Br. J. Pharmac. (1983), **78**, 375–394

Calcium antagonist and the peripheral circulation: differences and similarities between PY 108-068, nicardipine, verapamil and diltiazem

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1 The effects of two dihydropyridines, PY 108-068 (PY) and nicardipine (N), and two other calcium antagonists, verapamil (V) and diltiazem (D), on regional blood flow were measured in open-chest cats, anaesthetized with chloralose-urethane.

2 Each substance was infused at 3 different dose rates, each for 10 min. The total doses given were 5 plus 10 plus 35 (total of 50) μg/kg for PY, 10 plus 20 plus 70 (total of 100) μg/kg for N and 100 plus 200 plus 700 (total of 1000) μg/kg for V and D.

3 All substances lowered blood pressure and increased total peripheral conductance. Heart rate was lowered only by V, D and PY. Cardiac output was markedly increased only by the diyhydroypridine derivatives; D had small and V almost no effects.

4 All substances increased coronary flow and redistributed it in favour of the subepicardial layer. All substances also increased blood flow to the brain. The effects of verapamil were comparatively small.

5 Skeletal muscle flow was increased strongly by the two dihydropyridine derivatives. D and V had negligible effects.

6 Blood flow to stomach and small intestine was only slightly increased. Flow to the kidneys increased slightly in diltiazem-treated animals but did not change with all other treatments. Flow to the liver, the adrenals, and the spleen remained unchanged or showed a tendency to decrease.

7 The organ conductances which reflect the active changes in vascular tone better than blood flow values, showed that there was a tendency towards vasodilatation even in most organs where blood flow tended to decrease.

8 Results obtained in an earlier series of experiments with nifedipine were very similar to those described here for N, except that nifedipine was about twice as potent.

9 Calcium antagonists were thus neither general peripheral vasodilators nor did they show a uniform pattern of preferential sites of action. The most important common features were increases in coronary and cerebral blood flow and the most important differences the divergent effects of the dihydropyridines on one side and V and D on the other side on skeletal muscle flow. The size of this vascular bed may help to explain why dihydropyridines appear to be particularly potent as peripheral vasodilators.

Introduction

Many calcium antagonists such as verapamil and nifedipine were originally described as coronary vasodilators (Haas & Haertfelder, 1962, Bossert & Vater, 1971). The heart has remained the focus of attention, even though it is now well known that these drugs have effects on other parts of the circulation (Gross, Kirchheim & von Olshausen, 1979; Ono & Hashimoto, 1979; Henry, 1980; Hof, Hof & Neumann, 1982). Vasodilator effects were found to occur in several organs in animal experiments, most of which were performed with flow probes placed around blood vessels of individual vascular beds. The microsphere method allows regional blood flow to many vascular beds to be measured at the same time (Heymann, Payne, Hoffman & Rudolph, 1977). We have recently described the effects of the new dihydropyridine derivative PY 108-068 (PY) and of nifedipine on many regional vascular beds in anaes-

0007-1188/83/020375-20 $01.00

thetized cats (Hof *et al.*, 1982). We have now extended these investigations to nicardipine (N), a further representative of the dihydropyridines, and two compounds of entirely different chemical structure, namely verapamil and diltiazem. Because of the relatively short duration of action of the latter two compounds the new studies were performed by infusing the substances rather than by administering bolus injections as in the earlier series. PY was included in the new series to facilitate the comparison of the results obtained following the two different protocols.

The results indicate that different calcium antagonists have distinct patterns of peripheral haemodynamic effects.

Methods

Experimental animals

Mongrel cats of 2.5–3.5 kg body weight were anaesthetized with a mixture of chloralose (43 mg/kg) and urethane (430 mg/kg), injected intramuscularly into the muscles of the shoulder (the muscles of the hindlegs were used for blood flow measurements). The cats were tracheotomized and ventilated with a Loosco Mk 2 infant ventilator operated with compressed room air. The rate of the ventilator was set according to the animal's own rate. A positive end-expiratory pressure of 2–4 mmHg was applied as soon as the thorax was opened and the volume was adjusted so that the end-expiratory CO_2, monitored with a Gould Godart MK 2 capnograph, remained between 4.2 and 4.7 volume percent. The blood gases, measured on an IL 213 blood gas analyzer, showed that this ventilation resulted in a good oxygenation of the blood ($P_{O_2} > 100$ mm Hg) and a slight respiratory alkalosis (pH: 7.35 to 7.45, P_{CO_2}: 20 to 25 mm Hg). With this slight hyperventilation we obtained good respiratory and ventilatory stability throughout the course of the experiments without muscle relaxants. Polyethylene catheters were inserted into a femoral artery and vein for measuring aortic blood pressure and administering drugs, and into the right jugular vein for measuring right atrial pressure. The pericardium was opened through a thoracotomy in the fourth left intercostal space. A thin polyethylene catheter (PE 90) was inserted through a small incision into the left atrium for microsphere injection. The ascending aorta was then carefully dissected free of its adventitia and a tightly fitting electromagnetic flow probe (Narco) with a diameter between 5 and 6.5 mm was placed around it. A Narco RT 500 electromagnetic flowmeter system was used to determine aortic flow. The first derivative of the flow signal, dQ/dt, i.e. acceleration of blood in the aorta, was obtained with an HSE 401 differentiator. Peak acceleration (PA), mean blood pressure (BP), heart rate (HR), derived from the phasic blood pressure signal, right atrial pressure (RAP), phasic and mean aortic flow and acceleration of blood in the aorta were recorded on a Beckman R 612 8-channel recorder. Cardiac output (CO) was calculated from the aortic flow. The electromagnetic flow probe was calibrated *in vivo* by the reference flow method at the time of the last microsphere injection, as described below. Total peripheral conductance (TPC) was calculated by dividing cardiac output by mean arterial pressure, neglecting the small right atrial pressure (always equal to or smaller than 3 mmHg, as shown in the table with the baseline values). CO and TPC are expressed per kg of body weight throughout.

Microspheres

The microsphere method as used in this laboratory has recently been described in considerable detail (Hof, Wyler & Stalder, 1980; Hof, Hof, Salzmann & Wyler, 1981). In short, about 1.5×10^5 15 μm spheres (3M Company), suspended in 10% dextran and labelled with ^{125}I, ^{141}Ce, ^{51}Cr, ^{85}Sr or ^{46}Sc having a specific activity between 0.5 and 5 ct/min per sphere, were filled into mixing chambers. Care was taken, that the isotopes with higher energy photopeaks always had lower specific activities than isotopes wih photopeaks in the lower energy range. The chambers were shaken vigorously in an ultrasonic bath for 5 min and the microspheres were then injected into the left atrium with 1 ml of 0.9% w/v NaCl solution (saline). The catheter was quickly flushed with a further 1 ml of saline. This procedure had no effect on blood pressure, heart rate or aortic flow. In order to eliminate systematic errors due to small differences between different batches of microspheres, the sequence of isotopes was changed for each cat within each group. Each batch of spheres was used once for each measuring time with the exception of one batch which was used twice (6 cats and 5 different isotopes for each cat). The exact number of microspheres injected was determined by counting the radioactivity in the chambers before and after the injection and correcting these counts for variations due to counter geometry and counting efficiency. To calibrate the electromagnetic flow probe we drew a reference sample from the femoral artery at a flow rate of approximately 5 ml/min, using a Harvard apparatus withdrawal pump. The exact rate was determined from the weight of the blood withdrawn, and the number of microspheres was carefully adjusted to yield an accuracy of the order of $\pm 5\%$ or better (Hof & Hof, 1981a). At the end of the experiment, the organs to be counted were weighed

and placed in plastic vials. Samples of skeletal muscle were obtained from the hindlegs. All other organs mentioned were counted *in toto*. The heart was dissected to obtain samples of the free wall of the left ventricle. The apex (about 5 mm) was removed and the base was cut away just beneath the insertion of the mitral valve, the septum was removed and the remaining free wall was cut into strips of about 4 mm width which were then divided into 3 layers, a subendocardial (Endo), a middle (Mid) and a subepicardial (Epi) layer. The papillary muscles were cut away before slicing and counted with the subendocardial layer. The counting equipment consists of a Packard gamma counter (Mod. 5921) with a 3 × 2.5 inch NaI cristal and a Mod. 9012 pulse height analyzer (1024 channels, 25 MHz digitizing rate). The spectra were

