0.44	8.8
10	0.65	0.17	0.12	0.08	0.28	139.4	0.60	0.17	0.12	0.09	0.27	68.3
11	0.75	0.33	0.21	0.14	0.58	81.2	0.71	0.33	0.21	0.13	0.62	41.0
12	0.55	0.20	0.17	0.15	0.28	89.5	0.50	0.17	0.14	0.12	0.18	70.1
Mean	0.62	0.22	0.16	0.12	0.37	87.8	0.59	0.22	0.16	0.11	0.35	49.4*
SD	0.08	0.06	0.04	0.02	0.11	25.7	0.10	0.07	0.04	0.02	0.16	21.6

between the two groups depended upon the relationship between PEEPi and ventilator-PEEP. In the patients in whom the PEEP applied by the ventilator exceeded PEEPi, significant increases in airway pressures and EEV were found associated with the application of ventilator-PEEP. In this group of patients ventilator-PEEP is considered to exceed the critical pressure: significant increases in both end-inspiratory pressures and total PEEP were also found. In the patients in whom PEEPi exceeded ventilator-PEEP, the changes in airway pressures and EEV were not significant.

In most investigations concerning PEEPi and ventilator-PEEP only volume changes derived from spirometry of respiratory inductive plethysmography are reported [6, 15]. In contrast, we determined end-expiratory lung volumes, assuming that in the process of flow limitation lung volume is a key variable. We found that the level of PEEPi did not correlate with the magnitude of EEV, despite the presence of hyperinflation. Relatively low end-expiratory volumes were found in patients suffering from obesity, and in those with a history of tuberculosis and thoracoplasty. However, a reduction in FRC is well-established when supine position is compared with seated position [16]. In this study the loss of tonic activity of the inspiratory muscles may have contributed to this decrease.

Previous investigations have claimed detrimental increases in lung volumes and airway pressures associated with ventilator-PEEP [6]. In our study a group of patients could be discerned in whom application of PEEP by the ventilator was not associated with significant increases in EEV or airway pressures. This contradiction can be explained if we assume that in the previous investigation the PEEP applied by the ventilator surpassed the PEEPi in all patients studied [6].

We also studied PEEPi and ventilator-PEEP in relation to relaxed flow-volume curves. Relaxed expiratory flow-volume curves have been suggested to determine the presence of PEEPi [1]. In patients who can not expire to their elastic equilibrium volume, the flow-volume relationship does not pass through zero but has an intercept on the flow axis i.e. an end-expiratory flow associated with PEEPi [11]. Moreover, in all patients studied a downward concavity in the expiratory flow-volume relationship was found consistent with dynamic airway compression. In previous studies the concavity in the

flow-volume curve has been encountered in ventilated patients with COPD but not in patients ventilated for other forms of respiratory failure [7, 11, 17].

In order to estimate the concavity in the flow-volume relationship the peakflow, the V'50 ex, the V'25 ex, the flows at 50% respectively 25% of expiration volume and the V'endex, the flow at the moment the valve of the ventilator closed was measured. By measuring these flows the expiratory flow-volume relationship is considered as 'free floating'; in order to examine flow-volume curves as volume-based, i.e. in relation to the end-expiratory lung volume, isovolume expiratory flows were obtained.

The effect of ventilator-PEEP on the expiratory flow-volume curves differed between the two patient groups. In the patients in whom ventilator-PEEP exceeded the critical pressure, the shape of the flow-volume curve was changing as indicated by slight but significant increases in V'50 ex and V'25 ex and decreases in V'endex. The changing pattern indicated a marked decrease or disappearance of expiratory flow limitation.

Although in the former group the expiratory flows increased due to application of PEEP by the ventilator, these changes in flow should be considered in relation to total lung volume. In contrast with the increase in V'50 ex and V'25 ex, the isovolume flows were significantly decreased due to the increase in end-expiratory lung volume. In the patient group with the high PEEPi level, in whom ventilator-PEEP did not increase EEV, the shape of the expiratory flow-volume curve remained unchanged as did the isovolume flow comparing the two ventilator settings.

Considering these expiratory flows the resistance of the endotracheal tubes and ventilator tubings have to be taken into account. In order to calculate the transpulmonary resistance at end-expiration the flow-resistance of the equipment was estimated and subtracted from the total resistance.

In both patient groups the R,endex, the transpulmonary resistance calculated at end-expiration from driving pressure and flow was significantly reduced. In the patient group in whom the EEV was unchanged, the decrease in resistance can be elucidated by the hypothesis that during flow limitation the driving pressure can be diminished without a change in expiratory flow [7]. It has to be underlined that the decrease in resistance should be considered

mainly as reduction of energy dissipation within the airways.
Considering these results, two major issues should be taken into account. PEEP was applied by means of the scissor type PEEP device of the Siemens Servo ventilator. Although this PEEP device has been considered to exert a low resistance during passive expiration, the effects of ventilator-PEEP on the expiratory flow-volume relationship could be related to the device used [12].
Secondly, the flow-volume relationship was studied under muscle paralysis. However, we have reasons to believe that the results of our study can be extrapolated to clinical circumstances without muscle relaxation. We could reproduce the results in patients without muscle paralysis during controlled mechanical ventilation. Moreover, relaxed flow-volume curves have been obtained in previous investigations in patients without muscle paralysis [7, 11]. Recently, a paper has been published on the effects of continuous positive airway pressure showing the effects of ventilator-PEEP on flow-volume curves during spontaneous breathing [18].
In mechanically ventilated patients with COPD application of PEEP by the ventilator in order to reduce PEEPi has been challenged in view of increasing hyperinflation. This study suggests that ventilator-PEEP can reduce PEEPi without increasing EEV and this could be identified from the effect of ventilator-PEEP on the expiratory flow-volume curve. The concavity of the flow-volume curve remained unchanged when a ventilator-PEEP level was applied which did not increase EEV. However, when a level of ventilator-PEEP did increase EEV, a change in the shape of the expiratory flow-volume curve was found.

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Chapter 9

Continuous positive airway pressure (CPAP) in intubated patients with COPD

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Adapted from a manuscript submitted for publication.

Abstract

In 10 intubated patients with chronic obstructive pulmonary disease (COPD) who had been ventilated for acute respiratory failure, continuous positive airway pressure (CPAP) was compared with spontaneous breathing without positive pressure. The aim of the study was to relate the effects of a CPAP of 0.5 kPa on work of breathing and volume-flow relationships to the intrinsic PEEP-levels of the patients.

Intrinsic PEEP-levels were found during tracheal occlusions, ranging from .26 to 1.31 kPa. Compared to spontaneous breathing without positive pressure, CPAP reduced the total inspiratory work per liter of ventilation (Witot) from 1.66 ± .02 to 1.49 ± .16 J.l-1 (means ± SE $p < 0.005$). This decrease was found to be related to the intrinsic PEEP-levels: the largest reductions were found in the patients with an intrinsic PEEP-level close to the CPAP-level applied. During spontaneous breathing without positive pressure the expiratory flow-volume curves of all patients disclosed a concavity suggestive of flow limitation, which was diminished by CPAP. No correlation was found however between the intrinsic PEEP-levels and the changes in the variables describing the shape of the flow-volume curve.

In intubated patients with COPD, CPAP leaded to significant decreases in Witot, related to the intrinsic PEEP-levels measured during tracheal occlusions. Expiratory flow-volume curves were not found to be useful to estimate these effects.

