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The cardiovascular pharmacology of the phenyldihydropyridine elgodipine

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The global and regional cardiovascular responses to intravenous (0.3, 1.0, 3.0 and 10.0 $\mu g\ kg^{-1}\ min^{-1}$, i.v.) and intracoronary (0.3, 0.9, 3.0 and 4.5 $\mu g\ kg^{-1}\ min^{-1}$, i.c.) infusions of the phenyldihydropyridine elgodipine and its solvent were studied in open-chest anaesthetized pigs. Elgodipine (i.v., n = 7) caused dose-dependent decreases in arterial blood pressure (from 91 ± 3 to 52 ± 3 mmHg) and systemic vascular resistance (from 40 ± 5 to 21 ± 2 $mmHg.l^{-1}.min$), whereas heart rate (102 ± 7 $beats.min^{-1}$), LV dP/dt max (2780 ± 350 $mmHg.s^{-1}$), left ventricular filling pressure (8 ± 1 mmHg), cardiac output (2.3 ± 0.3 $l.min^{-1}$) and myocardial segment length shortening (SLS, $19 \pm 1\%$) did not change. The absence of a negative inotropic effect with the employed intravenous doses was confirmed by the intracoronary infusions (n = 7). With the lowest intracoronary dose (0.3 $\mu g\ kg^{-1}\ min^{-1}$, n = 7) both LV dP/dt max and SLS decreased by less than 10%. With 0.9 $\mu g\ kg^{-1}\ min^{-1}$ (i.c.) the negative inotropic properties of the drug became apparent as LV dP/dt max and SLS decreased by 20% and 33%, respectively, whereas heart rate and left ventricular filling pressure were not affected. Transmural myocardial blood flow did not change during intravenous infusion of elgodipine, as vasodilatation which was more pronounced in the subepicardial than in the subendocardial layers, compensated for the decrease in arterial perfusion pressure. The intracoronary infusions also revealed that the decrease in normalized subendocardial/subepicardial blood flow ratio was not secondary to the fall in arterial blood pressure. Myocardial oxygen consumption decreased during both i.v. and the i.c. administration of elgodipine. With the i.v. administration the decrease was secondary to the hypotensive action of the drug, whereas with the i.c. administration the negative inotropic properties played the dominant role. Elgodipine (i.v.) did not affect total cardiac output but caused a redistribution in favour of the nutritional blood flow at the expense of the arteriovenous anastomotic (AVA) blood flow. Up to an infusion rate of 3.0 $\mu g\ kg^{-1}\ min^{-1}$ the decrease in AVA-flow was secondary to a fall in arterial blood pressure, but at the highest infusion rate both the decrease in arterial perfusion pressure and an increase in the vascular resistance of the AVA's contributed to a further decrease in AVA blood flow. The skeletal muscles benefited most from the elgodipine-induced increase in nutritional blood flow, but vasodilatation was not uniform for all muscle groups (ten, seven and two fold increases in flow in the masseter, iliopsoas and abdominal muscle, respectively). Up to an infusion rate of 3.0 $\mu g\ kg^{-1}\ min^{-1}$ the vasodilatation in the renal vascular bed was more pronounced in the inner than in the outer cortex but, at 10 $\mu g\ kg^{-1}\ min^{-1}$, vascular resistances of both cortical layers returned to baseline values. In all regions of the brain, blood flow was maintained until the highest infusion rate was given. With 10 $\mu g\ kg^{-1}\ min^{-1}$ only flow to the vital parts of the brain (diencephalon and brain stem) was maintained. Blood flows to the skin and various abdominal organs were well maintained up to 3.0 $\mu g\ kg^{-1}\ min^{-1}$ but, at the highest dose, a decrease was observed in blood flow to the adrenals and spleen. Vascular resistances of all these organs and tissues decreased dose-dependently.

The potent systemic and coronary vasodilatory actions of elgodipine during i.v. administration, which were not accompanied by negative inotropic and positive chronotropic properties or decreases of the perfusion of vital organs, warrant further study on the application of the compound in essential hypertension, myocardial ischaemia and possibly in moderate chronic heart failure.