ACUTE CORONARY HEMODYNAMIC EFFECTS OF EQUIPHYPOTENSIVE DOSES OF NISOLDIPINE AND DILTIAZEM

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Abstract:
The hemodynamic effects of nisoldipine and diltiazem were investigated in two groups of patients undergoing investigation for suspected coronary artery disease. Emphasis was placed on the coronary hemodynamic changes. Approximately equihypotensive doses of these two calcium channel blockers, nisoldipine (6 μg/kg) and diltiazem (500 μg/kg) were given intravenously.

Although both drugs decreased peak systolic pressure by 28% and 24%, respectively, heart rate increased with nisoldipine (68 ± 9 to 82 ± 12 bpm) and remained unchanged with diltiazem (70 ± 9 to 67 ± 10 bpm). Nisoldipine increased mean coronary sinus blood flow from 146 ± 40 to 176 ± 35 ml/min and great cardiac vein flow from 87 ± 20 to 109 ± 24 ml/min, producing a significant reduction in the calculated global (from 0.79 ± 0.2 to 0.43 ± 0.12 mmHg min/ml) and regional (from 1.43 ± 0.2 to 0.70 ± 0.13 mmHg min/ml) coronary vascular resistances. There were no significant flow changes when corrected for heart rate. Global and regional myocardial oxygen consumptions were not significantly altered. Diltiazem had no significant effects on heart rate or global and regional blood flows, although the vascular resistances decreased by 32% and 35%, respectively. Diltiazem reduced global and regional arterio-coronary sinus oxygen differences, resulting in significant decreases in global (from 14.9 ± 4.7 to 12.1 ± 2.3 ml/min) and regional (from 5.6 ± 0.9 to 5.2 ± 1.2 ml/min) myocardial oxygen consumptions.

The major difference between the drugs was in heart rate, despite the similar reductions in aortic pressure. The lack of a positive chronotropic response after diltiazem may explain the reduction in myocardial oxygen consumption. (Aust NZ J Med 1985; 15: 685-690.)

Key words: Calcium channel blockers, nisoldipine, diltiazem, hemodynamic effects.

INTRODUCTION

Calcium channel blockers are an incongruous group of drugs which inhibit the transmembranous movement of calcium from the extra- to the intracellular space in cardiac and vascular smooth muscle. They characteristically decrease systemic and coronary vascular resistances and uncouple myocardial excitation–contraction.[1,2]

Nisoldipine and diltiazem are calcium channel blockers with dissimilar structures and physicochemical properties. Both produce *in vitro* relaxation of isolated coronary and peripheral blood

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TABLE 1
Clinical Data, Nisoldipine Group ($N=13$).

Patient	Age/sex	Coronary lesion	Coronary score*	EF %	ESVI ml/m²	Previous MI
1	48/M	Main stem + CABG	9	51	38	+
2	49/M	0	0	38	64	–
3	52/M	3 VD	10	52	27	–
4	68/F	2 VD	11.5	59	26	–
5	57/M	Main stem + 3 VD	15.5	34	115	+
6	73/F	Main stem	12.5	59	26	–
7	47/M	0	0	62	42	–
8	45/M	3 VD	12	54	40	–
9	69/M	1 VD	1	49	36	+
10	59/M	1 VD	2.5	53	44	+
11	50/M	0	0	59	30	–
12	44/F	2 VD	18	48	43	–
13	66/F	3 VD	25.5	60	23	+

Abbreviations: M = male; F = female; CABG = coronary artery bypass graft; VD = vessel disease; EF = ejection fraction; ESVI = end-systolic volume index; MI = myocardial infarction; *Coronary score calculated according to Leaman.[8]

vessels, and suppress sinoatrial and atrioventricular nodal function.[3-6] Whereas nisoldipine has three times the potency of diltiazem in depressing atrioventricular conduction, it has approximately 30 times the potency of diltiazem in the relaxation of coronary and peripheral blood vessels, when the two are compared on a weight for weight basis.[7]

This study was undertaken to investigate and compare the hemodynamic responses induced by approximately equihypotensive doses of nisoldipine and diltiazem, with particular emphasis on the changes in coronary circulation.