1. Introduction

Dynamic hyperinflation is frequently encountered in patients with respiratory failure and chronic obstructive pulmonary disease (COPD). This phenomenon occurs in severe airway obstruction, if the rate of lung emptying is decreased and the expiration is terminated by the next inspiration before the functional residual capacity i.e. the relaxed static equilibrium of the respiratory system has been reached [1]. Consequently, dynamic hyperinflation is associated with a lung volume at the end of expiration exceeding functional residual capacity. This condition also leads to the presence of a positive alveolar pressure at end-expiration, a pressure known as "intrinsic" or "auto" PEEP. At first the occurrence of intrinsic PEEP was established in mechanically ventilated patients, but subsequently this condition was also described in stable patients with COPD during spontaneous breathing [2, 3]. As intrinsic PEEP acts as an inspiratory threshold to the respiratory muscles, the presence of this condition leads to an increased work of breathing [4]. Hence, the consequences of intrinsic PEEP have been studied in particular in ventilator-dependent patients both during mechanical ventilation and during weaning modes [4-10].

It is well-established that patient effort to "trigger" ventilator breaths can be considerably enhanced by high level levels of intrinsic PEEP, when for instance assisted mechanical ventilation is used [5]. In order to lower the inspiratory threshold induced by intrinsic PEEP in ventilated patients with COPD, the application of PEEP by the ventilator has been suggested [5, 6]. Low levels of ventilator-PEEP have been shown to reduce intrinsic PEEP in these patients without significant changes in airway pressures or end-expiratory lung volumes [7, 8]. These effects of ventilator-PEEP could be estimated by inspection of expiratory flow-volume curves [8].

It has also been suggested that the use of continuous positive airway pressure (CPAP) as a weaning mode for patients with COPD could reduce the level of intrinsic PEEP and consequently the inspiratory work of breathing [1, 9].

However, the reported effects of CPAP on respiratory system mechanics have been conflicting with respect to changes in pulmonary resistance and end-expiratory lung volume. During application of CPAP pulmonary resistance was found to be decreased and to remain unchanged [9, 10, 11]. Elevated and unchanged end-expiratory lung volumes have also been reported related to the CPAP applied [9, 11]. These discrepancies may be due to the type of CPAP-assembly used, the severity of respiratory disease in the patients studied and the presence or absence of an endotracheal tube. The usefullness of inspection of tidal flow-volume curves during CPAP has not been well established [9].

In view of these contradictory opinions on the effects of CPAP and the lack of data concerning expiratory flow-volume curves, we studied the effects of CPAP on work of breathing and volume-flow relationship in intubated patients with COPD during spontaneous breathing. The effects of CPAP were related to the intrinsic PEEP-levels of the individual patients. An experimental circuit with a CPAP-level of 0.5 kPa was compared to a circuit without positive pressure.

2. Patients and Methods

2.1. Patients

Ten patients with COPD aged 65 - 81 yrs were studied. Patient data are shown in Table 1. In seven patients vital capacity and forced expiratory volume in 1 s (FEV_1) could be obtained before the period of mechanical ventilation when the patients were breathing spontaneously without an endotracheal tube. Exacerbations of chronic bronchitis leading to acute respiratory failure with severe hypercapnia, prompted to the institution of mechanical ventilation in eight patients. In patient no.6 a cardiac arrest and in patient no.7 an atelectasis due to bronchial secretions prompted to endotracheal intubation and ventilatory support. All patients were alert during the study and informed consent was obtained.

TABLE 1
Patient data

Patient	Age	Sex	BH	BW	VC	FEV1	paCO2 at start of mechanical ventilation
no	yrs	m/f	m	kg	l	l	kPa
1	78	m	1.80	50	3.30	0.98	9.1
2	78	m	1.67	70	2.79	0.58	11.8
3	80	f	1.60	80	n.d.	n.d.	12.0
4	70	m	1.75	58	3.77	0.72	9.9
5	76	f	1.66	65	n.d.	n.d.	9.1
6	73	f	1.60	53	1.37	0.55	10.4
7	66	m	1.77	61	3.34	0.89	6.2
8	81	m	1.75	75	n.d.	n.d.	6.7
9	65	f	1.67	72	1.70	0.80	n.d.
10	73	m	1.83	71	2.44	0.54	11.5

BH = body height; BW = body weight; VC = vital capacity; FEV1 = forced expiratory volume in 1 s.; n.d. = not done.

2.2. Respiratory measurements

Flow (V') was measured with a heated pneumotachograph (Lilly) positioned at the endotracheal tube. Volume displacement was obtained by integration of the flow signal (Jaeger, Wurzburg, Germany). Tracheal pressure (Ptr) was recorded proximal to the pneumotachograph using a differential pressure transducer (Validyne). Esophageal pressure (Pes) was measured using another differential pressure transducer connected to an esophageal balloon attached to a nasogastric catheter. The esophageal balloon was filled with 0.5 - 1.0 ml of air and properly positioned using the "occlusion test" as previously described [12]. In order to perform the occlusion test the patients were breathing through a two-way valve connected to the endotracheal tube, with the facility to occlude the inspiratory and expiratory line separately.

In all patients the $\Delta Pes/\Delta Ptr$ ratio during the occlusion tests was close to unity (range .91 to 1.13) indicating that the measurements of the swings in

the Pes were a satisfactory index of the changes in pleural surface pressure. Using the same two-way valve, tracheal occlusions at end-expiration were performed and maintained for 2 inspiratory efforts. By measuring the plateau pressures between the occluded efforts in both Ptr and Pes, the elastic recoil pressures of respectively the total respiratory system and the chest wall at end-expiration were estimated. The static elastic recoil pressure of the total respiratory system at end-expiration is assumed to equal the level of intrinsic PEEP during spontaneous breathing [13]. The static elastic recoil pressure of the chest wall has been used for the computation of the elastic work of breathing [4] (vide infra).

2.3. Study protocol

The patients were studied in semirecumbent position. Mechanical ventilation was discontinued and patients were allowed to breath spontaneously through an experimental circuit consisting of a continuous high flow (approximately 100 l.min-1) generator (Downs Flow generator # 9250 Vital Signs Inc., Totowa, NJ). The inspiratory oxygen fraction (FI,O_2) was monitored (Oxygen Monitor 404, Instrumental Laboratory) and kept constant at 0.4 throughout the study. The flow resistance of the experimental circuit including the pneumotachograph, amounted to .23 kPa.l-1.s at flow of 1 l.s-1. A spring-loaded PEEP-valve of 0.5 kPa (Vital Signs) was added to the circuit in order to apply CPAP. This PEEP-valve is known to have a minimal resistance above its threshold, which is considered of critical importance in high flow, non-reservoir circuits [14].

The patients were allowed to breath spontaneously through the experimental circuit for approximately 10 minutes after which the respiratory measurements were obtained. Subsequently the PEEP-valve was added to or removed from the circuit and after a control period of 10 minutes the measurements were repeated.

At the end of two procedures arterial blood-gases were obtained and analyzed with a blood-gas analyzer (ABL3, Radiometer, Copenhagen).

