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Nimodipine-induced changes in the distribution of carotid blood flow and cardiac output in pentobarbitone-anaesthetized pigs

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1 In view of the claimed effectiveness of nimodipine in migraine and its possible selectivity for cerebral vessels, we investigated the effects of nimodipine in anaesthetized pigs on the fractionation of carotid arterial blood flow into non-nutrient (arteriovenous anastomoses; AVAs) and nutrient (capillary) parts, and on regional tissue blood flows and vascular conductances.

2 Intracarotid infusions of nimodipine ($0.05-1.25\ \mu g\ kg^{-1}\ min^{-1}$) redistributed carotid blood flow in favour of its nutrient compartment, particularly to the skeletal muscles and tongue. Vascular conductance in the non-nutrient (AVAs) compartment decreased (40%), most likely, as a result of 'steal' following profound (5.5 fold) arteriolar dilatation.

3 Intravenous infusions of nimodipine ($0.05-6.25\ \mu g\ kg^{-1}\ min^{-1}$) caused hypotension, bradycardia, a decrease in conduction in the non-nutrient fraction, and an increase in conduction in the nutrient fraction (mostly in the skeletal muscles, but also in the gastrointestinal tract, cerebral hemispheres, heart and adrenals).

4 Probably due to the hypotensive effect, only skeletal muscle blood flow increased. The nimodipine-induced increase in vascular conductance in the skeletal muscles showed regional variation; the effect was most pronounced in the cheek muscles, followed by the muscles of the chest, abdominal, trunk and gluteal regions.

5 We conclude that: (i) AVA flow seems to represent a 'reserve' perfusion which can be readily diverted to tissues in the case of increased metabolism and/or vasodilatation, (ii) though the overall response to nimodipine of carotid blood flow distribution qualitatively resembles that to some anti-migraine drugs, the relevance of such acute effects in the prophylactic usefulness of nimodipine in migraine remains to be ascertained, and (iii) nimodipine lacks a selective cerebral vasodilator action in the anaesthetized pig.

Introduction

One of the most significant recent advances in drug development has been the discovery of agents interfering with calcium (Ca^{2+}) channels. These drugs are now being used for the treatment of cardiovascular disorders such as angina pectoris, cardiac arrhythmias and hypertension (see Fleckenstein, 1983). The Ca^{2+} channel antagonists exhibit considerable heterogeneity with respect to their effects on the heart and different vascular smooth muscle preparations (Cauvin *et al.*, 1983; Fleckenstein, 1983; Nayler, 1983; Peroutka, 1983). The dihydropyridine derivative nimodipine appears to have a preferential action on cerebral vessels; it antagonizes vasoconstrictor effects of 5-hydroxytryptamine (5-HT), blood and carboxylic thromboxane A_2 on the rabbit basilar artery more effectively than on the rabbit saphenous artery (Towart, 1981; Towart & Perzborn, 1981; Towart *et al.*, 1982). Clinically, nimodipine has shown potential in the therapy of cerebral vascular spasm following subarachnoid haemorrhage (Auer *et al.*, 1982; Grotenhuis *et al.*, 1984; Kostron *et al.*, 1984) and in the treatment of migrainous headaches (Gelmers, 1983; Meyer & Hardenberg, 1983).

In the present investigation we have addressed

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ourselves to two questions. Firstly, in view of the possible involvement of cephalic arteriovenous anastomoses (AVAs) in the pathophysiology of migraine (Heyck, 1969; Saxena, 1978; 1984), we have studied the effects of local infusions of nimodipine on the fractionation of carotid blood flow into nutrient (capillary) and non-nutrient (AVA) parts in the anaesthetized pig. The second part of this study deals with regional haemodynamics. Though several studies have shown that basal cerebral blood flow may increase in some species (Harper *et al.*, 1981; Kazda *et al.*, 1982; McCalden *et al.*, 1984; Mohamed *et al.*, 1984), only Haws *et al.* (1983), using rabbits, have directly compared the cerebrovascular effects of nimodipine with those on some other tissues. Therefore, the effects of intravenous (i.v.) infusions of nimodipine have been studied on regional tissue blood flows and vascular conductances to determine whether the drug causes a selective vasodilatation in the cerebral vascular bed of another species (pig).

Methods

Three series of experiments were performed. In the first series, intracarotid administration of the drug solvent was used as a control for evaluation of the stability of the preparation. In a second group of animals, the effects of local infusions of nimodipine on the total common carotid artery blood flow and its distribution were determined. Finally, i.v. infusions were used to evaluate the effects of nimodipine on cardiac output and its distribution. A wide range of doses of nimodipine was selected; the difference between the first and last infusion rate was 25 and 125 fold in the intracarotid and i.v. experiments, respectively.

Experimental preparation

After an overnight fast, 25 Yorkshire pigs (mean body weight ± s.e.mean, 25.7 ± 0.8 kg; age 12–16 weeks) were initially sedated with 120 mg (i.m.) azaperone (Stresnil) and 150 mg (i.v.) metomidate (Hypnodil). After the animals had been intubated, they were connected to a respirator for intermittent positive pressure ventilation with oxygen and nitrous oxide (1:2). Respiratory rate and tidal volume were adjusted to keep arterial blood gases, measured with an ABL-3 (Radiometer, Copenhagen), within normal limits (pH, 7.35–7.45; P_{O_2}, 90–150 mmHg, P_{CO_2}, 35–45 mmHg); sodium bicarbonate (8.4%, w/v) was infused, if necessary, until base excess was near zero. An electric blanket was used to maintain the animal's temperature around 37°C. A continuous i.v. infusion of pentobarbitone sodium (15–25 mg kg^{-1} h^{-1}) and an i.v. bolus of 4 mg pancuronium bromide (Pavulon) were used to maintain anaesthesia. Arterial blood pressure (obtained via a 7F catheter placed in the left femoral artery and connected to a Statham pressure transducer) and heart rate (counted from ECG signals) were monitored on a Gould Brush recorder. Catheters in both femoral veins and the other femoral artery were used for i.v. administration of drugs and fluids, and for monitoring arterial blood gases.

