Eur J Clin Pharmacol (1989) 37: 443–447

European Journal of Clinical Pharmacology

Comparison of haemodynamic effects of nifedipine and molsidomine in patients with coronary artery disease

M. Kyriakidis, G. Vyssoulis, P. Sfikakis, C. Kyriakidis, C. Pitsavos, K. Valsamis, V. Nomikos, and P. Toutouzas

Hippokration Hospital, University of Athens, Athens, Greece

Summary. The haemodynamic effects of oral nifedipine 20 mg and molsidomine 4 mg were compared in 24 patients with coronary artery disease.

Molsidomine unlike nifedipine caused a significant fall in mean pulmonary artery pressure and left ventricular end-diastolic pressure. Both drugs caused a significant and comparable reduction in systolic and diastolic blood pressure. Although only nifedipine significantly reduced systemic vascular resistance the difference between the drugs was not significant. The heart rate was significantly increased by nifedipine but not by molsidomine. The ejection phase indices were all increased by molsidomine and the increment in the mean normalized systolic ejection rate was significantly greater than that due to nifedipine. The left ventricular end-systolic volume index decreased significantly after molsidomine but not nifedipine.

Neither drug significantly affected left ventricular end diastolic volume index, stroke volume index, maximal rate of rise of left ventricular pressure or left ventricular stroke work index.

Key words: nifedipine, molsidomine, ischaemic heart disease; vasodilators, haemodynamic-/cardiac effects

The ability of nifedipine to block calcium influx into vascular smooth muscle cells results in peripheral and coronary vasodilatation [1, 2]. The active metabolite of molsidomine SIN 1 A [3], formed in the liver, carries an N-terminal nitrosogroup characteristic of nitrovasodilators, such as nitroprusside [4]. SIN 1 A causes vasodilatation by direct stimulation of intracellular guanylate cyclase activity, which increases intracellular cyclic guanosine monophosphate and initiates relaxation, most probably by increasing calcium extrusion from the cell [3, 4]. Both nifedipine and molsidomine are orally effective, long-acting vasodilators with pronounced actions on the peripheral circulation, and they are clinically effective in the treatment of angina pectoris [5–10] and left ventricular failure [10–13].

The present single dose study was undertaken to detailed compare the haemodynamic effects of clinically equivalent doses of each drug in patients with coronary artery disease.

Materials and methods

Patients

Twenty-four patients, 18 men and 6 women, were studied during routine cardiac catheterization for investigation of ischaemic heart disease. Their ages ranged from 41 to 69 (mean 58 (10) years).

The inclusion criteria for the study were the presence of significant coronary artery disease, with a more than 75% occlusion of at least one coronary artery, a left ventricular ejection fraction greater than 40%, and left-ventricular end-diastolic pressure greater than 15 mm Hg. Patients with a history of myocardial infarction in the previous 3 months, cardiomyopathy or rheumatic or congenital heart disease were excluded. Cardioactive drugs, with the exception of short-acting nitrates, were discontinued 2 days before the study. Informed consent was obtained from all patients.

Protocol

Cardiac catheterization was performed in all patients by the percutaneous femoral route. Cournand catheters were used for the right heart and pigtail and Judkins catheters for the left heart. Direct pressure measurements (mm Hg) included right atrial, pulmonary arterial and pulmonary capillary wedge mean pressures and aortic systolic, diastolic and mean pressures. Maximal rate of rise of left ventricular pressure mm Hg/s was determined by electronic differentiation of the left ventricular pressure signal. Heart rate was recorded continuously by an ECG monitor. After making the haemodynamic measurements selective coronary arteriography and left ventriculography were performed. Left ventriculography was performed in the 30-degrees right anterior oblique position by injection of 76% Renografin 45 ml at 12 ml/s.

Twenty minutes after completion of ventriculography alternate patients were given molsidomine 4 mg or nifedipine 20 mg p.o. Thirty min later the haemodynamic measurements and left ventriculography were repeated.