2.4. Data analysis

Respiratory measurements were obtained from 6 to 8 breaths for each condition. The tidal excursions of Ptr were determined during both conditions in order to establish the performance of the experimental circuit with and without the PEEP-valve. From the breaths analyzed for each condition the tidal excursions of the esophageal pressure (ΔPestot) were determined. Graphical analysis of the volume-pressure diagrams of the breaths was used to calculate work of breathing (Figure 1). Between the values of the Pes at the start of inspiration and expiration a line was drawn, the slope of which

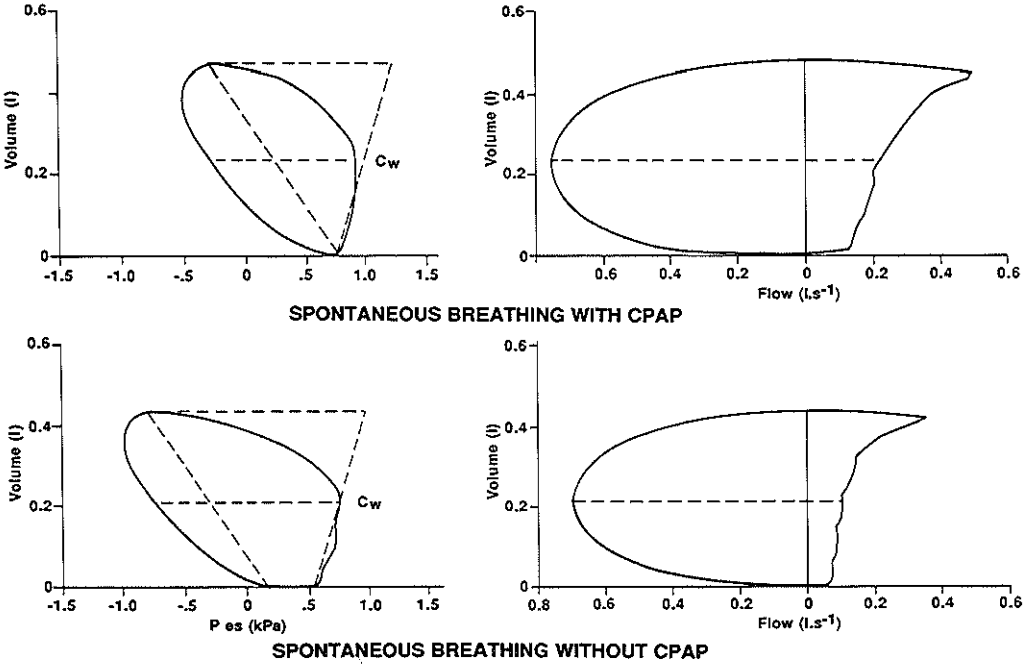

Figure 1. Pressure-volume and flow-volume relationships obtained during spontaneous breathing with and without CPAP. At the left side the esophageal pressure (Pes) on the abscissa plotted against volume on the ordinate. The Cw is the static chest wall compliance. At the right side the flow on the abscissa plotted against volume on the ordinate. For further explanation see text.

represented the dynamic lung compliance ($C_{L,dyn}$). The start of inspiration was defined as the change in the pressure-volume loop due to the start of the inspiratory volume-displacement. The inspiratory resistive work was obtained by integration of the area subtended by the dynamic changes in Pes and lung volume during inspiration and the $C_{L,dyn}$ line. The resistive work thus obtained, included work done in overcoming the resistance of the respiratory system, endotracheal tube and experimental circuit.

The elastic work of breathing was estimated using Campbell's diagram [15]. For this analysis the static volume-pressure relationship of the chest wall was used. According to the literature, the compliance of the chest wall (Cw) is assumed to be 4% of the vital capacity per cmH_2O [16]. The Cw in patients with COPD is considered to be within normal limits and therefore normal predicted values of vital capacity have been used [17].

The line of Cw was fitted on the volume-pressure diagrams of each breath by passing it through the abrupt change in the pressure-volume loop at end-expiration, that occurred before the beginning of the inspiration [18]. These elastic recoil pressures of the chest wall which were fitted on the pressure-volume loops at end-expiration, were compared to the static elastic recoil pressures of the chest wall obtained during tracheal occlusions. Since the tracheal occlusions have only been performed during breathing without positive airway pressure, these comparisons could not be obtained during CPAP. The elastic work (Wel) was obtained by integration of the area subtended by the $C_{L,dyn}$ and Cw lines.

Total inspiratory work (Wtot) was obtained by adding the inspiratory resistive work (Wres) to the inspiratory elastic work (Wel). Total inspiratory work per liter of ventilation was calculated by dividing work by tidal volume for the breaths studied.

For each condition 6 flow-volume curves obtained during tidal breathing were analyzed. Both the maximal expiratory flow (V'maxex) and the inspiratory and expiratory flow at 50% of tidal volume (V'50in and V'50ex) were measured.

To estimate the airway collapse during expiration, the ratio of the expiratory to the inspiratory flow at 50% of tidal volume was calculated (V'50ex/V'50in) [19]. Secondly, the ratio of the expiratory flow at 50% of

the tidal volume to the maximal expiratory flow was calculated to describe the concavity in the expiratory volume-flow relationship (V'50ex/V'maxex). The inspiratory pulmonary resistance at 50% of tidal volume was obtained from the Pes and V'50in. According to the method of Mead and Whittenberger the resistive pressure was measured in the volume-pressure diagram from the $C_{L,dyn}$ line to the dynamic change in Pes at 50% of tidal volume [20].

The pattern of breathing was determined at both conditions to assess the effects of CPAP on inspiratory and expiratory times and flows. From the recording of the flow signal in time, the duration of inspiration and expiration (TI and TE) was obtained to calculate mean inspiratory and expiratory flows (V_T/TI and V_T/TE). The TI/Ttot was calculated from the inspiration time and total breathing cycle.

2.5. Statistical analysis

The measurements obtained during breathing without positive pressure were compared to those during breathing with CPAP. Unless stated otherwise, all data are presented as mean values ± standard error. For statistical analysis paired T-tests were used. Differences with p-values less than 0.05 were considered statistically significant. Correlations were examined by linear regression analysis [20].

3. Results

The intrinsic PEEP-levels of the patients measured during tracheal occlusions, ranged from 0.26 to 1.31 kPa. When the patients were breathing through the experimental circuit with 0.5 kPa CPAP, the actual pressures measured at the endotracheal tube during expiration ranged from 0.4 to 0.5 kPa with a mean of 0.45 kPa. The tidal excursions in Ptr were calculated to assess the performance of the circuit with and without CPAP: the ΔPtr amounted to 0.22 ± 0.02 and 0.21 ± 0.02 kPa for the experimental circuits with and without CPAP respectively. The ΔPestot, the tidal excursions of the esophageal pressure were significantly reduced during the application of CPAP: the mean ΔPestot amounted to 1.69 ± 0.18 and 1.46 ± 0.19 kPa

for tidal breathing without and with CPAP respectively (p-value < 0.005). In Figure 1 the pressure-volume and flow-volume relationships of patient no. 5 during spontaneous breathing with and without CPAP are shown. In the pressure-volume of each breath the line of $C_{L,dyn}$ has been drawn passing through the values of Pes at the start of inspiration and expiration. The start of inspiration has been defined as the change in the pressure-volume loop due to the start of the inspiratory volume-displacement. The line of Cw has been drawn through the abrupt change in the pressure-volume loop at end-expiration. The elastic recoil pressures of the chest wall fitted in the pressure-volume loops at end-expiration were correlated with the static elastic recoil pressures of the chest wall obtained during tracheal occlusions: the correlation proved to be highly significant ($r = .94$ $p < 0.005$).

The elastic recoil pressure of the lung at the start of inspiration and the recoil pressure of the chest wall at end-expiration do not coincide in the pressure-volume loop of the breath obtained without positive pressure (Figure 1, lower part). The deflection in the esophageal pressure between the two elastic recoil pressures is assumed to equal intrinsic PEEP. At the breath obtained during CPAP the elastic recoil pressure of the lung at the start of inspiration and the recoil pressure of the chest wall at end-expiration do coincide in the pressure-volume loop: no intrinsic PEEP was found. Inspection of the expiratory flow-volume curves revealed that the downward concavity was diminished comparing the breath with CPAP to the breath without positive pressure.

