Evidence against a role for dopamine D₁ receptors in the myocardium of the pig

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1 We investigated the presence of dopamine D₁ receptors in the myocardium of anaesthetized pigs using intravenous infusions of dopamine, alone and after α - and β -adrenoceptor blockade and intracoronary infusions of the selective D₁ receptor agonist, fenoldopam.

2 Intravenous infusion of dopamine (2.5, 5 and 10 $\mu\text{g kg}^{-1} \text{min}^{-1}$ for 10 min, $n = 6$) caused dose-dependent changes in heart rate (from 94 ± 6 to 132 ± 10 beats min^{-1} , $P < 0.05$), the maximal rate of rise of left ventricular pressure ($\text{LVdP/dt}_{\text{max}}$; from 2280 ± 170 to 4800 ± 410 mmHg s^{-1} , $P < 0.05$), mean arterial blood pressure (from 87 ± 5 to 62 ± 3 mmHg) and systemic vascular resistance (from 40 ± 4 to 28 ± 2 mmHg $\text{l}^{-1} \text{min}$, $P < 0.05$). The increases in heart rate and $\text{LVdP/dt}_{\text{max}}$ were abolished when dopamine was infused after α - and β -adrenoceptor blockade. The vasodilator response was, however, only minimally affected.

3 Intravenous infusions of dopamine decreased coronary vascular resistance from 0.90 ± 0.06 to 0.53 ± 0.07 mmHg $\text{ml}^{-1} \text{min} 100 \text{ g}$ ($P < 0.05$). This action of dopamine was not observed when dopamine was infused after blockade of the α - and β -adrenoceptors.

4 Pretreatment with α - and β -adrenoceptor blockade had no effect or only slightly attenuated the dopamine-induced decrease in vascular resistance of the brain, kidneys, adrenals and small intestine.

5 In 7 animals, intracoronary doses of 0.04, 0.1, 0.2 and 0.4 $\mu\text{g kg}^{-1} \text{min}^{-1}$ of fenoldopam had no effect on coronary venous oxygen content, local myocardial oxygen consumption, coronary blood flow or coronary vascular resistance. However, systemic effects were observed at the highest two doses, as manifested by a drop in mean arterial blood pressure from 82 ± 4 to 72 ± 4 mmHg ($P < 0.05$) due to peripheral vasodilatation (e.g. cerebral vascular bed). Heart rate, $\text{LVdP/dt}_{\text{max}}$, regional myocardial segment length shortening and left ventricular end-diastolic pressure were not affected at these doses. In 2 animals the infusion rate was increased to 4 $\mu\text{g kg}^{-1} \text{min}^{-1}$, but again there was no evidence for coronary vasodilatation.

6 We conclude that the intravenous infusion of dopamine after α - and β -adrenoceptor blockade and the intracoronary infusion of fenoldopam provided no evidence for a major role of D₁ receptors in the coronary circulation of pigs. The absence of any effect of the employed doses of fenoldopam on $\text{LVdP/dt}_{\text{max}}$ and on regional myocardial segment length shortening also indicates that fenoldopam does not exhibit any inotropic action in this species.

Keywords: Dopamine; fenoldopam; D₁ receptors; systemic haemodynamics; regional blood flows; coronary blood flow; inotropy; pig myocardium

Introduction

Dopamine D₁ receptors have been identified in a number of vascular beds, including the renal, mesenteric and cerebral vasculature (Ueda *et al.*, 1982; Toda, 1983; Hughes & Sever, 1989). However, evidence for their presence in the coronary circulation is limited. Kopia & Valocik (1989) demonstrated a specific D₁ receptor-mediated vasodilatation in the coronary vascular bed of pentobarbitone-anaesthetized dogs following intracoronary infusion of the specific D₁ receptor agonist, fenoldopam. Hieble *et al.* (1987) showed that fenoldopam, in both dogs and rats, increased blood flow to various vascular beds, but not to the heart. Recently, Zhao *et al.* (1990) concluded from their experiments in pentobarbitone-anaesthetized dogs that coronary vasodilatation after intracoronary infusion of fenoldopam was due to a positive inotropic effect of the drug rather than to a direct effect on the coronary vasculature. Furthermore, fenoldopam has failed to relax isolated conduit coronary arteries of humans precontracted by noradrenaline (Hughes & Sever, 1989).

