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Nisoldipine and perfusion of post-stenotic myocardium in conscious pigs with different degrees of concentric stenosis

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1 The effects of oral nisoldipine on the perfusion and wall function of a myocardial segment distal to a fixed coronary artery stenosis were studied in 2 groups of conscious pigs with different degrees of stenosis. In group 1 ($n = 8$) systolic wall thickening (SWT) of the post-stenotic segment was more than 15% ($27 \pm 4\%$); in group 2 ($n = 7$) SWT was less than 10% ($7 \pm 1\%$).

2 The systemic haemodynamic profiles at baseline and during nisoldipine were similar in both groups. Dose-titrations of nisoldipine ($0.24 \pm 0.02\,mg\,kg^{-1}$ and $0.47 \pm 0.04\,mg\,kg^{-1}$) were performed to obtain increases in heart rate of 25% and 50%, respectively. These increases were accompanied by increases in cardiac output (up to 50%) and left ventricular (LV)*dP/dt max* (60%), while systemic vascular resistance (35%) and mean arterial blood pressure (10%) were reduced. Left ventricular systolic and end-diastolic blood pressure and stroke volume were not affected.

3 In both groups, nisoldipine caused increases in blood flow to the non-stenotic area which favoured the subepicardium more than the subendocardium. Blood flow to the post-stenotic area of group 1 was normal at baseline and was only slightly enhanced (preferentially to the subepicardium) by nisoldipine. In the post-stenotic area of group 2 transmural and subendocardial blood flow were lower at baseline compared to the control area. Nisoldipine did not affect subepicardial blood flow but reduced subendocardial blood flow.

4 In spite of the reflex-mediated positive chronotropic actions of nisoldipine, the acute post-stenotic systolic wall thickening was not affected by nisoldipine in either group.

5 We conclude that, under the experimental conditions employed (concentric stenosis, no coronary collaterals and acute drug administration), nisoldipine does not have a useful effect on post-stenotic myocardial blood flow, particularly in animals with severe stenosis. In view of a possible resetting of the baroreceptors (subsiding of the tachycardia) with chronic treatment and the presence of eccentric stenosis in many patients, additional studies are warranted.

Introduction

Since the myocardial vasculature possesses a large capacity for autoregulation, a coronary artery stenosis reduces coronary perfusion pressure but not necessarily perfusion (Berne & Rubio, 1979; Feigl, 1983). The autoregulatory capacity is most pronounced in the subepicardial layers of the myocardium as vasodilator reserve in these layers is greater than that in the subendocardium. Consequently, progressive narrowing of a coronary artery affects perfusion and causes ischaemia in the subendocardium earlier than in the subepicardium.

Until recently it was believed that during myocardial ischaemia, coronary vasodilator reserve is completely exhausted as vasodilatation in the post-stenotic segment is maximal (Berne & Rubio, 1979). Pharmacological interventions were therefore primarily aimed at reducing myocardial oxygen demand and at increasing myocardial oxygen supply by elevation of perfusion pressure or prolongation of diastolic perfusion time. Unless vasodilatation at the site of stenosis is possible (eccentric stenosis or

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spasm), vasodilatation is generally regarded as being potentially harmful since it may induce 'coronary steal' from ischaemic to non-ischaemic transmurium (Warltier *et al.*, 1980) or from post-stenotic subendocardium to subepicardium (Weintraub *et al.*, 1981; Gewirtz *et al.*, 1984). However, evidence is now emerging that coronary vasodilatation may not be maximal in ischaemic myocardium. In dogs (Aversano & Becker, 1985; Canty & Klocke, 1985) as well as in pigs (Pantely *et al.*, 1985) with myocardial ischaemia resulting from a fixed stenosis in a coronary artery, intracoronary administration of adenosine can increase myocardial blood flow. Furthermore, during exercise-induced ischaemia in dogs, both α_2-adrenoceptor blockade (Seitelberger *et al.*,, 1986) and nifedipine (Heusch *et al.*, 1987) improve blood flow to and function of the myocardium distal to the stenosis.

