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Systemic and splanchnic oxygen supply-demand relationship with fenoldopam, dopamine and noradrenaline in sheep

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Abstract

The effects of intravenous administration of fenoldopam (0.3–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$), dopamine (1–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and noradrenaline (0.1–1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) on systemic and splanchnic haemodynamics and oxygen supply-demand relationship were studied in 12 chronically instrumented, sedated sheep. Fenoldopam produced dose-dependent peripheral and splanchnic vasodilatation without change in arterial blood pressure. The coeliac trunk and portal vein blood flows were particularly sensitive to fenoldopam, whereas dopamine vasodilated these vascular beds only at high doses. Renal blood flow was not influenced by dopamine or fenoldopam, but decreased by noradrenaline. Fenoldopam maintained systemic oxygen extraction constant by increasing both oxygen supply and demand, while noradrenaline and dopamine increased oxygen supply more than demand, thus decreasing oxygen extraction. Both dopamine and fenoldopam increased oxygen delivery to the splanchnic organs while noradrenaline reduced it. Splanchnic oxygen consumption decreased with noradrenaline and increased with dopamine, resulting in a conserved oxygen extraction with both drugs, whereas oxygen consumption remained constant at all doses of fenoldopam infusion (i.e. dose-dependent decreased oxygen extraction). Both noradrenaline and fenoldopam, but not dopamine, were accompanied by increased portal lactataemia. We conclude that in sheep fenoldopam is a potent and selective splanchnic vasodilatator but without vasodilatator effect on the renal circulation. The portal lactataemia associated with a decreased splanchnic oxygen extraction may present a significant limitation for some clinical applications of this drug.

Keywords: Dopamine; Fenoldopam; Noradrenaline; Renal blood flow; Splanchnic blood flow; Oxygen demand; Oxygen supply; Oxygen extraction ratio

1. Introduction

The beneficial effects of dopamine on the splanchnic circulation result largely from stimulation of specific dopamine D_1 receptors of the renal and mesenteric vasculature producing vasodilatation (Hahn and Wardell, 1980) and a positive inotropic action which is probably mediated by β-adrenoceptor stimulation (Goldberg, 1972; Setler et al., 1975). At relatively small, vasodilating doses, when mesenteric blood flow is increased, dopamine has been shown to decrease tissue oxygen extraction (Giraud and Mac Cannell, 1984) as well as capillary density (Pawlick et al., 1976), suggesting a reduced oxygen delivery to the intestine. On the other hand, shunting mesenteric arterial blood flow into portal venous blood should increase the oxygen delivery to the liver (Angehrn et al., 1980).

Moreover, catecholamines, including dopamine, stimulate oxidative metabolism, thereby increasing tissue oxygen demand (Kvietys and Granger, 1982). Thus, it appears that dopamine, at small doses, increases hepatic oxygen delivery but at the same time might be associated with a concomitant increase in hepatic oxy-

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gen demand, whereas mesenteric oxygen delivery might be decreased.

At higher doses, dopamine stimulates α- and β-adrenoceptors resulting in regional vasoconstriction, increased arterial pressure and tachycardia (Goldberg, 1972), as well as dopamine D_1 and dopamine D_2 receptors (Goldberg et al., 1978). Dopamine D_2 receptor stimulation may have a number of additional effects that might be considered deleterious. These include pre-synaptic inhibition of sympathetic nerve terminals, which prevents neurotransmitter release and thus attenuates normal cardiovascular reflexes (Kohli et al., 1989). Secondly, and no less importantly, dopamine D_2 receptors regulate carotid body chemosensory discharge, so the use of dopamine may preclude a normal response to hypoxia. Finally, dopamine through inhibition of hypophyseal prolactin and thyroid stimulating hormone release (MacLeod and Login, 1977) may be partly responsible for some of the endocrine imbalance that occurs in severely ill patients.

Fenoldopam (6-chloro-7,8-dihydroxy-1-(*p*-hydroxyphenyl)-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine) is a selective dopamine D_1 receptor agonist (Hahn et al., 1982) approximately 10-fold more potent than dopamine as a renal vasodilatator (Nichols et al., 1987). But more importantly, fenoldopam does not prevent the vasoconstriction elicited by periarterial nerve stimulation, and this contrasts with the pre-synaptic effect of dopamine D_2 agonists which are able to inhibit such neurogenic vasoconstriction (Dupont et al., 1987). Fenoldopam has no direct α- or β-adrenergic effect, but there is a significant rise in plasma renin activity which is blocked by propranolol. This new selective renal vasodilatator might be useful in severe patterns of shock contributing to improvement of altered renal function.

Before undertaking a larger evaluation on the potential therapeutic benefit of a continuous intravenous infusion of fenoldopam over dopamine during pathologic conditions, particularly during sepsis-induced multiple organ failure, the present study was aimed at comparing in a randomised, sequential manner, the acute cardiovascular effects of dopamine and fenoldopam by determining dose-response curves of the systemic, pulmonary as well as renal and mesenteric blood flows and vascular resistances during normal conditions in sheep. We elected to use sheep because these animals are particularly suited for physiological studies requiring chronic preparations and because of our previous experience regarding the development of a reproducible animal model of septic shock that simulates human sepsis-induced multiple organ failure (Pittet and Morel, 1991; Weber et al., 1992). Dopamine and fenoldopam were further compared to noradrenaline, a pure sympatomimetic agent, to contrast the effect of both dopamine and fenoldopam with those of noradrenaline producing intrinsic α- and β-adrenergic effects (Brodde, 1990).

2. Material and methods

2.1. Surgical preparation

The experimental protocol conformed to the Guiding Principles in the Care and Use of Animals as approved by the Council of the American Physiological Society and reviewed by the Ethical Committee for Animal Research of our institution. Under halothane anaesthesia and mechanical ventilation, 12 Alpine sheep weighing 30–40 kg were surgically instrumented for chronic studies. Intravascular catheters were placed into the aorta, and femoral and jugular veins. A Swan-Ganz flow-directed thermodilution catheter (model 93A-131H-7F, Edwards Laboratories, Irvine, CA, USA) was inserted into the pulmonary artery for the measurement of cardiac output, central venous, mean pulmonary artery, and pulmonary capillary wedge pressures, for intermittent sampling of mixed venous blood and central body temperature. Through a right subcostal laparotomy, a transit-time ultrasonic blood flow probe (2R-Sil, Transonic System, Ithaca, NY, USA) was placed around the right renal artery for continuous renal artery blood flow measurement. Two other transit-time ultrasonic blood flow probes (2R-Sil or 3R-Sil in accordance with the vascular diameter) were placed around the superior mesenteric artery and the coeliac trunk, 2–5 cm from their origin, for continuous mesenteric blood flow determination. Total hepatic blood flow was continuously measured by two transit-time ultrasonic blood flow probes placed around the portal vein (12R-Sil) and the hepatic artery (2R-Sil). In addition, two Silastic catheters were inserted into the renal and portal veins for the measurements of renal vein and portal vein pressures and for intermittent sampling of renal and portal venous blood. The portal and renal vein catheters and the wires of the ultrasound tubings were exteriorized through the abdominal wall, tunnelled subcutaneously, and fixed on the right flank. The sheep were then awakened, extubated, and remained under frequent post-operative control in the laboratory for 24 h. The animals then had free access to food and water for a one-week period of recovery. The intravascular catheters were filled with heparin and their permeability frequently controlled. The sheep were additionally anticoagulated daily with $2 \times 10\,000$ units heparin administered subcutaneously up to the start of the experimental protocol; systemic antibiotic therapy (penicillin 5 million units and chloramphenicol 0.5 g twice a day) was administered over the first 3 days following surgery and local antibiotic therapy was applied on the wounds of skin incision.