Zhao *et al.* (1990) reported an increased inotropic state during infusion of fenoldopam in dogs, but Hieble *et al.* (1987) found that in the same species the drug reduced the maximal rate of rise of left ventricular pressure ($\text{LVdP/dt}_{\text{max}}$) and

ascribed the latter to a negative inotropic action of the drug. Kopia & Valocik (1989), however, could not confirm either observation, when they infused fenoldopam directly into a coronary artery.

In view of these discrepancies, we used two approaches to investigate the role of D₁ receptors in the myocardium of pigs, a species frequently used in biomedical research. We first determined the responsiveness to intravenous infusions of dopamine alone and after α - and β -adrenoceptor blockade. We then used intracoronary infusions of fenoldopam to evaluate the direct effects of fenoldopam on coronary blood flow and myocardial contractility.

Methods

General

After an overnight fast, 25 cross-bred Landrace $\times$ Yorkshire pigs (H.V.C., Hedel, The Netherlands) of either sex and weighing from 22–28 kg were sedated with intramuscular 5 mg kg^{-1} azaperone (Stresnil, Janssen Pharmaceutica, Beerse, Belgium), anaesthetized with intravenous 6 mg kg^{-1} metomidate (Hypnodil, Janssen Pharmaceutica, Beerse, Belgium), intubated and connected to a respirator for intermittent positive pressure ventilation with a mixture of oxygen and nitrous oxide (1 : 2). Respiratory rate and tidal volume were set to

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keep arterial blood gases within the normal range: $7.35 < \text{pH} < 7.45$; $35 \text{ mmHg} < \text{PCO}_2 < 45 \text{ mmHg}$ and $120 \text{ mmHg} < \text{PO}_2 < 160 \text{ mmHg}$. 7F catheters were placed in the superior caval vein for administration of 150 mg kg^{-1} α -chloralose (E. Merck, Darmstadt, Germany) followed by an infusion of a low dose ($5 \text{ mg kg}^{-1} \text{ h}^{-1}$) of sodium pentobarbitone (Apharma, Arnhem, The Netherlands); for administration of 4 mg of the muscle relaxant pancuronium bromide (Organon Teknika BV, Boxtel, The Netherlands) prior to thoracotomy; and for administration of haemaccel (Behringwerke A.G., Marburg, Germany) to compensate for loss of intravascular volume. Catheters were also positioned in the descending aorta for withdrawal of blood samples and measurement of central aortic blood pressure. A Sensodyn MTCP7 catheter (B. Braun, Medical BV, Uden, The Netherlands) inserted via the left carotid artery was used to measure left ventricular pressure and its first derivative (LVdP/dt). After thoracotomy, an electromagnetic flow probe (Skalar, Delft, The Netherlands) was placed around the ascending aorta, and the great cardiac vein was cannulated for subsequent collection of blood for determining haemoglobin concentration and oxygen saturation (OSM2, Radiometer, Copenhagen, Denmark). In 14 of the animals the proximal left anterior descending coronary artery was dissected free and a small cannula inserted for intracoronary infusions of fenoldopam or its solvent.