In the present investigation we studied the effects of the dihydropyridine calcium channel blocker nisoldipine on regional myocardial blood flow distribution and function of the post-stenotic myocardium in conscious pigs with a fixed chronic coronary artery stenosis. To investigate the possible dependency of these effects upon the severity of the stenosis the animals were divided into two groups, one with slight or almost no and the other with marked attenuation of myocardial wall motion. Nisoldipine was administered orally in doses up to $0.5\,mg\,kg^{-1}$ which corresponds with doses used in the clinical situation (Lam *et al.*, 1985; Lopez *et al.*, 1985). Furthermore, Drexler *et al.* (1986) showed that after oral administration of nisoldipine a more pronounced vasodilatation of the coronary bed is obtained than after intravenous application.

Methods

General

After an overnight fast Yorkshire pigs (18–20 kg), pretreated with a mixture of procaine penicillin-G and benzathine penicillin-G (Duplocillin, Gist-Brocades N.V., Delft, The Netherlands) both 300,000 units i.m., were sedated with $30\,mg\,kg^{-1}$ ketamine HCl i.m. (Aescoket, Aesculaap B.V., Boxtel, The Netherlands). The animals were intubated and connected to a respirator for artificial ventilation with a mixture of oxygen and nitrous oxide (1:2) to which 1% halothane was added. A jugular vein and a common carotid artery were cannulated for infusion of drugs and measurement of mean arterial blood pressure, respectively. The chest was opened via the left fifth intercostal space to expose the heart. A transducer ($P_{4.5}$, Konigsberg Instruments Inc. Pasadena, California, U.S.A.) was implanted into the left ventricle of the heart through its apex for recording of left ventricular blood pressure. The left atrium was cannulated for the injection of radioactive microspheres (see later) and for recording of left atrial pressure which, together with the aortic blood pressure, was used for calibration of the Konigsberg transducer signals. Regional myocardial function was assessed by sonomicrometry (Triton Technology, San Diego, Ca, U.S.A.). One pair of ultrasonic crystals (5 MHz) was implanted in the myocardial area perfused by the left anterior descending coronary artery (LADCA) to measure regional myocardial wall thickness. The wall thicknesses at end-diastole (EDT) and end-systole (EST) were used to calculate systolic wall thickening (SWT) as:

$$SWT(\%) = (EST - EDT)/EDT \times 100\%$$

and the mean velocity of SWT (V_{SWT}) as:

$$V_{SWT} = (EST - EDT)/DS$$

where DS is the duration of systole (isovolumic contraction phase and ejection time). Systolic wall thickening at the time of surgery (open-chest state) was $32 \pm 4\%$.

The aorta was approached through the third intercostal space and an electromagnetic flowprobe (Skalar, Delft, The Netherlands) was positioned around the ascending aorta. The proximal segment of the LADCA was dissected free from its surrounding tissue and a teflon constrictor, with an internal diameter varying from 1.0 to 2.0 mm, was positioned around the LADCA which resulted in different degrees of loss of systolic wall thickening. Catheters and wires were tunnelled subcutaneously to the back. The chest was closed and the animals allowed to recover. During the next two days the animals received intravenous bolus injections of 500 mg amoxicilline per day (Clamoxil, Beecham Farma B.V., Amstelveen, The Netherlands) to prevent infection. Catheters were flushed daily with an isotonic saline solution containing 500 unit heparin ml^{-1} (Thromboliquine, Organon Teknika B.V., Boxtel, The Netherlands) to avoid blood clotting. Before surgery the animals had been adapted to the laboratory and experimental facilities. An additional adaptation procedure was performed on the second day after surgery to confirm haemodynamic stability. This was the case in all but two animals showing ventricular arrhythmias (see results). On the next day the arrhythmias had disappeared and the experimental protocol could be executed. The animals were fasted for 18 h before the experiments. All tracings were written on a Graphtec Linearcorder (F WR 3701, Ankersmit, Breda, The Netherlands). Arterial

acid-base balance and oxygenation during the experiments were within the following limits: $7.37 < pH < 7.49$; $35\,mmHg < P_{CO_2} < 45\,mmHg$; $75\,mmHg < P_{O_2} < 95\,mmHg$. These values are in accordance with previous results (see Tumbleson & Schmidt, 1986).