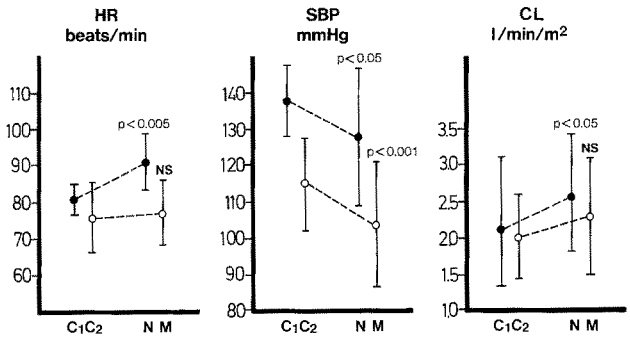

Fig. 1. Effects of nifedipine (N) and molsidomine (M) on heart rate (HR), systolic blood pressure (SBP) and cardiac index (CI). C_1 = control before nifedipine, C_2 = control before molsidomine

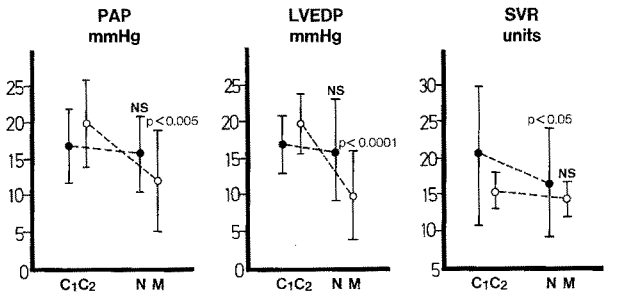

Fig. 2. Effects of nifedipine (N) and molsidomine (M) on mean pulmonary artery pressure (PAP), left ventricular end-diastolic pressure (LVEDP) and systemic vascular resistance (SVR). C_1 = control before nifedipine, C_2 = control before molsidomine

Haemodynamic indices

Left ventricular volume was calculated by the single-plane area length method. Volume indices were obtained by dividing the volume by the body surface area.

Left ventricular ejection fraction

$$= \frac{\text{left ventric. end-diastol. volume - left ventric. end-systol. volume} \times 100}{\text{left ventricular end-diastolic volume}}$$

Mean velocity of circumferential fibre shortening

$$= \frac{\text{end-diastolic circumference - end-systolic circumference}}{\text{end-diastolic circumference} \times \text{systolic ejection time}}$$

Mean normalized systolic ejection rate

$$= \frac{\text{Stroke volume}}{\text{Systolic left ventric. ejection time} \times \text{left ventric. end-diastolic volume}}$$

Cardiac output was calculated by the Fick method. Cardiac index = cardiac output divided by the body surface area. Stroke volume index = cardiac index divided by the heart rate · Systemic vascular resistance = mean arterial pressure minus right atrial pressure divided by the cardiac output.

Left ventricular stroke work index = Stroke volume index multiplied by mean arterial blood pressure minus left ventricular end-diastolic pressure multiplied by 0.0136.

Paired patient data were analyzed by Student's *t*-test for paired samples. The control data and the percent change from control for each drug were compared using the unpaired Student's *t*-test.

Results

Effects of nifedipine

The data are summarized in Table 1 and Figs. 1-3 as mean (standard deviation). Oral nifedipine 20 mg was followed by a significant fall in aortic pressure and systemic vascular resistance and an increase in heart rate and cardiac index. Systolic blood pressure fell from the control value of 138 (10) to 128 (19) mmHg ($p<0.05$), diastolic blood pressure fell from 76 (9) to 69 (8) mmHg ($p<0.01$) and systemic vascular resistance fell from 21.2 (9.4) to 16.9 (7.5) units ($p<0.05$). Heart rate increased from 81 (4) to 91 (7) beats · min^{-1} ($p<0.005$) and the cardiac index was increased from 2.2 (0.9) to 2.6 (0.8) l · min^{-1} · m^{-2} ($p<0.05$).

Ejection phase indices all increased following nifedipine. Left ventricular ejection fraction increased from 51.9 (6.5) to 56.2 (12.1)% (NS), mean velocity of circumferential fibre shortening increased from 0.9 (0.2) to 1.2 (0.4) circ/s ($p<0.01$) and mean normalized systolic ejection rate increased from 2.0 (0.4) to 2.3 (0.5) s^{-1} ($p<0.01$).

There was no significant change in pulmonary artery or wedge pressures, left ventricular pressures or volumes, maximal rate of rise of left ventricular pressure, stroke volume index or left ventricular stroke work index.

