

# The effects of nisoldipine (Bay K 5552) on cardiovascular performance and regional blood flow in pentobarbital – anaesthetized pigs with or without $\beta$ -adrenoceptor blockade

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1 The effects of the 1,4-dihydropyridine derivative nisoldipine, infused intravenously (i.v.) at 3 different rates (0.25, 0.5 and  $1.0 \mu\text{g kg}^{-1} \text{min}^{-1}$ ), were studied in anaesthetized pigs on cardiovascular performance with or without  $\beta$ -adrenoceptor blockade produced by propranolol.

2 Nisoldipine caused dose-dependent decreases in arterial blood pressure (30%), systemic vascular resistance (30%) and left ventricular filling pressure (15%), but raised heart rate (25%) and LV  $dP/dt_{\text{max}}$  (20%). Cardiac output was not significantly affected.

3 Transmural myocardial blood flow and vascular conductances increased dose-dependently after nisoldipine. The elevation in blood flow to the left ventricle favoured epicardial layers. Endocardial blood flow showed small increases as the changes in conductance of the endocardial layer more than compensated for the loss in perfusion pressure. The endo-epi blood flow ratio decreased from  $1.16 \pm 0.05$  to  $0.70 \pm 0.01$ . Myocardial  $\text{O}_2$ -consumption was unaltered as the decrease in arterial-coronary venous  $\text{O}_2$ -content difference (30%) was balanced by the increase in transmural blood flow.

4 Nisoldipine increased blood flow to skeletal muscle (500%), stomach (50%) and adrenals (25%), but decreased that to the liver (50%), spleen (25%) and kidneys (25%). No changes were noticed in the small intestine, skin and brain. In spite of differential effects on blood flow, vascular conductance in all organs and tissues, with the exception of the liver, increased.

5 After  $\beta$ -adrenoceptor blockade the responses of mean arterial blood pressure, cardiac output and systemic vascular resistance to nisoldipine remained virtually unchanged, but the elevations in heart rate and LV  $dP/dt_{\text{max}}$  were abolished, as was the decrease in left ventricular filling pressure.

6 A higher dose of nisoldipine was required after  $\beta$ -adrenoceptor blockade to elicit significant vasodilatation in the epi- and endocardial layers. However, the reduction in endo-epi blood flow ratio by nisoldipine was not affected by propranolol. Myocardial  $\text{O}_2$ -consumption tended to decrease as the diminution in the arterial-coronary venous  $\text{O}_2$ -content difference (30%) slightly exceeded the increase of left ventricular blood flow (30%).

7 Except for the brain and liver, effects of nisoldipine on regional vascular conductances were attenuated after  $\beta$ -adrenoceptor blockade.

## Introduction

$\beta$ -Adrenoceptor antagonists and calcium channel blockers are widely used in the treatment of hypertension and ischaemic heart disease. Since these drugs act through different mechanisms, their combined use might be attractive. Some of the 1,4 dihydropyridines (nisoldipine, felodipine), a subgroup of the calcium channel blocking agents, exert a strong vasodilator effect at concentrations that only slightly affect myocardial contractile behaviour.  $\beta$ -Adrenoceptor

antagonists usually lower cardiac output and thereby decrease perfusion of most organs and tissues (van Boom & Saxena, 1983). Since significant lowering of blood pressure can be expected with nisoldipine, combined use of these drugs could be detrimental for some of these organs particularly when their perfusion depends on perfusion pressure. The effects of nisoldipine on the distribution of cardiac output have been studied during rest and exercise by Drexler *et al.* (1985), but regional blood flow data on nisoldipine after  $\beta$ -adrenoceptor blockade have not been docu-

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mented. Furthermore, only limited experimental data are available on the effects of the combination of  $\beta$ -adrenoceptor antagonists and calcium channel blockers (Wolffenbuttel & Verdouw, 1983; Warltier *et al.*, 1984a). We therefore evaluated the cardiovascular effects, in particular the distribution of cardiac output, of varying doses of nisoldipine with and without  $\beta$ -adrenoceptor blockade in the domestic swine.

## Methods

### General

After an overnight fast Yorkshire pigs (20–30 kg) were anaesthetized with 120 mg azaperone i.m. and 150 mg metomidate i.v. (both compounds: Janssen Pharmaceutica, Beerse, Belgium), intubated and ventilated with a mixture of O<sub>2</sub> and N<sub>2</sub>O (1:2). Respiratory rate and tidal volume were adjusted in order to keep arterial blood gases within normal limits. A double lumen 8 French (F) catheter was placed in the superior caval vein for administration of sodium pentobarbitone (20 mg kg<sup>-1</sup> h<sup>-1</sup>), and pancuronium bromide (4 mg), while two 7F catheters were positioned in the inferior caval vein, for infusions of Haemaccel (to replace blood loss), propranolol and nisoldipine. Left ventricular and aortic pressures were obtained with 8F Millar micro-tipped catheters. Ascending aortic blood flow was measured by placing an electromagnetic flow probe around the vessel after thoracotomy. Cardiac output was derived by adding myocardial blood flow (measured with radioactive microspheres; see below) to ascending aorta blood flow. Oxygen (O<sub>2</sub>) saturation and haemoglobin were determined in blood samples withdrawn from the abdominal aorta and the great cardiac vein. Myocardial O<sub>2</sub>-consumption was calculated by multiplying the difference between the aortic O<sub>2</sub> content and that of the great cardiac vein, by myocardial blood flow. A stabilization period of at least 30 min was allowed before baseline data were collected.