The results of the measurements of respiratory work of the individual patients are shown in Table 2. A high correlation was found between the intrinsic PEEP-level and the inspiratory work per liter of ventilation obtained during breathing without positive pressure (Figure 2). Comparing the two conditions, a significant reduction for CPAP was found in total inspiratory work per liter of ventilation (p-value < 0.005). Subdividing inspiratory work in the resistive and elastic components revealed that the decrease in elastic ork accounted for 70% of the decrease in the total inspiratory work. When the measurements obtained in the individual patients are compared, the decrease in inspiratory work due to CPAP proved to be related to the intrinsic

TABLE 2
Respiratory measurements of the individual patients

	Breathing without CPAP				Breathing with CPAP		
	PEEPi	Wltot	Wel	Wres	Wltot	Wel	Wres
no	kPa	J.l^{-1}	J.l^{-1}	J.l^{-1}	J.l^{-1}	J.l^{-1}	J.l^{-1}
1	0.26	0.82	0.49	0.33	0.78	0.48	0.30
2	0.39	1.20	0.76	0.43	1.07	0.68	0.40
3	0.42	1.79	1.47	0.32	1.39	1.13	0.26
4	0.43	1.62	1.03	0.59	1.38	0.92	0.46
5	0.54	1.31	1.07	0.25	0.99	0.82	0.17
6	0.66	1.71	1.26	0.45	1.54	1.10	0.43
7	0.76	1.44	1.04	0.40	1.43	1.04	0.40
8	1.00	1.84	1.19	0.65	1.71	1.10	0.60
9	1.28	2.31	1.33	0.98	2.20	1.26	0.94
10	1.31	2.51	1.87	0.64	2.41	1.76	0.65
mean	0.71	1.66	1.15	0.50	1.49**	1.03**	0.46*
SE	0.12	0.02	0.12	0.07	0.16	0.11	0.07

PEEPi = intrinsic PEEP-level during spontaneous breathing without positive pressure; Wltot = total inspiratory work per liter of ventilation; Wel = elastic work per l of ventilation; Wres = resistive work per l of ventilation; SE = standard error of the mean.
Paired T-tests: * = $p < .05$
** = $p < .005$

PEEP-level measured during tracheal occlusions. In Figure 3 the decrease in inspiratory work due to CPAP with respect to breathing without positive pressure is shown. The decrease in inspiratory work is expressed as percentage of the values obtained during breathing without CPAP. In patients no. 2-5, with an intrinsic PEEP-level from 0.39 to 0.54 kPa, the largest reductions in inspiratory work were found.

In patient no. 1 with the lowest intrinsic PEEP-level CPAP was only associated with a minimal decrease in inspiratory work. Also in the patients with the highest levels of intrinsic PEEP above 0.6 kPa (patients no 6-10)

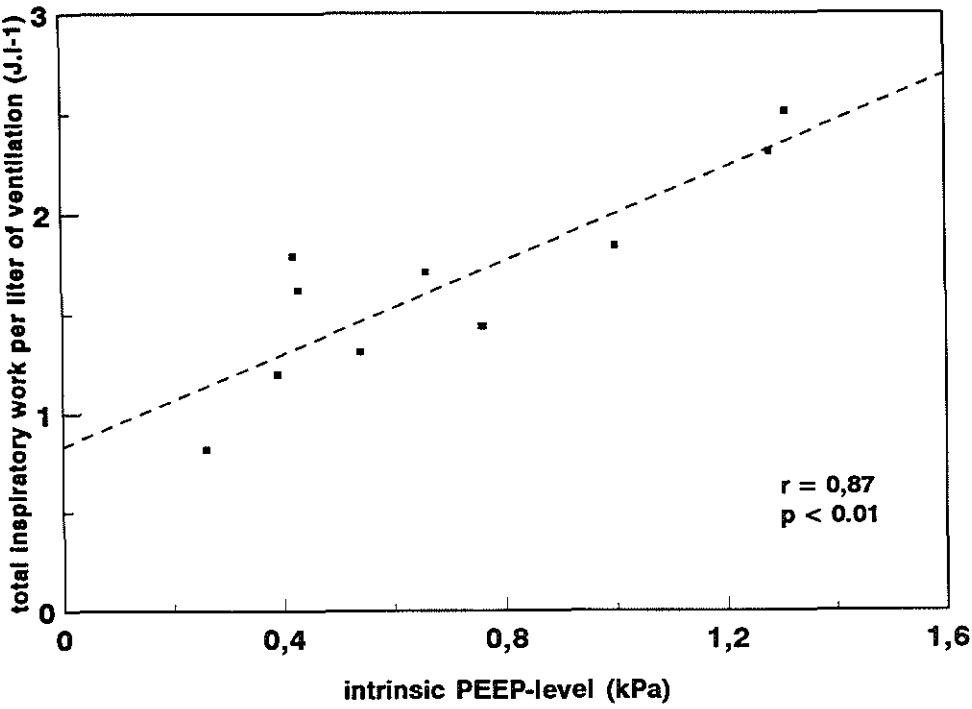

Figure 2. Relationship between the intrinsic PEEP-levels and the total inspiratory work per liter of ventilation of the individual patients obtained during spontaneous breathing without positive pressure. The regression line is also shown.

only moderate reductions in inspiratory work were found associated with the CPAP applied.

The results of the respiratory measurements are shown in Table 3. Comparing the two conditions, no significant differences were found in tidal volume, respiratory frequency or minute ventilation. A slight but significant increase in TI/Ttot was demonstrated during the application of CPAP: the TI/Ttot amounted to 0.31 ± 0.02 and 0.33 ± 0.02 for tidal breathing without and with CPAP respectively (p-value < 0.05).

In all patients a downward concavity in the expiratory flow-volume curve during tidal breathing without CPAP was found (Figure 1). No correlation was found between the level of intrinsic PEEP and the concavity in the

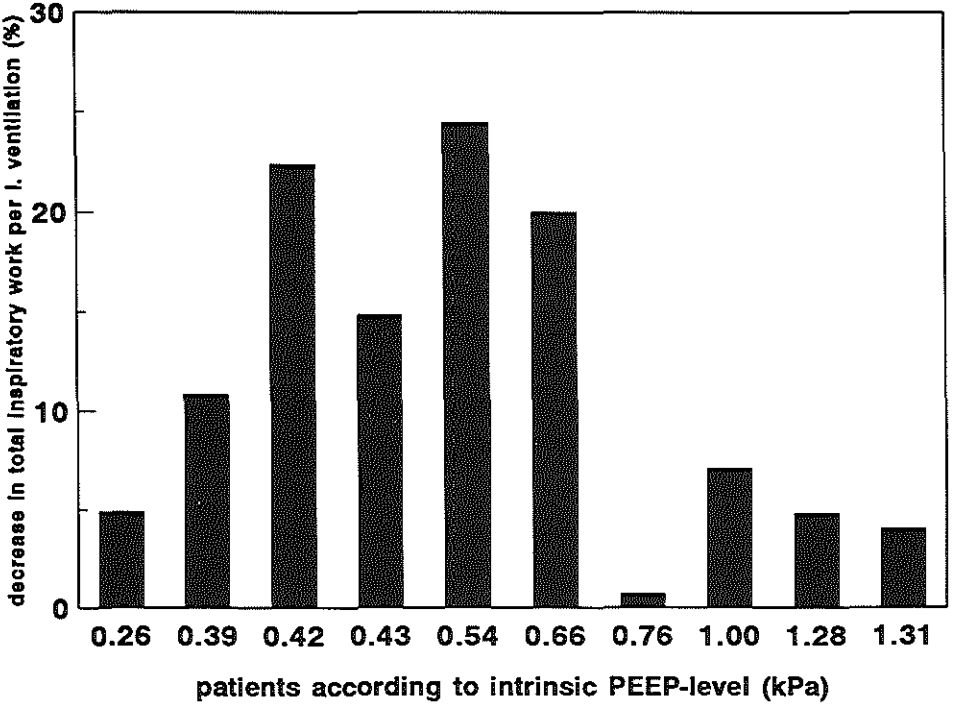

Figure 3. The decreases in total inspiratory work per liter of ventilation (Witot) due to CPAP displayed according to the intrinsic PEEP-levels of the individual patients. The decrease in Witot is expressed as percentage of the values obtained during spontaneous breathing.