2.2. Haemodynamic measurements

Mean systemic and pulmonary arterial pressures as well as central venous, renal and portal venous pressures were measured using calibrated pressure transducers (Honeywell, model 156-PC-06-GW2, Zürich, Switzerland) positioned at the level of the third of the distance from the brisket to the top of the back. Cardiac output was recorded every 10 min as the mean of triplicate determinations by thermodilution injecting 5 ml of 0°C saline, and measured by an Edwards Laboratories model 9520A Cardiac Output Computer. Mean renal artery, coeliac trunk, superior mesenteric artery, hepatic artery and portal vein blood flows were measured with transit-time flow meters (T101CDS, Transonic System, Ithaca, NY, USA). Vascular pressures and regional blood flows were simultaneously and continuously recorded on a thermal chart recorder (Gould Electronics, model 8000 S, Zürich, Switzerland) as well as connected via an analog/digital interface converter (SICMU, Centre Médical Universitaire, Geneva, Switzerland) to a microcomputer (ALR AT-386, CPI, Geneva, Switzerland). Sampling rate of each channel was 0.5 Hz and the digitised data were stored on the hard disk of the computer. Systemic vascular resistance was calculated as the difference between mean arterial and central venous pressure divided by cardiac output, pulmonary vascular resistance as the difference between mean pulmonary arterial and pulmonary capillary wedge pressure divided by cardiac output, renal artery vascular resistance as the difference between mean arterial and renal venous pressure divided by renal artery blood flow, superior mesenteric artery vascular resistance as the difference between mean arterial and portal venous pressure divided by superior mesenteric artery blood flow, coeliac trunk vascular resistance as the difference between mean arterial and portal venous pressure divided by coeliac trunk blood flow, hepatic artery vascular resistance as the difference between mean arterial and central venous pressure divided by hepatic artery blood flow, and finally portal vein vascular resistance as the difference between portal venous and central venous pressure divided by portal vein blood flow. All the resistances were multiplied by 79.9 to express results in standard units (dynes $\cdot$ s $\cdot$ cm^{-5}). Non-splanchnic blood flow was calculated by subtracting the sum of the measured arterial splanchnic blood flows (i.e. superior mesenteric artery blood flow, coeliac trunk blood flow, renal artery blood flow) from cardiac output. Stroke volume was calculated by dividing cardiac output by heart rate $\times 1000$. Right and left ventricular stroke works were calculated multiplying respectively mean pulmonary arterial pressure or mean arterial pressure by stroke volume $\times 0.0031$. A standard 3-lead electrocardiogram via chronically implanted subcutaneous electrodes was continuously displayed on a Hewlett-Packard monitor and heart rate intermittently recorded from the digital readout of the monitor.

2.3. Oxygen delivery and consumption

Systemic, renal and portal oxygen deliveries (DO_2) were calculated as the product of arterial or portal venous oxygen contents (taking the respective haemoglobin concentrations) and the respective blood flows; systemic oxygen consumption (VO_2) was calculated as the product of cardiac output and the difference between arterial and mixed venous blood oxygen contents, renal VO_2 as the product of renal blood flow and the difference between arterial and renal venous blood oxygen contents, and finally portal venous VO_2 as the product of portal vein blood flow and the difference between arterial and portal venous blood oxygen contents. Systemic, renal and portal oxygen extraction ratios were calculated by dividing the respective DO_2 by VO_2.

2.4. Additional measurements

Blood gas tensions and pH were analysed by an automated AVL 940 oximeter. Haematocrit was measured after centrifugation. Total haemoglobin concentration and oxygen haemoglobin saturation in arterial, mixed venous, renal venous and portal venous blood were measured by a CO-oximeter (Corning 2005, Ciba-Corning, Switzerland). The alveolar-arterial oxygen gradient and intrapulmonary venous admixture were calculated by standard formulae. White blood cell count was measured by phase microscopy. The activated clotting time of whole blood was measured with a Haemochron 400D system (International Technidyne, Edison, NJ, USA). Plasma lactate concentration was determined by absorption spectrometry (Boehringer UV test, Mannheim, Germany).

2.5. Experimental protocol

The studies began at least 8 days after the surgical preparation, with the animals in a documented stable baseline respiratory and haemodynamic state ($< 10\%$ variation of physiological variables during a 4-h control recording period). The study was postponed if the animals presented signs of infection (arterial white blood cell count > 12000, core temperature > 40°C) or a pulmonary hypertension (mean pulmonary arterial pressure > 22 mm Hg) at the beginning of the experiment. After connecting the different catheters and blood flow probes to the recording devices, the animals were first sedated with a benzodiazepine (midazolam, Hoffmann-La Roche, Basel, Switzerland) given as a continuous intravenous infusion at the rate of 0.6 mg $\cdot$

$kg^{-1} \cdot h^{-1}$ after an initial bolus of 0.4 mg/kg. In addition, a continuous infusion of bovine lung heparin (Hoffmann-La Roche, Basel, Switzerland) was started at an initial rate of 40 units $\cdot kg^{-1} \cdot h^{-1}$ and thereafter adjusted to maintain the activated clotting time of whole blood between 300–400 s in order to avoid clotting of the various intravascular catheters.

After a 30-min period of baseline measurements during which normal saline chloride was infused at the same volume and rate as during drug administration, the drugs were injected by means of a constant rate infusion pump (Vickers, model SP 55, Schoch Electronics, Zürich, Switzerland) for a period of 20 min for each infusion rate in a running intravenous infusion of sodium chloride 0.9% (3 ml $\cdot kg^{-1} \cdot h^{-1}$) connected to the jugular vein catheter in increasing doses (0.1, 0.3, and 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for noradrenaline, 0.3, 1.0, 3.0, and 10.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for fenoldopam and 1.0, 3.0, and 10.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for dopamine). The drugs were prepared in a dilution suitable for obtaining a flow rate of 100 ml/h for the highest drug concentration, i.e., 21 μg/ml for noradrenaline and 210 μg/ml for fenoldopam and dopamine in a 35-kg sheep. At the end of each 20-min period and just before changing to a higher drug infusion rate, 1.5 μl of arterial, mixed venous, renal venous and portal venous blood samples were taken for blood gas analysis, haemoglobin oxygen saturation and plasma lactate measurements.