Table 1. Haemodynamic effects of nifedipine

Parameter	Baseline C_1	After nifedipine	*p*
HR (beats · min^{-1})	81 (4)	91 (7)	<0.005
SBP (mm Hg)	138 (10)	128 (19)	<0.05
DBP (mm Hg)	76 (9)	69 (8)	<0.01
LVEDP (mm Hg)	17 (4)	16 (7)	NS
PAP (mm Hg)	17 (5)	16 (5)	NS
PCWP (mm Hg)	18 (6)	17 (8)	NS
dP/dt max. (mm Hg · s^{-1})	1288 (423)	1293 (395)	NS
LVESVI (ml · m^{-2})	25.3 (10.9)	23.9 (15.4)	NS
LVEDVI (ml · m^{-2})	52.5 (21.1)	52.3 (19.2)	NS
LVEF (%)	51.9 (6.5)	56.2 (12.1)	NS
Mean Vcf (circ · s^{-1})	0.9 (0.2)	1.2 (0.4)	<0.01
MNSER (s^{-1})	2.0 (0.4)	2.3 (0.5)	<0.01
CI (l · min^{-1} · m^{-2})	2.2 (0.9)	2.6 (0.8)	<0.05
SVI (ml · m^{-2})	27.2 (10.9)	28.4 (7.7)	NS
SVR (units)	21.2 (9.4)	16.9 (7.5)	<0.05
LVSWI (g · m · m^{-2})	32.6 (14)	31.1 (12.7)	NS

Abbreviations: HR = Heart rate; SBP = aortic systolic blood pressure; DBP = aortic diastolic blood pressure; LVEDP = left ventricular end-diastolic pressure; PAP = mean pulmonary artery pressure; PCWP = mean pulmonary capillary wedge pressure; dP/dt max = maximal rate of rise of left ventricular pressure; LVESVI = left ventricular end-systolic volume index; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; mean Vcf = mean velocity of circumferential fiber shortening; MNSER = mean normalised systolic ejection rate; CI = cardiac index; SVI = stroke volume index; SVR = systemic vascular resistance; LVSWI = left ventricular stroke work index

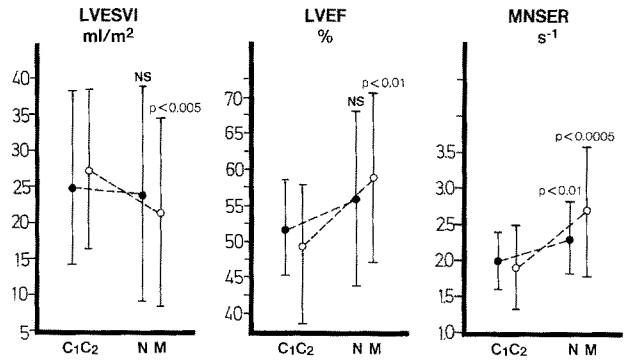

Fig. 3. Effects of nifedipine (N) and molsidomine (M) on left ventricular end-systolic volume index (LVESVI), left ventricular ejection fraction (LVEF) and mean normalized systolic ejection rate (MNSER)

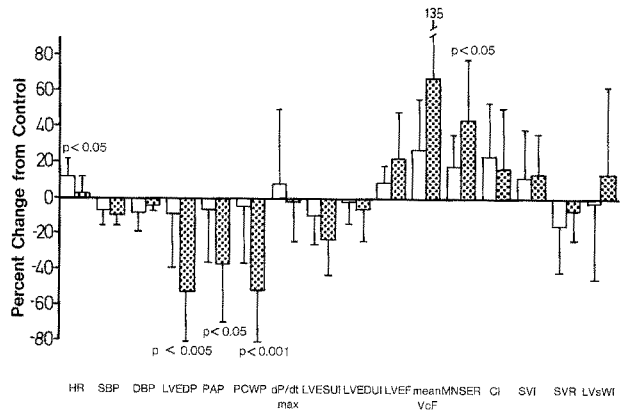

Fig. 4. Comparison of percentage changes from control after nifedipine and molsidomine therapy. □ oral nifedipine; ⊠ oral molsidomine

Effects of molsidomine

The data are summarized in Table 2 and Figs. 1–3. Following oral molsidomine 4 mg there was a significant fall in pulmonary artery and wedge pressure, and left ventricular end-diastolic and aortic systolic pressures. Thus, pulmonary artery pressure fell from 20 (6) to 12 (7) mmHg ($p<0.005$), pulmonary wedge pressure fell from 20 (6) to 10 (7) mmHg ($p<0.0005$), left ventricular end-diastolic pressure fell from 20 (4) to 10 (6) mmHg ($p<0.001$) and systolic blood pressure fell from 115 (13) to 104 (17) mmHg ($p<0.001$). There was a clinically insignificant fall in diastolic blood pressure ($p<0.01$).