In the animals which received intracarotid infusions of nimodipine, both common carotid arteries were dissected free in the neck and bilateral cervical vagosympathectomy was performed to avoid reflex influences on the carotid circulation. Two 0.5 mm (external diameter) needles, connected to suitable polyethylene tubings, were inserted directly into one of the common carotid arteries for the infusion of nimodipine and the injection of microspheres, respectively. Blood flow in this artery was measured with a 2.5 or 3 mm (i.d.) calibrated flow probe connected to a sine wave electromagnetic blood flowmeter (Skalar, Delft). In the animals used to study the effects of i.v. administration of nimodipine on the distribution of cardiac output, a mid-sternal thoracotomy was performed. A cannula was inserted into the left atrial appendage for injection of the microspheres and a catheter in the femoral artery was employed to withdraw a reference blood sample during microsphere injection (Saxena *et al.*, 1980). Ascending aorta blood flow was measured with a suitable electromagnetic flow probe placed around the vessel. Cardiac output was derived by adding myocardial blood flow (measured with radioactive microspheres; see below) to the ascending aorta blood flow.

Distribution of common carotid blood flow and cardiac output

Injection of radioactive microspheres Radioactive microspheres (15 ± 1 [s.d.] μm diameter), labelled with ^{141}Ce, ^{113}Sn, ^{103}Ru, ^{95}Nb or ^{46}Sc (NEN Chemicals GmbH, Dreieich, West Germany) and suspended in saline containing a drop of Tween 80, were used (for details, see Saxena & Verdouw, 1982, 1984). Prior to use, the spheres were deaggregated by mechanical agitation. The distribution of common carotid arterial blood flow was determined by injecting $1-2 \times 10^5$ microspheres into the artery against the direction of blood flow over a period of 15–20 s. The distribution of cardiac output was determined similarly except that $1-2 \times 10^6$ microspheres were injected into the left atrium. Starting about 5 s before the injection of microspheres, blood was withdrawn (rate: 12 ml min^{-1}) from a femoral artery for a total period of 60–65 s.

Counting of radioactivity At the end of each experiment the animal was killed with an overdose of

pentobarbitone sodium and the various tissues, as specified later, were dissected out, weighed and placed in vials. The radioactivity in the vials containing the tissues and blood samples was counted for 5–10 min in a γ-scintillation counter (Packard, model 5986) equipped with a multichannel pulse height analyser (Conrac) using suitable windows for discriminating the different isotopes used (Saxena *et al.*, 1980).

Calculations The microsphere and other data were processed by a PDP-11/70 computer using a set of programmes especially developed for the microsphere technique (Saxena *et al.*, 1980). The amount of carotid blood distributed to the individual tissues ($\dot{Q}_{tis[car]}$) was calculated by: $\dot{Q}_{tis[car]}$ (ml min^{-1}) = (I_{tis}/I_{tot}) × $\dot{Q}_{car}$ and $\dot{Q}_{tis[car]}$ (%) = (I_{tis}/I_{tot}) × 100, where I_{tis} and I_{tot} are, respectively, the radioactivity (c.p.m.) in a particular tissue and that detected in all tissues (i.e. tissues of the head, including the complete brain, and the neck and lungs) collectively, and $\dot{Q}_{car}$ is carotid blood flow (ml min^{-1}) (see Saxena & Verdouw, 1982). The amount of cardiac output distributed to the various tissues ($\dot{Q}_{tis}$) was calculated as: $\dot{Q}_{tis}$ (ml min^{-1}) = (I_{tis}/I_{art}) × $\dot{Q}_{art}$ and $\dot{Q}_{tis}$ (%) = ($\dot{Q}_{tis}/CO$) × 100, where I_{tis} and I_{art} are, respectively, the radioactivity (c.p.m.) in a particular tissue and that of the arterial blood sample, while $\dot{Q}_{art}$ is the rate of withdrawal of blood samples and CO is cardiac output in ml min^{-1}. The various tissues selected were: heart, kidneys, adrenal glands, skeletal muscles from several regions, skin, spleen, liver, small and large intestine, including caecum and rectum (gastrointestinal tract), eyes and a large part of the brain (cerebral hemispheres). Tissue vascular conductance was calculated by dividing respective blood flow values by mean arterial blood pressure.

The values determined for lungs, when microspheres were injected into the carotid artery, represent the AVA part of the carotid circulation (see Johnston & Saxena, 1978; Saxena & Verdouw, 1982). In the case of left atrial injection, the lungs receive microspheres via both peripheral AVAs and bronchial arteries; however, the contribution via the latter route appears to be only about 1% (Baile *et al.*, 1982). Thus, even in this case, the values for 'lung blood flow' can be used as an index of peripheral AVA flow (i.e. the non-nutrient part of cardiac output). The nutrient part of cardiac output was calculated by subtracting 'lung blood flow' from cardiac output.