Each drug was used sequentially in all animals with the order of drug infusion determined randomly. The dose-response curves were produced by sequentially increasing infusion rates of the same drug, during a 20-min period of recording, after which a blood sample was taken and the next infusion rate applied. After each dose-response determination, a recovery period of at least 3 h was allowed before starting the next drug session. The overall length of the whole experimental period was about 12 h. Haemodynamic data were collected by an on-line data acquisition system to obtain an average of 120 data points collected at a rate of 0.5 Hz during the last 4 min of each 20-min dose infusion period.

2.6. Statistical analysis

Group data are presented as mean ± S.E.M. values of the 12 sheep. Statistical comparisons were conducted by analysis of variance for repeated measures, followed by Dunnet's test for comparison with baseline values, and by Scheffe's test for comparison between drugs. Inter-drug comparisons were conducted at equipotent doses of all three amines regarding their effect on cardiac output, i.e. fenoldopam and dopamine were approximately equipotent at the same concentrations in this respect, and compared with noradrenaline at 10-fold higher concentrations. Analysis of variance resulting in a P value < 0.05 was considered significant.

3. Results

Baseline values of the different measured variables were not different between the three drug dose-response studies, indicating stable experimental conditions.

Table 1
Effect of stepwise increase of constant rate i.v. infusions of dopamine, fenoldopam and noradrenaline on haemodynamic variables

	Heart rate (beats min^{-1})	Mean arterial pressure (mm Hg)	Central venous pressure (mm Hg)	Mean pulmonary arterial pressure (mm Hg)	Pulmonary capillary wedge pressure (mm Hg)
Dopamine					
Baseline	124 ± 7	121 ± 4	2.1 ± 0.6	17.5 ± 0.9	6.0 ± 0.9
1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	125 ± 5	120 ± 4	2.3 ± 0.6	17.4 ± 1.0	6.3 ± 0.9
3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	126 ± 6	121 ± 5	2.8 ± 0.8	21.3 ± 1.5 [a]	7.0 ± 1.0
10.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	136 ± 9	124 ± 5	3.1 ± 0.8	22.6 ± 1.2 [a]	8.0 ± 1.1 [a]
Fenoldopam					
Baseline	124 ± 6	118 ± 4	1.0 ± 0.8	17.2 ± 1.2	6.7 ± 0.6
0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$	126 ± 5	118 ± 4	1.3 ± 0.9	17.7 ± 1.1	7.6 ± 1.1
1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	134 ± 5 [d]	113 ± 5	1.1 ± 0.8	19.3 ± 1.2	7.1 ± 0.8
3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	153 ± 8 [a,b,d]	117 ± 3 [d]	0.7 ± 0.9 [d]	19.5 ± 1.2	7.8 ± 0.8
10.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	151 ± 9 [a]	119 ± 3 [d]	1.6 ± 0.9 [d]	18.8 ± 1.5 [b,d]	7.9 ± 1.0
Noradrenaline					
Baseline	121 ± 5	119 ± 5	2.8 ± 0.9	18.3 ± 1.0	8.3 ± 1.0
0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	123 ± 7	122 ± 6	3.1 ± 0.9	18.4 ± 1.2	8.5 ± 1.2
0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$	115 ± 9	131 ± 7 [a]	5.1 ± 0.9	19.4 ± 0.7	10.1 ± 1.2
1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	133 ± 11	150 ± 8 [a,c]	5.9 ± 1.0 [a,c]	25.0 ± 1.5 [a]	11.4 ± 1.3 [a]

Values are means ± S.E.M.; $n = 12$. [a] $P < 0.05$ compared with baseline by Dunnet's test. [b] $P < 0.05$ between fenoldopam and dopamine by Scheffe's test. [c] $P < 0.05$ between noradrenaline and dopamine by Scheffe's test. [d] $P < 0.05$ between fenoldopam and noradrenaline by Scheffe's test.

3.1. Systemic and pulmonary haemodynamics

Mean arterial pressure was significantly increased with noradrenaline infusion (from 119 ± 5 to 150 ± 8 mm Hg at the 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ rate), while mean arterial pressure remained at baseline values with both dopamine and fenoldopam at all infusion rates (Table 1). Heart rate increased significantly under high fenoldopam infusion rates (3 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) but was not modified by noradrenaline or dopamine infusions (Table 1). The three drugs increased cardiac output to a similar degree at their highest infusion rates (dopamine, +33%; fenoldopam, +33%; noradrenaline, +28%), but at lower infusion rates cardiac output was significantly increased only by fenoldopam (+20% and +28%, at the 1 and 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rates, respectively; Fig. 1). Systemic vascular resistance was significantly and similarly decreased by 25% at the 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rate with both fenoldopam and dopamine, but at lower infusion rates systemic vascular resistance was significantly reduced only by fenoldopam. Noradrenaline infusion did not significantly change systemic vascular resistance (Fig. 2).

Mean pulmonary arterial pressure was significantly elevated during the higher doses of dopamine (3 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and noradrenaline (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and was accompanied by a rise in pulmonary capillary wedge pressure (Table 1), whereas pulmonary vascular resistance remained at baseline levels (Table 2). In contrast, fenoldopam infusion produced no rise in mean pulmonary arterial pressure and was followed by a 27% decrease in pulmonary vascular resistance at the 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rate.