PATIENTS AND METHODS

Patients undergoing investigation of suspected coronary artery disease were studied during cardiac catheterisation. The mean age of the 27 patients was 57 years (range 43-73 years). All were in sinus rhythm, had no signs of cardiac failure, and gave informed consent to the study. Nisoldipine was given to 13 consecutive patients and diltiazem to 14 consecutive patients, thus forming two groups.

Previous myocardial infarction had occurred in 11 patients of whom five were in the nisoldipine group. There were four females in the nisoldipine group and none in the diltiazem group. Four patients had no significant coronary artery disease. An unpaired Student's *t* test detected no significant differences between the two groups in patient age, degree of coronary artery disease as assessed by coronary score,[8] resting ejection fraction, coronary sinus blood flows, and coronary vascular resistances. Patient data are summarised in Tables 1 and 2.

All medications were withheld for 36 hours before cardiac catheterisation, which was performed with the patient fasting and without premedication. Heart rate was available from continuous electrocardiogram (ECG) monitoring. Aortic and left ventricular (LV) pressures were recorded with a tip manometer mounted on an 8F pigtail catheter. The on-line computer system assessed aortic pressure, peak LV pressure, left ventricular end-diastolic pressure (LVEDP), and the

TABLE 2
Clinical Data, Diltiazem Group ($N=14$).

Patient	Age/sex	Coronary lesion	Coronary score*	EF %	ESVI ml/m²	Previous MI
14	59/M	3 VD	17	56	37	–
15	56/M	2 VD	10.5	42	44	+
16	67/M	3 VD	8.5	56	31	+
17	61/M	2 VD	9.5	57	23	–
18	56/M	2 VD	12	62	28	+
19	61/M	CABG + 3 VD	33.5	59	25	–
20	62/M	0	0	62	24	–
21	68/M	3 VD	20	49	31	–
22	50/M	3 VD	9	64	22	–
23	62/M	3 VD	14.5	63	25	+
24	61/M	2 VD	6.5	58	28	+
25	60/M	3 VD	27	63	18	–
26	52/M	CABG + 2 VD	2.5	44	37	–
27	43/M	3 VD	17	–	–	+

Abbreviations: M = male; CABG = coronary artery bypass graft; VD = vessel disease; EF = ejection fraction; ESVI = end-systolic volume index; MI = myocardial infarction; *Coronary score calculated according to Leaman.[8]