The ejection phase indices were all considerably increased after molsidomine. Left ventricular ejection fraction increased from 50 (11) to 59 (12)% ($p<0.01$), mean velocity of circumferential fibre shortening increased from 0.9 (0.4) to 1.3 (0.5) circ/s ($p<0.001$) and mean normalised systolic ejection rate increased from 1.9 (0.6) to 2.7 (0.9) s^{-1} ($p<0.001$).

There were no significant changes in heart rate, cardiac index, stroke volume index, systemic vascular resistance, maximal rate of rise of left ventricular pressure or left ventricular stroke work index.

Comparison of the percentage changes from control after nifedipine and molsidomine (Fig. 4)

Although resting systolic blood pressure was higher in the nifedipine C_1 than in the molsidomine controls C_2 ($p<0.0001$), the percentage reduction in systolic blood pressure from control was comparable with both drugs, viz. 7 (10)% with nifedipine and 10 (8)% with molsidomine (difference not significant (NS).

There was no statistically significant difference between any of the other resting haemodynamic parameters in C_1 and C_2. Heart rate, systolic and diastolic blood pressure, left ventricular end-diastolic pressure, pulmonary artery and wedge pressures, dP/dt max, left ventricular end systolic and diastolic volume indices, left ventricular ejection fraction, mean velocity of circumferential fibre shortening, mean normalised systolic ejection rate, cardiac index, stroke volume index, systemic vascular resistance and left ventricular stroke work index were comparable in the 2 groups ($p=$ NS). The number and severity of coronary stenoses in C_1 and C_2 were also comparable ($p=$ NS) and the ages of the patients were similar ($p=$ NS).

Heart rate was increased by 12 (11)% after nifedipine ($p<0.005$) and by 2 (10)% after molsidomine (NS). The difference in effect on heart rate between the two drugs was significant ($p<0.05$). Cardiac index increased by 23 (30)% after nifedipine ($p<0.05$) and by 16 (35)% after molsidomine (NS) and there was no significant difference between the drugs.

Molsidomine caused a fall in pulmonary artery pressure, pulmonary wedge pressure and left ven-

Table 2. Haemodynamic effects of molsidomine

Parameter	Baseline C_2	After nifedipine	p
HR (beats·min^{-1})	76 (10)	77 (9)	NS
SBP (mm Hg)	115 (13)	104 (17)	<0.001
DBP (mm Hg)	70 (8)	66 (8)	<0.01
LVEDP (mm Hg)	20 (4)	10 (6)	<0.0001
PAP (mm Hg)	20 (6)	12 (7)	<0.005
PCWP (mm Hg)	20 (6)	10 (7)	<0.0005
dP/dt max. (mm Hg·s^{-1})	1608 (514)	1583 (463)	NS
LVESVI (ml·m^{-2})	27.6 (11.1)	21.6 (12.9)	<0.005
LVEDVI (ml·m^{-2})	54.1 (14.2)	51.2 (20.2)	NS
LVEF (%)	49.6 (10.9)	59.0 (11.8)	<0.01
Mean VcF (circ·s^{-1})	0.9 (0.4)	1.3 (0.5)	<0.001
MNSER (s^{-1})	1.9 (0.6)	2.7 (0.9)	<0.0005
CI (l·min^{-1}·m^{-2})	2.0 (0.6)	2.3 (0.8)	NS
SVI (ml·m^{-2})	26.4 (6.8)	29.5 (10.2)	NS
SVR (units)	15.8 (2.6)	14.6 (2.6)	NS
LVSWI (g·m·m^{-2})	30.9 (10.9)	33.9 (15.4)	NS

Abbreviations as in Table 1

tricular end-diastolic pressure of 37 (33%) ($p<0.005$), 52 (29)% ($p<0.0005$) and 53 (28)% ($p<0.0001$) respectively. For the same parameters the corresponding figures for nifedipine were only 7 (29)% (NS), 5 (32)% (NS) and 9 (30)% (NS).