Regional blood flows

In order to determine regional blood flows, the left atrial appendage was cannulated for injection of a batch of $1-2 \times 10^6$ carbonized plastic microspheres [$15 \pm 1 \mu\text{m}$ (s.d.) in diameter] labelled with ^{46}Sc , ^{95}Nb , ^{103}Ru , ^{113}Sn or ^{141}Ce . Starting 15 s before the injection of microspheres, blood was withdrawn from a femoral artery at a rate of 10 ml min^{-1} until 60–65 s after completion of the injection of the microspheres. In the animals which received the intracoronary infusions of fenoldopam, the area perfused by the left anterior descending coronary artery (LADCA) was identified by an intracoronary injection of patent blue violet (Sigma, St. Louis, MO, U.S.A.) at the end of the experiment. Animals were killed with an overdose of sodium pentobarbitone and the heart, the brain (divided into hemispheres, diencephalon, cerebellum and brainstem) adrenals, kidneys and aliquots of the skeletal muscle, skin and small intestine were excised. The heart was fixed in formaldehyde (10% v/v) for 48 h at which point of time the left ventricle was divided into three layers of equal thickness. From the radioactivity in the tissue, blood flows were determined by standard procedures (Saxena *et al.*, 1980).

Myocardial oxygen consumption and contractile function

Myocardial oxygen consumption (MVO_2) of the LADCA perfused area was calculated as the product of coronary blood flow (microsphere measurements) and the difference in the oxygen contents of the arterial and coronary venous blood.

In the animals in which fenoldopam was infused, regional myocardial segment length shortening was assessed by sonomicrometry (Triton Technology Inc., San Diego, CA, U.S.A.) with a pair of ultrasonic crystals implanted approximately 10 mm apart in the subendocardial layers of the myocardium perfused by the LADCA. From the tracings, systolic segment length shortening (SLS) was calculated as:

$$\text{SLS (\%)} = 100 \times (\text{EDL} - \text{ESL})/\text{EDL},$$

in which EDL and ESL are the segment length at end-diastole and end-systole, respectively.

Experimental protocols

Two series of experiments were performed. In the first series of experiments the effects of dopamine on systemic haemodynamics and regional blood flows were evaluated. To this

end 6 pigs received three consecutive 10 min intravenous infusions (2.5 , 5 and $10 \mu\text{g kg}^{-1} \text{ min}^{-1}$) of dopamine and 5 other animals received four consecutive 10 min intravenous infusions (2.5 , 5 , 10 and $20 \mu\text{g kg}^{-1} \text{ min}^{-1}$) of dopamine after α - and β -adrenoceptor blockade with phentolamine (1 mg kg^{-1}) and propranolol ($0.5 \text{ mg kg}^{-1} + 0.5 \text{ mg kg}^{-1} \text{ h}^{-1}$), respectively. Systemic haemodynamics, arterial and coronary venous oxygen contents and regional blood flows were determined at baseline and at the end of each infusion rate. In the second series of experiments, the direct effects of fenoldopam on the coronary circulation and the myocardium were evaluated. Hitherto, four incremental doses of fenoldopam (0.04 , 0.1 , 0.2 and $0.4 \mu\text{g kg}^{-1} \text{ min}^{-1}$) were infused directly into the left anterior descending coronary artery for 10 min each in the experimental group ($n = 7$) and the results were compared with those of a control group ($n = 7$), which received equal volumes of the solvent. Systemic haemodynamics, regional myocardial function, arterial and coronary venous oxygen contents and coronary blood flow were determined again at baseline and at the end of each infusion rate.

Drugs

Dopamine hydrochloride (Department of Pharmacy, Academic Hospital Dijkzigt, Rotterdam, The Netherlands), propranolol hydrochloride (gift: ICI-Pharmaceuticals, Rotterdam, The Netherlands) and phentolamine methane-sulphonide (gift: Ciba-Geigy B.V., Arnhem, The Netherlands) were dissolved in physiological saline. Fenoldopam mesylate (gift: Dr F. Lippens, Smith, Kline and Beecham, Rijswijk, The Netherlands) was dissolved in physiological saline containing 1% v/v ethanol and the required doses were obtained by adjusting the infusion rate (from 0.13 ml min^{-1} to 2 ml min^{-1}).

Statistical evaluation

All data are presented as arithmetic mean $\pm$ s.e.mean. Statistical analysis was performed by use of a parametric two-way of analysis of variance (random-block design), followed by the Duncan new multiple range test. Statistical significance was accepted for $P < 0.05$.