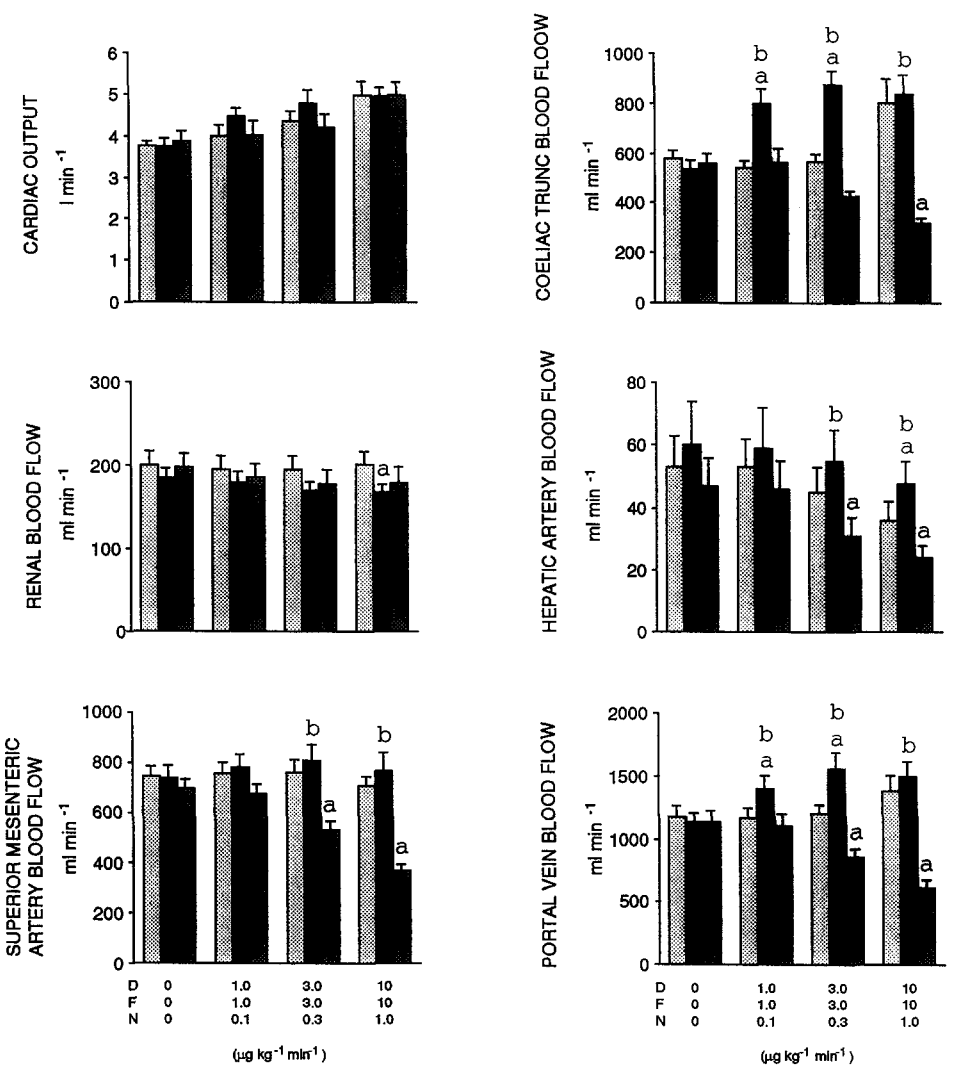

Fig. 1. Effect of stepwise increase of constant rate i.v. infusions of dopamine (D), fenoldopam (F), and noradrenaline (N) on systemic and regional blood flows. Data are given as means ± S.E.M.; $n = 11$. [a] $P < 0.05$ compared with dopamine; [b] $P < 0.05$ compared with noradrenaline (one-way analysis of variance for repeated measures followed by Scheffe's test for multiple comparisons).

Left ventricular stroke work was significantly increased by dopamine (+23%) and noradrenaline (+51%) at their highest infusion rates but remained unchanged by fenoldopam infusion (Table 2). Right ventricular stroke work was significantly increased by all three drugs, but noradrenaline (+68%) and dopamine (+59%) had a more pronounced effect than fenoldopam (+21%; Table 2).

Estimated non-splanchnic blood flow was increased by all three drug infusions indicating a preferential distribution of cardiac output towards the non-splanchnic vascular beds, although fenoldopam (+32%) showed significantly less effect than noradrenaline (+62%) in this respect.

3.2. Splanchnic haemodynamics

Stepwise increase of intravenous noradrenaline infusion caused a dose-dependent decrease of the blood flows in the different splanchnic vascular beds, with a proportional increase in corresponding vascular resistances (Figs. 1 and 2). The effect of noradrenaline on the different territories was very similar (superior mesenteric artery blood flow, −47%; coeliac trunk blood flow, −43%; hepatic artery blood flow, −50%; portal vein blood flow, −46%, at the 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rate). In contrast, dopamine and fenoldopam influenced the different splanchnic territories to various degrees. Whereas superior mesenteric

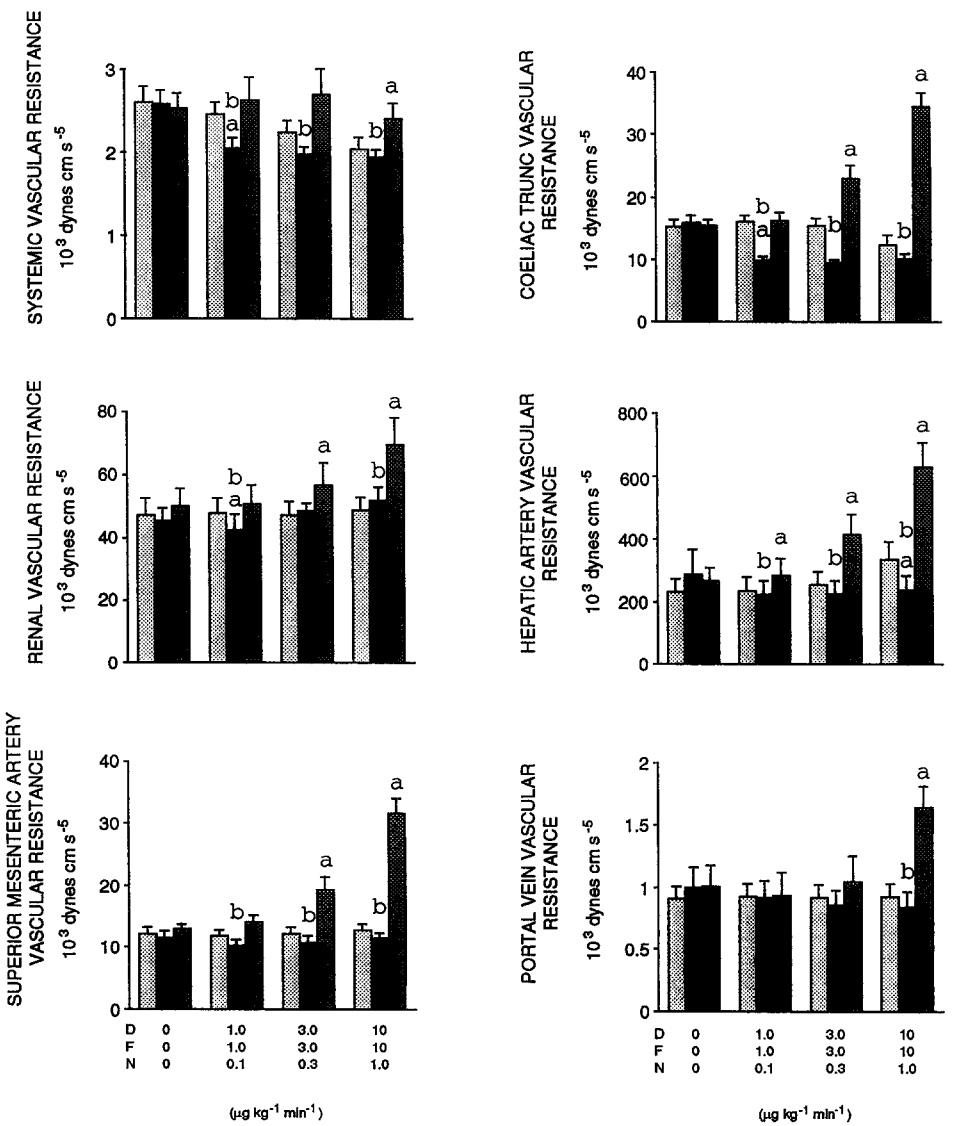

Fig. 2. Effect of stepwise increase of constant rate i.v. infusions of dopamine (D), fenoldopam (F), and noradrenaline (N) on systemic and regional vascular resistances. Data are given as means ± S.E.M.; $n = 11$. [a] $P < 0.05$ compared with dopamine; [b] $P < 0.05$ compared with noradrenaline (one-way analysis of variance for repeated measures followed by Scheffe's test for multiple comparisons).