Experimental protocol

In all experiments, the baseline values were obtained following a stabilization period of 60 min after completion of the surgical procedures. The measurements consisted of recordings of the heart rate, mean arterial blood pressure and common carotid artery blood flow (or cardiac output), while a batch of microspheres was injected into the carotid artery (or into the left atrium). In the common carotid blood flow distribution experiments, three successively increasing intracarotid infusions of nimodipine (0.05, 0.25 and 1.25 μg kg^{-1} min^{-1}) were then administered for 10 min each. Microspheres were injected at the end (10 min) of the 0.05 and 0.25 μg kg^{-1} min^{-1} infusions, and 2 and 10 min after the last infusion step (1.25 μg kg^{-1} min^{-1}). In the cardiac output distribution experiments, successively increasing i.v. doses of 0.05, 0.25, 1.25 and 6.25 μg kg^{-1} min^{-1} of nimodipine were infused for a period of 10 min each; microspheres were injected at the end of each i.v. infusion period. Control experiments were performed with the drug solvent which was injected into the common carotid artery in amounts (0.5, 2.5 and 12.5 μl kg^{-1} min^{-1}) which corresponded to the three intracarotid doses of nimodipine; 10 min after each infusion, microspheres were injected into the carotid artery.

Data presentation and statistical analysis

Except as mentioned otherwise, all data in the text and

Table 1 Effects of intracarotid administration of nimodipine (n = 9) and equivalent amounts of its solvent (n = 6) on mean arterial blood pressure and heart rate in pigs

		% change by nimodipine (μg kg^{-1} min^{-1}) or solvent[a]			
	Baseline values	*0.05*	*0.25*	*1.25 (2 min)*	*1.25 (10 min)*
		Mean arterial pressure (mmHg)			
Solvent	104 ± 7	−2 ± 1	−3 ± 1		−4 ± 1*
Nimodipine	105 ± 4	−14 ± 3*'**	−24 ± 4*'**	−34 ± 4*	−47 ± 5*'**
		Heart rate (beats min^{-1})			
Solvent	100 ± 4	−8 ± 1*	−11 ± 1*		−12 ± 2*
Nimodipine	114 ± 8	−7 ± 2	−17 ± 5*	−18 ± 4*	−23 ± 4*'**

[a]The corresponding doses of solvent were 0.5, 2.5 and 12.5 μl kg^{-1} min^{-1}; *Significantly different from the respective baseline value; **Change significantly more than the respective change caused by the drug solvent.

illustrations are presented as means ± s.e.mean. In general absolute values have been given but in order to facilitate comparison between the effects of nimodipine and its solvent (carotid blood flow distribution experiments), we have presented data in Tables 1 and 2 as % changes from the respective baseline values. These values are means of the % changes in each animal, as are the other % changes included in the text. The significance of the effects of the solvent or nimodipine on the different variables was evaluated by Duncan's new multiple-range test once an analysis of variance (randomized block design) had revealed that the samples represented different populations. The baseline values and the effects of the solvent were compared similarly but, in this case, one-way analysis of variance was used (Saxena, 1985). A P value of 0.05 or less (two-tailed) was considered statistically significant.

Drugs

No drugs other than the anaesthetics and nimodipine (Bay e 9736; Bayer, Wuppertal) were used in this study. The nimodipine solvent used was a mixture of polyethylene glycol 400, glycerol and water. The nimodipine solution (0.1 mg ml^{-1}) and the solvent were diluted with 0.9% w/v NaCl solution immediately before use.

Results

Effects of intracarotid infusions of solvent and nimodipine

Arterial blood pressure and heart rate Baseline mean arterial blood pressure and heart rate did not differ

Table 2 Effects of intracarotid administration of nimodipine (n = 9) and equivalent amount of its solvent (n = 6) on total carotid blood flow and its distribution in pigs

		% change by nimodipine (μg kg^{-1} min^{-1}) or solvent[a]			
	Baseline values	*0.05*	*0.25*	*1.25 (2 min)*	*1.25 (10 min)*
		Blood flow (% carotid flow)			
AVA-fraction					
Solvent	82 ± 1	3 ± 2	2 ± 3		1 ± 3
Nimodipine	82 ± 2	−31 ± 6*'**	−48 ± 5*'**	−63 ± 5*	−65 ± 5*'**
Nutrient-fraction[b]					
Solvent	18 ± 1	−13 ± 9	−11 ± 13		−1 ± 16
Nimodipine	18 ± 2	122 ± 18*'**	232 ± 23*'**	323 ± 32*	268 ± 29*'**
		Blood flow (ml min^{-1})			
Total carotid					
Solvent	166 ± 17	2 ± 1	3 ± 2		2 ± 2
Nimodipine	232 ± 20	4 ± 8	10 ± 7	9 ± 7	−14 ± 7*
AVA-fraction					
Solvent	137 ± 15	6 ± 2	5 ± 3		3 ± 3
Nimodipine	190 ± 18	−31 ± 4*'**	−44 ± 5*'**	−60 ± 6*	−70 ± 4*'**
Nutrient-fraction					
Solvent	29 ± 3	−11 ± 10	−8 ± 13		1 ± 18
Nimodipine	40 ± 5	135 ± 34*'**	264 ± 29*'**	323 ± 32*	208 ± 14*'**
		Conductance (ml min^{-1} mmHg^{-1})			
Total carotid					
Solvent	1.6 ± 0.2	5 ± 1	7 ± 3*		7 ± 3*
Nimodipine	2.2 ± 0.2	21 ± 10	47 ± 10*'**	67 ± 8*	68 ± 16*'**
AVA-fraction					
Solvent	1.3 ± 0.2	8 ± 2*	8 ± 4*		7 ± 3*
Nimodipine	1.8 ± 0.2	−20 ± 4*'**	−27 ± 4*'**	−40 ± 7*	−44 ± 5*'**
Nutrient-fraction					
Solvent	0.28 ± 0.02	−9 ± 10	−5 ± 13		6 ± 20
Nimodipine	0.38 ± 0.04	175 ± 42*'**	385 ± 48*'**	551 ± 53*	512 ± 68*'**

[a]The corresponding doses of solvent were 0.5, 2.5 and 12.5 μl kg^{-1} min^{-1}; [b]Includes both extracerebral and cerebral (2%) components. *Significantly different from the respective baseline value; **Change significantly more than the respective change caused by the drug solvent.

significantly in the animals subsequently treated with the solvent or nimodipine (Table 1). Intracarotid administration of the solvent had little or no effect on mean arterial blood pressure but caused slight decreases in heart rate. Nimodipine produced substantial decreases in arterial blood pressure at all three infusion rates, but heart rate decreased significantly more than that with the equivalent amount of solvent only at the highest rate ($1.25\,\mu g\,kg^{-1}\,min^{-1}$) of infusion (Table 1).