Results

Intravenous infusions of dopamine without and after α - and β -adrenoceptor blockade

Systemic haemodynamics Intravenous infusion of dopamine caused an increase in heart rate from 94 ± 6 to $132 \pm 10 \text{ beats min}^{-1}$ ($P < 0.05$) and a decrease in mean arterial blood pressure from 87 ± 5 to $62 \pm 3 \text{ mmHg}$ ($P < 0.05$); both changes were dose-dependent (Figure 1). Cardiac output did not change, which implies that the hypotensive effect was caused by a reduction of the systemic vascular resistance ($P < 0.05$). $\text{LVdP/dt}_{\text{max}}$ increased by more than 100%, while left ventricular end-diastolic pressure showed a decrease from 10 ± 1 to $7 \pm 1 \text{ mmHg}$ ($P < 0.05$).

The animals in which the α - and β -adrenoceptors were blocked had a 20% lower $\text{LVdP/dt}_{\text{max}}$ at baseline, but other systemic haemodynamic parameters were not significantly different from the animals without adrenoceptor blockade (Figure 1). When dopamine was infused in these animals, the increases in heart rate and in $\text{LVdP/dt}_{\text{max}}$ were inhibited, but the systemic vasodilator response was only minimally affected (Figure 1).

Myocardial blood flow and oxygen consumption During infusion of the lowest dose of dopamine ($2.5 \mu\text{g kg}^{-1} \text{ min}^{-1}$) there was a 10% decrease in left ventricular transmural blood flow, but during the infusion of 5 and $10 \mu\text{g kg}^{-1} \text{ min}^{-1}$, transmural blood flow was, respectively, 20% and 50% higher than the baseline flow (Figure 2). The subepicardial layers benefited

Figure 1 Systemic haemodynamic effects of dopamine alone (○, $n = 6$) and after α - and β -adrenoceptor blockade (●, $n = 5$) in anaesthetized pigs. HR = heart rate (beats min^{-1}); CO = cardiac output (l min^{-1}); MAP = mean arterial blood pressure (mmHg); LV dP/dt_{max} = maximum rate of rise in left ventricular pressure (mmHg s^{-1}); LVEDP = left ventricular end-diastolic pressure (mmHg). SVR = systemic vascular resistance ($\text{mmHg l}^{-1} \text{min}$). Note that after α - and β -adrenoceptor blockade the dopamine-induced increases in heart rate and LV dP/dt_{max} were almost completely abolished, but that dilatation of the systemic vascular bed was much less affected. * $P < 0.05$ vs baseline.

more from the increase in blood flow than the subendocardial layers as the ratio of the normalized subendocardial and subepicardial blood flows decreased from 1.07 ± 0.04 to 0.97 ± 0.06 ($P < 0.05$). Calculation of the coronary vascular

Figure 2 The effect of dopamine on transmural left ventricular blood flow (LV) and left ventricular vascular resistance (LV resistance) and left ventricular oxygen consumption ($M\dot{V}O_2$) in anaesthetized pigs. Data were obtained without (○, $n = 6$) and after α - and β -adrenoceptor blockade (●, $n = 5$). * $P < 0.05$ vs baseline.

resistance revealed no change at $2.5 \mu\text{g kg}^{-1} \text{min}^{-1}$, but decreases of 30% and 50% were observed during the dopamine infusions of 5 and $10 \mu\text{g kg}^{-1} \text{min}^{-1}$, respectively. Myocardial oxygen consumption decreased (by 20%) during infusion of the lowest dose, was not different from baseline during infusion of the middle dose and increased (by 30%) during infusion of the highest dose. The left ventricular systolic pressure-heart rate product, a measure of myocardial oxygen demand, followed a similar pattern.

After blockade of the α - and β -adrenoceptors, the dopamine-induced increases in coronary blood flow were abolished and the decrease in coronary vascular resistance was attenuated. Myocardial oxygen consumption tended to decrease slightly, but levels of statistical significance were not reached. The decrease in myocardial efficiency did not reach levels of statistical significance also.