Regional myocardial blood flow

Carbonized plastic microspheres (15 ± 1 (s.d.) μm in diameter) labelled with ^{141}Ce, ^{113}Sn, ^{103}Rn or ^{95}Nb (NEN Chemicals GmbH, Dreieich, F.R.G.) and suspended in saline containing a drop of Tween 80, were injected in random order into the left atrium over a period of 30 s, while an arterial reference sample was drawn for calibration of the microsphere data.

At the end of each experiment the animals were killed with an overdose of pentobarbitone sodium, the heart excised, the left anterior descending coronary artery (LADCA) cannulated for injection of methylene blue dye to delineate between LADCA and non-LADCA perfused areas, and the heart fixed in 10% formalin for at least 48 h. The left ventricle was then divided into LADCA and non-LADCA perfused areas. To avoid mixing the two areas, border zone tissue was not sampled. Both areas were separated into three layers of equal thickness from endocardium to epicardium. Details of the radioactive microsphere method and of the calculation of flow data have been described previously (Saxena *et al.*, 1980; Verdouw *et al.*, 1985).

Experimental protocols

The experiments were performed in 18 instrumented pigs. In 12 of these animals stability of systemic haemodynamic variables and regional myocardial wall function was evaluated over a 150 min period. The effects of orally administered nisoldipine on systemic haemodynamics, myocardial blood flows and regional left ventricular wall function of the LADCA perfused segment were studied in 15 pigs. The two doses of nisoldipine (0.24 ± 0.02 and 0.47 ± 0.04 mg kg^{-1}) were selected in each animal before surgery and were such that they elicited peak increases in heart rate (30–60 min after drug administration) of approximately 30 and 60 beats min^{-1}, respectively. Measurements consisting of systemic haemodynamics and regional myocardial wall function were made and a batch of microspheres injected at baseline and at peak heart rate effects of the first dose of nisoldipine. In all but the first three animals systemic haemodynamic measurements were repeated at 30 min, 60 min and 120 min after peak-effect. Twenty four hours later, when it is known that previously-administered nisoldipine is no longer detectable in the plasma (see Duncker *et al.*, 1987) the same protocol was performed, but the higher dose of the drug was used.

Data presentation and statistical analysis

Animals were categorized into two groups defined by the systolic wall thickening of the post-stenotic segment at the time of the experiment; each group was analysed separately. Group 1 consisted of animals with a systolic wall thickening of 15% or more; group 2 consisted of animals with a systolic wall thickening of 10% or less. No animals with a systolic wall thickening between 10% and 15% were present.

All data have been presented as mean $\pm$ s.e. mean. Statistical analysis was performed by use of Duncan's New Multiple range-test once a parametric two-way analysis of variance (randomized block design) had revealed that the samples represented different populations.

Drugs

Except for the anaesthetics during surgery and the antibiotics during the post-surgical period the only drug used in this study was nisoldipine (Bayer A.G., Wuppertal, F.R.G.).

Results

Arrhythmias during the post-surgical period

Two animals died the night following surgery. Because *post mortem* examination was negative ventricular fibrillation might have been the cause of death. In two other animals ventricular arrhythmias (>5 premature ventricular contractions min^{-1}) were observed during the first adaptation session after surgery, but not on the following days. Arrhythmias were not observed in any of the other animals, either during adaptation, or during the course of the experiments.