Fractionation of carotid blood flow into non-nutrient and nutrient parts The effects of nimodipine and its solvent on the distribution of carotid blood flow are shown in Table 2. Though the baseline values of total carotid blood flows in the two series differed significantly, none of the other baseline values was significantly different. Infusions of the solvent caused little or no change in either the blood flow to or the conductance in the carotid vascular bed (both in non-nutrient and nutrient parts). On the other hand, there was a marked redistribution of blood flow with nimodipine. AVA blood flow and conductance decreased dose-dependently by up to 70 and 44%, respectively, but these decreases were associated with marked increases in nutrient blood flow and conductance (Table 2). Therefore, total carotid artery blood flow was not affected until 10 min after the infusion of the highest dose when flow had significantly decreased by 14%. Since mean arterial blood pressure had decreased with nimodipine, there were increases in the calculated total carotid conductance, but these were much smaller than the increases observed in the nutrient part.

Tissue distribution of the nutrient part of carotid blood flow Figures 1 and 2 show that the various tissues in the head were not equally affected by nimodipine. The

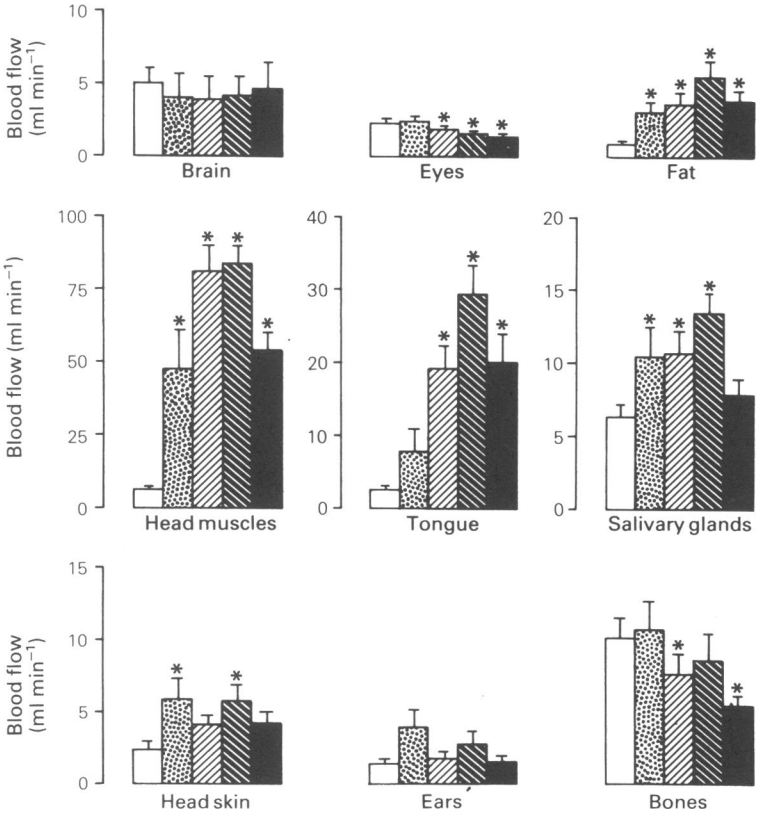

Figure 1 Effects of intracarotid administration of nimodipine on tissue distribution of carotid nutrient blood flow in pigs ($n = 9$). The five columns represent values at baseline (open columns), and after nimodipine ($\mu g\,kg^{-1}\,min^{-1}$) infusions of 0.05 (stippled columns), 0.25 (hatched, dark lines on white background, columns) and 1.25 at 2 min (hatched, white lines on dark background columns) and at 10 min (solid columns). *Significantly different from the respective baseline value.

contribution via the carotid artery to nutrient blood supply of the eyes and bones decreased, but that to the fat, skeletal muscles, tongue, salivary glands and skin increased. The increases in the blood flow to the skeletal muscles (6–14 fold) and tongue (2–12 fold) were particularly marked. No significant change was noticed in the brain and ears (Figure 1).

Vascular conductance increased in all tissues except the eyes and bones (Figure 2). The magnitude of the vasodilator response varied greatly. The largest increase in conductance (20 fold) was observed in skeletal muscles and tongue, followed by fat (9 fold), skin (4 fold) and salivary glands (3 fold). Conductance of the cerebral vascular bed showed the least increase (1.6 fold) and that, too, only after 10 min of the highest infusion rate.