### Regional blood flow

Distribution of cardiac output was determined by the radioactive microsphere method (for details, see Saxena & Verdouw, 1985). Microspheres of  $15 \pm 1 \mu\text{m}$  (mean  $\pm$  s.d.) diameter, labelled with 5 different isotopes (<sup>103</sup>Ru; <sup>113</sup>Sn; <sup>46</sup>Sc; <sup>95</sup>Nb and <sup>141</sup>Ce), were injected in random order via a cannula inserted into the left atrial appendage. To calibrate flow measurements, an arterial reference blood sample was withdrawn (10 ml min<sup>-1</sup>) starting 10 s before and continuing until 1 min after completion of each microsphere injection. At the end of each experiment the animal was killed and various organs and tissues

(see later) were dissected out, weighed, and placed in plastic vials for counting radioactivity. Data were processed by use of a set of computer programmes described elsewhere (Saxena *et al.*, 1980).

### Experimental protocol

Fifteen animals received three continuous 10 min infusions of nisoldipine (0.25, 0.5 and 1.0  $\mu\text{g kg}^{-1} \text{ min}^{-1}$ ), seven without and eight after  $\beta$ -adrenoceptor blockade with propranolol (0.5 mg kg<sup>-1</sup>  $\pm$  0.5 mg kg<sup>-1</sup> h<sup>-1</sup>). Microspheres were injected and haemodynamic data obtained at baseline and at the end of each infusion rate. An additional batch of microspheres was injected 15 min after administration of propranolol in the animals that received the  $\beta$ -adrenoceptor antagonist. The adequacy of the dose of propranolol to provide  $\beta$ -adrenoceptor blockade and the stability of the preparation have been described in an earlier communication (Wolffenbuttel & Verdouw, 1983).

### Statistical analysis

Statistical analysis was performed by use of a two-way analysis of variance followed by the Duncan new multiple range test (Steel & Torrie, 1980). *P* values less than 0.05 were considered to be statistically significant.

### Drugs

Apart from the anaesthetics, the only drugs used were propranolol hydrochloride (ICI-Farma, Rotterdam, The Netherlands) and nisoldipine (Bay K 5552, Bayer AG, Wuppertal, West-Germany), dissolved in a mixture of polyethylene glycol 400, glycerol and water. The nisoldipine solution (0.1 mg ml<sup>-1</sup>) was diluted with 0.9% w/v NaCl immediately before use. The effects of the solvent on haemodynamics were negligible (unpublished data from this laboratory).

## Results

Baseline values of the two groups of animals and the effects of propranolol are presented in Tables 1 and 2.

### Systemic haemodynamics

Nisoldipine caused dose-dependent increases in heart rate (up to 25%), while mean arterial blood pressure decreased dose-dependently up to 30% (Figure 1). The decline in blood pressure was mainly due to vasodilatation in peripheral vascular beds since cardiac output was virtually unchanged. Myocardial contractility (assessed as LV  $dP/dt \text{ max}$ ), was not compromised by this calcium channel blocker. Left

**Table 1** Baseline values of cardiovascular parameters for the animals that received nisoldipine without (group 1,  $n = 7$ ) and after  $\beta$ -adrenoceptor blockade (group 2,  $n = 8$ )

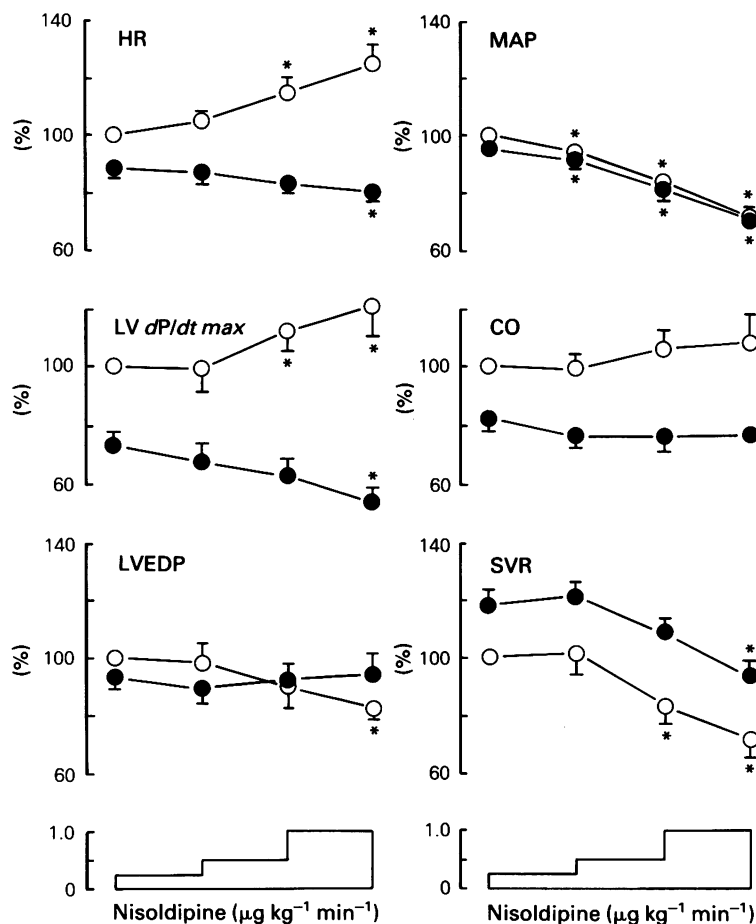
	Group 1	Group 2	
		Before propranolol	After propranolol
<i>Systemic circulation</i>			
Heart rate (beats $\text{min}^{-1}$ )	92 $\pm$ 4	96 $\pm$ 3	84 $\pm$ 3*
Mean arterial blood pressure (mm Hg)	84 $\pm$ 3	81 $\pm$ 2	77 $\pm$ 2
LV $dp/dt$ max (mm Hg $\text{s}^{-1}$ )	2450 $\pm$ 250	2330 $\pm$ 270	1660 $\pm$ 170*
Cardiac output ( $\text{l min}^{-1}$ )	2.8 $\pm$ 0.2	3.1 $\pm$ 0.3	2.6 $\pm$ 0.2*
LV end-diastolic pressure (mm Hg)	10.1 $\pm$ 0.9	12.1 $\pm$ 0.8	11.4 $\pm$ 1.0
Systemic vascular resistance (mm Hg $\text{l}^{-1} \text{min}$ )	31 $\pm$ 4	27 $\pm$ 2	32 $\pm$ 3*
<i>Coronary circulation</i>			
LV transmural blood flow ( $\text{ml min}^{-1} \text{g}^{-1}$ )	1.41 $\pm$ 0.18	1.45 $\pm$ 0.10	1.15 $\pm$ 0.12*
Endo-epi blood flow ratio	1.16 $\pm$ 0.05	1.10 $\pm$ 0.03	1.09 $\pm$ 0.04
Arterial-coronary venous oxygen content difference ( $\text{mmol l}^{-1}$ )	3.4 $\pm$ 0.2	3.7 $\pm$ 0.3	3.4 $\pm$ 0.2
Myocardial $\text{O}_2$ consumption ( $\mu\text{mol min}^{-1} \text{g}^{-1}$ )	4.6 $\pm$ 0.3	5.4 $\pm$ 0.5	3.8 $\pm$ 0.4*