Table 1 Baseline values for all groups of cats

	Control		*PY 108-068*		*Nicardipine*	
Systemic variables	*Mean*	*s.e.mean*	*Mean*	*s.e.mean*	*Mean*	*s.e.mean*
HR	209.5	12.1	217.5	8.6	207.5	6.8
BP	117.2	6.4	121.1	5.6	120.6	7.9
RAP	1.9	0.5	2.8	0.6	3.0	0.6
C0/kg	124.5	8.9	126.0	11.5	116.6	7.5
TPC/kg	1.1	0.08	1.0	0.09	1.0	0.10
Peak acc	585.8	70.1	511.6	22.7	663.3	63.9
	Flow (ml min^{-1} per 100 g of tissue)					
Organ	*Mean*	*s.e.mean*	*Mean*	*s.e.mean*	*Mean*	*s.e.mean*
Heart total	142.1	25.2	151.9	6.0	165.2	16.8
Epi	203.8	46.1	198.5	12.6	214.8	37.6
Mid	205.5	35.5	214.0	11.6	244.8	38.6
Endo	217.4	57.4	206.3	11.0	250.2	37.4
Brain total	32.0	2.9	30.4	2.2	32.1	3.1
Cortex	31.2	2.7	28.8	2.0	31.9	3.3
Cerebellum	34.0	2.9	34.9	3.1	32.5	3.6
Brainstem	33.3	3.3	32.8	3.1	32.5	3.0
Lungs	204.4	37.2	78.9	23.5	108.2	28.0
Kidneys	287.1	39.9	321.0	33.4	327.5	28.9
Skin	4.1	0.5	3.2	0.9	4.5	0.8
Leg muscle	3.1	0.6	3.8	0.6	2.8	0.9
Spleen	184.4	40.6	248.8	62.3	209.5	31.0
Liver	82.4	7.3	83.2	1.3	92.2	16.2
Adrenals	339.0	21.7	613.1	55.2	537.7	61.9
Small intestine	41.8	7.8	49.4	4.9	36.2	5.2
Stomach	27.8	9.2	23.2	4.8	17.7	2.1
	Conductance (ml min^{-1} $mmHg^{-1}$ per 100 g of tissue)					
Organ	*Mean*	*s.e.mean*	*Mean*	*s.e.mean*	*Mean*	*s.e.mean*
Heart total	1.23	0.23	1.27	0.10	1.37	0.10
Epi	1.80	0.48	1.66	0.17	1.75	0.13
Mid	1.79	0.38	1.80	0.18	1.97	0.19
Endo	1.82	0.41	1.73	0.17	2.02	0.23
Brain total	0.28	0.03	0.26	0.03	0.27	0.03
Cortex	0.27	0.03	0.25	0.03	0.26	0.03
Cerebellum	0.30	0.04	0.30	0.04	0.27	0.04
Brainstem	0.29	0.04	0.28	0.04	0.27	0.03
Lungs	1.73	0.31	0.68	0.17	0.93	0.27
Kidneys	2.47	0.34	2.68	0.33	2.75	0.28
Skin	0.04	0.01	0.03	0.01	0.03	0.01
Leg muscle	0.03	0.01	0.03	0.01	0.02	0.01
Spleen	1.61	0.40	1.99	0.50	1.78	0.31
Liver	0.73	0.10	0.70	0.04	0.78	0.14
Adrenals	2.91	0.20	5.12	0.58	4.65	0.72
Small intestine	0.35	0.06	0.41	0.03	0.31	0.06
Stomach	0.23	0.08	0.19	0.04	0.14	0.02

Table 1 Baseline values of all groups of cats – *continued*

	Diltiazem		*Verapamil*	
Systemic variables	*Mean*	*s.e.mean*	*Mean*	*s.e.mean*
HR	219.0	12.2	220.1	10.7
BP	122.8	8.2	129.5	5.9
RAP	2.7	0.4	2.2	0.7
CO/kg	129.3	6.8	115.5	6.9
TPC/kg	1.1	0.11	0.9	0.07
Peak acc	623.3	67.8	568.3	43.3
	Flow (ml min^{-1} per 100 g of tissue)			
Organ	*Mean*	*s.e.mean*	*Mean*	*s.e.mean*
Heart total	155.5	15.7	164.2	18.3
Epi	207.3	27.4	226.5	39.7
Mid	213.3	22.6	210.0	28.8
Endo	212.1	23.3	220.7	26.9
Brain total	33.1	2.4	32.4	2.5
Cortex	31.6	2.4	32.0	2.8
Cerebellum	35.0	3.2	35.0	2.1
Brainstem	34.9	2.9	31.5	2.6
Lungs	110.5	29.0	49.7	10.7
Kidneys	287.1	27.7	353.2	32.9
Skin	4.1	0.9	3.7	0.8
Leg muscle	6.8	2.1	4.6	1.2
Spleen	224.8	49.6	220.0	60.9
Liver	105.4	10.6	71.5	15.3
Adrenals	518.5	98.7	606.0	109.0
Small intestine	40.4	5.7	48.0	6.4
Stomach	21.0	3.9	20.7	3.8
	Conductance (ml min^{-1} $mmHg^{-1}$ per 100 g of tissue)			
Organ	*Mean*	*s.e.mean*	*Mean*	*s.e.mean*
Heart total	1.30	0.13	1.28	0.15
Epi	1.70	0.18	1.79	0.35
Mid	1.77	0.12	1.64	0.23
Endo	1.75	0.17	1.72	0.21
Brain total	0.28	0.03	0.26	0.02
Cortex	0.26	0.03	0.25	0.03
Cerebellum	0.29	0.04	0.28	0.03
Brainstem	0.29	0.02	0.25	0.03
Lungs	0.88	0.21	0.38	0.08
Kidneys	2.42	0.35	2.76	0.32
Skin	0.03	0.01	0.03	0.01
Leg muscle	0.06	0.02	0.04	0.01
Spleen	1.88	0.42	1.71	0.48
Liver	0.90	0.14	0.58	0.13
Adrenals	4.51	1.14	4.77	0.89
Small intestine	0.35	0.07	0.37	0.04
Stomach	0.18	0.03	0.16	0.02

Abbreviations and units: HR: heart rate (beats/min); BP: blood pressure, (mmHg); RAP: right atrial pressure (mmHg); CO/kg: cardiac output per kg of body weight (ml min^{-1} kg^{-1}); TPC/kg: total peripheral conductance per kg of body weight (ml min^{-1} $mmHg^{-1}$ kg^{-1}).
Peak acc: peak acceleration of blood in the aorta (ml s^{-2}); Epi, Mid, Endo: subepicardial, middle and subendocardial layer of the left ventricular free wall of the heart. $n = 6$ for all experiments.

recorded on a Kennedy 1610/360R tape recorder and processed on a Hewlett Packard 21 MX minicomputer. Our system of resolving complex spectra follows the method of Rudolph & Heymann (1967) with modifications of the calculations described by Schaper, Lewi, Flameng & Gijpen (1973).

Experimental protocol and statistics

Before starting the experiments the cats were allowed to recover from the preparation for at least one hour. During this time all drug solutions were prepared fresh. The calcium antagonists were dissolved in a mixture of ethanol and polyethyleneglycol 400 (0.5 or 1 ml per mg of active substance). This solution was then diluted with saline. Doses of the active substances or an equivalent amount of vehicle were infused intravenously in three periods of 10 min. The amounts administered during each period were: 5, 10, 35 (total 50) μg/kg of PY; 10, 20, 70 (total 100) μg/kg of N; and 100, 200, 700 (total 1000) μg of V and D. In the figures the cumulative doses are indicated. It should be kept in mind, however, that the duration of action of the compounds was different. The amount of vehicle was the same for all experiments, so that only one control group was needed. Changes in BP, HR, CO, PA and RAP were measured and TPC was calculated just before each microsphere injection, that is at the end of each 10 min infusion period and at the end of the experiment 30 min later (i.e. 60 min after the start of the first infusion). Six cats were used for each group of experiments.

The effects of placebo or of the active substances were calculated as changes from baseline. These changes due to the different treatments were compared by the Kruskal-Wallis test. When it was significant ($P < 0.05$), the Mann-Whitney test was used to test between which of the groups the differences occurred. Since we performed up to 4 comparisons with the same control group, a $P < 0.01$ was chosen as significance level. In order to facilitate visual comparison the results (mean and s.e.mean) were converted into percent changes from baseline for the figures and mean values and standard errors of the mean (s.e.mean) are shown.

Results

Changes occurring in the control group

Table 1 contains the baseline values for systemic haemodynamic variables, blood flow and conductance of all experimental animals. The statistical comparison of the groups belonging to the individual treatments showed that for most variables there were

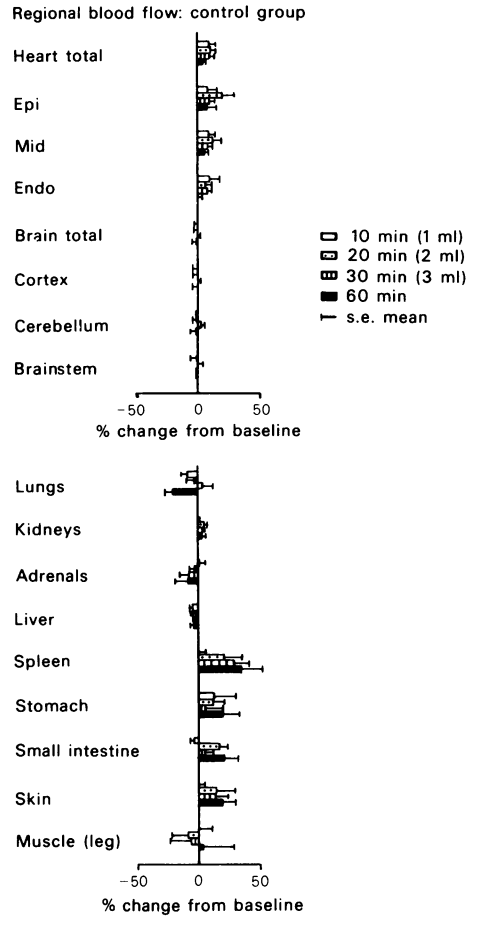

Figure 1 Changes in regional blood flow in the control group. The vehicle used to dissolve the active drugs containing alcohol and polyethyleneglycol 400 was infused during three 10 min periods to a total volume of 3 ml. Measurements were obtained at the end of each infusion period and 30 min after the end of the infusions. Changes in drug-treated animals were compared statistically with these spontaneous changes, $n = 6$ for all measurements.

no significant differences. Exceptions were the blood flow and conductance values of the adrenals (significant difference between the PY and N group in the Mann-Whitney test), and the lungs (significant difference between the PY and V group). In the latter case it should be remembered, that microsphere accumulation in the lungs represents bronchial flow plus a contribution, estimated at 90% or more from microspheres crossing through arterio-venous shunts in this cat model (Hof, Wyler & Stalder, 1980).