Table 2
Effect of stepwise increase of constant rate i.v. infusions of dopamine, fenoldopam and noradrenaline on derived haemodynamic variables

	Pulmonary vascular resistance (dynes · cm · s^{-5})	Left ventricular stroke work (J)	Right ventricular stroke work (J)	Non splanchnic blood flow (ml · min^{-1})
Dopamine				
Baseline	241 ± 14	51.4 ± 3.7	7.4 ± 0.7	2355 ± 174
1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	236 ± 30	53.9 ± 5.5	7.7 ± 0.8	2556 ± 330
3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	271 ± 29	59.6 ± 6.2	10.6 ± 1.4 [a]	2878 ± 210
10.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	239 ± 24	63.3 ± 4.8 [a]	11.8 ± 1.3 [a]	3515 ± 336 [a]
Fenoldopam				
Baseline	230 ± 42	49.9 ± 3.9	7.0 ± 0.5	2460 ± 198
0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$	214 ± 31	51.7 ± 3.2	7.6 ± 0.4	2567 ± 203
1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	232 ± 26	53.1 ± 5.1	8.8 ± 0.6 [a]	2916 ± 303
3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	196 ± 29	52.2 ± 5.4	8.5 ± 0.7 [a]	3146 ± 330 [a]
10.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	167 ± 27 [a]	55.6 ± 4.4 [d]	8.5 ± 0.7 [a,d]	3253 ± 324 [a,d]
Noradrenaline				
Baseline	218 ± 35	54.1 ± 4.0	8.0 ± 0.4	2613 ± 268
0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	199 ± 32	57.0 ± 7.9	8.1 ± 0.9	2817 ± 516
0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$	195 ± 31	62.6 ± 5.0	9.2 ± 0.5	3179 ± 244
1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	202 ± 27	81.5 ± 8.7 [a]	13.4 ± 2.0 [a]	4246 ± 360 [a]

Values are means ± S.E.M.; $n = 12$. [a] $P < 0.05$ compared with baseline by Dunnet's test. [b] $P < 0.05$ between fenoldopam and dopamine by Scheffe's test. [c] $P < 0.05$ between noradrenaline and dopamine by Scheffe's test. [d] $P < 0.05$ between fenoldopam and noradrenaline by Scheffe's test.

artery blood flow was not affected by either dopamine or fenoldopam, coeliac trunk blood flow was particularly sensitive to fenoldopam being increased by 50% already at the 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rate, with no further increase at higher infusion rates (Figs. 1 and 2). Dopamine was less effective, it significantly increased coeliac trunk blood flow only at the 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ rate infusion (+39%). Venous splanchnic outflow assessed by portal vein blood flow showed a similar response to the one observed in coeliac trunk blood flow, but was attenuated by the relative insensitivity of the superior mesenteric vascular territory to dopamine and fenoldopam. Contrasting with superior mesenteric, coeliac and portal vascular beds, the hepatic arterial vasculature responded by a dose-dependent vasoconstriction to dopamine (−32% decrease in hepatic artery blood flow and a corresponding 45% increase in hepatic artery vascular resistance at the 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rate) while fenoldopam at the same dosage caused only a moderate though signif-

Table 3
Effect of stepwise increase of constant rate i.v. infusions of dopamine, fenoldopam and noradrenaline on femoral artery, pulmonary artery and portal vein haemoglobin concentrations

	Femoral artery haemoglobin (g · l^{-1})	Portal vein haemoglobin (g · l^{-1})	Pulmonary artery haemoglobin (g · l^{-1})
Dopamine			
Baseline	86.9 ± 3.7	84.3 ± 3.8	85.8 ± 4.2
1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	85.0 ± 3.7	84.5 ± 3.3	84.5 ± 3.9
3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	88.5 ± 3.4	88.1 ± 3.3	85.8 ± 4.1
10.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	105.0 ± 4.2 [a]	100.3 ± 4.0 [a,e]	97.4 ± 3.7 [a,e]
Fenoldopam			
Baseline	91.8 ± 3.2	91.3 ± 3.4	88.8 ± 3.5
0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$	92.2 ± 3.4	90.2 ± 4.1	89.2 ± 3.9
1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	99.0 ± 3.1 [a,b]	97.0 ± 3.5 [b]	93.6 ± 3.6 [b,f]
3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	97.8 ± 3.8 [a,b]	96.4 ± 4.0 [a,b]	95.3 ± 3.5 [a]
10.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	98.7 ± 3.0 [a,b,d]	95.2 ± 3.4 [a,d,e]	97.5 ± 3.4 [a,d]
Noradrenaline			
Baseline	89.8 ± 3.9	88.9 ± 4.7	90.8 ± 4.2
0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$	93.3 ± 4.8 [c]	92.6 ± 4.6 [c]	90.1 ± 3.9 [c]
0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$	102.2 ± 4.1 [a,c]	100.2 ± 4.2 [a,c]	95.9 ± 6.3 [c]
1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$	112.2 ± 3.9 [a]	110.6 ± 3.9 [a,c]	106.6 ± 4.7 [a,c,f]

Values are means ± S.E.M.; $n = 12$. [a] $P < 0.05$ compared with baseline by Dunnet's test. [b] $P < 0.05$ between fenoldopam and dopamine by Scheffe's test. [c] $P < 0.05$ between noradrenaline and dopamine by Scheffe's test. [d] $P < 0.05$ between fenoldopam and noradrenaline by Scheffe's test. [e] $P < 0.05$ compared with femoral artery by Dunnet's test. [f] $P < 0.05$ compared with both femoral artery and portal vein by Dunnet's test.

icant decrease in hepatic artery blood flow (−20%, $P < 0.05$ compared to dopamine) without changing hepatic artery vascular resistance (Figs. 1 and 2).

3.3. Renal haemodynamics

Infusion of noradrenaline caused dose-dependent renal artery vasoconstriction (39% increase in renal artery vascular resistance at the 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rate; Fig. 2). Fenoldopam produced a slight though significant 15% increase in renal artery vascular resistance at the 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rate, whereas dopamine had no effect on the renal vascular bed (Figs. 1 and 2).

3.4. Systemic, pulmonary and splanchnic haemoglobin concentrations

Stepwise increase of noradrenaline infusion induced a dose-dependent significant increase of haemoglobin concentration in the systemic, pulmonary and splanchnic vascular beds (Table 3). At the highest noradrenaline dosage (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$), haemoglobin concentration in the pulmonary artery was significantly less increased than in the femoral artery or in the portal vein. Dopamine infusion did not change haemoglobin concentrations, except for the highest infusion rate (10 $\mu g \cdot kg^{-1} \cdot min^{-1}$), although this effect was significantly less pronounced than under noradrenaline infusion. In contrast, administration of fenoldopam was associated with significant elevation of haemoglobin concentration already at lower infusion rates, with a significant gradient between femoral and pulmonary artery haemoglobin concentration. At the 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rate, however, haemoglobin concentration remained significantly lower with fenoldopam than with corresponding dopamine and noradrenaline dosages.