expiratory volume-flow relationship. As end-expiratory lung volumes were not estimated during the study, the flow-volume curves obtained during breathing with CPAP, could not be compared volume-based to those during breathing without CPAP. The variables describing the flow-volume curves are shown in table 3. The peak flow (V'max ex) did not change comparing CPAP to breathing without positive pressure. The downward concavity in the flow-volume curves was significantly decreased during the application of CPAP.

The V'50ex, the expiratory flow at 50% of tidal volume increased significantly during tidal breathing with CPAP ($p < 0.005$). Both the ratio of the V'50ex to the V'50in (V'50ex/V'50in) and the ratio of the V'50ex to the V'maxex (V'50ex/V'maxex) increased significantly comparing CPAP to breathing without positive pressure (p-values both < 0.005). Between the patients with lower and higher levels of intrinsic PEEP, no difference was established in the change of the shape of the expiratory flow-volume curves associated with the application of CPAP. The increase in V'50ex was not associated with significant changes in the V_T/TE, calculated from tidal volume and expiration time. Despite the slight increase in TI/Ttot no significant differences were found in the V_T/TI or V_T/TE.
Comparing the two conditions no significant differences were found in the dynamic compliance calculated from the pressure-volume curves or in the inspiratory resistance at 50% of the tidal volume.
The arterial blood-gases revealed no significant differences between the experiments: the Pa,CO_2 amounted to 6.30 ± 0.26 and 6.32 ± 0.35 kPa at the end of period of spontaneous breathing without positive pressure and with CPAP respectively.

4. Discussion

In our study the application of CPAP of 0.5 kPa was associated with a reduction in the inspiratory work of breathing predominantly due to a reduction in the elastic component. This finding is in agreement with a previous study and supports the hypothesis that CPAP will reduce the inspiratory threshold induced by the presence of intrinsic PEEP [9].
In addition, we established that the effect of CPAP on the inspiratory work of breathing depended on the level of intrinsic PEEP obtained during tracheal occlusions when no positive airway pressure was applied. The largest reductions in inspiratory work associated with CPAP were found in the patients with intrinsic PEEP-levels in the range of the CPAP-level applied. The effects of CPAP on inspiratory work were found to be only moderate in

TABLE 3
Respiratory mechanics
Data given are means ± SEM

		Without CPAP	With CPAP
Vtex	l.	.430 ± .050	.420 ± .046
Respiratory Rate	min^{-1}	23.4 ± 1.8	23.6 ± 1.7
V'e	$l.min^{-1}$	9.47 ± .70	9.48 ± .80
TI/Ttot		.31 ± .02	.33 ± .02 *
V'max ex	$l.s^{-1}$	.463 ± .035	.468 ± .028
V'50 ex	$l.s^{-1}$	.216 ± .015	.270 ± .014 **
V'50 ex/V'50 max		.48 ± .04	.59 ± .03 **
V'50 ex/V'50 in		.35 ± .03	.43 ± .02 **
VT/TI	$l.s^{-1}$	.494 ± .047	.479 ± .048
VT/TE	$l.s^{-1}$	.215 ± .019	.233 ± .018
Pes tot	kPa	1.69 ± .18	1.46 ± .19 **
R50 in	$kPa.l^{-1}.s$	1.02 ± .12	.96 ± .13
CLdyn	$l.kPa^{-1}$	.46 ± .07	.54 ± .08
paCO2	kPa	6.30 ± .26	6.32 ± .35

Vtex = expiratory tidal volume; V'e = expiratory minute volume; TI/Ttot = inspiratory time divided by total cycle time; V'max ex = peak expiratory flow; V'50 ex = expiratory flow at 50% of expiration volume; V'50 in = inspiratory flow at 50% of inspiration volume; VT/TI = mean inspiratory flow; VT/TE = mean expiratory flow; Pes tot = tidal swings of the esophageal pressure; R50 in = inspiratory resistance at 50% of tidal volume; CLdyn = dynamic lung compliance.
Paired T-tests: * = $p < 0.05$
** = $p < 0.005$

patient no. 1 with the lowest intrinsic PEEP-level and in the patients with the highest intrinsic PEEP-levels. These findings should be interpreted in view of the results of previous studies in which dynamic hyperinflation and intrinsic PEEP were investigated in ventilated patients with COPD [7, 8, 22]. In these patients the occurrence of intrinsic PEEP was associated with dynamic airway compression leading to expiratory flow limitation. Expiratory flow limitation might be present when the application of ventilator-PEEP is associated with an unchanged expiratory flow at the same lung volume [7, 22]. It is assumed that the increase in airway pressure downstream of the critical site of flow limitation (the "equal pressure point") does not influence

the expiratory flow until the applied ventilator-PEEP exceeds the level of the extramural pressure surrounding the airway [22].

In the present study, the patients with the intrinsic PEEP-levels in the range of the CPAP-level applied, demonstrated the largest reductions in inspiratory work. Although intrinsic PEEP was only measured during tracheal occlusions without positive pressure and not with CPAP in this study, it is assumed that in these patients intrinsic PEEP was counterbalanced by CPAP associated with a reduction in the elastic component of the inspiratory work. In contrast, in the patients with the high levels of intrinsic PEEP, CPAP is assumed to reduce intrinsic PEEP only slightly, resulting in only a moderate reduction in inspiratory work.

It is well-established that the application of CPAP increases the end-expiratory lung volume in healthy subjects and patients with acute respiratory failure [24, 25]. In patients with COPD, a progressive hyperinflation due to CPAP would be deleterious in view of a decrease in respiratory compliance with attendant increases in elastic work. In this study no end-expiratory lung volumes were obtained. However, in a study of patients with COPD the application of 0.5 kPa of CPAP was associated with only minor increases in end-expiratory lung volumes [9]. Considering the effects of ventilator-PEEP on lung volumes in ventilated patients with COPD, it is assumed that a level of CPAP equal to or below the intrinsic PEEP-level will not induce major increases in lung volumes [8].

As increases in lung volumes are known to alter respiratory compliance and resistance, CPAP should not be expected to lead to changes in compliance or resistance in this study. In agreement with this assumption no consistent changes in respiratory compliance were found, neither if the patients with the low and high levels of intrinsic PEEP were analyzed separately. Also, the inspiratory resistance calculated at 50% of tidal volume did not change; the inspiratory resistive work per liter of ventilation proved however to be significantly reduced due to the application of CPAP. This decrease in resistive work was predominantly found in the patients with an intrinsic PEEP-level in the range of the CPAP-level applied. This result could still suggest a slight increase in end-expiratory lung volume. In previous studies of patients with COPD and asthma, it has been suggested that the respiratory resistance did

decrease due to CPAP unrelated to changes in end-expiratory lung volumes [10, 11]. In those studies however, resistance was calculated using the isovolume method, dividing the difference between inspiratory and expiratory pressures by the difference in corresponding flows [26]. It is well-established that the calculation of the expiratory resistance in the presence of flow limitation is spurious [7]. In this case a decrease in the pressure gradient over the flow-limiting segment can be applied without a change in the flow.