Effects of i.v. infusions of nimodipine

Systemic haemodynamics The effects of nimodipine on systemic haemodynamic variables are shown in Table 3. The drug decreased mean arterial blood pressure and heart rate dose-dependently (by up to 60 ± 4 and $36 \pm 5\%$, respectively). During baseline condition, $55 \pm 2\%$ of cardiac output ($2.91\,min^{-1}$) was used for the nutrition of tissues, while $45 \pm 2\%$ bypassed tissues via AVAs. Nimodipine decreased cardiac output but, except for the highest dose ($38 \pm 7\%$), these effects were relatively minor (<15%). The decrease in cardiac output was entirely in the AVA-part which was reduced by 12 ± 3, 41 ± 5, 70 ± 4 and $87 \pm 3\%$, respectively, by the four infusion rates (0.05, 0.25, 1.25 and $6.25\,\mu g\,kg^{-1}\,min^{-1}$) used. The nutrient part of cardiac output remained unchanged, or even increased (after $1.25\,\mu g\,kg^{-1}\,min^{-1}$ of nimodipine). Systemic vascular conductance increased (up to $65 \pm 13\%$) after the two highest doses of the drug. This increase in the systemic conductance (Table 3) was due to the increase in conductance of the nutrient part of the vascular beds of the various tissues

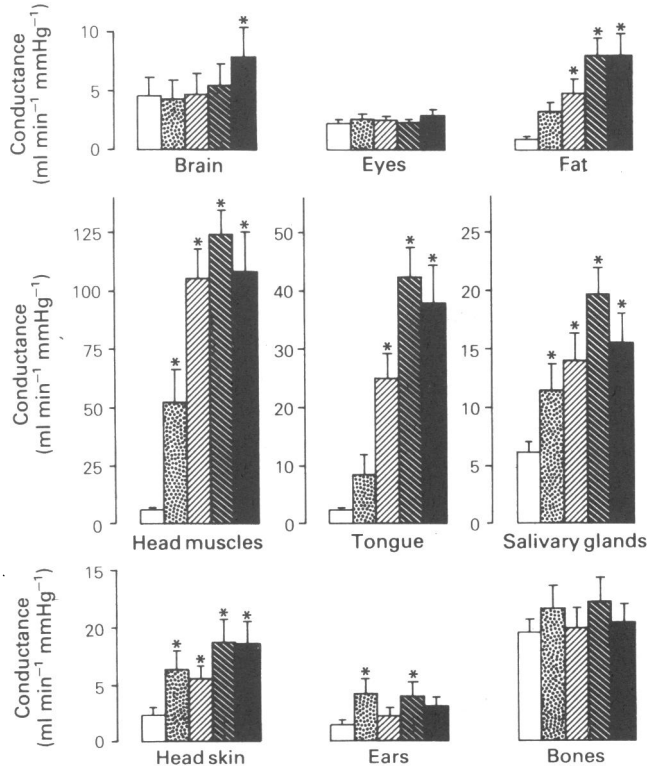

Figure 2 Effects of intracarotid administration of nimodipine on tissue conductance in the nutrient part of carotid vascular bed of pigs ($n = 9$). The five columns represent values at baseline (open columns), and after nimodipine ($\mu g\,kg^{-1}\,min^{-1}$) infusions of 0.05 (stippled columns), 0.25 (hatched, dark on white background, columns) and 1.25 at 2 min (hatched, white lines on dark background, columns) and at 10 min (solid columns). *Significantly different from the respective baseline value.

Table 3 Systemic haemodynamic effects of i.v. administration of nimodipine in pigs (n = 10)

		Nimodipine ($\mu g\,kg^{-1}\,min^{-1}$)			
	Baseline values	0.05	0.25	1.25	6.25
MAP (mmHg)	84 ± 4	78 ± 4	63 ± 4*	45 ± 2*	34 ± 3*
HR (beats min^{-1})	98 ± 3	95 ± 3	92 ± 4	87 ± 5*	63 ± 5*
CO (l min^{-1})	2.9 ± 0.2	2.5 ± 0.1	2.4 ± 0.1*	2.4 ± 0.1*	1.7 ± 0.2*
AVA flow (l min^{-1})	1.3 ± 0.1	1.1 ± 0.1*	0.7 ± 0.1*	0.3 ± 0.04*	0.2 ± 0.04*
NCO (l min^{-1})	1.6 ± 0.1	1.4 ± 0.1	1.7 ± 0.1	2.1 ± 0.1*	1.5 ± 0.2
SVC (ml min^{-1} $mmHg^{-1}$)	35 ± 3	34 ± 3	41 ± 3	54 ± 3*	51 ± 5*
AVAC (ml min^{-1} $mmHg^{-1}$)	16 ± 1	15 ± 2	12 ± 1*	8 ± 1*	5 ± 1*
NVC (ml min^{-1} $mmHg^{-1}$)	19 ± 2	19 ± 2	29 ± 3*	46 ± 3*	46 ± 5*

MAP, mean arterial blood pressure; HR, heart rate; CO, cardiac output; AVA flow, peripheral arteriovenous anastomoses blood flow; NCO, nutrient part of cardiac output. SVC, AVAC and NVC are conductances of, respectively, total systemic, peripheral AVA and nutrient channels.
*Significantly different from the respective baseline value.

(2.4 fold with the highest dose), as the conductance of AVAs decreased dose-dependently to 30% of baseline values.

Tissue blood flow and conductance The changes in nutrient cardiac output were not equally distributed (Figure 3). The perfusion of the skeletal muscles

