Alterations in angina threshold with nifedipine during pacing induced angina

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SUMMARY Changes in coronary haemodynamics and angina threshold were determined during atrial pacing in 11 patients with fixed obstructive coronary artery disease with effort angina before and after the administration of 20 mg of oral nifedipine. Coronary vascular resistance decreased at resting and at "subangina" heart rates but not at "angina" rates. Primary coronary vasodilatation with nifedipine was also suggested by higher coronary sinus oxygen content whether at rest or at subangina or angina heart rates. After nifedipine angina occurred at a lower double product and lower myocardial oxygen consumption.

These findings suggest that nifedipine is a coronary vasodilator, but angina can occur at a lower angina threshold in some patients with obstructive coronary artery disease.

The imbalance between myocardial oxygen supply and demand is the principal mechanism of angina—the clinical manifestation of myocardial ischaemia. Primary decrease in coronary blood flow (oxygen supply), due to increased vasomotor tone or frank spasm of the epicardial conduit coronary arteries, appears to be the cause of myocardial ischaemia and spontaneous angina in patients with variant angina and in some patients with unstable angina.^{1,2} Pharmacological agents, such as calcium entry blocking drugs, which can decrease coronary resistance and relieve coronary artery spasm, are therefore useful in the management of variant and unstable angina.³⁻⁵ In patients with atherosclerotic coronary artery stenosis the capacity to increase coronary blood flow with increased myocardial oxygen requirements, as during effort induced angina, appears to be limited.⁶ The pharmacological treatment for effort angina has therefore usually relied

on decreasing myocardial oxygen demand. If, however, coronary blood flow can also be increased concomitantly the myocardial angina threshold is likely to improve. Nifedipine increases coronary blood flow in experimental animals and in humans by dilating epicardial coronary arteries and coronary arterioles.⁷⁻¹⁷ Thus the potential exists that nifedipine can improve angina threshold in patients with atherosclerotic obstructive coronary artery disease and effort angina. Angina threshold and coronary haemodynamics can be assessed during atrial pacing studies.⁶ The purpose of this study, therefore, was to evaluate the effects of oral nifedipine on pacing induced angina threshold in patients with atherosclerotic obstructive coronary artery disease and a history of stable effort angina.

Patients and methods

The study protocol was approved by the Human Research Committee at the University of California, San Francisco, and all patients gave written informed consent. The patient population consisted of 11 men (age range 48-65 (mean 58) years) with New York Heart Association class II or III chronic stable angina. Angina was classified as chronic if it had been present longer than three months and stable if the functional class had not recently deteriorated, there were no

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Nifedipine and angina threshold

symptoms at rest, and the work threshold at which angina appeared was consistent by history. All patients had undergone coronary arteriography within the preceding three months. Nine patients had significant coronary artery disease ($\geq 70\%$ luminal narrowing) of the three major epicardial coronary arteries and two patients two vessel disease. Three patients had old myocardial infarctions. No patient had previously been treated with a calcium entry blocking agent. Beta adrenergic blocking drugs were withheld for at least 24 hours and nitrates for at least 12 hours before the study.

All patients were admitted to the coronary care unit for placement of a triple lumen balloon flotation thermodilution catheter into the pulmonary artery and a coronary sinus thermodilution pacing catheter into the coronary sinus and for radial artery cannulation. The coronary sinus catheter was advanced into the midcoronary sinus to prevent reflux,¹⁸ and its position was checked fluoroscopically by injecting radiopaque dye before and after the study. After a brief rest, resting systemic and coronary haemodynamic data were collected and termed "baseline." Supraventricular pacing was then initiated at a rate 50% higher than the resting heart rate for five minutes and measurements at this time were defined as "subangina." The heart rate was then increased by 10 beats/min every minute until angina occurred or until a rate of 170 beats/min was achieved, and data collected at this pacing rate were defined as "angina." Electrocardiographic lead V5 was continuously monitored. Pacing was then discontinued. After a brief rest period, 20 mg of nifedipine was given orally, and 30 minutes later the pacing protocol was repeated. The subangina pacing rate was the same as that used before drug administration. If patients did not develop angina at the predrug angina rate the pacing rate was further increased until angina occurred.

The following systemic haemodynamic measurements were recorded: systolic, diastolic, and mean arterial blood pressure (SBP, DBP, and MAP respectively); heart rate (HR); thermodilution cardiac output (CO); mean right atrial pressure (RAP); and pulmonary capillary wedge pressure (PCWP). The following variables were calculated: cardiac index (CI) (l/min/m^2) = CO/BSA , where BSA is body surface area; stroke volume index (SVI) (ml/m^2) = CI/HR ; stroke work index (SWI) (g m/m^2) = $\text{SVI} \times (\text{MAP} - \text{PCWP}) \times 0.0136$; systemic vascular resistance (SVR) (dyn s cm^{-5}) = $(\text{MAP} - \text{RAP})/\text{CO} \times 80$; and double product (DP) ($\text{mm Hg/min} \times 10^{-3}$) = $\text{HR} \times \text{SBP}$. The double product at the onset of angina and electrocardiographic manifestation of myocardial ischaemia was defined as the angina threshold. Coronary sinus blood flow (CSBF) was determined by the constant infusion thermodilution technique¹⁹ using