No differences were found in tidal volumes, respiratory rate or minute ventilation between the two conditions. This is in agreement with previous studies in which patients with COPD or acute respiratory failure were investigated [9, 10, 27]. A slight increase in TI/Ttot was however demonstrated comparing breathing with CPAP to breathing without positive pressure. This increase just reached significance, but in contrast the differences in mean inspiratory and expiratory flows between the two procedures were not significant. The latter results are in agreement with results previously published [9, 10]. Neither differences were found in arterial blood-gases. Considering these results it should be taken into account that the patients were breathing spontaneously for only short periods of time, which could preclude differences in arterial blood-gases. In a previous study however, neither changes in arterial blood-gases were observed despite significant reductions in inspiratory work [10].

In all patients studied a concavity was found in the expiratory flow-volume curve during spontaneous breathing without positive pressure. This concavity has also been demonstrated during relaxed expiration in mechanically ventilated patients with COPD and is considered to be suggestive of flow limitation during expiration [7, 8]. In the ventilated patients the inspection of the relaxed expiratory flow-volume curve could be used to estimate the effects of ventilator-PEEP on respiratory mechanics [8]. The concavity of the expiratory flow-volume curve remained unchanged when a level of ventilator-PEEP was applied, which did not increase the end-expiratory lung volume. However, when the level of ventilator-PEEP applied did increase the end-expiratory lung volume, a change in the shape of the expiratory flow-volume curve of the patients was found, indicated by significant increases in the V'50ex, the flow at 50% of expiration volume

[8].

In the present study the application of CPAP was associated in all patients with an increase in the V'50ex, which proved to be significant, but was unrelated to the level of intrinsic PEEP measured during spontaneous breathing without positive pressure. In this study we obtained the ratio between the V'50ex and the V'maxex in order to describe the shape of the expiratory flow-volume curves. Although the concavity estimated from this ratio was found to be decreased in all patients due to CPAP, inspection of the flow-volume curves revealed that during CPAP a concavity was still present, suggesting that flow limitation was not abolished. This finding, which is in contradiction with earlier observations, may be explained by the assumption already mentioned that in the patients with a low intrinsic PEEP-level the end-expiratory lung volume did not increase substantially due to the application of CPAP [8]. In the study of Petrof et al. was stated that the flow-volume relationship was be virtually identical comparing weaning with CPAP to weaning without positive positive pressure [9]. The V'50ex was however not measured in that study.

Considering these results, it should be taken into account that the effects of CPAP on work of breathing and expiratory flow-volume relationships could be well related to the CPAP-assembly used. It is well-established that both the physical properties of the CPAP-circuit and the PEEP-valve affect work of breathing [14, 28]. A CPAP-assembly was considered optimal if the change in Ptr during respiration was minimized [14]. In this study the mean ΔPtr amounted to 0.22 $\pm$ 0.02 and 0.21 $\pm$ 0.02 kPa during breathing with and without CPAP respectively, indicating that the addition of the PEEP-valve did not increase the ΔPtr.

In conclusion, application of a CPAP of 0.5 kPa in intubated patients with COPD can reduce the inspiratory work of breathing predominantly by decreasing the elastic component. The effect of CPAP depends on the relationship between the level of positive pressure applied and the level of intrinsic PEEP obtained during tracheal occlusions. In this study, expiratory flow-volume curves did not prove to be useful to estimate these effects of CPAP.

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Chapter 10

Summary

The purpose of this thesis was to evaluate various aspects of metabolism and respiratory mechanics related to the process of withdrawal of mechanical ventilatory support in patients with respiratory failure.
In the first part of the thesis the effects of nutritional support in ventilated patients were studied, with emphasis on changes in gas-exchange during weaning attempts. The role of nutrition was also studied in patients during a prolonged period of weaning from the ventilator with respect to nutritional status and respiratory muscle function.
In the second part of the thesis respiratory mechanics was studied in patients with chronic obstructive pulmonary disease (COPD) both during mechanical ventilation and weaning attempts in order to facilitate the weaning process.

In chapter 1 the various aspects of the process of weaning from the ventilator are reviewed. The importance of cardio-pulmonary diseases and the nutritional status prior to the start of ventilatory support is emphasized as is the pathophysiology of the acute respiratory failure leading to ventilatory support and the effects of mechanical ventilation on respiratory muscle function. Then the pathophysiology related to the discontinuation of ventilatory support is described with emphasis on work of breathing, oxygen cost of breathing and respiratory muscle function. At last the various effects of nutritional support on the process of withdrawal from mechanical ventilation are discussed.

In chapter 2 the effects of nutrition on measures of nutritional status and respiratory muscle function during the period of withdrawal of ventilatory support were examined. Patients were included in this retrospective study, in whom weaning attempts were made during a prolonged period. These patients had a marked weight loss during the weaning period. This weight

loss was found to be inversely related to the caloric intake of the patients, underlining the importance of nutritional support. In all patients studied, respiratory muscle strength, estimated by the measurement of the maximum inspiratory pressure against an occluded airway (PImax) improved during the weaning period. This improvement in PImax was found to be positively related to the caloric intake. The clinical outcome of the patients was however unrelated to the caloric intake or weight loss. We concluded from this study that nutritional support did not affect clinical outcome in ventilator-dependent patients. Nutritional support appeared however to reduce weight loss and to be associated with improvements in respiratory muscle strength.

In chapter 3 a system for continuous long-term determination of oxygen uptake ($V'O_2$) and carbon dioxide excretion ($V'CO_2$) during mechanical ventilatory support and weaning from mechanical ventilation is described. Tests on accuracy, stability, reproducibility and feasibility of the system are described and results of clinical application are shown. The advantages of this system with respect to commercial equipment are illustrated. This system was used in the clinical studies described in the chapters 4, 5 and 6.

In chapter 4 the effects of enteral nutrition on $V'O_2$ and $V'CO_2$ were investigated in 9 ventilated patients. Two enteral diets with the same ratio between protein, carbohydrate and fat but with a moderate and high caloric intake were administered. Significantly higher increases in $V'O_2$, $V'CO_2$ and RQ were found during the high caloric intake, compared to the moderate caloric intake. In 4 patients gas-exchange and arterial blood-gases were determined after discontinuation of ventilatory support. The increase in $V'CO_2$, induced by the high caloric intake, resulted in an elevated Pa,CO_2 and respiratory distress during spontaneous breathing. It was concluded that high caloric enteral feeding can induce significant increases in $V'CO_2$, and consequently respiratory distress during spontaneous breathing in patients in whom weaning attempts are made.

In chapter 5 the effects of enteral nutrition with a high protein content on

measures of ventilatory drive were investigated in patients after discontinuation of mechanical ventilation. Nutritional support with a high protein content was compared to enteral nutrition with a moderate protein content. Gas-exchange and arterial blood-gases were determined both during ventilatory support and during spontaneous breathing applied as weaning from the ventilator. High protein intake was associated with significantly higher CO_2-excretion during spontaneous breathing and smaller increases in Pa,CO_2 from mechanical ventilation to the end of the weaning period, compared to the moderate protein intake. It was concluded that in mechanically ventilated patients high protein nutrition may facilitate withdrawal from ventilatory support.