Regional vascular beds Figure 3 demonstrates the existence of peripheral dopamine receptors in the pig as the decreases in vascular resistances of, in particular the kidneys, adrenals, brain and small intestine, were only minimally affected when dopamine was infused after α - and β -adrenoceptor blockade. The regional differences in the brain were relatively small as after α - and β -adrenoceptor blockade the dopamine-induced decreases in the vascular resistances of the diencephalon, hemispheres, cerebellum and brainstem were maximally $16 \pm 4\%$, $16 \pm 3\%$, $13 \pm 3\%$ and $11 \pm 7\%$, respectively.

Intracoronary infusions of fenoldopam

Systemic haemodynamics As shown in Table 1, intracoronary infusions of fenoldopam up to $0.4 \mu\text{g kg}^{-1} \text{min}^{-1}$ had no effect on cardiac output, heart rate, LV dP/dt_{max} and left ventricular end-diastolic pressure. Mean arterial blood pressure decreased from 82 ± 4 to 72 ± 4 mmHg (12%, $P < 0.05$) with an associated reduction in systemic vascular resistance from 41 ± 3 to 35 ± 3 $\text{mmHg l}^{-1} \text{min}$ (15%, $P < 0.05$). In 2 of the experiments intracoronary infusions up to $4 \mu\text{g kg}^{-1} \text{min}^{-1}$ were

Figure 3 The effect of dopamine on the regional vascular resistance of regional vascular beds. Data were obtained without (○, $n = 6$) and after α - and β -adrenoceptor blockade (●, $n = 5$). * $P < 0.05$ vs baseline.

Table 1 Systemic haemodynamics after continuous intracoronary 10 min infusions of fenoldopam or its solvent in anaesthetized pigs

		Fenoldopam ($\mu\text{g kg}^{-1} \text{min}^{-1}$) or equal volumes of its solvent				
		0	0.04	0.1	0.2	0.4
HR	Solvent	112 $\pm$ 7	110 $\pm$ 6	110 $\pm$ 5	112 $\pm$ 5	113 $\pm$ 6
	Fenoldopam	118 $\pm$ 8	114 $\pm$ 9	114 $\pm$ 8	118 $\pm$ 9	115 $\pm$ 8
MAP	Solvent	89 $\pm$ 5	86 $\pm$ 9	84 $\pm$ 4	85 $\pm$ 4	85 $\pm$ 6
	Fenoldopam	82 $\pm$ 4	80 $\pm$ 5	79 $\pm$ 4	72 $\pm$ 4*	73 $\pm$ 6*
CO	Solvent	2.5 $\pm$ 0.3	2.5 $\pm$ 0.3	2.5 $\pm$ 0.3	2.5 $\pm$ 0.3	2.4 $\pm$ 0.3
	Fenoldopam	2.1 $\pm$ 0.2	2.0 $\pm$ 0.2	2.1 $\pm$ 0.2	2.1 $\pm$ 0.2	2.1 $\pm$ 0.1
SVR	Solvent	37 $\pm$ 3	36 $\pm$ 3	36 $\pm$ 3	36 $\pm$ 3	38 $\pm$ 4
	Fenoldopam	41 $\pm$ 3	41 $\pm$ 3	40 $\pm$ 3	35 $\pm$ 3*	35 $\pm$ 3*
LVdP/dt _{max}	Solvent	2360 $\pm$ 390	2330 $\pm$ 310	2260 $\pm$ 330	2430 $\pm$ 410	2400 $\pm$ 410
	Fenoldopam	2010 $\pm$ 320	1850 $\pm$ 260	1850 $\pm$ 270	1790 $\pm$ 280	1880 $\pm$ 280
LVEDP	Solvent	7.3 $\pm$ 1.1	6.4 $\pm$ 1.1	6.5 $\pm$ 1.1	6.4 $\pm$ 1.1	6.4 $\pm$ 1.0
	Fenoldopam	6.9 $\pm$ 0.8	7.1 $\pm$ 0.8	7.1 $\pm$ 0.8	6.8 $\pm$ 0.8	7.5 $\pm$ 1.0

Data are mean $\pm$ s.e.mean; $n = 7$ for the solvent-treated and $n = 7$ for the fenoldopam-treated animals. HR = heart rate (beats min^{-1}); MAP = mean arterial blood pressure (mmHg); CO = cardiac output (l min^{-1}); SVR = systemic vascular resistance ($\text{mmHg l}^{-1} \text{min}$); LVdP/dt_{max} = maximal rate of rise of left ventricular blood pressure (mmHg s^{-1}); LVEDP = left ventricular end-diastolic blood pressure (mmHg).