LV  $dp/dt$  max = maximal rate of rise of left ventricular pressure; LV = left ventricular. Endo-epi blood flow ratio = ratio of the endocardial and epicardial blood flows. Data are presented as mean  $\pm$  s.e.mean; \* $P < 0.05$  vs before propranolol.

**Table 2** Baseline values of organ blood flows and vascular conductances for the animals which received nisoldipine without (group 1,  $n = 7$ ) and after  $\beta$ -adrenoceptor blockade (group 2,  $n = 8$ )

	Flow ( $\text{ml min}^{-1} 100 \text{g}^{-1}$ )			Conductance ( $10^{-2} \text{ml min}^{-1} \text{mm Hg}^{-1} 100 \text{g}^{-1}$ )		
	Group 1	Group 2		Group 1	Group 2	
		Before propranolol	After propranolol		Before propranolol	After propranolol
LA	115 $\pm$ 31	123 $\pm$ 9	108 $\pm$ 4	140 $\pm$ 42	153 $\pm$ 12	139 $\pm$ 19
LVT	141 $\pm$ 18	145 $\pm$ 10	115 $\pm$ 12*	172 $\pm$ 28	178 $\pm$ 11	147 $\pm$ 13*
LV-endo	149 $\pm$ 15	150 $\pm$ 11	117 $\pm$ 12*	180 $\pm$ 23	185 $\pm$ 11	150 $\pm$ 13*
LV-epi	132 $\pm$ 20	137 $\pm$ 10	110 $\pm$ 12*	161 $\pm$ 29	168 $\pm$ 11	141 $\pm$ 14
RA	133 $\pm$ 32	155 $\pm$ 22	146 $\pm$ 26	163 $\pm$ 44	191 $\pm$ 26	185 $\pm$ 31
RV	110 $\pm$ 21	120 $\pm$ 11	106 $\pm$ 14	134 $\pm$ 29	148 $\pm$ 13	135 $\pm$ 16
Liver	46 $\pm$ 7	54 $\pm$ 10	43 $\pm$ 10*	56 $\pm$ 9	65 $\pm$ 12	55 $\pm$ 12
Spleen	131 $\pm$ 17	96 $\pm$ 12	73 $\pm$ 9*	131 $\pm$ 17	118 $\pm$ 14	94 $\pm$ 10*
Stomach	15.2 $\pm$ 1.6	21 $\pm$ 3	17.4 $\pm$ 2.5	18 $\pm$ 2	26 $\pm$ 4	23 $\pm$ 3
Small intest.	30 $\pm$ 4	32 $\pm$ 6	27 $\pm$ 4*	36 $\pm$ 5	40 $\pm$ 8	35 $\pm$ 5
Kidneys	277 $\pm$ 47	304 $\pm$ 28	265 $\pm$ 24	339 $\pm$ 66	375 $\pm$ 34	341 $\pm$ 29
Adrenals	214 $\pm$ 39	237 $\pm$ 49	188 $\pm$ 39*	260 $\pm$ 54	293 $\pm$ 60	238 $\pm$ 47
Skel. muscle	4.6 $\pm$ 0.9	4.0 $\pm$ 0.4	3.0 $\pm$ 0.5	5.6 $\pm$ 1.1	4.9 $\pm$ 0.5	3.8 $\pm$ 0.6
Skin	0.65 $\pm$ 0.13	1.10 $\pm$ 0.39	0.68 $\pm$ 0.13	0.82 $\pm$ 0.20	1.41 $\pm$ 0.52	0.88 $\pm$ 0.18
Brain	29 $\pm$ 5	26 $\pm$ 2	24 $\pm$ 2	35 $\pm$ 7	32 $\pm$ 2	30 $\pm$ 2

LA = left atrium; LVT = left ventricular transmural; LV-endo = left ventricular endocardium; LV-epi = left ventricular epicardium; RA = right atrium; RV = right ventricle; small intest. = small intestine; Skel. muscle = skeletal muscle. Data are presented as mean  $\pm$  s.e.mean; \* $P < 0.05$  vs before propranolol.