Spontaneous changes occurring during the experiment in the control group were generally small. Figure 1 shows the changes in regional blood flow in the

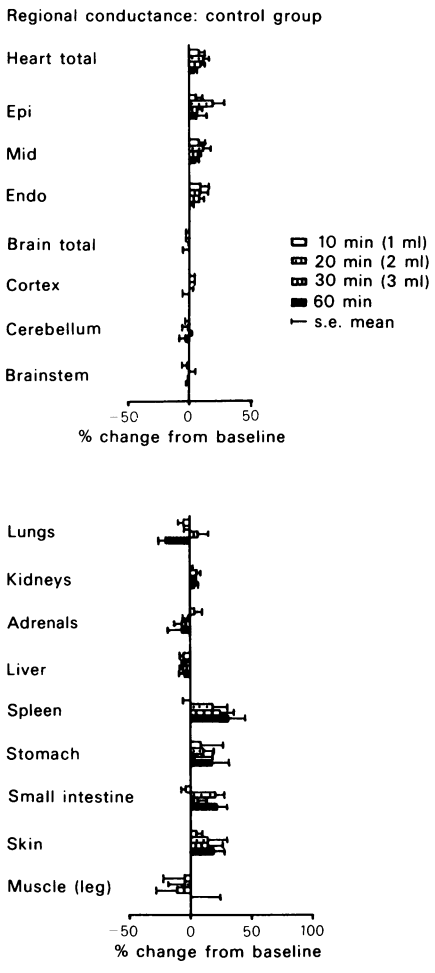

Figure 2 The changes in regional conductance paralleled the changes in blood flow since blood pressure remained almost unchanged during the experiments. Same experiments as in Figure 1.

control animals. Small increases in blood flow to the heart, spleen, stomach, small intestine and skin were observed, other organs showing no consistent changes. Since arterial pressure remained constant, changes in conductance (Figure 2) closely reflected the changes in flow. Changes in other haemodynamic variables were also small as can be seen from the control curves (open circles) in Figures 3–6.

Systemic haemodynamic effects of the calcium antagonists

Figures 3–6 show the results obtained during the infusion of PY, N, V and D, as well as the values obtained at the end of the experiment. PY (Figure 3) and N (Figure 4) effected very similar changes on all haemodynamic variables with the exception of heart rate, where N caused a minimal tachycardia (not significantly different from the controls) whereas PY caused a significant and dose-related bradycardia. The comparison of the HR effects of PY and N showed a significant difference at 10 min. The effects of PY on CO and PA were well maintained 30 min after the end of the infusion. RAP had returned to baseline and the other effects to about half of their peak changes. The duration of action of N appeared to be somewhat shorter and similar for all variables.

The effects of V (Figure 5) and D (Figure 6) were different from those of the two dihydropyridines. V decreased HR and increased RAP whereas most other effects were comparatively modest or absent. The open stars in Figure 5 indicate that V lowered heart rate significantly more, decreased BP less and increased CO, TPC and PA less than PY. The effects of D were intermediate between those of V and the dihydropyridines since it increased CO and PA slightly.

Changes in regional blood flow

PY and N, the two dihydropyridines, elicited similar changes in regional blood flow and conductance so that they will be presented together. Both PY and N strongly increased blood flow to heart (Figures 7 and 8, top) and the effects were most prominent in the subepicardial layer (Epi) of the left ventricular free wall. The effects on the subendocardial layer, however, were different. PY increased flow dose-dependently in both parts of the heart, whereas no appreciable dose-dependence was found with N so that flow increased less than expected after the two higher doses.

The effects on cerebral blood flow were very similar with both compounds. Interestingly, with both compounds as well as with V and D the blood flow increased most strongly in the brainstem. PY in contrast to the other substances maintained its effects on blood flow to the brain fully to the end of the experiment.

The lower part of the two figures shows the effects of PY and N on blood flow to many other organs. The general similarity of the pattern is obvious. The only difference was a tendency of small intestinal blood flow to decrease under the influence of PY and to increase with N. Whereas neither effect reached significance in comparison to the control group (except with 10 μg/kg N) there was a significant difference between the effects of PY and N at two dose levels.

Both compounds produced large increases in skeletal muscle blood flow. The variability between individual animals was considerable as shown by the relatively large s.e.mean.

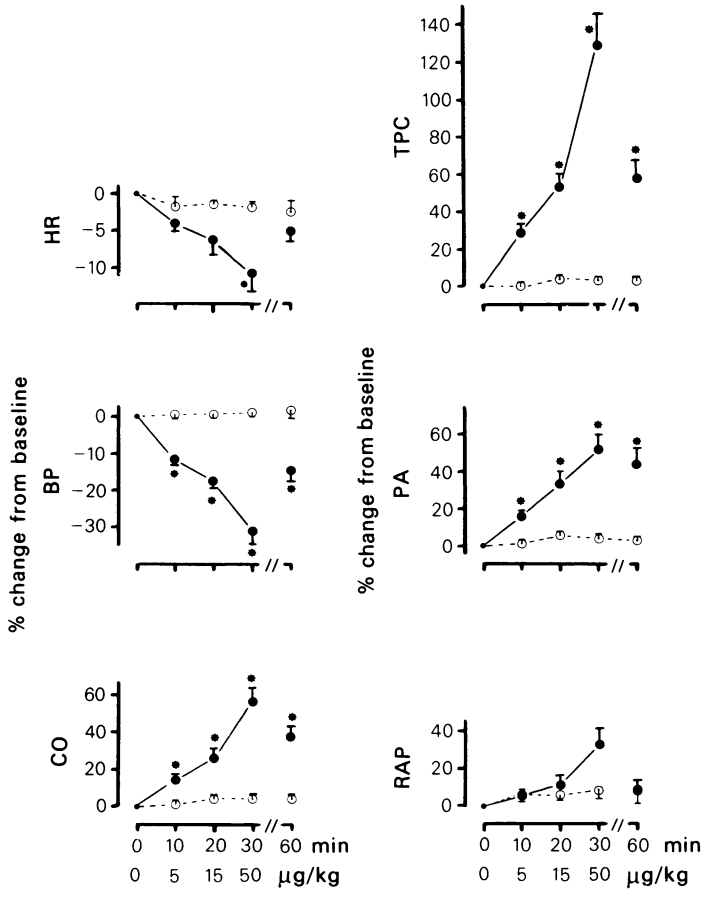

Figure 3 Systemic haemodynamic effects of PY 108-068 (PY). In figures 3–6 (○) indicate measurements in the control animals, expressed as % changes from the initial baseline value, at 10, 20, 30 and 60 min after the baseline measurement; (●) show measurements in the drug-treated animals. Drug infusion was started at time zero and continued at a constant rate for 10 min. The rate of infusion was increased during the second and third 10 min periods and stopped at 30 min, a final measurement being taken at 60 min. The cumulative dose of the drug infused prior to each measurement is shown on the lower abscissa scale. Bars show s.e.mean ($n = 6$). Asterisks indicate a significant difference from control.

Since the fall in blood pressure was also dose-related, the effects on regional conductance shown in Figures 9 (PY) and 10 (N) generally followed the pattern described for the organ blood flows. In the N-treated group the conductance in the subendocardial layer also increased dose-dependently. The figures show furthermore that even in organs where blood flow tended to decrease, no vasoconstriction occurred (with the exception of the spleen in the PY group).

Figure 11 shows the effects of V on regional blood flow. All effects were rather small; only the effects on total coronary flow, on flow to the two outer layers of the heart and on the brain stem were significantly different from the control g oup at the highest dose-level. The crosses indicate, that most regional heart and brain flows increased significantly less than with the doses of PY used. A further important finding was the absence of any effect of V on leg muscle blood flow.

The regional conductances (Figure 12) show more clearly that V dilated dose-dependently the coronary and the cerebral vascular beds. Again the lack of effects on the skeletal muscle vascular bed is obvious.