Stability of systemic haemodynamics and regional myocardial wall function

Data relating to the haemodynamics obtained during the 150 min in which the animals received no treatment have been presented in Figure 1. In both group 1 and group 2 none of the parameters changed significantly from its baseline value during

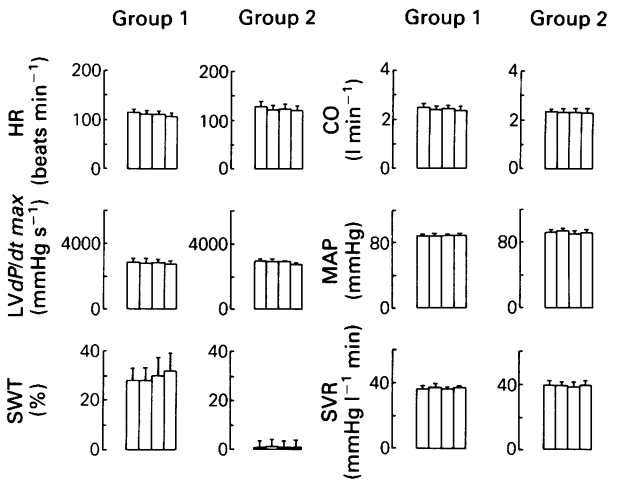

Figure 1 Systemic haemodynamics of untreated animals of group 1 (SWT > 15%; $n = 6$) and group 2 (SWT < 10%; $n = 6$). The four columns represent: baseline; 30 min, 90 min and 150 min after baseline, respectively. HR = heart rate; CO = cardiac output; LV*dP/dt max* = maximal rate of rise of left ventricular blood pressure; MAP = mean arterial blood pressure; SWT = systolic wall thickening; SVR = systemic vascular resistance. Data have been presented as mean with vertical lines indicating s.e. mean.

the course of the experiment. Moreover, there were no differences between the systemic haemodynamic parameters of the two groups despite the difference in regional systolic wall function.

Nisoldipine-induced responses

Systemic haemodynamics The nisoldipine-induced increases in heart rate were accompanied by responses that were very similar in both groups (Figure 2). Calculated systemic vascular resistance decreased dose-dependently (up to $36 \pm 4\%$ and $37 \pm 4\%$ after the highest dose in group 1 and 2, respectively), as mean arterial blood pressure was reduced from 98 ± 5 to 88 ± 5 mmHg and from 95 ± 4 to 83 ± 5 mmHg after the highest dose and cardiac output increased considerably ($43 \pm 5\%$ and $46 \pm 7\%$). The increase in cardiac output resulted primarily from a dose-dependent increase in heart rate (up to $53 \pm 6\%$ and $50 \pm 7\%$, in group 1 and 2, respectively) as stroke volume was unchanged from its baseline value (21 ± 1 ml and 19 ± 2 ml). Left ventricular systolic (124 ± 8 mmHg and 122 ± 2 mmHg) and end-diastolic (12.1 ± 1.0 mmHg and 12.8 ± 1.9 mmHg) blood pressure were also unchanged from their respective baseline values. Finally LV*dP/dt max* increased dose-dependently up to $67 \pm 8\%$ and $53 \pm 7\%$ in group 1 and 2, respectively. The doses needed to elicit these responses were similar for group 1 (0.22 ± 0.03 mg kg^{-1} and 0.44 ± 0.05 mg kg^{-1}, p.o.) and group 2 (0.25 ± 0.02 mg kg^{-1} and 0.51 ± 0.05 mg kg^{-1}, p.o.).

Regional myocardial blood flows Baseline myocardial blood flow values and the nisoldipine-induced responses in the control area of both groups were similar (Figure 3). Myocardial blood flow to the control areas was dose-dependently enhanced in both groups (up to $76 \pm 18\%$ and $64 \pm 12\%$ after the highest dose in group 1 and 2, respectively). The increase in transmural blood flow favoured the subepicardial ($96 \pm 22\%$ and $88 \pm 13\%$, respectively) over the subendocardial ($70 \pm 21\%$ and $40 \pm 13\%$) layers.