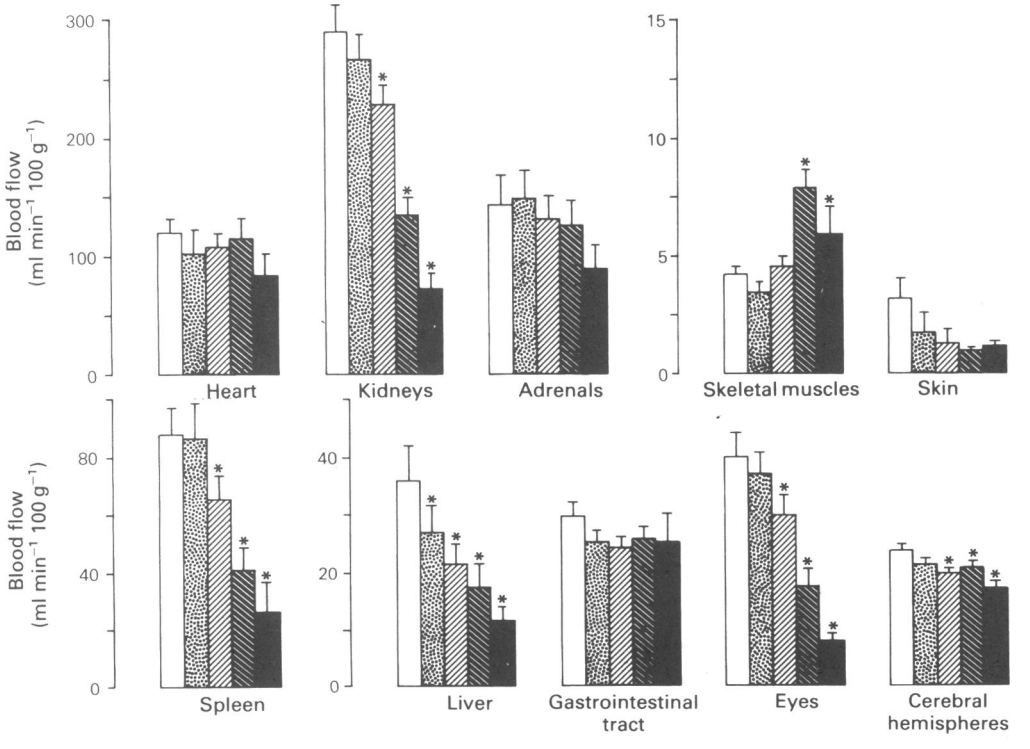

Figure 3 Effects of i.v. administration of nimodipine on tissue distribution of nutrient cardiac output in pigs (n = 10). The five columns represent values at baseline (open columns), and after infusions of 0.05 (stippled columns), 0.25 (hatched, dark lines on white background, columns), 1.25 (hatched, white lines on dark background, columns) and 6.25 (solid columns) $\mu g\,kg^{-1}\,min^{-1}$ of nimodipine. *Significantly different from the respective baseline value.

increased, while that of other organs either did not change (heart, adrenal glands, skin and gastrointestinal tract) or even decreased (kidneys, spleen, liver, eyes and cerebral hemispheres). Consequently, nutrient vascular conductance (Figure 4) of some organs increased (heart, adrenal glands, skeletal muscles, gastrointestinal tract and cerebral hemispheres) and of others either remained unchanged (skin and liver) or decreased (kidneys, spleen and eyes). The most pronounced increase was in the conductance of skeletal muscles (271 ± 57%) which was followed by gastrointestinal tract (124 ± 19%) and cerebral hemispheres (98 ± 16%). On the other hand, conductance of the vascular bed of the eye was reduced by 49 ± 7%, which was followed by the renal vascular bed (41 ± 6%).

Skeletal muscles of different regions As shown in Table 4, the effects of nimodipine varied in the skeletal muscles obtained from different regions. With the highest dose the average increase in vascular conductance was 9 fold in the cheek muscles, 4 fold in the chest muscles, 3 fold in the abdominal muscles and only 2 fold in the trunk and gluteal muscles.

Discussion

Systemic haemodynamics

Both intracarotid and i.v. administration of nimodipine caused a fall in arterial blood pressure. Since even the local intracarotid infusions of the drug substantially lowered blood pressure, it would appear that the drug quickly appeared in the systemic circulation. Whether the cervical vagosympathetic nerves were sectioned (intracarotid infusions) or not (i.v. infusions), the hypotensive effect of nimodipine was