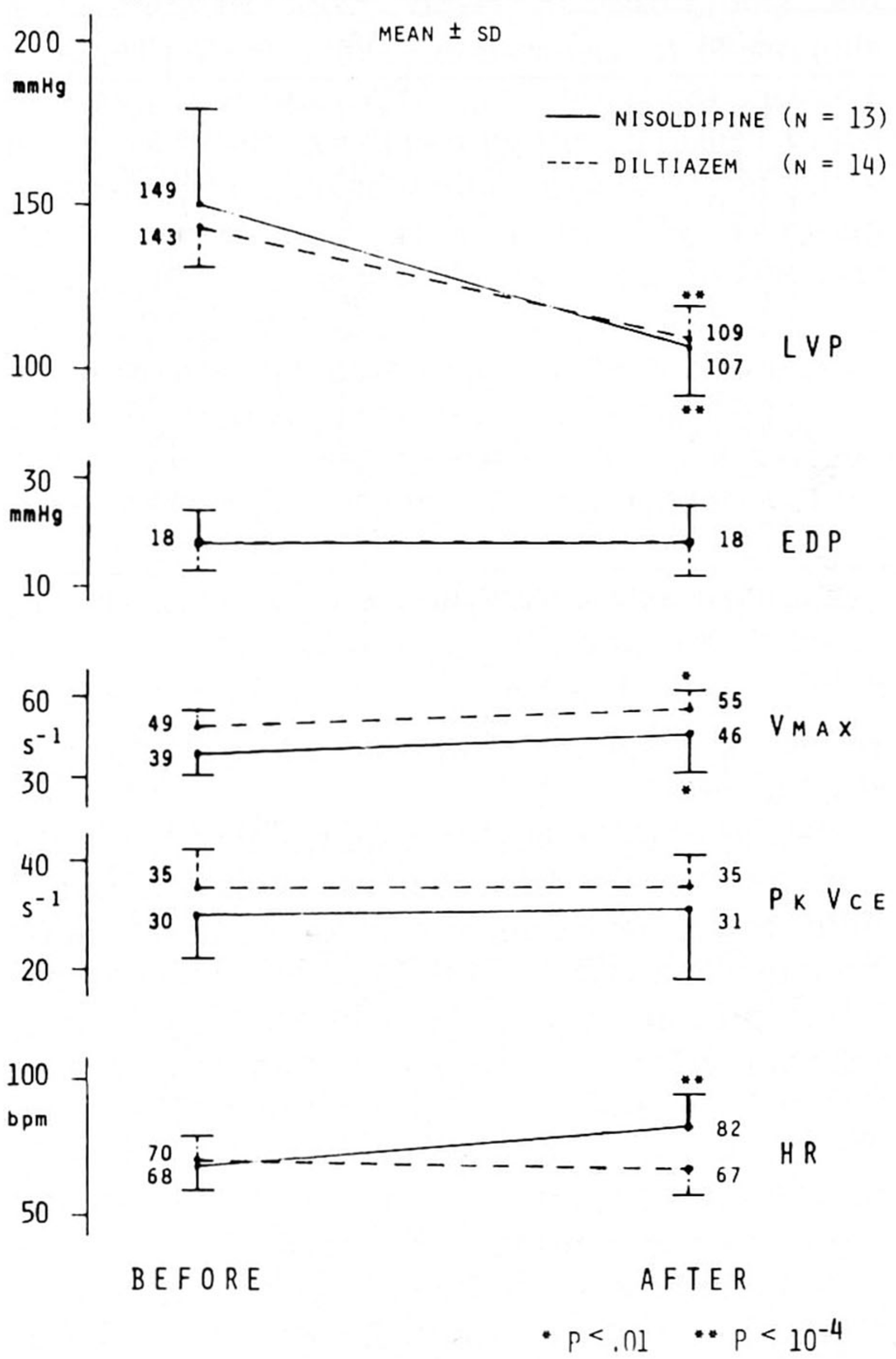

Figure 1: Hemodynamic changes during acute administration of intravenous nisoldipine and diltiazem. LVP = left ventricular peak systolic pressure. EDP = left ventricular end-diastolic pressure. pk Vce = peak Vce. HR = heart rate. Values represent mean ± SD.

pressure-derived indices of LV contraction *V*max and peak *V*ce.[9] A Baim[10] coronary sinus and great cardiac vein flow catheter, or a Ganz coronary sinus flow catheter was inserted into the coronary sinus by a right antecubital venous approach. Using a constant infusion thermodilution technique, blood flow could be measured in either coronary sinus (CS) or great cardiac vein (GCV).

Simultaneous measurements of heart rate, aortic and LV pressures, CS and GCV blood flows, and systemic and coronary venous O_2 saturations were taken in a resting state 20 minutes after left ventriculography but before coronary angiography. Nisoldipine (2 μg kg^{-1} min^{-1}) was then infused intravenously over three minutes or diltiazem (100 μg kg^{-1} min^{-1}) over five minutes by the same route. The measurements were repeated as close as possible to two minutes after drug administration. Systemic, CS, and GCV blood O_2 saturations were measured spectrophotometrically (Lex-O_2-Con, Lexington Instruments Corp.), and O_2 contents calculated. Regional (from GCV) and global (from CS) myocardial O_2 consumptions were given by the product of the respective coronary blood flow and the arterio-coronary venous O_2 difference. Regional (from CS) and global (from CS) coronary vascular resistances were given by the ratios of the mean aortic pressure to coronary venous blood flow. Coronary angiography was performed after the study. Significant coronary artery disease was defined as luminal diameter narrowing of at least 70% in a major vessel. Results are expressed as the mean ± SD. Group data before and after drug administration were compared by paired *t* tests. A *p* value less than 0.05 was considered significant.