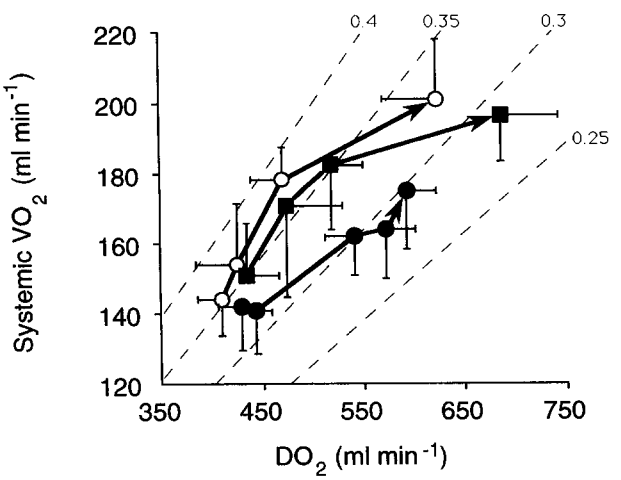

Fig. 3. Effect of stepwise increase (arrows) of constant rate i.v. infusions of dopamine (○; 0, 1, 3, 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$), fenoldopam (●; 0, 0.3, 1, 3, 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and noradrenaline (■; 0, 0.1, 0.3, 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) on the relationship between systemic oxygen consumption (VO_2) and oxygen delivery (DO_2). Dotted lines represent isopleths of constant oxygen extraction ratios. Data are given as means ± S.E.M.; $n = 11$.

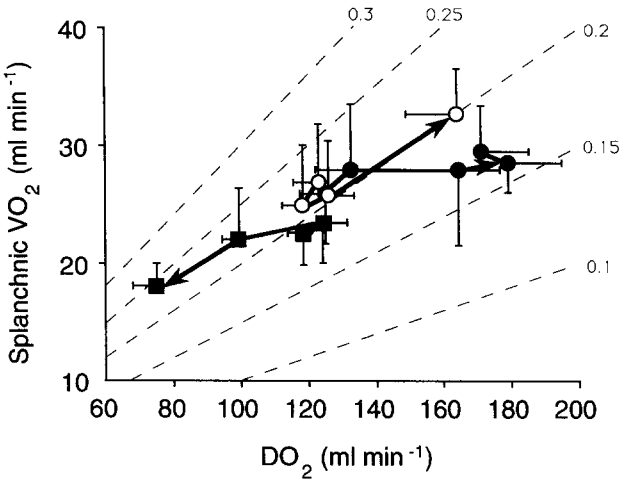

Fig. 4. Effect of stepwise increase (arrows) of constant rate i.v. infusions of dopamine (○; 0, 1, 3, 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$), fenoldopam (●; 0, 0.3, 1, 3, 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and noradrenaline (■; 0, 0.1, 0.3, 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) on the relationship between splanchnic oxygen consumption (VO_2) and oxygen delivery (DO_2). Dotted lines represent isopleths of constant oxygen extraction ratios. Data are given as means ± S.E.M.; $n = 11$.

3.5. Systemic and splanchnic oxygen delivery, consumption, and extraction ratio

Systemic DO_2 was significantly increased by fenoldopam, and this already at the 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rate. This was associated with a proportional increase in systemic VO_2 resulting in a constant systemic O_2 extraction ratio (Fig. 3). In contrast, both dopamine and noradrenaline significantly increased DO_2 at their highest dosage only, so that systemic DO_2 at 1 and 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rates was significantly higher with fenoldopam than with dopamine. In addition, the increase in DO_2 with high doses of either dopamine or noradrenaline was associated with a proportionally lesser increase in VO_2 than with fenoldopam, leading to a reduction in systemic O_2 extraction ratio with the former drugs Fig. 4.

Contrasting with its effects on systemic DO_2, noradrenaline decreased instead of increased mesenteric DO_2 by 21 ± 4% at 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and by 37 ± 5% at 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, with a slight increase in mesenteric O_2 extraction ratio. Dopamine increased mesenteric DO_2 at the high infusion rate only, whereas fenoldopam caused a significant increase in DO_2 of more than 50% already at low infusion rates, with an unchanged VO_2, so that mesenteric O_2 extraction ratio was decreased.

Table 4
Effect of stepwise increase of constant rate i.v. infusions of dopamine, fenoldopam and noradrenaline on femoral artery, pulmonary artery, renal and portal veins lactate concentrations

	Femoral artery lactate (mmol · l^{-1})	Pulmonary artery lactate (mmol · l^{-1})	Renal vein lactate (mmol · l^{-1})	Portal vein lactate (mmol · l^{-1})
Dopamine				
Baseline	0.60 ± 0.05	0.59 ± 0.08	0.56 ± 0.06	0.58 ± 0.07
1.0 μg · kg^{-1} · min^{-1}	0.61 ± 0.09	0.59 ± 0.07	0.57 ± 0.05	0.62 ± 0.06
3.0 μg · kg^{-1} · min^{-1}	0.54 ± 0.06	0.60 ± 0.10	0.54 ± 0.14	0.57 ± 0.06
10.0 μg · kg^{-1} · min^{-1}	0.84 ± 0.23	0.78 ± 0.20	0.61 ± 0.08	0.79 ± 0.21
Fenoldopam				
Baseline	0.46 ± 0.08	0.45 ± 0.07	0.47 ± 0.05	0.48 ± 0.06
0.3 μg · kg^{-1} · min^{-1}	0.47 ± 0.06	0.41 ± 0.06	0.49 ± 0.07	0.54 ± 0.08
1.0 μg · kg^{-1} · min^{-1}	0.52 ± 0.08	0.53 ± 0.09	0.47 ± 0.06	0.58 ± 0.06
3.0 μg · kg^{-1} · min^{-1}	0.50 ± 0.08	0.51 ± 0.08	0.52 ± 0.07	0.65 ± 0.10
10.0 μg · kg^{-1} · min^{-1}	0.66 ± 0.08 [a]	0.72 ± 0.07 [a]	0.66 ± 0.05 [a]	0.84 ± 0.08 [a]
Noradrenaline				
Baseline	0.56 ± 0.05	0.55 ± 0.08	0.56 ± 0.06	0.67 ± 0.07 [d]
0.1 μg · kg^{-1} · min^{-1}	0.59 ± 0.08	0.55 ± 0.07	0.54 ± 0.11	0.64 ± 0.06
0.3 μg · kg^{-1} · min^{-1}	0.66 ± 0.06	0.82 ± 0.23	0.76 ± 0.11	0.76 ± 0.06
1.0 μg · kg^{-1} · min^{-1}	0.96 ± 0.13 [a]	1.05 ± 0.20 [a]	0.87 ± 0.09 [a,c]	1.06 ± 0.15 [a]

Values are means ± S.E.M.; $n = 12$. [a] $P < 0.05$ compared with baseline by Dunnet's test. [b] $P < 0.05$ between fenoldopam and dopamine by Scheffe's test. [c] $P < 0.05$ between noradrenaline and dopamine by Scheffe's test. [d] $P < 0.05$ between fenoldopam and noradrenaline by Scheffe's test.