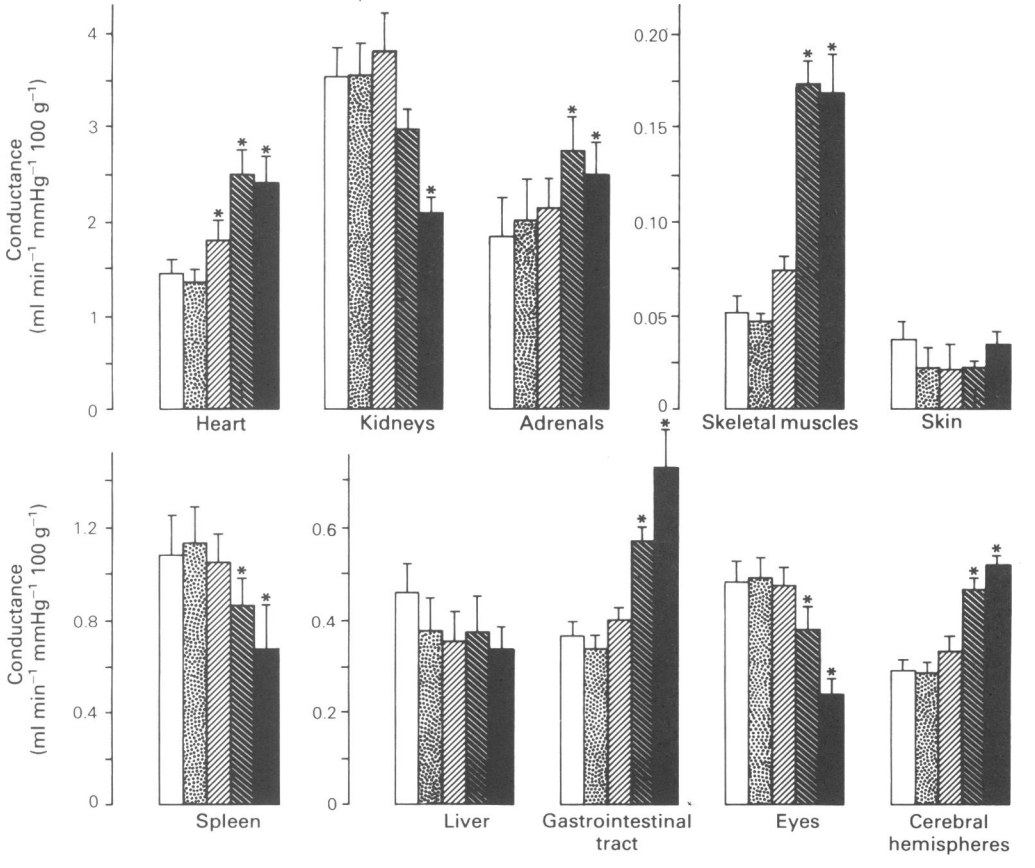

Figure 4 Effects of i.v. administration of nimodipine on nutrient regional vascular conductance in pigs ($n = 10$). The five columns represent values at baseline (open columns), and after infusions of 0.05 (stippled columns), 0.25 (hatched, dark lines on white background, columns), 1.25 (hatched, white lines on dark background, columns) and 6.25 (solid columns) $\mu g\,kg^{-1}\,min^{-1}$ of nimodipine. *Significantly different from the respective baseline value.

Table 4 Effect of i.v. administration of nimodipine on skeletal muscles of different regions of pigs ($n = 10$)

	Baseline values	*Nimodipine* ($\mu g kg^{-1} min^{-1}$) 0.05	0.25	1.25	6.25
		Blood flow ($ml\ min^{-1}\ 100\ g^{-1}$)			
Cheek	3.5 ± 0.6	3.1 ± 0.4	4.5 ± 1.2	14 ± 2*	11 ± 2*
Chest	2.6 ± 0.4	2.1 ± 0.4	2.9 ± 0.5	4.8 ± 0.7*	4.3 ± 1.1*
Abdomen	2.0 ± 0.2	1.7 ± 0.2	1.7 ± 0.3	3.2 ± 0.4*	2.7 ± 0.8
Right trunk	5.5 ± 0.5	4.6 ± 0.9	5.3 ± 1.0	9.0 ± 1.3*	6.6 ± 1.8
Left trunk	5.9 ± 0.8	4.4 ± 0.8	5.4 ± 1.0	8.9 ± 1.9*	6.1 ± 1.8
Right gluteus	4.4 ± 0.5	3.7 ± 0.5	5.0 ± 0.7	6.9 ± 1.2*	5.4 ± 1.6
Left gluteus	5.3 ± 0.4	4.5 ± 0.6	6.7 ± 0.8	9.6 ± 1.3*	6.6 ± 1.4
		Conductance ($ml\ min^{-1}\ mmHg^{-1}\ 100\ g^{-1}$)			
Cheek	0.04 ± 0.01	0.04 ± 0.01	0.07 ± 0.02	0.31 ± 0.05*	0.32 ± 0.04*
Chest	0.03 ± 0.01	0.03 ± 0.01	0.05 ± 0.01	0.11 ± 0.01*	0.12 ± 0.02*
Abdomen	0.02 ± 0.004	0.02 ± 0.004	0.03 ± 0.005	0.07 ± 0.1*	0.07 ± 0.02*
Right trunk	0.07 ± 0.01	0.06 ± 0.01	0.09 ± 0.01	0.19 ± 0.02*	0.19 ± 0.03*
Left trunk	0.07 ± 0.01	0.06 ± 0.01	0.08 ± 0.01	0.19 ± 0.03*	0.17 ± 0.03*
Right gluteus	0.05 ± 0.01	0.05 ± 0.01	0.08 ± 0.01	0.15 ± 0.03*	0.15 ± 0.04*
Left gluteus	0.06 ± 0.01	0.06 ± 0.01	0.11 ± 0.01*	0.21 ± 0.02*	0.19 ± 0.03*

*Significantly different from the respective baseline value.

not accompanied by any evidence of reflex activation of the sympathetic nervous system via the baroreceptors; both heart rate and cardiac output decreased in the present experiments (Tables 1 and 3). The decrease in cardiac output (largely, if not entirely, confined to the non-nutrient part) was moderate and, therefore, the hypotensive effect of nimodipine was mainly due to an increase in systemic vascular conductance.

The lack of reflex effects during nimodipine-induced hypotension in anaesthetized pigs is in contrast to the effects of the structurally related Ca^{2+} channel antagonists nifedipine (Gross *et al.*, 1979) and felodipine (Bolt & Saxena, 1984) in conscious animals, where both heart rate and cardiac output increase prominently. This discrepancy appears to be, at least partly, due to the anaesthetic agents used in the present experiments; in conscious or anaesthetized (fentanyl plus etomidate) patients undergoing cardiac bypass surgery, nimodipine increases cardiac output (Boldt *et al.*, 1985), and therefore causes less hypotension. However, heart rate is not or only slightly elevated by nimodipine, even in conscious rabbits (Haws *et al.*, 1983) or man (Boldt *et al.*, 1985), but is increased by nisoldipine, another related Ca^{2+} channel antagonist, in anaesthetized pigs (Duncker *et al.*, 1986).

Carotid haemodynamics

The results obtained in the present experiments confirm our previous observations that a large (about 80%) fraction of common carotid blood flow in the pig is shunted via AVAs (Saxena & Verdouw, 1982; 1984; Verdouw *et al.*, 1984a,b), which are mainly located in the skin and ears (Saxena & Verdouw, 1985). Local infusions of nimodipine, but not of its solvent, redistributed carotid arterial blood flow in favour of the nutrient (tissue, arteriolar) component at the expense of the non-nutrient (AVA) component. Unlike 5-HT where the increased nutrient flow is mainly distributed to the skin and ears (Saxena and Verdouw, 1982; 1984), nimodipine enhanced primarily that to the skeletal muscles and tongue.