RESULTS

The hemodynamic responses after the infusions are summarised in Figure 1. Nisoldipine and diltiazem decreased peak systolic pressure by 28 and 24%, respectively. The chronotropic response induced by these approximately equihypotensive doses was quite different. Nisoldipine increased heart rate by 14 bpm ($p < 10^{-4}$), while heart rate remained unchanged after diltiazem. LVEDP was unchanged and similar LV contractile responses were evoked, with *V*max increased by 18% ($p < 0.01$) after nisoldipine and by 12% ($p < 0.01$) after diltiazem.

After nisoldipine (Table 3), CS blood flow increased (146 ± 40 to 176 ± 35 ml/min, $p < 0.02$), as did GCV blood flow (87 ± 20 to 109 ± 24 ml/min, $p < 0.005$). When corrected for the changes in heart rate, CS and GCV blood flows were unchanged. Simultaneously, mean aortic pressure decreased (107 ± 20 to 72 ± 9 mmHg, $p < 10^{-6}$) with marked falls in the calculated global coronary vascular resistances (0.79 ± 0.20 to 0.43 ± 0.12 mmHg min/ml, −46%) and in the regional coronary vascular resistances (1.43 ± 0.20 to 0.70 ± 0.13 mmHg min/ml, −51%). Although the mean arterio-CS (−22%, $p < 0.002$) and arterio-GCV (−23%, $p < 0.005$) O_2 differences fell, there were no significant changes in the global and regional myocardial O_2 consumptions.

Diltiazem (Table 4) produced no change in GCV flow and the fall in CS flow (165 ± 62 to 149 ± 45 ml/min) was not significant. When corrected for heart rate, there was also no change in CS and GCV blood flows. The mean aortic pressure decreased (107 ± 12 to 75 ± 5 mmHg), as did the global vascular resistance (−32%, $p < 0.02$) and the regional vascular resistance (−35%,

TABLE 3
Myocardial O_2 Consumption, Coronary Flow and Resistance Following Nisoldipine ($N=13$).

	Before	After	Δ%	p value
CS flow (ml/min)	146 ± 40	176 ± 35	+21	<0.02
CS flow/beat	2.2 ± 0.6	2.3 ± 0.6	+5	NS
GCV flow (ml/min)	87 ± 20	109 ± 24	+25	<0.005
GCV flow/beat	1.3 ± 0.3	1.3 ± 0.3	0	NS
MVO_2 CS (ml/min)	15.1 ± 4.8	13.9 ± 3.2	−8	NS
MVO_2 GCV (ml/min)	9.2 ± 3.2	8.8 ± 2.5	−4	NS
O_2 Content CS (ml%)	8.9 ± 2.3	11.1 ± 2	+25	<0.002
O_2 Content GCV (ml%)	8.3 ± 1.8	10.6 ± 1.7	+28	<0.005
(Art-CS) O_2diff (ml%)	10.3 ± 1.6	8 ± 1.5	−22	<0.002
(Art-GCV) O_2diff (ml%)	10.4 ± 2.3	8 ± 1.4	−23	<0.005
O_2 Content Art (ml%)	19.2 ± 1.8	19.2 ± 1.90	0	NS
MAP (mmHg)	107 ± 20	72 ± 9	−33	$<10^{-6}$
Resist CS (mmHg min/ml)	0.79 ± 0.2	0.43 ± 0.12	−46	$<10^{-4}$
Resist GCV (mmHg min/ml)	1.43 ± 0.2	0.70 ± 0.13	−51	$<10^{-4}$

Abbreviations: CS = coronary sinus; GCV = great cardiac vein; MVO_2 = global (CS) or regional (GCV) myocardial oxygen consumption; MAP = mean aortic pressure; resist = resistance.

$p<0.0005$). Mean arterio–CS (−11%, $p<0.005$) and arterio–GCV O_2 (−9%, $p<0.05$) content differences fell. With the decrease in CS blood flow, this resulted in a decrease in the calculated global myocardial O_2 consumption (−19%, $p<0.02$).