**Figure 1** Effects of continuous 10 min infusions of nisoldipine without (○) or after (●)  $\beta$ -adrenoceptor blockade with propranolol on heart rate (HR), mean arterial blood pressure (MAP), myocardial contractility (LV  $dP/dt \text{ max}$ ), cardiac output (CO), left ventricular end-diastolic pressure (LVEDP) and systemic vascular resistance (SVR). Data are expressed as percentage of baseline values (pre-propranolol values in the  $\beta$ -blocked animals). \* $P < 0.05$  vs pre-nisoldipine values.

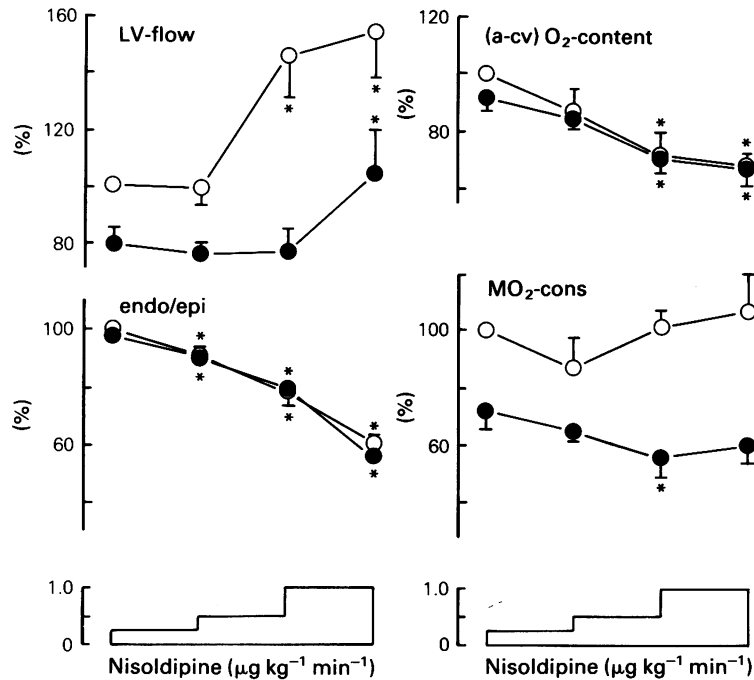
ventricular end-diastolic pressure (LVEDP) declined by 15% after the highest dose.

After propranolol the effects of nisoldipine on systemic haemodynamics were only slightly modified. Instead of an increase, we now observed either no changes (first 2 doses) or slight decreases (highest dose) in heart rate and LV  $dP/dt \text{ max}$  during increasing nisoldipine infusion rates. These decreases, however, were not statistically different from those observed at the same time period in animals that received propranolol only; compare data reported earlier by Wolffenbuttel & Verdouw (1983). Mean arterial blood pressure and cardiac output responses to nisoldipine were similar to those without  $\beta$ -adrenoceptor blockade, while LVEDP did not change.

#### *Coronary haemodynamics and myocardial $O_2$ -consumption*

Nisoldipine caused a considerable elevation of left ventricular blood flow (up to 55% at the end of the highest infusion rate, Figure 2). The microsphere data revealed that the epicardial layers especially benefited from the increase in flow and, as a result, the endo-epi blood flow ratio decreased dose-dependently by up to 40%. The combined effects of the changes in the determinants of myocardial  $O_2$ -demand resulted in unaltered  $O_2$ -consumption as the decrease in arterial-coronary venous  $O_2$ -content difference was balanced by the increase in blood flow.

The nisoldipine-induced increases in blood flow



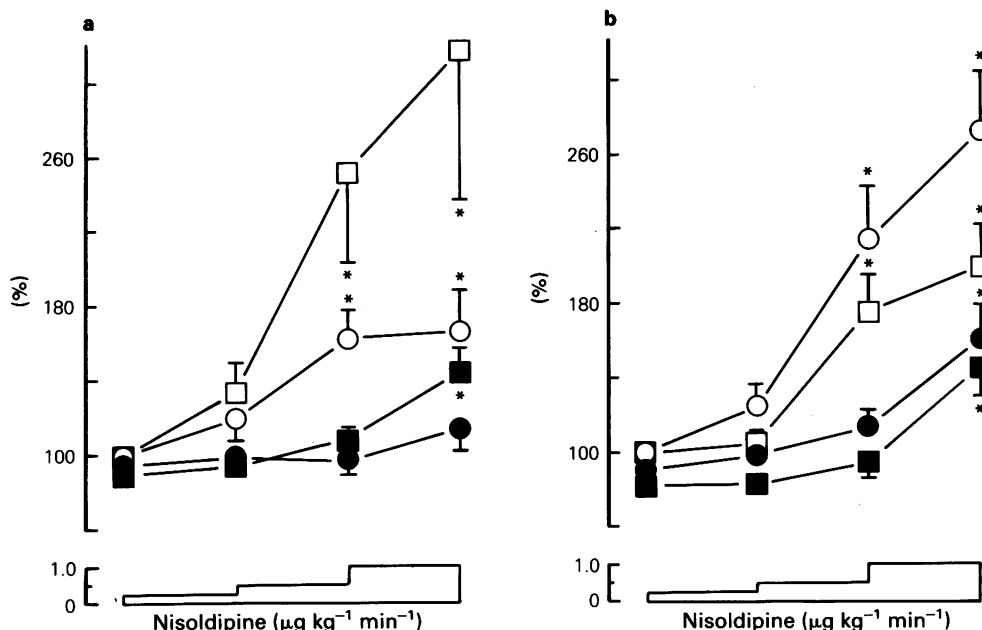
**Figure 2** Effects of continuous 10 min infusions of nisoldipine without (O) or after (●)  $\beta$ -adrenoceptor on left ventricular (LV) blood flow, myocardial O<sub>2</sub>-consumption (MO<sub>2</sub>-cons), the ratio of blood flows in the endo- and epicardium (endo/epi) and the arterial-coronary venous O<sub>2</sub>-content difference ((a-cv) O<sub>2</sub>-content). Data are expressed as percentage of baseline values (pre-propranolol values in the  $\beta$ -blocked animals). \* $P < 0.05$  vs pre-nisoldipine values.