The effects of D (Figure 13) on regional blood flow in the heart and the brain were more marked than those of V. Flow to most other organs was changed little. The effects on skeletal muscle blood flow were modest and did not reach statistical significance. Regional conductances are shown in Figure 14. The

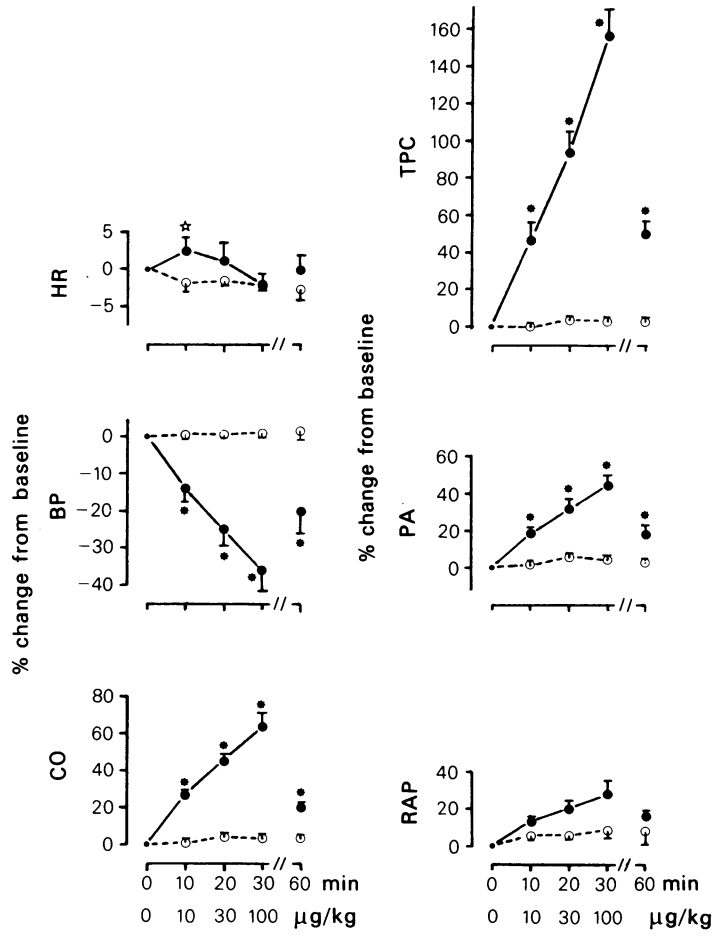

Figure 4 Systemic haemodynamic effects of nicardipine (N), plotted as in Figure 3. Except for the lack of an effect on heart rate with N (the open asterisk indicates a significant difference from the PY group) effects were very similar to those of PY (Figure 3).

overall pattern was rather similar to that of other calcium antagonists. There was a tendency for skeletal muscle vasodilatation and the vascular beds of the adrenals, the liver, the spleen an the skin remained unaffected.

Discussion

Flow measurements were obtained by the microsphere method which differs from other methods used to measure blood flow in several important aspects. With many other methods (e.g. electromagnetic or ultrasonic flowmeters) the investigator gets an immediate and often a continuous feedback about the blood flow to the target organ. He can start his experiment, when the flow is stable or he can reject an experiment if he detects unexpected abnormalities. With the microsphere method all flow measurements are done 'blind'. There is no indication as to the most suitable moment for obtaining the baseline and the later flow measurements. This is one of the reasons why values obtained with this method tend to be more variable than with other methods. On the positive side, this blindness eliminates a potential observer bias.

There is another point worth considering. The microsphere method allows measurement of blood flow to many vascular beds simultaneously. The wealth of results requires an unusually large number of statistical tests. The conventional criteria for significance allow 5% of the results to be significant by

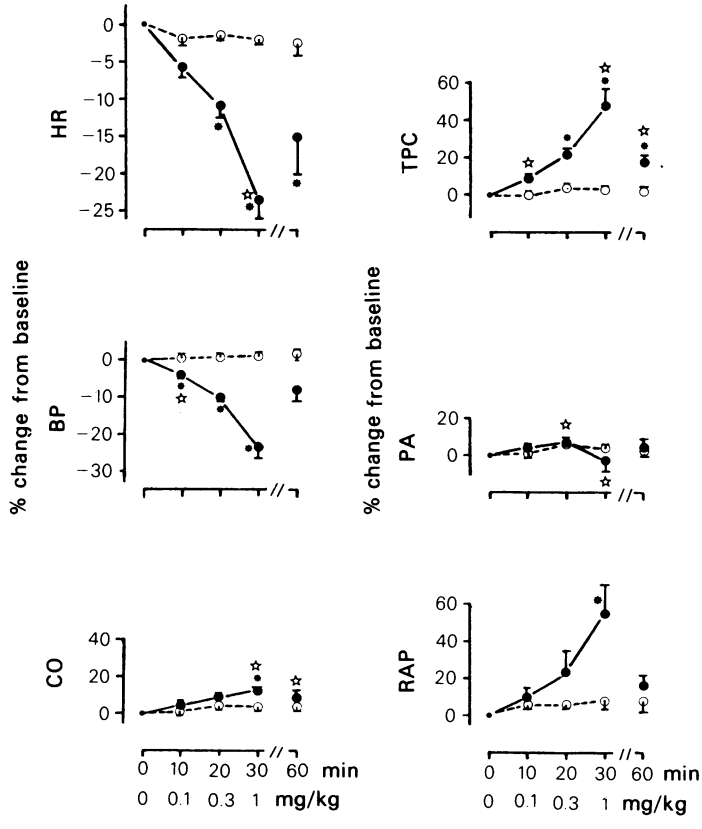

Figure 5 Systemic haemodynamic effects of verapamil (V), plotted as in Figure 3. Closed and open asterisks have the same meaning as in Figures 3 and 4. Compared with PY and N, V is much less effective as a vasodilator, does not increase cardiac output, but more effectively reduces heart rate.

chance. In these experiments measurements were made of 6 systemic haemodynamic variables and 17 regional blood flows at 5 different occasions in each of the 5 groups. One hundred and ten Kruskal-Wallis tests were performed and, for each positive one, 8 Mann-Whitney tests (each drug group against the control group, the PY group against the N, D and V groups and finally the V against the D group). On the other side, we used very conservative criteria of signficance since we had only one control group. A clear dose-dependence of an effect will therefore facilitate the interpretation of drug-induced changes.

The systemic haemodynamic effects of the dihydropyridines were rather different from those of the two other drugs. The increase in TPC was the most prominent effect of the former whereas bradycardia and bradycardia plus cardiodepression were the most important systemic effects of D and V respectively. The doses of V and D that could be tested were in fact limited by these actions; D induced bradyarrhythmias and V severe cardiodepression when an infusion of 3 mg/kg was tried in preliminary experiments. We obtained our results in anesthetized cats which hardly show reflex tachycardia. However, in man, even V and D caused no or only slight bradycardia (Burgess, Hamer & Johnston, 1979, Henry 1980). Results obtained with N in earlier experiments (Hof *et al.*, 1982) were similar to the effects found here with PY and N and support the impression, that the dihydropyridines, in contrast to V and D, primarily affect the peripheral circulation rather than the myocardium.

Coronary vasodilatation was prominent with all antagonists used in these experiments. Unfortunately, doses of each drug that caused comparable effects could not be chosen for the reasons given above. All substances increased blood flow to the outer more than flow to the inner layer of the left ventricular free wall. This effect was seen at all dose levels and has also been described for nifedipine and PY in experiments similar to the ones reported here (Hof *et al.*, 1982). The effects of a number of calcium antagonists

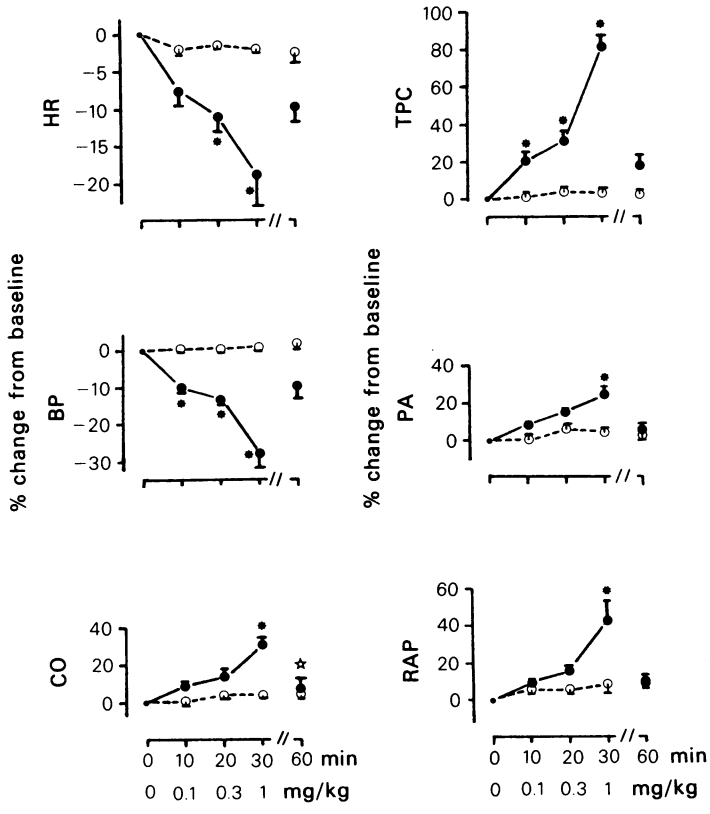

Figure 6 Systemic haemodynamic effects of diltiazem (D), plotted as in Figure 3. Closed and open asterisks have the same meaning as in Figures 3 and 4. The effects of D appear to be midway between those of V (Figure 5) and the dihydropyridines (Figures 3 and 4).

on transmural distribution of blood flow in dog left ventricles appear to be less consistent. Nifedipine was reported to leave the endo/epi distribution unchanged (Henry, Schuchleib, Borda, Roberts, Williamson & Sobel, 1978), or to decrease it (Brueckner, Keller, Mittmann & Wirth 1980, Jolly, Hardman & Gross 1981, Ribeiro, Brandon, Debauche, Maroko & Miller, 1981). Similar findings were obtained with several other dihydropyridine derivatives (Jolly *et al.*, 1981; Warltier, Meils, Gross & Brooks, 1981). Diltiazem did not change it or, like verapamil, tended to favour the subendocardium (Millard, 1980; Ribeiro *et al.*, 1981, Bache & Dymek, 1982; Futamura, Nomura, Nagata, Hama & Yasui, 1982). To some extent at least, the results appear to depend on the experimental situation. In many of the experiments mentioned, an acute coronary occlusion was performed before or after the drug administration, and it is well documented that the effect of nifedipine may depend on the degree of stenosis (Weintraub, Haltori, Agorwal, Bodenheimer, Banka & Helfant, 1981), or on dose administered (Selwyn, Welman, Fox, Horlock, Pratt & Klein, 1979).