DISCUSSION

Calcium channel blockers produce relaxation of cardiac and vascular smooth muscle by inhibiting the transmembranous influx of calcium from the extra cellular space. *In vitro* studies on cardiac muscle preparations have demonstrated negative chronotropic, inotropic, and dromotropic actions for all the calcium antagonists[1,3,4,11] as might be expected from their basic and common pharmacological action. The *in vivo* effects of the individual drugs are not as predictable, and result from a complex interplay between direct effects and reflex responses such as sympathetic stimulation. The nature of the direct effect and the balance with reflex responses varies with dose levels[7] and from drug to drug.

Results of this study have shown the structurally unrelated calcium channel blockers, nisoldipine and diltiazem, to have some similar and some dissimilar hemodynamic effects. Both caused a fall in systemic blood pressure after a short infusion by a direct relaxant effect on arterial smooth muscle thus reducing systemic vascular resistance. The doses chosen had produced equihypotensive effects in previous investigations,[7,12] and produced a similar degree of hypotension in this study.

Nisoldipine is a new dihydropyridine derivative, related in structure to nifedipine. The profile of hemodynamic response, *i.e.* systemic and coronary vasodilatation, a decrease in blood pressure, and increases in heart rate and stroke volume, is similar to that of nifedipine and has been attributed in part, to afterload reduction and reflex sympathetic activity.[13] Both nisoldipine and nifedipine are

TABLE 4
Myocardial O_2 Consumption, Coronary Flow and Resistance Following Diltiazem ($N=14$).

	Before	After	Δ%	p value
CS flow (ml/min)	165 ± 62	149 ± 45	−10	NS
CS flow/beat	2.5 ± 0.9	2.4 ± 1.0	−4	NS
GCV flow (ml/min)	58 ± 11	61 ± 21	+5	NS
GCV flow/beat	0.8 ± 0.2	0.9 ± 0.3	+12	NS
MCO_2 CS (ml/min)	14.9 ± 4.7	12.1 ± 2.3	−19	<0.02
MVO_2 GCV (ml/min)	5.6 ± 0.9	5.2 ± 1.2	−7	NS
O_2 Content CS (ml%)	9.2 ± 1.5	10.1 ± 1.8	+10	<0.02
O_2 Content GCV (ml%)	9 ± 1.5	9.6 ± 1.6	+7	<0.05
(Art-CS) O_2 diff (ml%)	9.5 ± 1.0	8.5 ± 1.3	−11	<0.005
(Art-GCV) O_2 diff (ml%)	9.9 ± 1.6	9.0 ± 2.1	−9	<0.05
O_2 Content Art (ml%)	19 ± 1.1	18.7 ± 1.3	−2	NS
MAP (mmHg)	107 ± 12	75 ± 5	−30	$<10^{-6}$
Resist CS (mmHg min/ml)	0.82 ± 0.41	0.56 ± 1.16	−32	<0.02
Resist GCV (mmHg min/ml)	2.05 ± 0.54	1.34 ± 0.41	−35	<0.0005

Abbreviations: CS = coronary sinus; GCV = great cardiac vein; MVO_2 = global (CS) or regional (GCV) myocardial oxygen consumption; MAP = mean aortic pressure; resist = resistance.

equipotent *in vitro* in producing negative inotropic effects. Nisoldipine has a higher vascular specificity and relatively lower doses of nisoldipine will produce the vascular responses free of observable negative inotropic effects.[6] The slight positive inotropic effect, as shown by the increased *V*max we observed with nisoldipine, may be explained by reflex sympathetic activity or LV afterload reduction.[14] These may be masking an intrinsic direct negative inotropic effect of the drug, a mechanism suggested to explain the *in vivo* lack of negative inotropic effects of nifedipine.[6,15] Nisoldipine does not appear to have any intrinsic beta adrenergic activity[6] to explain a positive inotropic effect.