In the post-stenotic area of group 1 baseline blood flow values were very similar to those in the control segment, but the nisoldipine-induced responses were markedly different. Nisoldipine caused only slight increases in transmural (25%) and subepicardial (40%) blood flows. However, subendocardial flow remained unchanged (Figure 3). In the post-stenotic segment of group 2 transmural and subendocardial blood flows at baseline were significantly lower compared with flows of the control area. Nisoldipine did not affect transmural and subepicardial blood flow but reduced subendocardial blood flow by 30% with the highest dose.

Regional myocardial wall function The effects of nisoldipine on regional wall function are shown in Figure 4. In neither of the two groups did nisoldipine affect myocardial wall thickness at end-diastole and at end-systole (baseline values: 10.0 ± 0.8 mm and 12.8 ± 0.9 mm in group 1; 10.6 ± 1.1 mm and 11.3 ± 1.2 mm in group 2). Systolic wall thickening

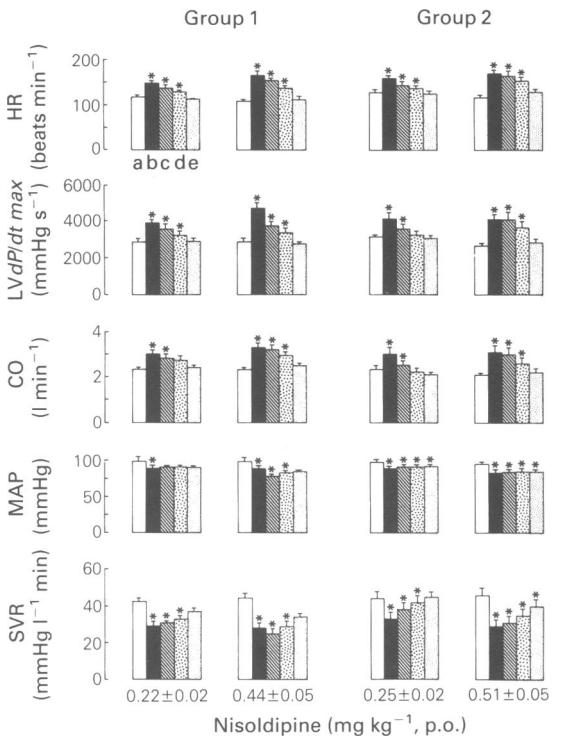

Figure 2 Effects of nisoldipine on systemic haemodynamics in group 1 (SWT > 15%; $n = 8$) and in group 2 (SWT < 10%; $n = 7$). The five columns represent: baseline (a), peak-response to nisoldipine (b) and 30 min (c), 60 min (d) and 120 min (e) after peak-response, respectively. HR = heart rate; LV$dP/dt\,max$ = maximal rate of rise of left ventricular blood pressure; MAP = mean arterial blood pressure; CO = cardiac output; SVR = systemic vascular resistance. Data have been presented as mean with vertical lines indicating s.e. mean. $^{*}P < 0.05$ vs baseline.