were considerably less after  $\beta$ -adrenoceptor blockade (up to 30% after the highest dose). Inspection of Figure 2 reveals that, after propranolol, a higher infusion rate of nisoldipine was required to enhance transmural myocardial blood flow. Although transmural flow was reduced by propranolol, the latter had no effect on the nisoldipine-induced decrements in endo-epi blood flow ratio. The arterial-coronary venous O<sub>2</sub>-difference again decreased, causing slight accentuation on nisoldipine-induced decreases in myocardial O<sub>2</sub>-consumption. After  $\beta$ -adrenoceptor blockade, nisoldipine caused lesser increments in transmurial conductance (flow/pressure), more so in the right ventricle than in the left ventricle (Figure 3). Right and left atria showed responses similar to those of the ventricles. Although the endo-epi blood flow ratio decreased, endocardial blood flow was maintained under both experimental conditions and was even augmented after the second dose of nisoldipine in untreated animals (Figure 4). Vascular conductances in the endo- and epicardial layers of the left ventricle increased during nisoldipine infusions, but the responses weakened in the  $\beta$ -blocked animals.

#### Cardiac output distribution

Nisoldipine infusions did not exert a uniform effect on the various regional vascular beds (Figure 5). Perfusion of some organs and tissues increased (skeletal muscles, stomach and adrenals), decreased (liver, spleen and kidneys), or was maintained (small intestine, brain and skin). Decreases in flow were, with the exception to the liver, always less than the drop in mean arterial blood pressure. Therefore, vascular conductance in all organs and tissues, except the liver, increased (Figure 6). The greatest vasodilator response was elicited in the skeletal muscles (up to 700% increase), followed by the skin (140% with the highest dose), stomach (120%), adrenals (60%) and brain (50%). The increases in vascular conductance in the spleen and kidneys were significant only at the second dose.

After  $\beta$ -adrenoceptor blockade the changes in conductances were less pronounced at the higher doses of nisoldipine, except for the brain and liver. The vasodilator response remained most marked in the skeletal muscle as conductance still increased by



**Figure 3** Effects of continuous 10 min infusions of nisoldipine without (open symbols) or after (closed symbols)  $\beta$ -adrenoceptor blockade on vascular conductance in the myocardium. In (a) are shown the conductances in the left ( $\square, \blacksquare$ ) and right ( $\circ, \bullet$ ) atrium. In (b) are shown the conductances in the left ( $\square, \blacksquare$ ) and right ( $\circ, \bullet$ ) ventricle. Data are expressed as percentage of baseline values (pre-propranolol values in the  $\beta$ -blocked animals). \* $P < 0.05$  vs pre-nisoldipine values.

600%, followed by the skin (70%), brain (60%) and stomach, small intestine and adrenals (40%). Conductance in the liver again decreased.