Effects on heart rate and diastolic perfusion pressure are factors known to influence selectively subendocardial perfusion (Hoffman & Buckberg, 1975; Hoffman, 1978). The effects of drugs on these variables may depend on the species, the anaesthetic used and the surgical preparation (open chest animals, for example, may show little tachycardia (Hof & Hof, 1981b). All this may contribute to the different results. A more pronounced reflex tachycardia expected to occur in conscious animals and man may therefore strongly modify the effects on coronary blood flow.

Nifedipine has been reported to induce angina pectoris in a few patients (Jariwalla & Anderson, 1978, Deanfield, Fox, Wright & Maseri, 1981). It is conceivable that the redistribution of coronary flow favouring the subepicardium contributes to this paradoxical effect in susceptible patients.

The present results show that the redistribution is

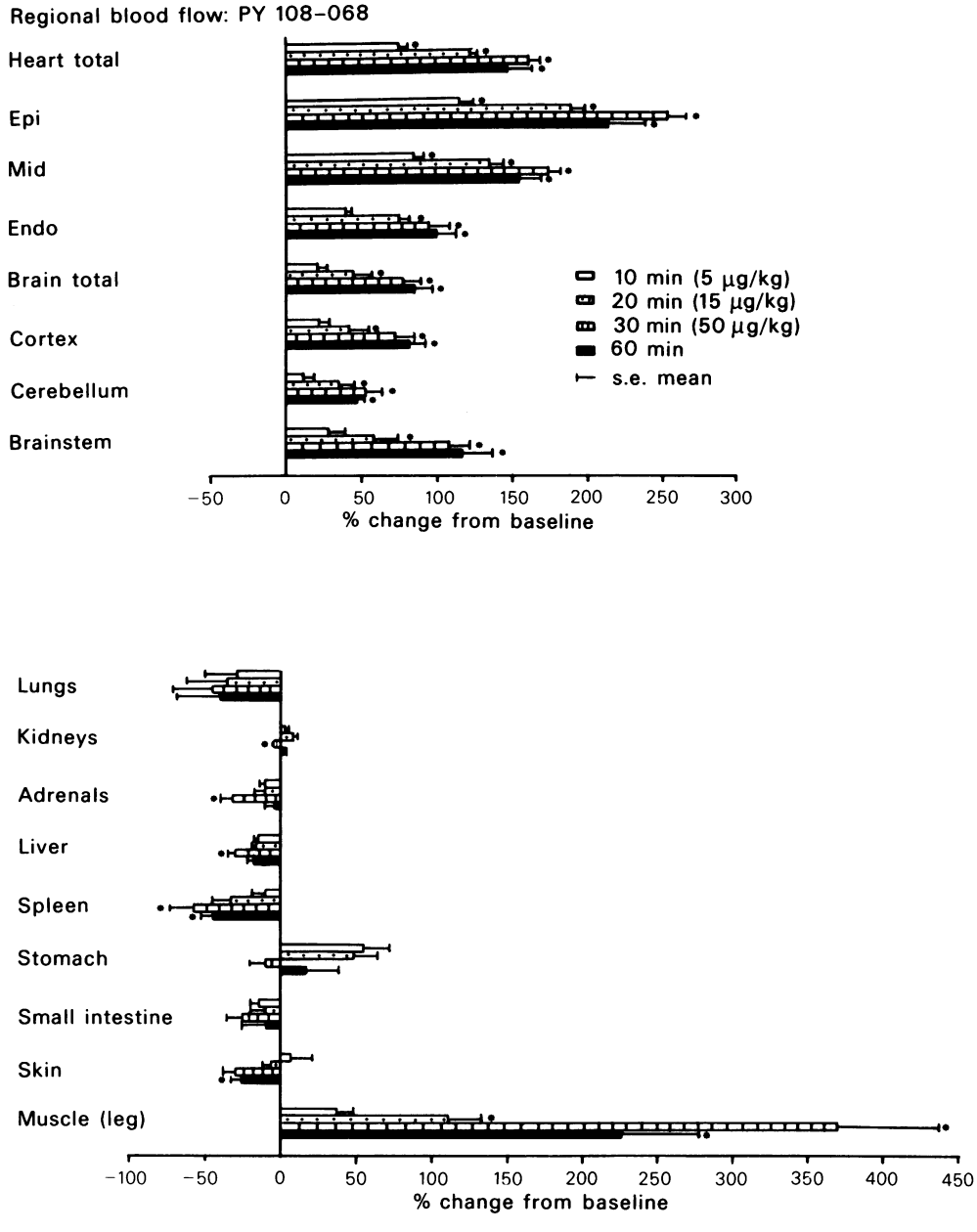

Figure 7 Changes in regional blood flow induced by PY 108-068: PY increased blood flow to the heart and the different layers of the left ventricular free wall dose-dependently. The effects were more pronounced in the subepicardial (Epi) than in the middle (Mid) and the subendocardial (Endo) layer. The flow to the brain and especially to the brain stem was also increased dose-dependently. The effects were maintained to the end of the experiment. In some regions flow even increased slightly as blood pressure tended to return at 60 min. Below: blood flow to leg muscle increased strongly and dose-dependently, whereas flow to the other vascular beds was little affected. $n = 6$ for all measurements. In this and the subsequent figures closed and open asterisks have the same meaning as in Figures 3 and 4.

qualitatively similar with all calcium antagonists examined. Quantitative differences, which are difficult to evaluate, might exist as suggested by the results obtained with N. Systemic haemodynamic changes such as the lack of bradycardia and the very pronounced fall of blood pressure in the N-treated group, are probably sufficient to account for this difference.

All calcium antagonists examined dilated the vessels of the brain. The two dihydropyridine derivatives increased flow most strongly. N and other dihydropyridines such as nimodipine and nifedipine have