3.6. Systemic and splanchnic plasma lactate concentrations

Noradrenaline infusion produced a dose-dependent increase in systemic and splanchnic plasma lactate concentrations, being significantly different from baseline at the 1 μg · kg^{-1} · min^{-1} infusion rate (Table 4). Systemic and splanchnic lactate levels were also significantly increased during the high fenoldopam infusion rate, though less than with noradrenaline, whereas remaining unchanged during dopamine infusion (Table 4).

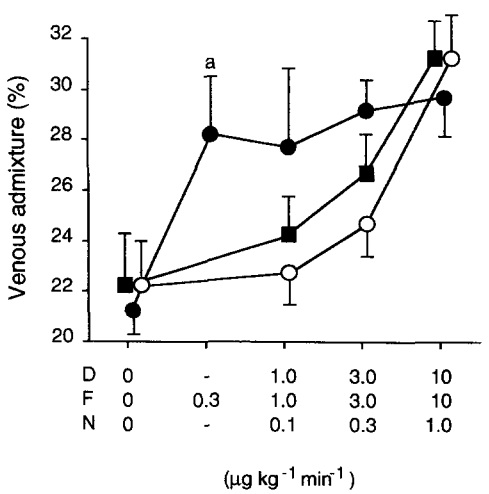

Fig. 5. Effect of stepwise increase of constant rate i.v. infusions of dopamine (D; ○; 0, 1, 3, 10 μg · kg^{-1} · min^{-1}), fenoldopam (F; ●; 0, 0.3, 1, 3, 10 μg · kg^{-1} · min^{-1}), and noradrenaline (N; ■; 0, 0.1, 0.3, 1 μg · kg^{-1} · min^{-1}) on the intrapulmonary venous admixture. Data are given as means ± S.E.M.; $n = 11$. [a] $P < 0.05$ compared to dopamine (1.0 μg · kg^{-1} · min^{-1}) and noradrenaline (0.1 μg · kg^{-1} · min^{-1}).

3.7. Alveolar-arterial oxygen gradient and intrapulmonary venous admixture

Alveolar-arterial oxygen gradient was unchanged with both dopamine and noradrenaline infusion, but increased significantly with the high dose of fenoldopam infusion (from 9.8 ± 2.9 to 17.3 ± 2.0 mm Hg). Intrapulmonary venous admixture was elevated with high dosages of dopamine and noradrenaline in a similar fashion (Fig. 5); in contrast, fenoldopam increased venous admixture from 21.0 ± 1.6 to 27.6 ± 2.2 already at the 0.3 μg · kg^{-1} · min^{-1} infusion rate, with only minimal further increase at higher infusion rates (Fig. 5).

4. Discussion

Already 20 years ago, Goldberg showed that at small dopamine doses, when α-adrenergic vasoconstriction is absent, renal and splanchnic vasodilatation predominate, cardiac contractility and output increase, and total peripheral resistance decreases whereas heart rate and blood pressure remain unchanged (Goldberg, 1972). More recently, the discovery that vascular receptors responded specifically to dopamine D_1 receptor led to the development of pure dopamine D_1 agonist molecules such as fenoldopam which proved to be an important and specific mesenteric and renal vascula-

ture relaxant (Hahn et al., 1982). Dopamine D_1 receptors were also located on renal tubular cells were they promoted sodium excretion (Goldberg and Rajfer, 1985).

As presented in Tables 1 and 2 and in Fig. 1, cardiac output and left and right ventricular stroke work increased under stepwise infusion rates of dopamine, whereas fenoldopam also increased cardiac output to a similar degree but without changing left ventricular stroke work. Systemic vascular resistance decreased with both drugs. In contrast to dopamine, fenoldopam increased heart rate while mean arterial pressure remained constant. These findings suggest that the peripheral vasodilatation mediated by both fenoldopam and dopamine via dopamine D_1 receptor stimulation was compensated either by a β_1-mediated increase in myocardial contractility (dopamine mechanism), or by activation of the baroreceptor reflex (fenoldopam mechanism; Murphy et al., 1988), maintaining blood pressure constant in both situations.

In contrast, noradrenaline did not modify heart rate, but increased mean arterial pressure at high infusion rates while maintaining systemic vascular resistance constant under all infusion rates. This noradrenaline-induced positive inotropic action was most probably mediated by direct β_1 agonist activity which increased cardiac output and blood pressure in the absence of peripheral vasodilatation, while systemic vascular resistance remained unchanged (noradrenaline mechanism). Recent human studies demonstrated that the fall in blood pressure under continuous fenoldopam infusion was accompanied by an increase in heart rate – as in the present study – and an increase in plasma noradrenaline concentration, both of which were thought to result from activation of the baroreceptor reflexes (Murphy et al., 1988; Stote et al., 1983a,b); the same authors suggested that the reflex sympathetic activation might partially negate the beneficial effect of dopamine D_1 receptor activation and represent a disadvantage of pure dopamine D_1 receptor agonists.

The lack of dopamine D_1-mediated inotropic effect of fenoldopam found in the present study confirms previous results by Van Woerkens et al. (1991) who recently demonstrated that intracoronary infusion of fenoldopam did not exhibit any inotropic action in anaesthetised pig myocardium. These findings suggest that pure dopamine D_1 receptor agonists may be more effective in combination with a positive inotropic agent when used for treatment of pathologic conditions with impaired myocardial function (Horn and Murphy, 1990). In agreement with Goldberg's conclusions on dopamine cardiovascular actions (Goldberg, 1972), our results suggest that the difference between dopamine and its analogs on the chronotropic and inotropic effects reside in the fact that dopamine's effects are α- or β-adrenoceptor-mediated, whereas the effects of dopaminergic analogs such as fenoldopam are essentially dopamine D_1 receptor-dependent.