Figure 4 Intracoronary infusions of fenoldopam into the left anterior descending coronary artery (LADCA) had no effect on coronary blood flow, coronary vascular resistance, regional systolic segment length shortening (SLS) or regional myocardial O₂-consumption (MVO₂); open columns, solvent infusion ($n = 7$); hatched columns, fenoldopam infusion ($n = 7$). Columns represent means and vertical bars represent the standard errors.

used. In these animals there was a further decrease in mean arterial blood pressure by 12 and 18 mmHg, respectively, with a further reduction in systemic vascular resistance. Cardiac output, heart rate and LVdP/dt_{max} were not affected (data not shown in Table 1).

Resistance of the cerebral vascular bed decreased dose dependently from 2.93 ± 0.33 to 2.24 ± 0.23 mmHg $\text{ml}^{-1} \text{min} 100 \text{g}$ (25%, $P < 0.05$) during the fenoldopam infusions. The resistance of the renal vascular bed was 0.45 ± 0.10 mmHg $\text{ml}^{-1} \text{min} 100 \text{g}$ at baseline and decreased gradually to 0.32 ± 0.04 mmHg $\text{ml}^{-1} \text{min} 100 \text{g}$ at $0.4 \mu\text{g kg}^{-1} \text{min}^{-1}$ fenoldopam. This decrement, however, was not significant compared to the changes in the solvent-treated animals.

Myocardial blood flow, oxygen consumption and contractile function Intracoronary infusions of fenoldopam did not alter transmural blood flow or vascular resistance in the LADCA-perfused region (Figure 4). Since coronary venous oxygen saturation (baseline value: $27 \pm 3\%$) was also not affected, myocardial oxygen consumption was maintained (Figure 4). This observation is not surprising as global and regional parameters of myocardial contractile function, LVdP/dt_{max} (Table 1) and segment length shortening (Figure 4), respectively, did not change.

In the two animals in which fenoldopam was infused at $4 \mu\text{g kg}^{-1} \text{min}^{-1}$, coronary venous oxygen saturation and regional segment length shortening remained constant.

Discussion

The principal findings of this study are that intracoronary infusions of fenoldopam (up to a dose of $0.4 \mu\text{g kg}^{-1} \text{min}^{-1}$) neither affected myocardial blood flow nor myocardial function and oxygen consumption in anaesthetized pigs. The doses used were high enough to cause changes in the peripheral vasculature as reflected by decreases in mean arterial blood pressure and systemic vascular resistance. Furthermore, in two animals the rate of the intracoronary infusions of fenoldopam was increased to $4 \mu\text{g kg}^{-1} \text{min}^{-1}$ without causing any changes in regional myocardial wall motion and coronary venous oxygen saturation, which is a sensitive parameter to detect coronary vasodilatation provided myocardial oxygen consumption does not increase (Duncker *et al.*, 1986; Verdouw *et al.*, 1987; Sassen *et al.*, 1990a,b). These observations suggest that D₁ receptors are of minor importance in the coronary circulation of the anaesthetized pig.