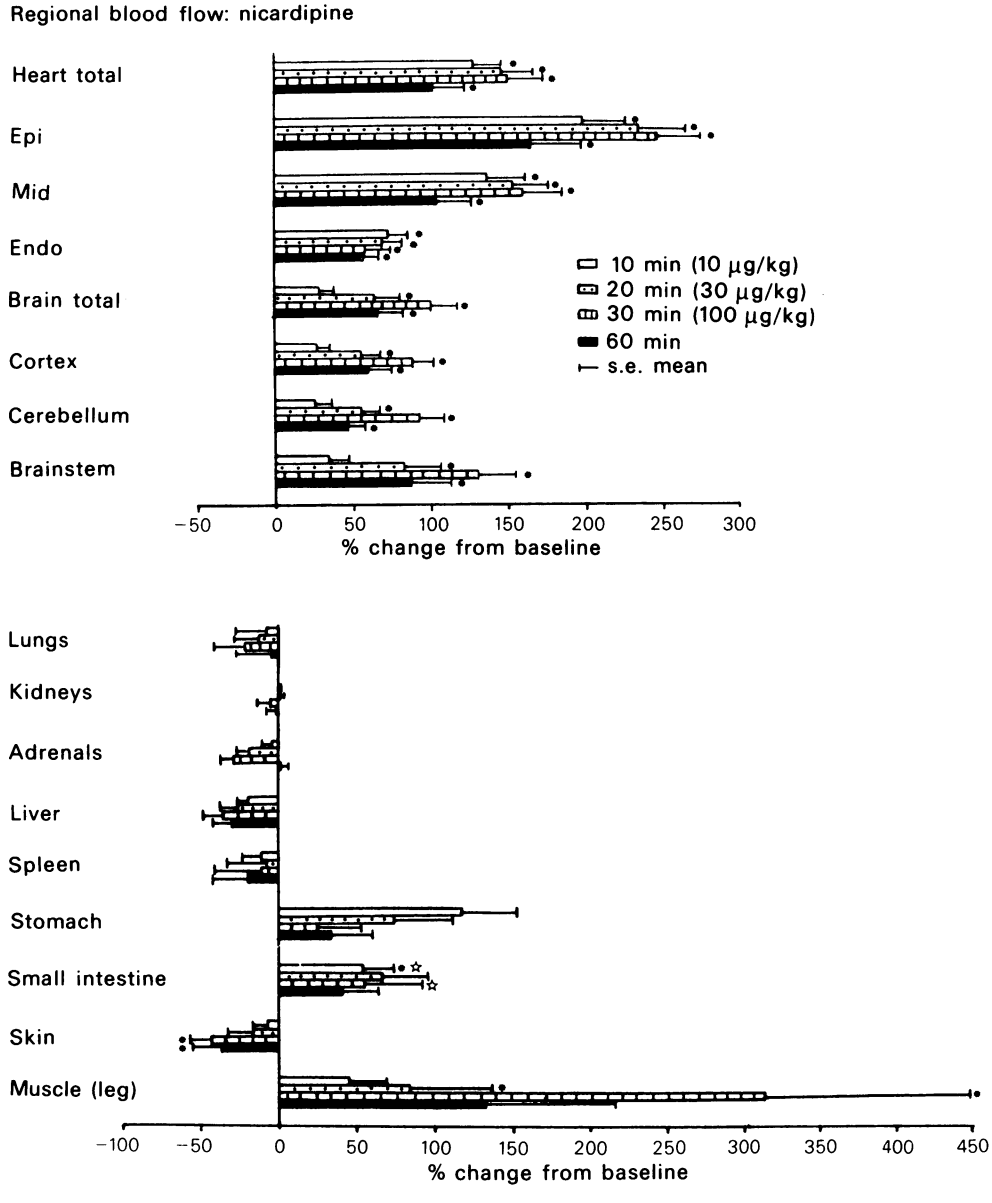

Figure 8 Nicardipine-induced changes in regional blood flow almost as potently as Py 108-068 (Figure 7). The smallest dose used had submaximal effects on myocardial flows and the increases in the subendocardial layer were not dose-dependent. The pattern of effects was rather similar to those of PY with the exception of flow to the small intestine, which tended to increase. $n = 6$ for all measurements.

been reported to increase cerebral blood flow or to relax constricted cerebral arteries *in vitro* (Edvinsson, Brandt, Andersson & Bengtsson, 1979; Takenaka & Handa, 1979; Tanaka, Gotoh, Muramaatsu, Fukuvchi, Amano, Okayasu & Suzuki, 1980; Towart, 1981; Kazda & Towart, 1981; Bevan, 1982; Kazda, Garthoff, Krause & Schlossmann, 1982).

The last measurement obtained at the end of the experiment indicated, that the effects of PY on blood flow to the brain were especially well maintained. Also some other effects of PY appeared to have a longer duration than others, e.g. the effects on CO, PA and coronary blood flow. With the other compounds at least the prominent effects showed no such divergent time course. The findings with PY are difficult to comment on at this time and open to

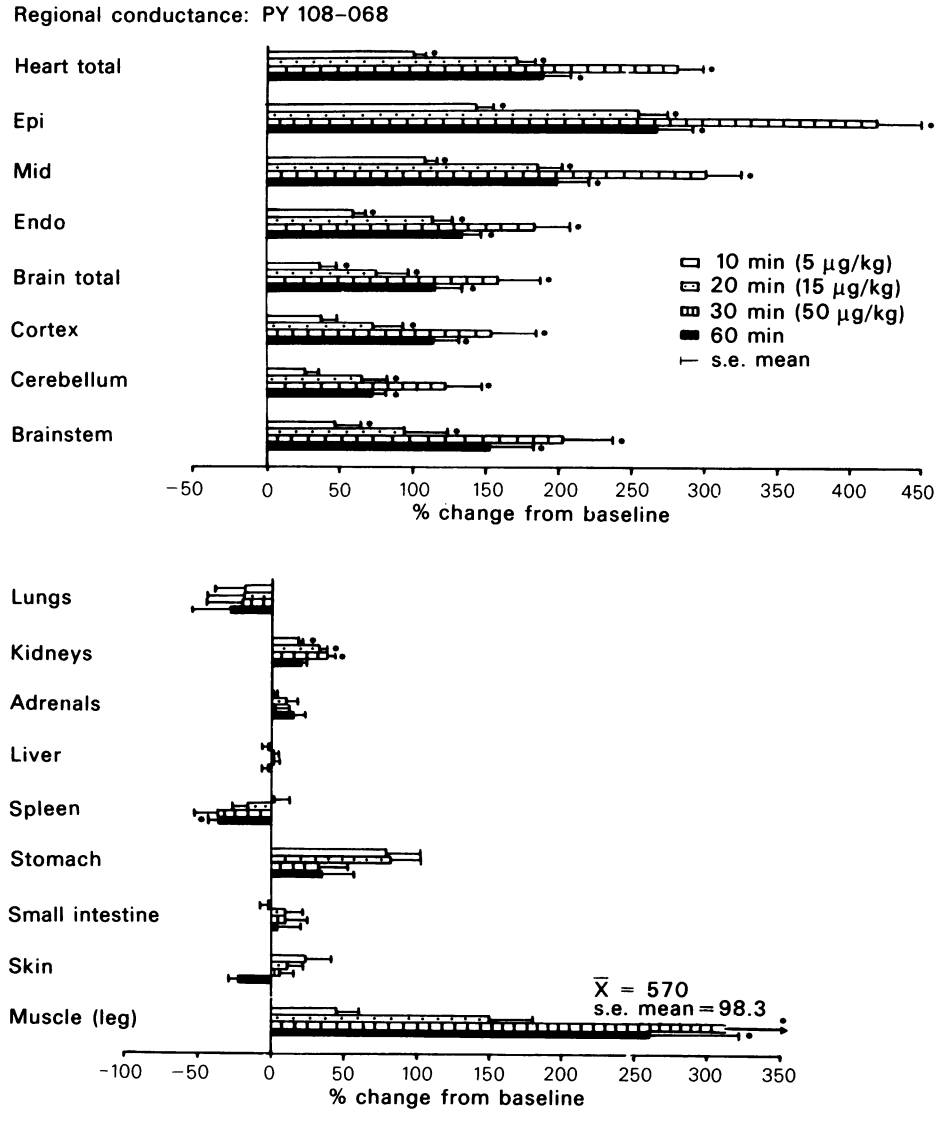

Figure 9 The changes in regional conductance induced by PY 108-068 were similar in the pattern but more pronounced than the changes in blood flow indicating considerable selectivity for certain vascular beds. Frank vasoconstriction was found only in the spleen. In other organs where flow tended to decrease this was due to the fall in perfusion pressure and not to a decrease in conductance. A striking vasodilatation was observed in the vascular bed of leg muscle (570% increase, off scale). Same experiments as in Figure 7.

several interpretations. They might mean a selective distribution of the compound based on a selective affinity for certain calcium channels or on physicochemical properties.

Increases in renal blood flow have been reported for several calcium antagonists including verapamil, nifedipine and diltiazem (Ishikawa, Matsushima, Matsui, Shindo, Morifuji & Okabayashi, 1978; Hashimoto, Takeda, Katano, Nakagawa, Tsukada, Hashimoto, Shimamoto, Sakai, Otarii & Imai, 1979; O'Hara, Ono, Oguro & Hashimoto, 1981). Surprisingly small effects on blood flow were found in the present experiments. Due to the fall in blood pressure the conductance increased dose-dependently with all antagonists examined. How much of this effect is attributable to autoregulation and how much to the effects of the drugs remains uncertain. In an earlier series of experiments we have found similar effects for nifedipine (Hof *et al.*, 1982).