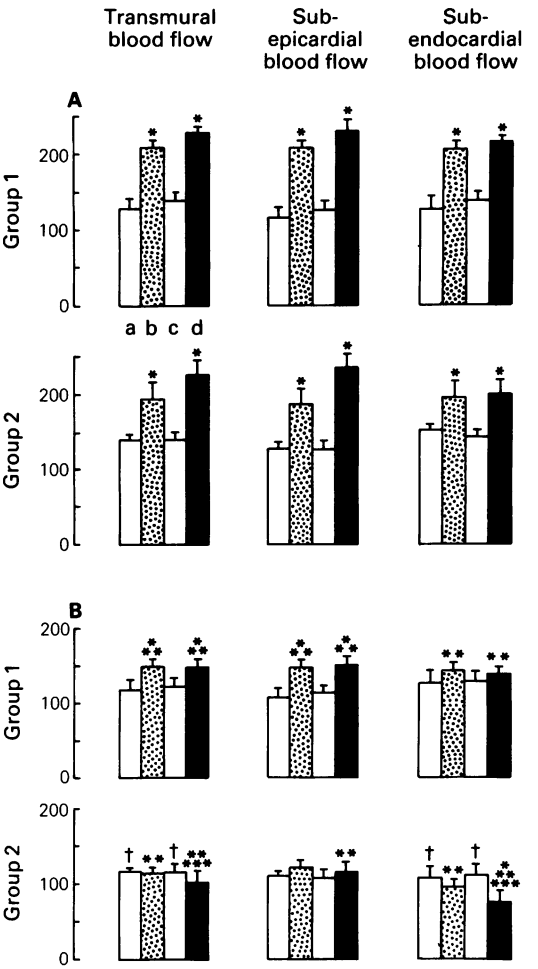

Figure 3 Regional myocardial blood flow (ml min^{-1} 100 g^{-1}) responses to nisoldipine of the control (A) and post-stenotic (B) areas of group 1 (SWT > 15%; $n = 8$) and group 2 (SWT < 10%; $n = 7$). The four columns represent: control (a), peak-response to nisoldipine (0.22 ± 0.03 mg kg^{-1} and 0.25 ± 0.02 mg kg^{-1} p.o. in group 1 and 2, respectively; b), control (c) and peak-response to nisoldipine (0.44 ± 0.05 mg kg^{-1} and 0.51 ± 0.05 mg kg^{-1} p.o. in group 1 and 2, respectively; d). Data have been presented as mean with vertical lines indicating s.e. mean. $^{*}P < 0.05$ vs baseline; ** nisoldipine-induced response significantly different ($P < 0.05$) from that in the corresponding control area; *** nisoldipine-induced response in group 2 significantly ($P < 0.05$) different from that in group 1. $^{\dagger}P < 0.05$ vs corresponding control area.

($27 \pm 4\%$ for group 1 and $7 \pm 1\%$ for group 2 during baseline) was also not affected by the drug in either group. Velocity of wall thickening was enhanced in group 1 but unaffected in group 2.

Discussion

In this investigation nisoldipine was administered orally at two doses which were titrated in each animal on the basis of peak heart rate responses of 30 and 60 beats min^{-1}, respectively. The tachycardiac effect of the lower dose (25% of baseline value) corresponds well with heart rate changes observed in the clinical situation (Silke *et al.*, 1985; Serruys *et al.*, 1985). Moreover, the peak tachycardiac response to nisoldipine correlate with drug concentrations in the plasma (Duncker *et al.*, 1987).

As demonstrated by many investigators (see Verdouw *et al.*, 1988) we also observed that nisoldi-