In chapter 6 the effects of high fat, low carbohydrate enteral nutrition on gas-exchange was studied in ventilated patients. High fat feeding was compared to a standard isocaloric regimen with respect to $V'CO_2$ and arterial blood-gases during ventilatory support and periods of weaning from the ventilator. In a prospectively randomized controlled study 15 patients received the high fat feeding and 17 patients the standard isocaloric feeding. High fat feeding was associated with significantly lower RQ-values during ventilatory support, compared to the standard feeding; the difference in $V'CO_2$, failed to reach significancy. During weaning significantly lower values of CO_2-excretion and RQ were found with the high fat feeding. The Pa,CO_2-values of the two feeding groups were not different during weaning. Neither difference was found between the two feeding groups in the time required to wean from mechanical ventilation. It was concluded that high fat, low carbohydrate enteral nutrition was associated with decreases in $V'CO_2$ and RQ in ventilated patients, but failed to reduce the time required to wean from the ventilator.

In chapter 7 the respiratory measurements used in these studies are reviewed. These measurements were obtained in intubated patients with COPD both during ventilatory support and weaning attempts. The phenomenon intrinsic PEEP, the "occult" positive end-expiratory pressure found in ventilated patients with COPD, is described. The various techniques

to determine intrinsic PEEP during ventilatory support and spontaneous breathing are reviewed. The determination of the functional residual capacity is described with emphasis on the techniques applied in ventilated patients, and the method determining work of breathing in intubated patients with COPD is elucidated. The various respiratory measurements, applied in the chapters 8 and 9 of this thesis, are described.

In chapter 8 the effects of positive end-expiratory pressure (PEEP) applied by the ventilator were studied in ventilated patients with COPD. Airway pressures, end-expiratory lung volumes (EEV) and relaxed expiratory flow-volume curves during ventilatory support with PEEP were compared with findings during support without PEEP. In all patients, when ventilated without PEEP, intrinsic PEEP and a concavity in the expiratory flow-volume curve was found. Ventilator-PEEP was associated with decreases in intrinsic PEEP in all cases. When a ventilator-PEEP was applied above the level of intrinsic PEEP, significant increases were found in airway pressures and EEV. This was associated with changes in the shape of the expiratory flow-volume curve. In patients in whom a ventilator-PEEP lower than the level of intrinsic PEEP was applied, no changes in airway pressures, EEV or expiratory flow-volume curves could be established. It was concluded that intrinsic PEEP could be reduced by ventilator-PEEP without significant changes in airway pressures or EEV. Expiratory flow-volume curves could be used to estimate the effects of ventilator-PEEP in these patients.

In chapter 9 the effects of continuous positive airway pressure (CPAP) applied as mode of weaning from mechanical ventilation were investigated in patients with COPD. CPAP was compared to spontaneous breathing without positive pressure with respect to estimations of work of breathing and flow-volume curves. Intrinsic PEEP was established during tracheal occlusions in all cases. CPAP was associated with significant reductions in inspiratory work of breathing, compared to breathing without positive pressure. This decrease in inspiratory work was related to the intrinsic PEEP-levels present during tracheal occlusions. During spontaneous breathing without positive pressure, a concavity was found in the expiratory flow-

volume curves of the patients; this concavity was diminished due to CPAP in all cases. No correlation could be established between the intrinsic PEEP-levels and the changes in the shape of the expiratory flow-volume curves. It was concluded that CPAP leads to significant decreases in inspiratory work in intubated patients with COPD. This decrease in inspiratory work was found to be related to the intrinsic PEEP-levels. Expiratory flow-volume curves were not useful to estimate these effects.

Samenvatting

Het doel van dit proefschrift was het bestuderen van verschillende aspecten die van invloed zijn op het ontwennen van de beademing, teneinde dit proces beter te laten verlopen. Hiertoe werden een aantal onderzoeken verricht met betrekking tot de stofwisseling en de ademmechanica bij patiënten die wegens acute respiratoire insufficiëntie beademd werden en vervolgens spontaan ademden via de endotracheale tube met als doel de ademhalingsondersteuning te beëindigen.
In het eerste gedeelte van het proefschrift werden de effecten van verschillende soorten voeding op de gaswisseling bestudeerd bij patiënten tijdens de beademing en het ontwennen van de beademing. De rol van voeding werd ook onderzocht bij patiënten bij wie gedurende langere tijd pogingen werden ondernomen van de beademing te ontwennen.
In het tweede gedeelte van het proefschrift werden verschillende aspecten van de ademmechanica bestudeerd bij patiënten met CARA, zowel tijdens de beademing als tijdens perioden van spontaan ademen opgelegd om de beademing te beëindigen.

In hoofdstuk 1 wordt een overzicht gegeven van de verschillende factoren die van belang zijn bij het ontwennen van de beademing. De betekenis van hart- en longaandoeningen en de voedingstoestand vóór de start van de beademing worden beschreven, evenals de pathofysiologie van de respiratoire insufficiëntie in relatie tot de beademing, en de effecten van die beademing op de ademhalingsspieren. Vervolgens worden de pathofysiologische veranderingen vermeld die samenhangen met het hervatten van de spontane ademhaling bij de beademde patiënt: hierbij wordt ingegaan op het functioneren van de ademhalingsspieren, de ademarbeid en het zuurstofverbruik van de ademhalingsspieren. Tenslotte worden de verschillende effecten van voeding op het proces van ontwenning beschreven.

In hoofdstuk 2 werden de effecten van voeding onderzocht op de voedingstoestand en de spierkracht van de ademhalingsspieren tijdens de

fase van ontwenning van de beademing. Hiertoe werden gegevens van patiënten verzameld, bij wie de ontwenning van de beademing geruime tijd in beslag nam. Bij deze patiënten werd een aanzienlijk gewichtsverlies gevonden tijdens de ontwenningsfase. Dit gewichtsverlies bleek omgekeerd evenredig te zijn aan de hoeveelheid toegediende voeding, hetgeen het belang van die voeding onderstreept. Bij alle patiënten verbeterde de spierkracht van de ademhalingsspieren tijdens de ontwenningsfase. De verbetering van de spierkracht bleek eveneens samen te hangen met de hoeveelheid toegediende voeding. Het resultaat van de ontwenning en de overleving van de patiënten bleken echter niet gerelateerd te zijn aan de hoeveelheid toegediende voeding of het gewichtsverlies. Aan de hand van deze resultaten werd geconcludeerd dat voeding het resultaat van de ontwenning bij beademde patiënten niet beïnvloedde. Bij deze patiënten bleek echter zowel het gewichtsverlies als de toename van de kracht van de ademhalingsspieren samen te hangen met de hoeveelheid toegediende voeding.

In hoofdstuk 3 wordt een systeem beschreven, waarmee continu en gedurende langere tijd de zuurstofopname ($V'O_2$) en de kooldioxide afgifte ($V'CO_2$) kan worden bepaald tijdens de beademing en de ontwenningsfase. De verschillende methoden waarmee de betrouwbaarheid, de stabiliteit en de reproduceerbaarheid van het systeem zijn getest, worden vermeld. Voorbeelden van toepassingen bij beademde patiënten worden getoond. De voordelen van het beschreven systeem ten opzichte van commerciële apparatuur worden uiteengezet. Het systeem is gebruikt bij de verschillende onderzoeken, beschreven in de hoofdstukken 4, 5 en 6.