Thus, molsidomine caused a significantly greater reduction of pulmonary artery pressure ($p<0.05$), pulmonary wedge pressure ($p<0.001$) and left ventricular end-diastolic pressure ($p<0.005$) than nifedipine.

Although nifedipine produced a greater reduction in diastolic blood pressure than molsidomine, 9 (10)% ($p<0.01$) compared to 4 (4)% ($p<0.01$) the difference between the 2 drugs was not significant. Systemic vascular resistance was reduced by 16 (26)% by nifedipine ($p<0.05$) and by only 7 (17)% with molsidomine (NS), but the difference between the two drugs was not significant. Left ventricular end-systolic volume index was reduced by 24 (20)% with molsidomine ($p<0.005$) compared to only 10 (17)% with nifedipine (NS) but the difference was not significant.

Molsidomine caused large increases in the ejection phase indices. After molsidomine there were increments in left ventricular ejection fraction, mean velocity of circumferential fibre shortening and mean normalised systolic ejection rate of 22 (26)% ($p<0.01$), 67 (68)% ($p<0.001$) and 44 (35)% ($p<0.0005$), respectively, whereas nifedipine caused corresponding increments of only 8 (16)% (NS), 27 (29)% ($p<0.01$) and 17 (19)% ($p<0.01$). Only the difference between the two drugs in mean normalized systolic ejection rate reached significance ($p<0.05$).

Neither drug significantly affected left ventricular end-diastolic volume index, stroke volume index, maximal rate of rise of left ventricular pressure or left ventricular stroke work index, and there was no significant difference between the drugs in any of these parameters.

Discussion

The present results are in agreement with non-comparative data in the literature about the haemodynamic effects of nifedipine and molsidomine [14–25].

As expected, molsidomine significantly reduced preload, whereas nifedipine caused only a small and insignificant reduction in the pulmonary artery and left ventricular end-diastolic pressures. Molsidomine caused a significantly greater reduction in mean pulmonary artery pressure ($p<0.05$) and left ventricular end-diastolic pressure ($p<0.005$) than nifedipine.

Surprisingly, the present study did not demonstrate any significant difference between the effects of nifedipine and molsidomine on afterload. Since molsidomine is known to act predominantly as a venodilator, and to have less effect on arterioles [24, 25], it was anticipated that nifedipine would cause a significantly greater reduction of afterload than molsidomine. In the present study, however, both drugs caused a significant and comparable percentage reduction in the systolic and diastolic blood pressures. Systemic vascular resistance did fall significantly after nifedipine ($p<0.05$) but not molsidomine, but no statistically significant difference between the 2 drugs was demonstrated. This may be associated with the inequality of the resting systolic blood pressures in the nifedipine control group and the molsidomine control group.

The reduction in afterload due to nifedipine, unlike that with molsidomine, was not accompanied by any concomitant reduction in the elevated left ventricular filling pressure. This could potentially lead to a reduction in coronary perfusion [26]. The associated tachycardia (not seen with molsidomine, difference between drugs $p<0.05$) might contribute to ischaemia, and also by increasing myocardial energy consumption it might aggravate the impaired ventricular pump function.

These potentially deleterious effects of nifedipine might account for some of the adverse responses reported in angina pectoris [27–29] and left ventricular failure [30–32]. There might also be a coronary-steal phenomenon. Nifedipine increases coronary flow by reducing coronary arteriolar resistance and there are varying reports in the literature about whether it dilates [32, 33] or even constricts [29] coronary epicardial vessels and stenoses.

There is at present no account of the effects of oral molsidomine on coronary blood flow in man. Intracoronary injection of SIN 1 in patients with coronary artery disease is followed by vasodilatation of epicardial coronary arteries and stenoses [34, 35] but not of coronary arterioles.

In the present study symptomatic ischaemia was not observed in any patients either after molsidomine or nifedipine.

Molsidomine unlike nifedipine increased the left ventricular ejection fraction and increased all the ejection phase indices more than nifedipine, significantly for the mean normalised systolic ejection rate ($p<0.05$). Unlike nifedipine, molsidomine significantly reduced left ventricular size, but no significant difference between the two drugs was demonstrated. Neither drug significantly affected contractility.