Increases in CS and GCV flows with nisoldipine appeared in part to be due to the heart rate changes and were associated with large falls in the global and regional coronary vascular resistances. LV afterload reduction occurred after the fall in aortic pressure but the small fall in O_2 consumption was not significant. Increase in O_2 supply and decrease in O_2 demand are means by which calcium channel blockers may be beneficial in treating myocardial ischemia. Some seem to offer vascular specificity by inducing greater degrees of dilatation in the coronary vasculature than elsewhere,[16] and this specificity may be greater for the dihydropyridine derivatives than for other calcium channel blockers such as diltiazem or verapamil.[6,17]

Although diltiazem produced a similar fall in blood pressure, the heart rate remained unchanged whereas it increased with nisoldipine. This suggests that reflex sympathetic stimulation was offset to a greater degree by diltiazem, possibly by a direct sinoatrial nodal effect.[11,18-20] Decreases in CS flow, coronary vascular resistance, and myocardial O_2 consumption after diltiazem are findings of a study measuring coronary flow using the Argon method.[21] Other studies using lower doses of diltiazem found increases in coronary blood flow with a fall in resistance but no change in myocardial O_2 consumption.[22,23] These changes occurred without alteration in the cardiac output, suggesting a redistribution of blood flow to the coronary circulation. The dose and infusion rate relationship to coronary flow has been investigated.[7]

An increase in coronary collateral flow after nisoldipine and diltiazem has been demonstrated in dogs with separately controlled and perfused circumflex and left anterior descending coronary arteries. The required dosage of diltiazem to produce similar effects was, however, 20 times that of nisoldipine when compared with hypotension-inducing potency.[4] In other animal studies, diltiazem has been shown to increase blood flow in the normal and in the mildly ischemic myocardium surrounding an ischemic zone.[12,24,25] Nisoldipine increased blood flow in the central ischemic zone by increasing collateral flow.[12]

CONCLUSION

In the approximately equihypotensive doses used, nisoldipine and diltiazem in acute intravenous administration had some differing effects on coronary hemodynamics. Both were free of observed negative inotropic effects. Nisoldipine increased heart rate which remained unchanged after diltiazem despite the similar falls in aortic pressure. The reduction in myocardial O_2 consumption after diltiazem may result from the lack of positive chronotropic responses.

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References

1. Fleckenstein A. Specific pharmacology of calcium in myocardium, cardiac pacemakers, and vascular smooth muscle. Annu Rev Pharmacol Toxicol 1977; 17: 49-66.
2. Tritthart HH. Pharmacology and electrophysiology of calcium ion antagonists. Clin Invest Med 1980; 3: 1-7.
3. Millard RW, Lathrop DA, Grupp G, Ashraf M, Grupp IL, Schwartz A. Differential cardiovascular effects of calcium channel blocking agents: potential mechanisms. Am J Cardiol 1982; 49: 499-506.
4. Schwartz A, Grupp G, Millard RW, *et al.* Calcium channel blockers: possible mechanisms of protective effects of the ischemic myocardium. In: Weiss GB, ed. Calcium antagonists. American Physiological Society Clinical Series 1981; 191-210.
5. Taira N. Effects of diltiazem and other calcium antagonists on cardiac functions and coronary blood flow assessed in blood-perfused dog-heart preparations. In: Bing RJ, ed. Diltiazem Hakone Symposium. New drug therapy with a calcium antagonist. Amsterdam: Excerpta Medica 1979; 91-105.
6. Kazda S, Garthoff B, Meyer H, *et al.* Pharmacology of a new calcium antagonistic compound, isobutyl methyl 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate (Nisoldipine, Bay k 5552). Arzneim Forsch (Drug Res) 1980; 30 (II) 12: 2144-62.
7. Lathrop DA, Valle-Aquilera JR, Millard RW, *et al.* Comparative electrophysiologic and coronary hemodynamic effect of diltiazem, nisoldipine and verapamil in myocardial tissue. Am J Cardiol 1982; 49: 613-20.
8. Leaman DM, Brower RW, Meester GT, Serruys PW, van den Brand M. Coronary artery atherosclerosis: severity of the disease, severity of angina pectoris and compromised left ventricular function. Circulation 1981; 63 (2): 285-92.
9. Meester GT, Bernard N, Zeelenberg C, Brower RW, Hugenholtz PG. A computer system for real time analysis of cardiac catheterization data. Catheterization Cardiovasc Diagn 1975; 1: 112-23.
10. Baim DS, Rothman MT, Harrison DC. Improved catheter for regional coronary sinus flow and metabolic studies. Am J Cardiol 1980; 46: 997-1000.
11. Henry PD. Comparative pharmacology of calcium antagonists: nifedipine, verapamil and diltiazem. Am J Cardiol 1980; 46: 1047-58.
12. Warltier DC, Meils CM, Gross GJ, Brooks HL. Blood flow in normal and acutely ischemic myocardium after verapamil, diltiazem and nisoldipine (Bay K5552), a new dihydropyridine calcium antagonist. J Pharmacol Exp Ther 1981; 218: 296-302.
13. Maxwell GM, Crompton S, Rencies V. Effect of nisoldipine upon the general and coronary hemodynamics of the anesthetized dog. J Cardiovasc Pharmacol 1982; 4: 393-7.
14. Serruys PW, Suryapranata H, Planellas J, *et al.* Effects of short-term intravenous administration of nisoldipine on left ventricular function and coronary hemodynamics in patients with coronary artery disease. In press.