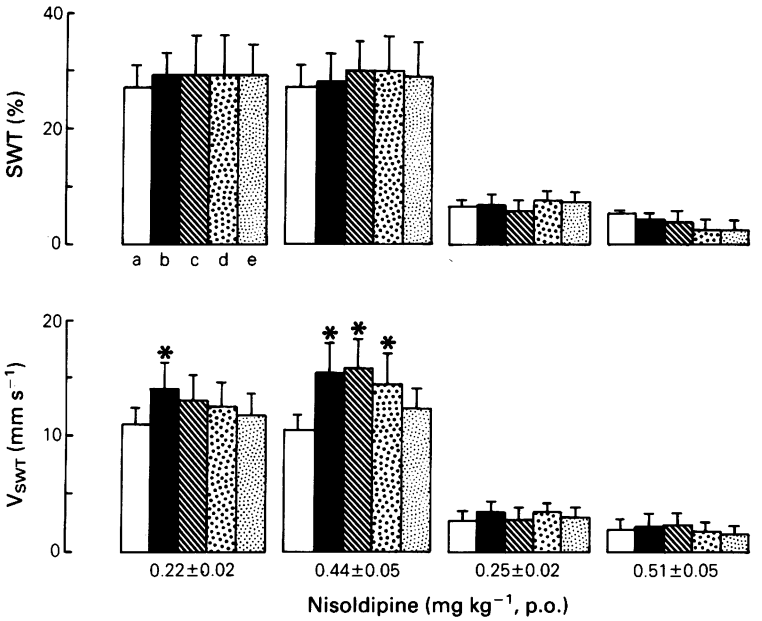

Figure 4 Regional left ventricular myocardial wall function responses to nisoldipine of pigs in group 1 (SWT > 15%; $n = 8$) and group 2 (SWT < 10%; $n = 7$). The five columns represent: baseline (a), peak response to nisoldipine (b) and 30 min (c), 60 min (d) and 120 min (e) after peak-response, respectively. SWT = normalized systolic wall thickening; V_{SWT} = mean velocity of wall thickening. Data have been presented as mean with vertical lines indicating s.e. mean. $^*P < 0.05$ vs baseline.

pine induced a pronounced systemic vasodilatation, which resulted in only a moderate reduction in mean arterial blood pressure as cardiac output was markedly elevated. The increase in cardiac output was the result of a reflex-mediated increase in heart rate as stroke volume was maintained. Due to the baroreceptor-reflex LV*dP/dt max* was also enhanced. Left ventricular end-diastolic blood pressure was unchanged, which is in accordance with earlier findings (see Verdouw *et al.*, 1988). Nisoldipine, like other dihydropyridine calcium antagonists, does not have an effect on pre-load unless elevated end-diastolic pressures are present (Verdouw *et al.*, 1984; Kimchi *et al.*, 1985). In both groups the cardiovascular profile of nisoldipine was not different from that observed in conscious pigs with a normal coronary circulation (Duncker *et al.*, 1987), which implies that the myocardial ischaemia in the present study was not severe enough to produce chronic reduction in global left ventricular pump function. Nisoldipine potently enhanced myocardial blood flow to the normally perfused areas which is in agreement with data obtained in animals with a normal coronary circulation (for references see Verdouw *et al.*, 1988) or in the control area of ischaemic canine hearts (Warltier *et al.*, 1981). The increase in blood flow favoured the subepicardial layers, a finding observed with many vasodilators (Verdouw *et al.*, 1986; 1987a, b), and this most likely resulted from the moderate hypotension and the reflex-mediated tachycardia (see Feigl, 1983).

In group 1 the stenosis did not affect basal blood flow which correlates well with the almost normal systolic wall thickening of the post-stenotic area. In group 2, however, the stenosis severely reduced systolic wall thickening, while basal transmural and subendocardial, but not subepicardial, blood flow were decreased. These findings are supported by Gallagher *et al.* (1985) who demonstrated a severe impairment of systolic wall thickening in the presence of a coronary stenosis, despite a normal subepicardial blood flow and function.

In the post-stenotic segment of group 1 in which the stenosis caused almost no or slight loss of wall function, nisoldipine caused a moderate increase in transmural blood flow which was solely confined to the subepicardial layers. In the post-stenotic myocardial area of the animals in which the stenosis caused marked loss of wall function (group 2), nisoldipine failed to cause an increase in blood flow to

the subepicardial layers whereas subendocardial blood flow was decreased. This decrease probably resulted from the hypotension and increase in heart rate. Although subepicardial blood flow was not affected by the drug, vasodilatation must have occurred as mean aortic blood pressure and hence perfusion pressure was decreased.