We observed surprisingly few changes in blood

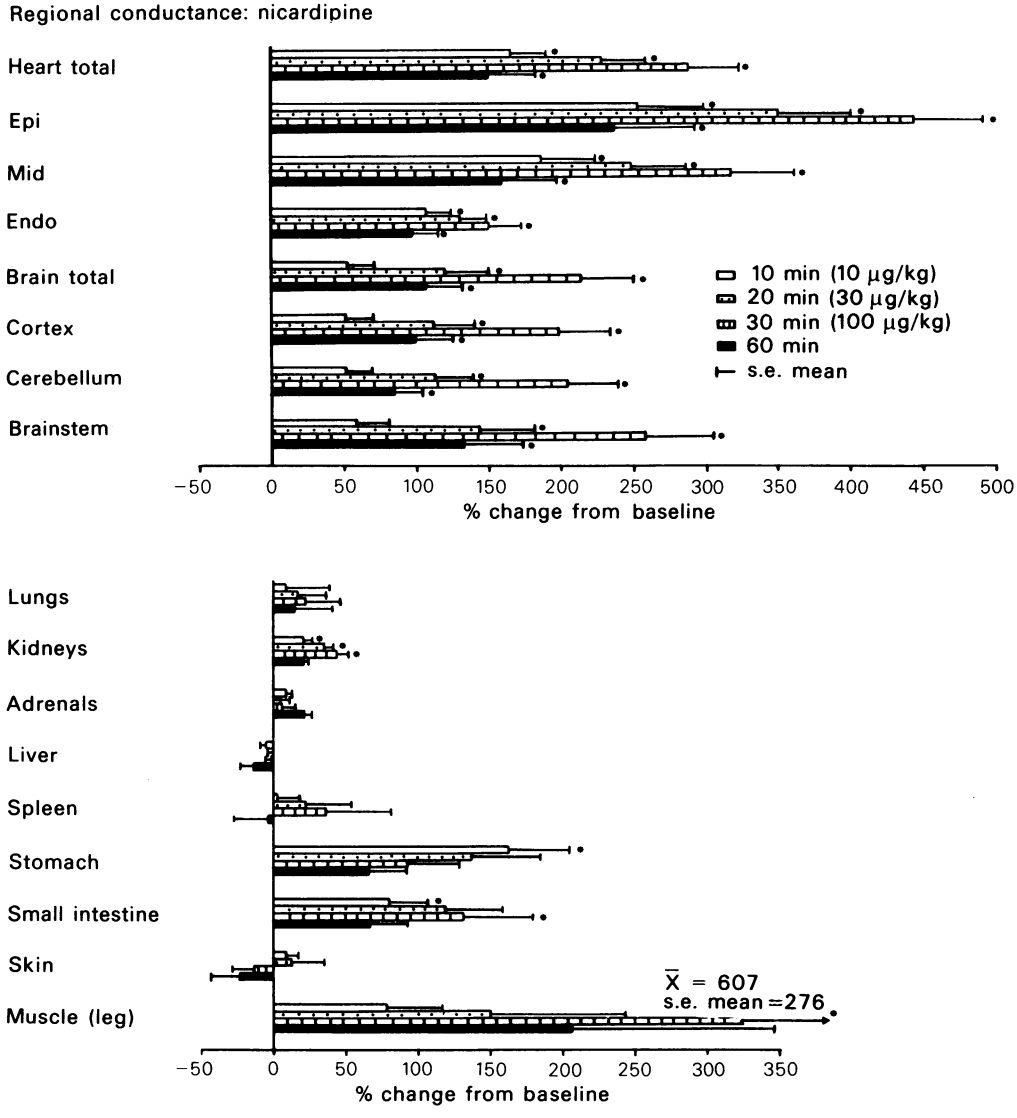

Figure 10 The changes in regional conductance induced by nicardipine (N) were similar to the effects of PY 108-068 (Figure 9) except that there was also a vasodilatation in the stomach and the small intestine and that conductance tended to increase even in the spleen. Same experiments as in Figure 9.

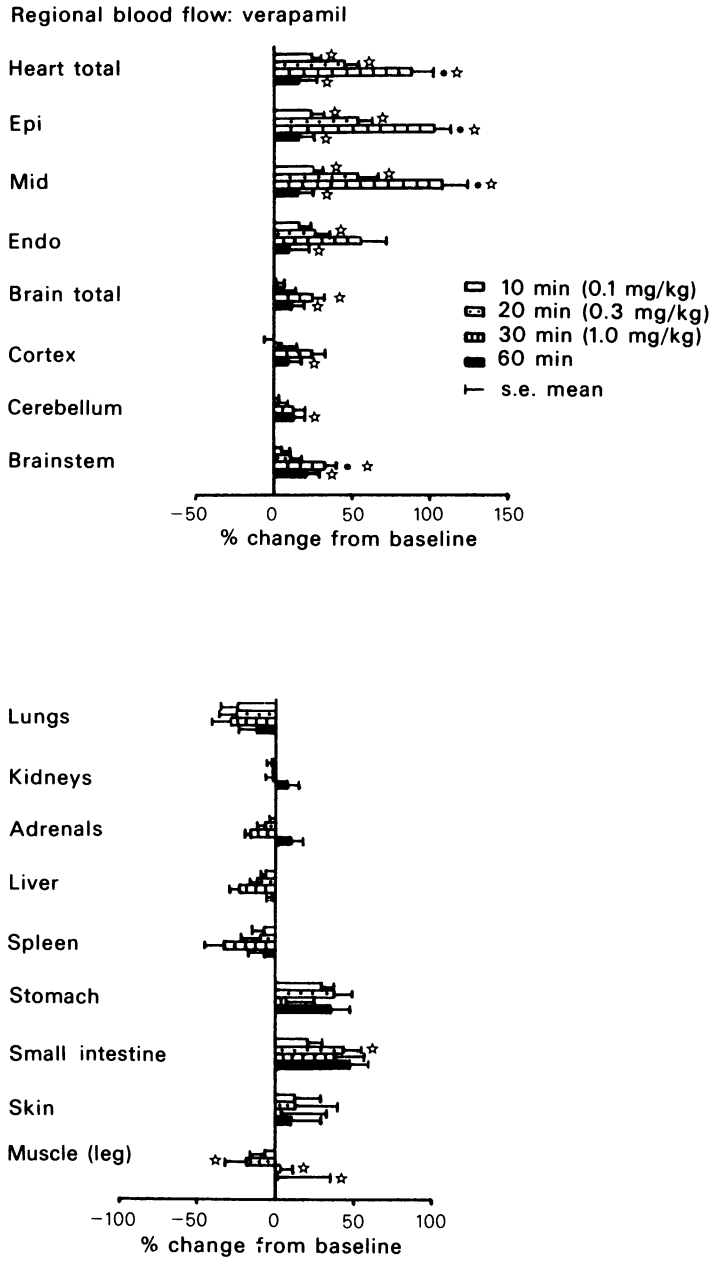

Figure 11 Changes in regional blood flow induced by verapamil (V). Top: this calcium antagonist had essentially similar but smaller effects than PY 108-068 and nicardipine on blood myocardial blood flow. Only few changes were significantly different from the control group (solid asterisks) but many were significantly smaller than the effects of PY (open asterisks). Below: verapamil did not influence blood flow to any of the organs examined to a significant extent. The absence of an effect on leg muscle flow is especially striking in comparison to the effects of the dihydropyridine derivatives. $n = 6$ for all measurements.

flow to the splanchnic vascular beds. Blood flow to the liver and the spleen in general tended to decrease, as the conductances indicate, probably due to the decrease in the perfusion pressure and not because of active vasoconstriction in these beds. Flow to the stomach and the small intestine remained almost unchanged after PY and V. N and D tended to dilate both vascular beds, but the effects were not dose-related. In earlier experiments, PY had also increased blood flow to the small intestine (Hof *et al.*, 1982). Only few results have appeared in the literature indicating that calcium-antagonists tend to increase blood flow to the liver (nifedipine) and the small intestine (Ishikawa *et al.*, 1978; O'Hara *et*

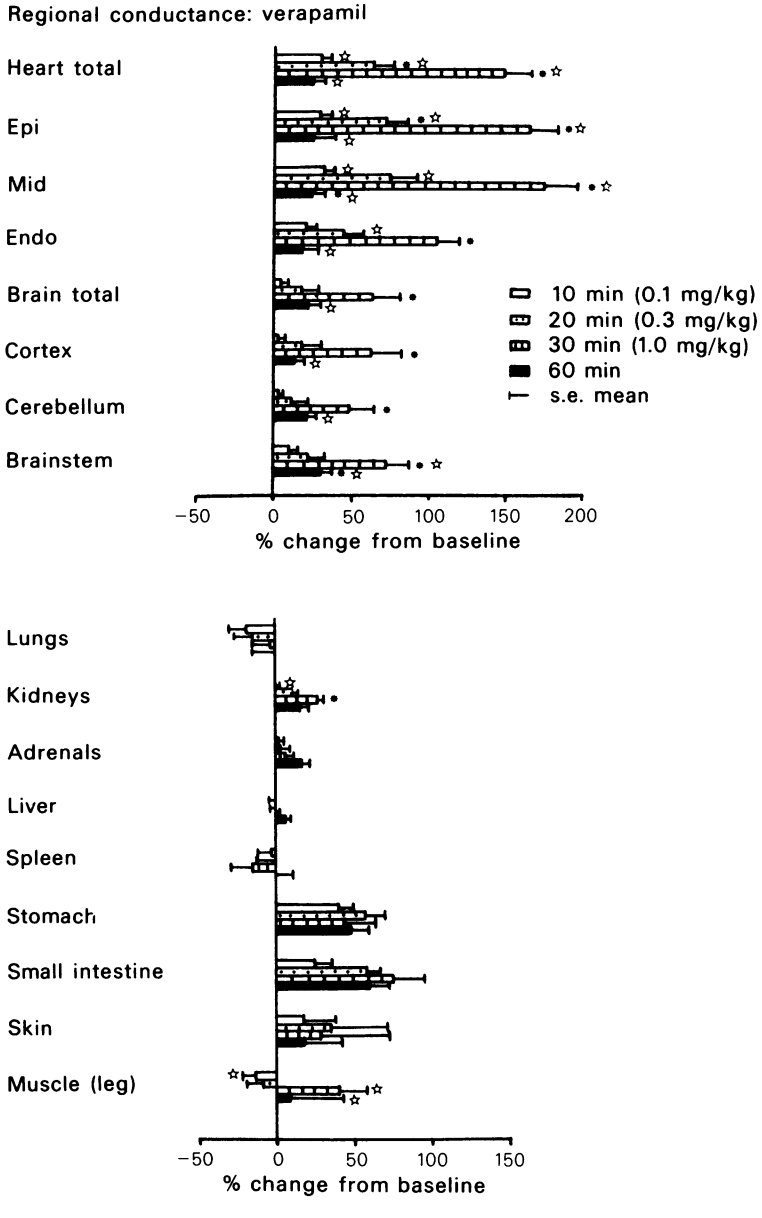

Figure 12 Changes in regional conductance induced by verapamil (V). Dose-related yet relatively weak vasodilatation was observed in all regions of the heart and the brain examined; but only minor changes in conductance were found in all other organs examined, especially in skeletal muscle. Same experiments as in Figure 11.

al.,1981; Walus, Fondacaro & Jacobson, 1981). Comparatively high concentrations of nifedipine and verapamil were needed to relax human mesenteric arteries *in vitro* (Mikkelsen, Andersson & Pedersen, 1979). The effects were minor under the present experimental circumstances, but this does not exclude the possibility that under pathological conditions these drugs could be useful. It has been shown, that even small doses of verapamil antagonized a digoxin-induced vasoconstriction of the mesenteric artery (Brobmann, Mikosch & Mayer 1976).