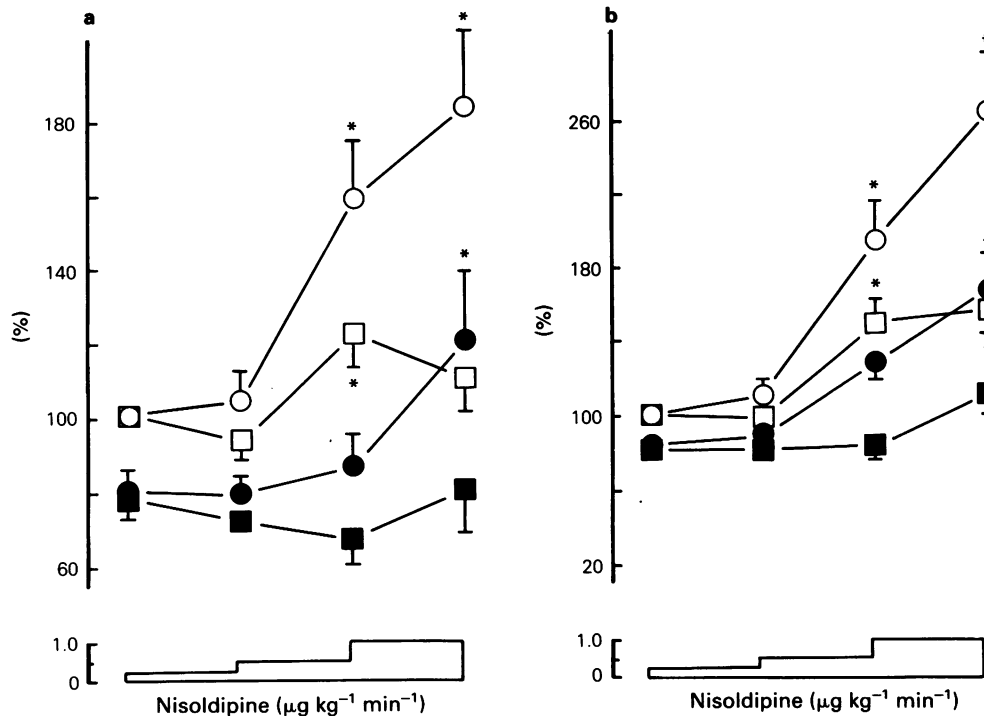
## Discussion

### *Effects of nisoldipine without $\beta$ -adrenoceptor blockade*

As reported by many investigators (Kazda *et al.*, 1980; Vogt *et al.*, 1980; Warltier *et al.*, 1981; Vogt & Kreuzer, 1983; Verdouw *et al.*, 1984; Warltier *et al.*, 1984a,b; Drexler *et al.*, 1985) the major haemodynamic effect of nisoldipine was a reduction of the systemic vascular resistance leading to a decline in mean arterial blood pressure. Presumably due to the baroreceptor reflex, heart rate increased, which is consistent with the findings of some investigators (Kazda *et al.*, 1980; Vogt *et al.*, 1980; Warltier *et al.*, 1984a), but at variance with those of others (Vogt & Kreuzer, 1983; Verdouw *et al.*, 1984). The absence of an increase in heart rate after oral administration of nisoldipine reported by Vogt & Kreuzer (1983) might be the result of the moderate decrease in mean arterial blood pressure reported in that study. Also the already enhanced sympathetic drive might have played a role,

as the patients in their study suffered from chronic congestive heart failure. An explanation for the discrepancy in heart rate responses with an earlier study performed in our laboratory (Verdouw *et al.*, 1984), might be the higher infusion regimen (2 and  $4 \mu\text{g kg}^{-1} \text{min}^{-1}$ ) used in those experiments. Warltier *et al.* (1981) also reported in anaesthetized dogs dissimilar effects on heart rate as a 15% increase was observed after  $1 \mu\text{g kg}^{-1} \text{min}^{-1}$  whereas there was virtually no change after  $3 \mu\text{g kg}^{-1} \text{min}^{-1}$ . Higher doses might lead to a greater direct negative chronotropic effect (Kazda *et al.*, 1980; Hof & Scholtysik, 1983) and a stronger suppression of the baroreceptor reflex (Warltier *et al.*, 1984b). That the experimental conditions are important is illustrated by Warltier *et al.* (1984a) who found an increase in heart rate in conscious dogs after intravenous nisoldipine in doses up to  $25 \mu\text{g kg}^{-1} \text{min}^{-1}$ , while we observed similar changes after oral administration up to  $500 \mu\text{g kg}^{-1}$  in the conscious pig (unpublished data).

Nisoldipine did not affect myocardial  $\text{O}_2$ -consumption, as the elevation of heart rate was balanced by decreases in arterial blood pressure and preload. Rousseau *et al.* (1984) also described no effect on myocardial  $\text{O}_2$ -consumption in angina pectoris patients in spite of a decline in pressure-rate product.



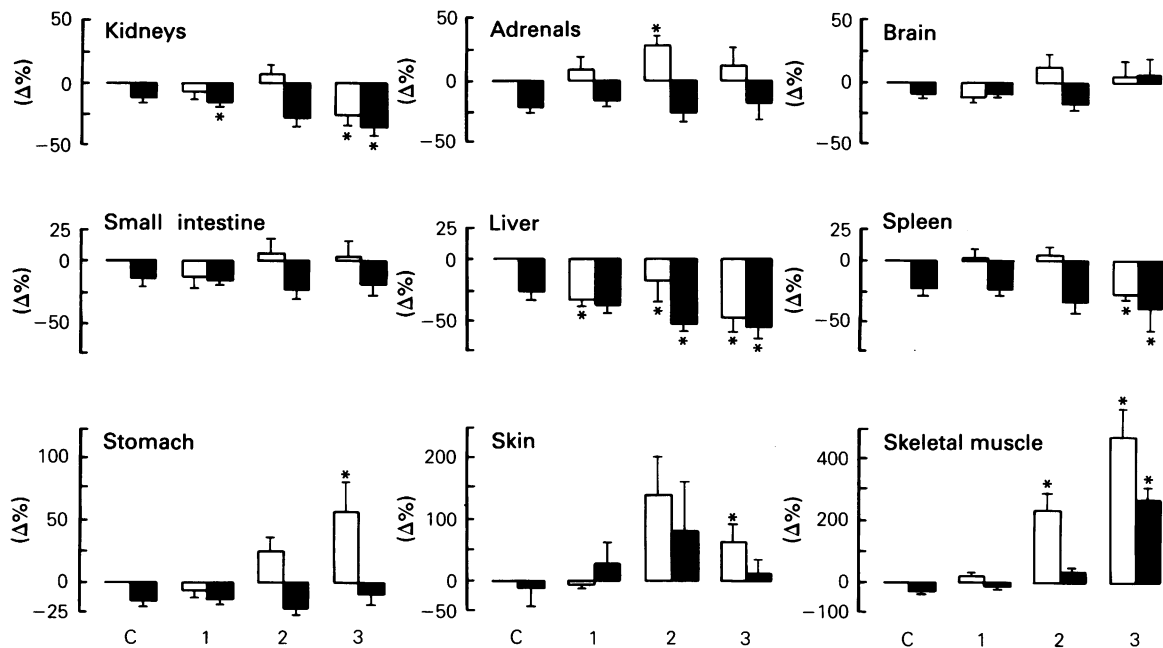
**Figure 4** Effects of continuous 10 min infusions of nisoldipine without (open symbols) or after (closed symbols)  $\beta$ -adrenoceptor blockade on blood flows to (a) and conductances in (b) the left ventricular epicardial (O, ●) and endocardial (□, ■) layers. Data are expressed as percentage of baseline values (pre-propranolol values in the  $\beta$ -blocked animals). \* $P < 0.05$  vs pre-nisoldipine values.