In conclusion, molsidomine appears to have a similar effect to nifedipine on left ventricular performance with fewer potentially disadvantageous haemodynamic effects. Its influence on coronary blood flow in man and its value in clinical practice remain to be clarified.

References

1. Braunwald E (1982) Mechanism of action of calcium-channel-blocking agents. N Engl J Med 307: 1618-1627
2. Stone PH, Antman EM, Muller JE, Braunwald E (1980) Calcium channel blocking agents in the treatment of cardiovascular disorders. Part II. Hemodynamic effects and clinical applications. Ann Intern Med 93: 886-904
3. Kukovetz WR, Holzmann S (1985) Mechanism of vasodilation by molsidomine. Am Heart J 109: 637-640
4. Kukovetz WR, Holzmann S, Wurn A, Pöch G (1979) Evidence for cyclic GMP-mediated relaxant effects of nitrocompounds in coronary smooth muscle. Naunyn Schmiedebergs Arch Pharmacol 310: 129-138
5. Rubenfire M, Tabaznik B, Liang CS, Heupler F, Achuff S, Reichek N, Geltman E, Kerin NZ, Neff RK, Braunwald E (1980) Nifedipine therapy for coronary-artery spasm. Experience in 127 patients. N Engl J Med 302: 1269-1273
6. Mueller HS, Chahine RA (1981) Interim report of multicenter double-blind placebo-controlled studies of nifedipine in chronic stable angina. Am J Med 71: 645-657
7. Gerstenblith G, Ouyang P, Achuff SC, Bulkley BH, Becher LC, Mellits ED, Baughman KL, Weiss JL, Fleherty JT, Kallman CH, Llewellyn M, Weisfeldt MI (1982) Nifedipine in unstable angina. A double-blind randomized trial. N Engl J Med 306: 885-889
8. Dalla-Volta S, Scorzelli L, Razzolini R (1985) Evaluation of the chronic antianginal effect of molsidomine. Am Heart J 109: 682-687
9. Guerchicoff S, Vazquez A, Kunik H, Drajer S, Diaz F (1978) Acute double-blind trial of a new anti-anginal drug: Molsidomine. Eur J Clin Pharmacol 13: 247-250
10. Rudolph W, Dirschinger J (1985) Effectiveness of molsidomine in the long-term treatment of exertional angina pectoris and chronic congestive heart failure. Am Heart J 109: 670-674
11. Klugmann S, Salvi A, Camerini F (1980) Hemodynamic effects of nifedipine in heart failure. Br Heart J 43: 440-446
12. Bellocci F, Ansalone G, Santarelli P, Loperfido F, Scabbia E, Zecchi P, Manzoll U (1982) Oral nifedipine in the long-term management of severe chronic heart failure. J Cardiovasc Pharmacol 4: 847-855
13. Acar J, Kulas A, Escudier B (1985) Long-term clinical and hemodynamic results of molsidomine treatment in patients with refractory heart failure. Am Heart J 109: 685-687
14. Robinson BF, Dobbs RJ, Kelsey CR (1980) Effects of nifedipine on resistance vessels, arteries and veins in man. Br J Clin Pharmacol 10: 433-438
15. Ludbrook PA, Tiefenbrunn AJ, Reed FR, Sobel BE (1982) Acute hemodynamic responses to sublingual nifedipine: Dependence on left ventricular function. Circulation 65: 489-498
16. Matsumoto S, Ito T, Sada T, Takahashi M, Su KM, Veda A, Okabe F, Sato M, Sekine I, Ifo Y (1980) Hemodynamic effects of nifedipine in congestive heart failure. Am J Cardiol 46: 476-480
17. Elkayam U, Weber L, Torkan B, Berman D, Rahimtoola SH (1983) Acute hemodynamic effect of oral nifedipine in severe chronic congestive heart failure. Am J Cardiol 52: 1041-1045
18. Nelson GIC, Silke B, Ahuja RC, Verma SP, Hussain M, Taylor SH (1984) Hemodynamic effects of nifedipine during upright exercise in stable angina pectoris and either normal or severely impaired left ventricular function. Am J Cardiol 53: 451-455
19. Elkayam U, Weber L, Torkan B, McKay CR, Rahimtoola SH (1984) Comparison of hemodynamic responses to nifedipine and nitroprusside in severe chronic congestive heart failure. Am J Cardiol 53: 1321-1325