The presence of D₁ receptors in the renal, mesenteric and cerebral vascular beds has now been well established in a

number of species including man, dogs and pigs (Goldberg, 1972; Ueda *et al.*, 1982; Gootman *et al.*, 1983; Toda, 1983; Hughes & Sever, 1989). In contrast, evidence for D₁ receptors in the coronary circulation is inconclusive. In dogs pretreated with α - and β -adrenoceptor antagonists, dopamine has been reported to elicit a D₁ receptor-mediated vasodilatation in coronary conductance vessels (Toda & Hatano, 1979) as well as in arterioles (Schuelke *et al.*, 1971; Kopia & Valocik, 1989). However, in the present experiments in pigs, dopamine-induced coronary vasodilatation was accompanied by increases in heart rate and myocardial contractility, and these effects were absent in animals with α - and β -adrenoceptor blockade. Similarly, fenoldopam-induced coronary vasodilatation has not been consistently observed. While Kopia & Valocik (1989) found coronary vasodilatation after intracoronary administration of $1 \mu\text{g kg}^{-1} \text{ min}^{-1}$ fenoldopam in the dog, no such effect was noticed with this drug after intravenous infusion in the same species (Hieble *et al.*, 1987) or after intracoronary infusion in the pig (present experiments). In human isolated coronary arteries precontracted with nor-adrenaline, fenoldopam failed to elicit a vasodilator response in 6 out of 9 artery segments (6 out of 7 patients) (Hughes & Sever, 1989), implying that the human conduit coronary vessels are devoid of D₁ receptors.

Another controversial point is the potential effects of fenoldopam on myocardial contractility. Hieble *et al.* (1987) suggested that fenoldopam exerts a negative inotropic action as shown by a 26% decrease in $\text{LVdP/dt}_{\text{max}}$ during intravenous infusion of the drug. The authors did not take into account that $\text{LVdP/dt}_{\text{max}}$ depends not only on myocardial contractility but also on heart rate, left ventricular filling pressure and arterial blood pressure (afterload). Since in their study arterial blood pressure decreased by approximately 25%, the effect on $\text{dP/dt}_{\text{max}}$ cannot be assumed to be secondary to possible cardiodepressant actions of the drug only. In contrast, Zhao *et al.* (1990) observed that intracoronary infusion of fenoldopam at concentrations up to 5000 nM (equivalent to intracoronary

infusions of $1\text{--}2 \mu\text{g kg}^{-1} \text{ min}^{-1}$ fenoldopam in our experiments) at constant coronary perfusion pressure increased $\text{LVdP/dt}_{\text{max}}$ in anaesthetized dogs. Kopia & Valocik (1989), using a similar experimental set-up found no change in myocardial function. We also did not observe change in $\text{LVdP/dt}_{\text{max}}$ or in regional myocardial segment length shortening indicating the absence of a negative inotropic action. Furthermore, to achieve equivalent intracoronary concentrations via intravenous administration one would require a fifty-fold higher dose of the drug. This may be unacceptable because of severe hypotension.

Finally, two points deserve comment. First, it is theoretically possible that in our model a vasodilator response of fenoldopam could not be observed because the coronary vascular bed was already maximally dilated. This seems very unlikely as we have repeatedly shown that in the same model a number of drugs increased coronary blood flow up to 100% (Duncker *et al.*, 1986; Verdouw *et al.*, 1987; Sassen *et al.*, 1990a,b) while in the present study intravenous infusions of dopamine reduced coronary vascular resistance to 60% of baseline. Secondly, it could be argued that the butyrophenone derivative azaperone (Niemegeers *et al.*, 1974), used by us as anaesthetic premedication, may have antagonized a possible vasodilator effect of fenoldopam. This drug has indeed been shown to exhibit antidopamine activity, but the inhibition is at the D₂ receptor site (Fukuchi *et al.*, 1988). Furthermore, intravenous infusion of dopamine in the presence of α - and β -adrenoceptor blockade revealed the existence of dopamine receptors in several peripheral vascular beds.

In conclusion, the lack of effect of intracoronary infusions of high doses of fenoldopam as well as of intravenous infusions of dopamine (after adrenoceptor blockade) on coronary blood flow and myocardial performance provides evidence that D₁ receptors do not play a major physiological role in the coronary circulation and myocardium of pigs. This observation should be taken into account in the study of the effects of agents acting on dopamine receptors.

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(Received April 17, 1991
Revised May 21, 1991)