In hoofdstuk 4 werd bij 9 beademde patiënten het effect van sondevoeding op $V'O_2$ en $V'CO_2$ bestudeerd. Bij alle patiënten werd één type voeding toegediend in een lage en in een hoge dosering. Significant hogere $V'O_2$, $V'CO_2$ en respiratoire quotient-waarden werden gevonden bij toediening van de hoge dosis voeding ten opzichte van de lage dosis. Bij 4 patiënten werden gaswisseling en arteriële bloedgas-waarden bepaald tijdens spontaan ademen direct na het staken van de beademing. De toename in $V'CO_2$ veroorzaakt

door de hoge dosis voeding, leidde bij deze patiënten tot een verhoogde arteriële P,CO_2 en kortademigheid tijdens spontaan ademen. Hieruit werd geconcludeerd dat sondevoeding toegediend in hoge doses een sterke toename van $V'CO_2$ veroorzaakt, hetgeen aanleiding kan geven tot kortademigheid tijdens spontaan ademen bij patiënten die ontwend worden van de beademing.

In hoofdstuk 5 werd het effect van sondevoeding met een hoog eiwit-gehalte onderzocht op de ademprikkel van patiënten die werden ontwend van de beademing. Hiertoe werd sondevoeding met een hoog eiwit-gehalte vergeleken met voeding met een laag eiwit-gehalte. Zowel tijdens beademing als tijdens spontaan ademen in de ontwenningsfase werden gaswisseling en arteriële bloedgas-waarden bepaald. Tijdens spontaan ademen werd een significant hogere CO_2-afgifte gevonden bij toediening van voeding met een hoog eiwit-gehalte vergeleken met voeding met een laag eiwit-gehalte. Bovendien steeg tijdens spontaan ademen de arteriële P,CO_2 minder sterk bij eiwitrijke voeding. Uit deze resultaten werd geconcludeerd dat voeding met een hoog eiwit-gehalte gunstig kan zijn voor het ontwennen van de beademing.

In hoofdstuk 6 werden de effecten van sondevoeding met een hoog vetgehalte op de gaswisseling bij beademde patiënten onderzocht. Voeding met een hoog vet-gehalte werd vergeleken met voeding met een laag vet-gehalte. De effecten van deze voedingen op de $V'CO_2$ en de arteriële bloedgaswaarden werden bepaald tijdens beademing en ontwenning van de beademing. In een prospectief gerandomizeerd onderzoek kregen 15 patiënten de voeding met het hoge vet-gehalte tegen 17 patiënten de voeding met het lage vet-gehalte. In vergelijking met de laatstgenoemde voeding werd tijdens beademing een significant lagere respiratoire quotientwaarde gevonden bij de voeding met hoog vet-gehalte. Ook de $V'CO_2$ was tijdens de beademing lager bij de voeding met hoog vet-gehalte, doch dit was niet significant. Tijdens de ontwenning van de beademing werden significant lagere waarden van CO_2-afgifte en respiratoir quotient gevonden bij de patiënten die voeding met een hoog vet-gehalte kregen toegediend. Er kon

echter geen verschil worden aangetoond tussen beide groepen in de duur van de ontwenningsfase. Uit deze resultaten werd geconcludeerd dat sondevoeding met een hoog vet-gehalte tot lagere waarden van $V'CO_2$ en respiratoir quotient leidde bij beademde patiënten, doch dat dit niet gepaard ging met een vermindering van het aantal dagen nodig voor de ontwenning van de beademing.

In hoofdstuk 7 wordt een overzicht gegeven van de longfunctiemetingen die zijn toegepast in dit proefschrift. Deze metingen zijn gedaan bij geintubeerde patiënten met CARA, zowel tijdens beademing als tijdens spontaan ademen. Allereerst is het fenomeen intrinsieke PEEP, de "verborgen" positieve druk aan het eind van de uitademing beschreven, die frequent wordt gevonden bij geintubeerde patiënten met CARA. Vervolgens worden de verschillende technieken om intrinsieke PEEP te bepalen tijdens beademing en spontaan ademen besproken. Daarna wordt de bepaling van de functionele residuaal capaciteit beschreven, waarbij de verschillende technieken worden besproken die bij beademde patiënten kunnen worden toegepast. Tenslotte wordt de techniek om ademarbeid te bepalen bij geintubeerde patiënten met CARA beschreven. Aangegeven wordt welke longfunctiemetingen zijn toegepast in de hoofdstukken 8 en 9 van dit proefschrift.

In hoofdstuk 8 werden de effecten van PEEP, positieve druk aan het eind van de uitademing opgelegd door de ventilator onderzocht bij beademde patiënten met CARA. Beademing met PEEP werd vergeleken met beademing zonder PEEP wat betreft de effecten op beademingsdruk, longvolume aan het eind van de uitademing en de relatie tussen stroom en volume tijdens de uitademing. Bij alle patiënten werd tijdens beademing zonder PEEP de aanwezigheid van intrinsieke PEEP en een concaviteit in de expiratoire stroom-volume curve aangetoond. PEEP opgelegd door de ventilator leidde bij alle patiënten tot een daling van de intrinsieke PEEP. Indien de PEEP opgelegd door de ventilator hoger was dan de intrinsieke PEEP, werd een significante toename gevonden van de beademingsdruk en het longvolume. Hierbij werd een verandering in de vorm van de expiratoire stroom-volume curve aangetoond. Bij de patiënten bij wie een PEEP werd opgelegd door de

ventilator lager dan de intrinsieke PEEP, werden geen veranderingen aangetoond in beademingsdruk, longvolume of expiratoire stroom-volume curve. Uit deze resultaten werd geconcludeerd dat intrinsieke PEEP kan worden verlaagd door de PEEP opgelegd door de ventilator zonder veranderingen in beademingsdruk of longvolume. Expiratoire stroom-volume curven kunnen worden gebruikt om de effecten van PEEP opgelegd door de ventilator bij deze patiënten in te schatten.

In hoofdstuk 9 werden de effecten van continue positieve luchtweg druk (CPAP) bij spontaan ademen onderzocht bij patiënten met CARA die werden ontwend van de beademing. In dit onderzoek werd CPAP vergeleken met spontaan ademen zonder positieve luchtweg druk en werden ademarbeid en stroom-volume curven bepaald. Tijdens afsluiting van de trachea werd de aanwezigheid van intrinsieke PEEP vastgesteld bij alle patiënten. In vergelijking met spontaan ademen zonder positieve druk, werd bij toepassing van CPAP een significante afname van de inspiratoire ademarbeid aangetoond. De mate van daling van de ademarbeid was gerelateerd aan de hoogte van de intrinsieke PEEP. Tijdens spontane ademhaling zonder positieve druk werd een concaviteit gevonden in de expiratoire stroom-volume curve van alle patiënten: deze concaviteit verminderde door toepassing van CPAP. Er kon echter geen correlatie worden vastgesteld tussen de hoogte van de intrinsieke PEEP en de veranderingen in de vorm van de expiratoire stroom-volume curven. Uit dit onderzoek bleek dat CPAP leidde tot een significante daling van de inspiratoire ademarbeid bij geintubeerde patiënten met CARA. Deze afname van inspiratoire ademarbeid was gerelateerd aan de hoogte van de intrinsieke PEEP. Expiratoire stroom-volume curven bleken niet geschikt te zijn om deze effecten in te schatten.

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Curriculum Vitae

The author of this thesis was born in Pijnacker. After completing secondary school he graduated in 1974 at the Medical Faculty of the University of Utrecht. From 1975 till 1980 he was resident at the Department of Internal Medicine of the University Hospital Rotterdam (head: Prof. Dr. M. Frenkel). Since 1979 he is working at the Respiratory Intensive Care Unit of the University Hospital Rotterdam (head: Prof. Dr. C. Hilvering).