15. Gross R, Kirchheim H, von Olshausen K. Effects of nisoldipine on coronary and systemic hemodynamics in the conscious dog. Arzneim Forsch 1979; 29: 1361-8.
16. Henry PD, Schuchleir R, Borda LJ, Roberts R, Williamson JR, Sobel BE. Effects of nifedipine on myocardial perfusion and ischemic injury in dogs. Circ Res 1978; 43: 372-80.
17. Ono H, Himuri N, Taira N. Chronotropic effects of coronary vasodilators as assessed in the isolated blood-perfused sino-atrial node preparation of the dog. Tohoku J Exp Med 1977; 12: 383-90.
18. Ellrodt G, Chew CYC, Singh BN. Therapeutic implications of slow channel blockade in cardiocirculatory disorders. Circulation 1980; 62: 669-79.
19. Valette H, Barnay C, Lopez M, *et al.* Effects of intravenous diltiazem on sinus node function and atrioventricular conduction in patients. J Cardiovasc Pharmacol 1983; 5: 62-6.
20. Mitchell LB, Schroeder JS, Mason JW. Comparative clinical electrophysiologic effects of diltiazem, verapamil and nifedipine: a Review. Am J Cardiol 1982; 49: 629-35.
21. Bioamino G, Oeff M, Prokein E, Schröder R. *Verhalten von Hämodynamik und Koronardurchblutung nach intravenöser Gabe von Diltiazem bei koronarer Herzerkrankung.* In: Bender F, Greeff K, eds. *Calcium antagonisten zur behandlung der angina pectoris, hypertonie und arrythmie.* Amsterdam-Oxford-Princeton: Excerpta Medica 1982: 94-105.
22. Bourassa MG, Cote P, Theroux P, Tubau JF, Genain C, Waters DD. Hemodynamic and coronary flow following diltiazem administration in anesthetized dogs and humans. Chest 1980; 78: 224-30.
23. Bertrand ME, Dupuis BA, Lablanche JM, Tilmant PY, Thieleux FP. Coronary hemodynamics following intravenous or intracoronary injection of diltiazem in man. J Cardiovasc Pharmacol 1982; 4: 695-9.
24. Millard RW. Changes in cardiac mechanics and coronary blood flow of regionally ischemic porcine myocardium induced by diltiazem. Chest 1980; 78 (Suppl.): 193-9.
25. Nakamura M, Kikuchi Y, Senda Y, Yamada A, Koiwaya Y. Myocardial blood flow following experimental coronary occlusion. Effects of diltiazem. Chest 1980; 78 (Suppl.): 205-9.

Grading of Angina of Effort by the Canadian Cardiovascular Society

I. Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina occurs with strenuous or rapid or prolonged exertion at work or recreation.
II. There is slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and on climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
III. Marked limitation of ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace.
IV. There is inability to carry on any physical activity without discomfort — anginal syndrome *may be* present at rest.

Campeau L. Circulation 1976; 54: 522-3