20. Elkayam U, Weber L, McKay CR, Rahimtoola SH (1984) Differences in hemodynamic response to vasodilation due to calcium channel antagonism with nifedipine and direct-acting agonism with hydralazine in chronic refractory congestive heart failure. Am J Cardiol 54: 126-131
21. Juliard JM, Neukirch F, Zygelman M, Merillon JP, Michel PL, Pansard Y, Dahan M, Gourgon R (1985) Hemodynamic and coronary effects of molsidomine at basal state, during atrial pacing and during cold pressor test in patients with stable angina pectoris. Am Heart J 109: 662-666
22. Crexells C, Lidon RM, Augé JM, Bosch X, Pina C, Garcia J, Oriol A (1985) Haemodynamic effects of molsidomine in patients with severe chronic coronary disease. Eur Heart J 6: 1032-1039
23. Meinertz T, Brandstätter A, Trenk D, Jähnchen E, Ostrowski J, Gärtner W (1985) Relationship between pharmacokinetics and pharmacodynamics of molsidomine and its metabolites in humans. Am Heart J 109: 644-648
24. Drajer S, Vazquez A, Cercos H, Torres H, Cohn JL, Romero N, Faerman G, Soifer S, Nijensohn CM (1985) Molsidomine in the treatment of acute heart failure. Am Heart J 109: 712-715
25. Drajer S, Cercos H, Torres H, Vazquez A, Cohn JL, Romero N, Faerman G, Soifer S, Nijensohn CM (1984) Hemodynamic effects of oral molsidomine in pump failure complicating myocardial infarction. Eur J Clin Pharmacol 27: 419-422
26. Packer M, Meller J, Medina N, Yushak M, Gorlin R (1981) Provocation of myocardial ischemic events during initiation of vasodilator therapy for severe chronic heart failure. Clinical and hemodynamic evaluation of 52 consecutive patients with ischemic cardiomyopathy. Am J Cardiol 48: 939-946
27. Yokoyama M, Koizumi T, Fujitani K, Mizutani T, Fukuzaki H (1982) Adverse response to nifedipine in unstable angina pectoris. Chest 81: 646-648
28. Deanfield J, Wright C, Fox K (1983) Treatment of angina pectoris with nifedipine: Importance of dose titration. Br Med J 286: 1467-1470
29. Schanzenbächer P, Deeg P, Liebau G, Kochsiek K (1984) Paradoxical angina after nifedipine: Angiographic documentation. Am J Cardiol 53: 345-346
30. Gillmer DJ, Kark P (1980) Pulmonary edema precipitated by nifedipine. Br Med J 280: 1420-1421
31. Brooks N, Cattell M, Pidgeon J, Balcon R (1980) Unpredictable response to nifedipine in severe cardiac failure. Br Med J 281: 1324
32. Alves LE, Rose EP (1982) Use of nifedipine in older patients and patients with congestive heart failure. Am J Med 72: 462
33. Schulz W, Kaber G, Krams G, Kaltenbach M (1981) Influence of intracoronary and intravenous nifedipine on diameters of coronary vessels and stenoses. In: Rafflenbeul W, Lichtlen PR, Balcon R (eds) Unstable angina pectoris. Thieme, Stuttgart, pp 259-265
34. Feldman RL, Hill JA, Conti JB, Conti CR, Pepine CJ (1983) Analysis of coronary responses to nifedipine alone and in combination with intracoronary nitroglycerin in patients with coronary artery disease. Am Heart J 105: 651-657
35. Schulz W, Kober G, Bernauer R, Kaltenbach M (1985) Active and passive changes in coronary diameter after vasodilation with SIN-I, the active metabolite of molsidomine. Am Heart J 109: 694-699
36. Sobolski J, Vandermoten P, Stoupel E, Berkenboom G, Degre S (1985) The new long-acting coronary artery dilator molsidomine and its metabolite SIN-I. Am Heart J 109: 700-703

Received: September 16, 1988
accepted in revised form: May 8, 1989

Dr. Michael Kyriakidis
139-143 Karaiskou street
Piraeus (18535), Greece