The splanchnic vascular reactivity to fenoldopam and dopamine infusions (Figs. 1 and 2) resulted in radical differences between the different territories examined: coeliac trunk and portal vein blood flows increased preferentially due to significant vasodilatation, whereas the renal artery blood flow remained unchanged. This suggests that the distribution of dopamine receptors in the splanchnic vascular tree may not be homogeneous. Species differences in dopamine distribution in the splanchnic organs have been described (Anton and Sayre, 1964) but the distribution of dopamine receptors has not yet been determined in the ruminant mesenteric vascular tree. These results suggest that dopamine D_1 receptors are present in important quantities in the arterial tree that delivers blood to the sheep paunch, as well as in the portal venous tree irrigating the liver, when compared to other mesenteric vascular territories. At low infusions rates, and therefore low plasma concentrations, dopamine activates specific dopamine receptors. Increasing dopamine plasma concentration leads to sympatomimetic activity, first on β_1-adrenoceptors and finally on α-adrenoceptors (Kohli et al., 1988). Contrasting with dopamine, fenoldopam is clearly devoid of sympatomimetic activities and may act only on the post-synaptic dopamine D_1 receptor. The lack of homogeneous distribution of dopamine D_1 receptors in the sheep mesenteric vascular tree contrasts with the ubiquity of α-adrenoceptors in splanchnic vessels assessed by noradrenaline-induced vasoconstriction since the noradrenaline infusion homogeneously decreased all mesenteric blood flows, most likely due to the α agonist activity of noradrenaline. The results of the present study cannot readily be extrapolated to the human situation, since fenoldopam produces its preponderent effects on the coeliac vasculature in sheep whereas in humans, this effect might be far less important as compared to the renal circulation.

The oxygen supply-demand relationship as presented in Figs. 3 and 4 showed important differences between the systemic and splanchnic circulations. Noradrenaline increased DO_2 in the systemic circulation whereas it decreased oxygen supply to the splanchnic organs. In fact, noradrenaline infusion induced a decrease in splanchnic DO_2 which was associated with a relatively maintained VO_2 (Fig. 4). This implies an increase in oxygen extraction ratio which was however insufficient to meet metabolic needs since it was associated with higher lactate levels outflowing from the portal and renal venous territories. In contrast to the noradrenaline-induced decrease in splanchnic oxygen supply, both dopamine and fenoldopam increased DO_2 to the splanchnic organs. However, this was associated with a concomitant increase in splanchnic VO_2 with

the high dopamine infusion rate, that may represent at least two different possibilities. Either splanchnic DO_2 was less than the critical oxygen delivery resulting in a VO_2 beeing DO_2-dependent, suggesting a pre-existing hypoxic state, or dopamine increased oxygen metabolism mediated by the activation of the cyclic adenosine monophosphate, activation of active transport process within the mucosa, and/or uncoupling oxidative phosphorylation at the mitochondria (Kvietys and Granger, 1982). These could occur regardless of alterations in DO_2. Since lactataemia was not increased with dopamine administration, and since it has been demonstrated that high-dose dopamine can directly stimulate intracellular oxidative metabolism, thereby increasing tissue oxygen demand (Roytblat et al., 1990), we believe that the second possibility is most likely involved in the present situation. The rise in splanchnic DO_2 with the infusion of fenoldopam was not associated with a concomitant increase in splanchnic VO_2, but was nevertheless accompanied by increased portal lactataemia. This first indicates that fenoldopam does not directly stimulate intracellular oxidative metabolism promoting an increased splanchnic VO_2, and second suggests that fenoldopam may interfere with the cellular oxidative metabolism pathway since the inability of the splanchnic organs to make use of the increased oxygen supply was associated with increased lactataemia.

Systemic DO_2 increased under noradrenaline infusion and this increase was proportionally higher than the increase in systemic VO_2 resulting in a decreased oxygen extraction ratio (Fig. 3). The associated elevated systemic lactataemia is more likely due to the splanchnic production of lactic acid secondary to bowel ischemia than to a systemic failure of oxidative metabolism in peripheral muscles, as evidenced by the reduced systemic oxygen extraction ratio. Dopamine and fenoldopam increased systemic DO_2 to a similar extent, but VO_2 was simultaneously more increased with dopamine, yielding a constant oxygen extraction ratio with this drug. Fenoldopam infusion was thus accompanied by decreased systemic oxygen extraction and increased systemic lactataemia. This particular pattern probably results from the β_1-adrenergic cardiac inotropic increase in left ventricular stroke work observed with dopamine and noradrenaline, and not with fenoldopam.

Another striking aspect of the study was revealed by fluctuations in haemoglobin values under drug infusions. As evidenced in Table 3, the highest noradrenaline dosage induced an increase in haemoglobin values in the portal vein and femoral artery, which was significantly more pronounced than in the pulmonary artery, suggesting a splanchnic source of red blood cells and/or haemoconcentration by transudation in the lung. Red blood cell storage function of the spleen in sheep has already been demonstrated (Turner and Hodgetts, 1959). This observation suggests that the release of red blood cells from spleen storage may be mediated by α-adrenoceptors, as evidenced by the fact that only high dopamine dosages induced similar increases in haemoglobin, though significantly less pronounced than with noradrenaline infusion. In contrast, fenoldopam increased haemoglobin values even at low infusion rates, but the difference between portal vein, pulmonary artery and femoral artery haemoglobin values disappeared at higher fenoldopam infusion dosage, suggesting that haemoconcentration by transudation was accentuated.

The pulmonary vascular response to dopamine confirmed earlier studies showing that dopamine induced an increase in pulmonary vascular pressure associated with constant pulmonary vascular resistance due to a dose-dependent increase in cardiac output (Waaler, 1961). In contrast, fenoldopam increased cardiac output without increasing pulmonary arterial pressure resulting in decreased pulmonary vascular resistance. This suggests that the dopamine-induced increase in pulmonary arterial pressure is related to a β_1-mediated positive inotropic activity on the myocardium, while the dopaminergic-induced vasodilatation is insufficient to prevent the rise in pulmonary arterial pressure. In contrast, fenoldopam dilated the pulmonary vessels (probably dopamine D_1 receptor-mediated), maintained pulmonary arterial pressure constant in spite of a baroreceptor reflex-induced increase in cardiac output since fenoldopam is devoid of sympathomimetic positive inotropic effect on the myocardium. Finally, noradrenaline increased cardiac output and pulmonary arterial pressure while pulmonary vascular resistance remained constant probably by a synergistic effect of the β_1 activity on the heart and the α agonist activity on pulmonary vessels at high doses. The calculated intrapulmonary venous admixture was rapidly increased at low-dose fenoldopam infusion compared to dopamine and noradrenaline which increased the intrapulmonary venous admixture only at high infusion dosage. This indicates that the fenoldopam infusion induced an opening of pulmonary venous shunts and interfered, even at low doses, with gas exchange function of the lung.

In conclusion, the splanchnic vascular effects of fenoldopam are probably dependent on dopamine receptors and particularly the dopamine D_1 receptor distribution which is not only species dependent (Anton and Sayre, 1964), but also depends on the systemic effects of fenoldopam which induces a pure dopaminergic vasodilatation with reflex tachycardia. The dose-dependent response of fenoldopam shows that the mesenteric vasodilatation rapidly reaches a plateau that is reached with dopamine only at high infusion rates. Additional effects on oxidative metabolism and pul-

monary gas exchange were observed at high fenoldopam infusion rates, but the role of dopamine D_1 receptor activation in these latter effects is not yet known.

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