Kazda *et al.* (1980), however, found that nisoldipine lowered myocardial  $O_2$ -consumption in the anaesthetized dog, which might have been due to the decrease in heart rate in their experiments.

Augmented transmural myocardial blood flow, also demonstrated by other investigators (Kazda *et al.*, 1980; Warltier *et al.*, 1981; 1984a; Rousseau *et al.*, 1984) was completely accounted for by the increase in epicardial blood flow. Although the endo-epi blood flow ratio declined during infusions of higher concentrations of nisoldipine, no deleterious effect was exerted on the endocardium as endocardial blood flow was maintained or even enhanced. Warltier *et al.* (1981) also documented similar changes in endo-epi blood flow ratio, after  $1 \mu\text{g kg}^{-1} \text{min}^{-1}$ , while subendocardial perfusion was augmented in spite of tachycardia. Serruys *et al.* (1985) found in man that a 30% decrease in total systemic vascular resistance was accompanied by a 50% decrease in coronary vascular resistance. From these observations they prematurely concluded that nisoldipine is primarily a coronary vasodilator. In our study a dose of  $1 \mu\text{g kg}^{-1} \text{min}^{-1}$  produced a 30% and 50% decrease in systemic and

coronary vascular resistances, respectively. However, the various regions contributed very differently, as vascular conductance in skeletal muscle increased 7 fold, while that in the kidneys, spleen and liver was hardly affected, or even diminished.

The data on organ and tissue perfusion demonstrate that the vasodilator action of nisoldipine is most marked in skeletal muscle, as reported with other dihydropyridines (Hof, 1983; Bolt & Saxena, 1984a). Only in the liver was a vasoconstrictor response observed. Drexler *et al.* (1985) reported in rats a general vasodilatation, although at the dose used ( $1.6 \mu\text{g kg}^{-1} \text{min}^{-1}$ ) this was not always statistically significant. Higher organ and tissue conductances were in most cases sufficient to compensate for the loss of perfusion pressure. Blood flow was therefore maintained in most regions. The kidneys are known to possess an autoregulatory mechanism for maintaining stable blood flow, which is primarily myogenic in nature (Thurau & Kramer, 1959; Hashimoto *et al.*, 1980). Hashimoto *et al.* (1980) also reported the capacity of calcium channel blockers to interfere with this autoregulation. Our data show that only with the



**Figure 5** Effects of continuous 10 min infusions of nisoldipine (0.25; 0.5 and 1.0  $\mu\text{g kg}^{-1} \text{min}^{-1}$ , depicted as 1, 2 and 3 respectively) without ( $\square$ ) or after ( $\blacksquare$ )  $\beta$ -adrenoceptor blockade on tissue blood flows. C denotes control state or, in the  $\beta$ -blocked group, the effect of propranolol. Data are expressed as percentage of baseline values (pre-propranolol values in the  $\beta$ -blocked animals). \* $P < 0.05$  vs pre-nisoldipine values.

second dose was there an increase in conductance, while after the highest dose renal blood flow decreased significantly as conductance remained constant.

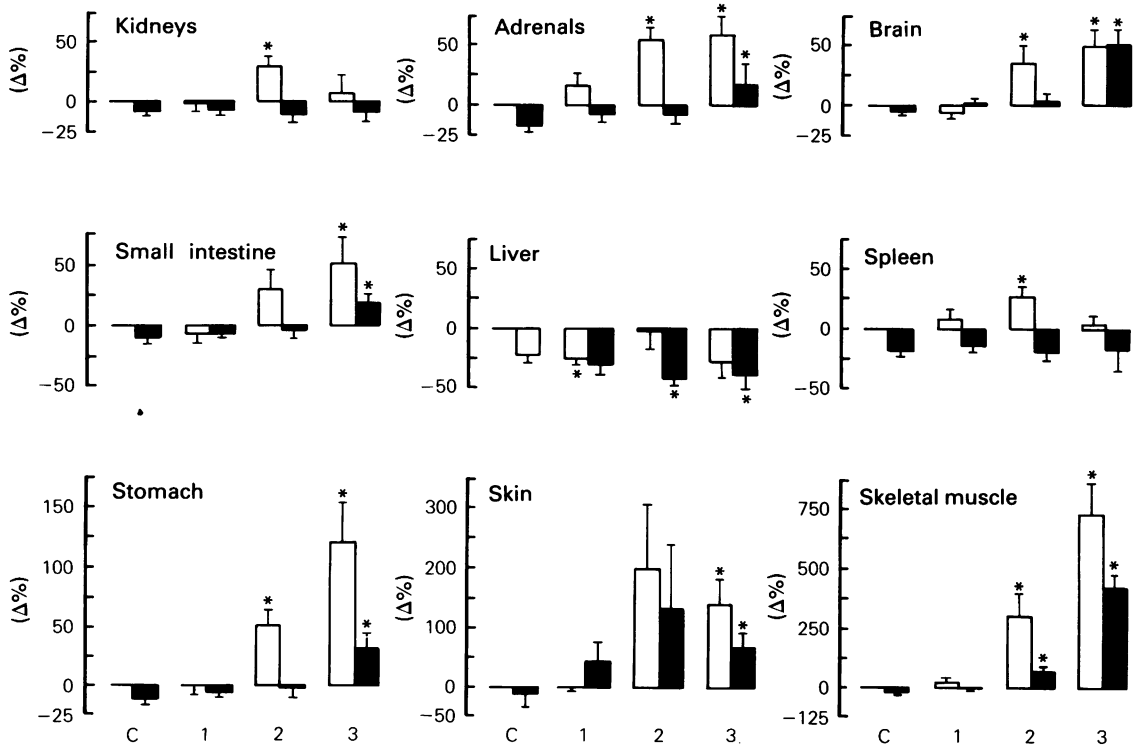
#### *Effects of nisoldipine after $\beta$ -adrenoceptor blockade*