The dilatation of arterioles by nimodipine is apparently due to Ca^{2+} channel blockade, but the mechanism responsible for the decrease in AVA flow and conductance needs further examination. A baroreceptor reflex-mediated stimulation of the sympathetic nervous system seems unlikely for the reasons discussed above and, moreover, in young pigs as used in the present experiments, AVAs are only poorly constricted via noradrenergic mechanisms (Verdouw *et al.*, 1984b). Another possibility may be that nimodipine in some way interferes with the release of an endogenous substance responsible for opening up AVAs in the pig. Though the formation of endothelium-derived relaxing factor (EDRF) in some arterial preparations *in vitro* is Ca^{2+}-dependent (Singer & Peach, 1982; Rubanyi *et al.*, 1985), and can be inhibited by Ca^{2+} channel antagonists (Singer & Peach, 1982), it is not yet known if such an effect of Ca^{2+} channel antagonists is observed *in vivo* or if EDRF can indeed relax AVAs. Thus, it follows that the reduction in AVA flow and conductance most probably results from 'steal' as a consequence of

profound dilatation in the nutrient vascular channels caused by nimodipine. This suggestion is indirectly supported by comparing similar data found with 5-HT, which elicits an 'active' constriction of AVAs. In the face of a 3 fold increase in nutrient vascular conductance, 5-HT reduces AVA conductance by over 80% (Saxena & Verdouw, 1982), whereas in association with an even greater increase (5.5 fold) in nutrient conductance, nimodipine decreased AVA conductance by only about 40% (Table 2). This haemodynamic redistribution as observed with nimodipine may be of physiological significance; the data in this study reinforce the idea that, in situations of increased metabolism and/or vasodilatation, nutrient blood supply to tissues can be readily made available from arteriovenous shunting which apparently represents 'reserve' perfusion.

Arteriovenous shunting has been implicated in the pathophysiology of migraine where profound vasodilatation in these large shunt vessels may lead to a reverse 'steal' (Heyck, 1969; Saxena, 1978; 1984). Indeed anti-migraine drugs, particularly the ergot alkaloids effective in the treatment of individual attacks (Johnston & Saxena, 1978; Schamhardt *et al.*, 1979; Spierings & Saxena, 1980), as well as 5-HT (Saxena & Verdouw, 1982) which may also alleviate migraine attacks (Kimball *et al.*, 1960; Lance, 1982), cause an 'active' constriction of AVAs. Though the overall effect of nimodipine on the distribution of carotid artery blood flow into nutrient and non-nutrient fractions qualitatively resembles that of the above drugs, nimodipine is less efficacious and, as discussed above, has a 'passive' effect on AVAs. Probably because of this passive and moderate effect of AVAs, in contrast to the ergot alkaloids, nimodipine has recently been found to be ineffective in the treatment of individual attacks of classic migraine (Jensen *et al.*, 1985). Whether the acute effects of nimodipine on carotid haemodynamics, as observed in this study, are related to the beneficial properties of the drug reported after long term prophylactic use in migraine (Gelmers, 1983; Meyer & Hardenberg, 1983) remains to be ascertained.

Regional haemodynamics

The regional haemodynamic effects of nimodipine on the nutrient fraction were not uniform. Only skeletal muscle blood flow increased. Since arterial blood pressure decreased, conductance increases (i.e. vasodilatation) were observed (in decreasing order of magnitude) in the skeletal muscles, the gastrointestinal tract, the cerebral hemispheres, the heart and the adrenals. Cerebral vasodilatation has been observed in all studies, but nimodipine, used in doses similar to those in the present experiments, causes variable effects on basal cerebral blood flow. In anaesthetized animals, the drug elicits no (Haws & Heistad, 1984) or a moderate (18–50%) increase in cerebral blood flow (Harper *et al.*, 1981; Kazda *et al.*, 1982; McCalden *et al.*, 1984; Mohamed *et al.*, 1984), probably due to a fall in systemic perfusion pressure. In unanaesthetized rabbits, however, the drug produced a 2 fold increase in cerebral blood flow despite the usual fall in blood pressure (Haws *et al.*, 1983). The other differences with respect to tissue blood flow changes were that Haws *et al.* (1983) observed an increase in the flow to the heart, no change in the flow to the kidneys and only a moderate increase in the flow to the skeletal muscles (masseter). In our experiments, renal blood flow decreased substantially and the increase in blood flow to the skeletal muscles, which showed a regional variation, was very pronounced in the cheek muscles. Skeletal muscle blood flow is also greatly increased by other dihydropyridine Ca^{2+} channel antagonists such as nifedipine, darodipine, felodipine and nisoldipine (Hof, 1983; 1984; 1985; Bolt & Saxena, 1984; Duncker *et al.*, 1986), but not by verapamil or diltiazem (Hof, 1983).

Lastly, though this study did not demonstrate a selective vasodilatation in the brain with nimodipine, it may be that when cerebral (and other) vessels are in spasm or have a higher basal tone (e.g. in animals without anaesthesia, or in clinical situations) nimodipine may show a different spectrum of activity. Hof (1984, 1985) has convincingly shown that the pattern of anti-vasoconstrictor effects of Ca^{2+} channel antagonists (darodipine and verapamil) differs considerably from their pattern of vasodilatation, indicating that the selectivity of action of these drugs, and the influx of extracellular Ca^{2+} (Deth & Van Bremen, 1977; Bolton, 1979), depend not only on the vascular bed but also on the presence of vasoconstrictor influences.

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