Our findings lend further support to the concept that during myocardial ischaemia due to a fixed concentric coronary artery stenosis, vasodilators, via dilatation in the subepicardial layers, can reduce post-stenotic coronary perfusion pressure and thereby perfusion of the subendocardial layers in which the vasculature is already maximally dilated and therefore perfusion-pressure dependent (Weintraub *et al.*, 1981; Gross & Warltier, 1981; Gewirtz *et al.*, 1984). However, recent data have shown that vasodilator reserve may be present in ischaemic myocardium distal to a severe coronary artery stenosis and that vasodilators may improve myocardial blood flow and myocardial function (Heusch & Deussen, 1984; Aversano & Becker, 1985, Seitelberger *et al.*, 1986; Heusch *et al.*, 1987). The different observations in those studies and in the present one might be the result of (i) different routes of administration, (ii) absence or presence of collateral circulation and (iii) different duration of ischaemia. In most studies intracoronary administration of drugs was used to minimize systemic effects (Heusch & Deussen, 1984; Aversano & Becker, 1985; Canty & Klocke, 1985; Pantely *et al.*, 1985; Seitelberger *et al.*, 1986). We, on the other hand, used oral administration as in the clinical situation. Systemic administration of a vasodilator results in hypotension which together with a reflex-tachycardia reduces autoregulatory capacity of the myocardial vasculature especially in the subendocardial layers (see Feigl, 1983). Only in the study of Heusch *et al.* (1987) was intravenous administration of nifedipine employed. However, during exercise-induced ischaemia, systemic haemodynamics of the untreated and the nifedipine-treated group did not differ. Furthermore, systemic administration of nifedipine might have enhanced blood flow through collateral vessels, which may be abundantly present in canine hearts. For example, Warltier *et al.* (1981) observed an increase in flow to a totally collateral-dependent area in acutely ischaemic dog hearts after intravenous administration of nisoldipine. Since pigs possess very few collaterals, and it is unlikely that after induction of ischaemia extensive collateral formation takes place within 5 days (Ramo *et al.*, 1970), such a beneficial effect of nisoldipine was not to be expected in our study. Finally, in all previous studies measurements were made up to a maximum of 3 h after induction of ischaemia, whereas in our study ischaemia was present for more than 2 days when the protocol was executed. To our knowledge, no information is available on the extent of vasodilator reserve during prolonged (more than 3 h) ischaemia. Therefore, it might be that in our animals vasodilator reserve was no longer present at the time of the experiment.

The nisoldipine-induced responses of myocardial blood flow were not accompanied by a worsening of wall function in group 1 and, surprisingly, also not in group 2. An explanation for this observation is not readily found. Nisoldipine might have decreased oxygen demand of the post-stenotic area, although the increase in heart rate suggests an increase in oxygen demand rather than a reduction. Another possibility arises from the investigation of Berdeaux *et al.* (1984) who observed an increase in wall function of severely ischaemic myocardium after a low dose of prenalterol, a β-adrenoceptor agonist, causing an increase in heart rate of 15 beats min^{-1}, while after a high dose of prenalterol an increase in heart rate of 40 beats min^{-1} was accompanied by an unchanged wall function. This suggests that the reflex-mediated increase in sympathetic activity can cause an increase in wall function even in severely ischaemic myocardium, provided that the increase in heart rate is minimal. In our experiments it is possible that these reflex-mediated chronotropic and inotropic actions of nisoldipine balance one another with respect to their effects on wall function.

In conclusion, the findings in the present study, although obtained in normotensive animals with a normal cardiac pump function, suggest that in patients with myocardial ischaemia caused by a concentric coronary artery stenosis and with few collaterals, vasodilators may not be beneficial. Therefore, it is important to stratify patients according to the status of their coronary circulation, i.e. presence or absence of collaterals and severity and type of stenosis. Because of its potent systemic vasodilator properties, the drug will most likely also be used in patients with hypertension. In view of this and the probable resetting of the baroceptors, long-term studies in models with hypertension and myocardial ischaemia appear to be worth while.

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