Consistent with the findings of Kazda *et al.* (1980), we observed that pretreatment of the animals with the  $\beta$ -adrenoceptor antagonist propranolol did not attenuate nisoldipine-induced decreases in arterial blood pressure and systemic vascular resistance, but abolished the increments in heart rate and LV  $dP/dt \text{ max}$ . It therefore appears that the latter effects are mediated primarily via a reflex augmentation of the sympathetic nervous system (Gross *et al.*, 1979; Spedding, 1982; Bolt & Saxena, 1984a). However, in certain circumstances, an additional mechanism resistant to  $\beta$ -adrenoceptor blockade, namely a withdrawal of parasympathetic tone, may also be involved (Nakaya *et al.*, 1983; Warltier *et al.*, 1984a).

After propranolol, nisoldipine caused a slight decrease in myocardial  $\text{O}_2$ -consumption and a less marked increase in coronary blood flow. This can partly be explained by a decreased metabolic demand, as shown by Vatner & Hintze (1982). In contrast,

Warltier *et al.* (1984a) found no difference in coronary blood flow responses to nisoldipine under the two experimental conditions but, in their experiments, the tachycardia following nisoldipine was not completely eliminated by  $\beta$ -adrenoceptor blockade. The endo-epi blood flow ratio showed similar responses to nisoldipine irrespective of the presence or absence of propranolol. However, individual vasodilator responses of epi- and endocardium were attenuated by propranolol. Except for the liver and brain, the same was the case in other organs and tissues. It is interesting to recall that  $\beta$ -adrenoceptor blockade interferes with vasodilator responses to another arteriolar vasodilator, hydralazine (Bolt & Saxena, 1984b).

Finally, we would like to compare the effects of nisoldipine in the present series of experiments with those of another dihydropyridine analogue, nifedipine, which was infused directly into the left anterior descending coronary artery (Wolffenbuttel & Verdouw, 1983). As can be expected, intracoronary infusions of nifedipine (up to 0.5  $\mu\text{g kg}^{-1} \text{min}^{-1}$ ) seem to produce a greater cardiodepressant effect (arterial pressure, cardiac output and LV  $dP/dt \text{ max}$  decreased up to 23%, 18% and 35%, respectively), which was either unchanged or attenuated in propranolol-treated animals. In spite of a slight additional cardiodepres-



**Figure 6** Effects of continuous 10 min infusions of nisoldipine (0.25; 0.5 and  $1.0 \mu\text{g kg}^{-1} \text{min}^{-1}$ , depicted as 1, 2 and 3 respectively) without (□) or after (■)  $\beta$ -adrenoceptor blockade on regional vascular conductances. C denotes control state or, in the  $\beta$ -blocked group, the effect of propranolol. Data are expressed as percentage of baseline values (pre-propranolol values in the  $\beta$ -blocked animals). \* $P < 0.05$  vs pre-nisoldipine values.

sant effect of nifedipine in the presence of propranolol, coronary blood flow increases were similar to those when nifedipine was given alone.

### Conclusions

Nisoldipine has been shown to be a potent vasodilator which lowers blood pressure but increases heart rate and coronary blood flow without changing myocardial  $\text{O}_2$  consumption. After propranolol, the reflex mediated cardiostimulatory responses to nisoldipine are eliminated but the cardiac function is not compromised. Therefore, a combination of nisoldipine and  $\beta$ -adrenoceptor antagonists is an attractive possibility when the therapeutic aim is to reduce the work of the heart and maintain cardiac perfusion. However, complications have been reported when calcium channel blockers and  $\beta$ -adrenoceptor antagonists are administered concurrently to patients with impaired cardiovascular performance (Opie & White, 1980; Robson & Vishwanath, 1982; Packer *et al.*, 1982;

Oesterle & Schroeder, 1982). Indeed, our data, although obtained in acute experiments in anaesthetized animals with normal cardiovascular performance, also show that perfusion of some organs (in particular adrenals, kidneys, liver, spleen and stomach) decrease after combined use of the two drugs. Therefore, when cardiovascular performance is already impaired, nisoldipine might better be employed without  $\beta$ -blockade as it improves myocardial  $\text{O}_2$ -balance, while myocardial function is maintained. Also, the reduction of afterload facilitates left ventricular emptying, while organ and tissue perfusion is better preserved than when  $\beta$ -blockade is present.

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