Different calcium antagonists had very different effects on the resistance vessels of skeletal muscle. Verapamil had no effects on skeletal muscle flow and

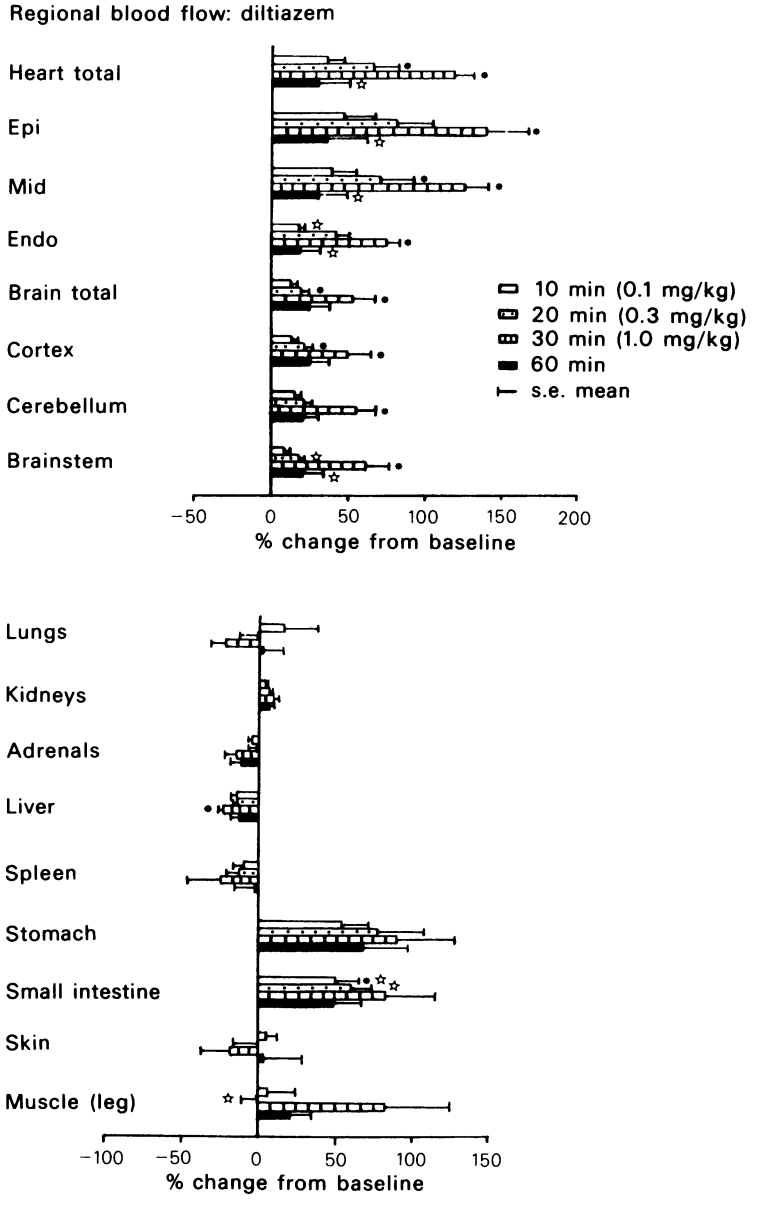

Figure 13 The changes in regional blood flow induced by diltiazen (D) were intermediate between those of PY 108-68 or nicardipine (N) and those of verapamil (V). Below: blood flow to the stomach and the small intestine showed a tendency to increase, whereas skeletal muscle flow was not consistantly increased. $n = 6$.

diltiazem caused a small increase only at the highest dose. Observations similar to the present ones were obtained in anaesthetized dogs where blood flow to several vascular beds were measured simultaneously. Diltiazem (Ishikawa *et al.*, 1978) and verapamil (O'Hara *et al.*, 1981) had comparatively small or biphasic effects on femoral blood flow. The two dihydropyridines increased flow strongly and similar effects have also been observed with nifedipine (Hof *et al.*, 1982). Skeletal muscle represents a large vascular bed and it is conceivable that the strong effects observed there contribute much to the prominent fall in BP and the increase in TPC observed in the present experiments.

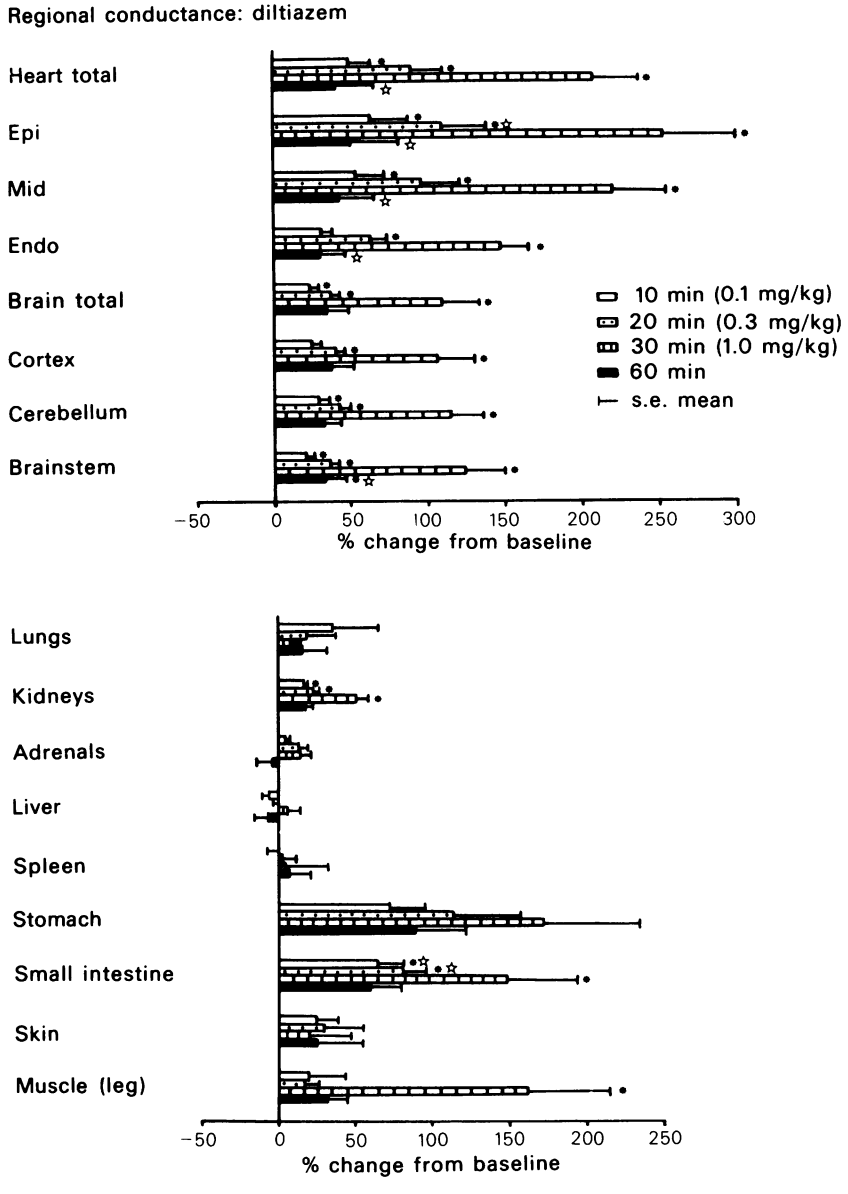

Figure 14 The changes in regional conductance induced by diltiazem (D) paralleled the effects on regional blood flow but were more pronounced due to the dose-dependent fall in blood pressure. Conductance of skeletal muscle was increased significantly following the highest dose of D.

These experiments have clearly shown that calcium antagonists are not general peripheral vasodilators. They all preferentially dilate certain vascular beds, especially the coronary and, to a lesser extent the cerebral bed. The profile of peripheral vascular activity in these experimental animals suggest considerable differences between different compounds. Little is known about regional vascular effects of different calcium antagonists in man. The results presented here were obtained in anaesthetized open-chest cats. It is certainly not possible to extrapolate to man effects observed in a single species under the conditions mentioned. The present findings might alert physicians to the possibility of such differences. Understanding them should ultimately contribute to a more rational knowledge of the therapeutic usefulness of each of these drugs.

I am very grateful to Professor H.P. Rang (London) for stimulating discussions and for his valuable comments on the manuscript.

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(Received August 10, 1982
Revised September 27, 1982.)