the equation: $\text{CSBF (ml/min)} = ((T_B - T_I/T_B - T_M) - 1) \times 1.08 \times 46$ where T_B is blood temperature, T_I injectate temperature, T_M temperature of the mixture, 1.08 a constant accounting for the specific heat and density of blood and injectate, and 46 ml/min the infusion rate of injectate (5% dextrose in water) by a Harvard constant infusion pump. Arterial and coronary sinus blood samples were drawn simultaneously for determination of oxygen saturation with a Corning 175 automated blood gas and pH analyser. Oxygen content (ml/100 ml) was calculated as follows: % oxygen saturation $\times$ haemoglobin (g/dl) $\times 1.34$. The transmural arteriovenous oxygen content difference ($(\text{ART} - \text{CS})\text{O}_2$, volume %) was calculated as the difference between arterial and coronary sinus oxygen content. Myocardial oxygen consumption (MVO_2 ml/min) was calculated as follows: $(\text{ART} - \text{CS})\text{O}_2 \times \text{CSBF}(\text{ml/min}) \times 10^{-3}$. Mean coronary vascular resistance (CVR) (dyn s cm^{-5}) was calculated as $(\text{MAP} - \text{RAP})/\text{CSBF} \times 80$.

Statistical significance was evaluated by analysis of variance using Tukey's method for multiple comparisons.²⁰

Results

During atrial pacing all patients developed angina both before and after nifedipine. After nifedipine angina occurred at a pacing rate higher than the predrug angina rate in only three patients. The angina heart rate in the remaining eight patients was unchanged after nifedipine. ST segment shifts in the electrocardiograms, indicative of myocardial ischaemia, occurred concurrently during angina. In all patients angina resolved promptly after pacing was stopped.

SYSTEMIC HAEMODYNAMIC EFFECTS

The systemic haemodynamic effects of nifedipine are summarised in the Table. After nifedipine, resting heart rate and systolic blood pressure decreased at baseline, subangina, and angina heart rates. In the group as a whole, the double product did not change at baseline but decreased significantly at subangina and angina rates. At angina rates in eight patients the double product was lower; in two patients it was unchanged and in only one was it slightly higher after nifedipine. Systemic vascular resistance was lower at subangina and angina rates. Left ventricular stroke work index decreased and pulmonary capillary wedge pressure increased at angina rates before nifedipine, and there was no significant change after nifedipine, indicating no change in left ventricular pump function.

Table Systemic and coronary haemodynamic effects of nifedipine at rest (baseline) and at two different atrial pacing rates before and after nifedipine. Values are mean (SD) ($n = 11$)

Variables measured	Baseline		Subangina rate		Angina rate	
	Before	After	Before	After	Before	After
<i>Systemic data</i>						
Double product (mm Hg/min $\times 10^{-3}$)	11.71(3.14)	11.43(2.97)	19.45(4.73)	16.91(3.53)**	23.30(3.36)	21.28(3.00)**
Stroke work index (g m/m ²)	58.8(17.2)	53.7(15.9)	47.8(11.3)	46.5(10.5)	40.0(13.2)	37.3(15.8)
Systemic vascular resistance (dyn s cm ⁻⁵)	1252(298)	1062(348)	1308(408)	1005(274)*	1355(457)	1028(291)***
Systolic blood pressure (mm Hg)	159(19)	146(28)*	176(18)	156(18)	177(17)	157(19)***
Pulmonary capillary wedge pressure (mm Hg)	9.7(5.1)	10.0(5.4)	10.5(7.3)	10.2(6.8)	13.6(10.6)	13.5(9.4)
Resting heart rate (beats/min)	73(15)	79(16)*				
<i>Coronary data</i>						
Coronary sinus blood flow (ml/min)	74.9(41.2)	84.4(42.7)	105.3(52.9)	108.5(43.2)	122.5(50.9)	126.9(55.5)
Coronary vascular resistance (dyn s cm ⁻⁵)	131(74)	98(45)***	101(60)	80(40)**	82(38)	70(38)
Coronary sinus oxygen content (volume %)	6.32(1.06)	8.19(1.55)****	6.67(1.65)	7.83(1.35)***	6.86(1.69)	7.56(1.42)**
Arterial coronary sinus oxygen content difference (volume %)	12.51(1.80)	10.34(1.70)****	12.19(1.65)	10.65(1.67)****	12.01(1.63)	11.22(1.31)**
Myocardial oxygen consumption (ml/min)	9.57(6.00)	8.91(5.10)	12.42(6.90)	11.11(5.25)	14.62(6.54)	13.10(5.94)**

* $p < 0.02$,** $p < 0.05$,*** $p < 0.01$,**** $p < 0.001$.

CORONARY HAEMODYNAMICS

The effects of nifedipine on coronary haemodynamics are summarised in the Table and the Figure. Coronary sinus blood flow increased as the heart rate was increased to subangina and angina rates before nifedipine, and there was no significant change after nifedipine (Figure *a*). Before nifedipine, coronary sinus oxygen content did not change when heart rate was increased to subangina and angina rates. After nifedipine, this value increased appreciably at baseline and remained higher at subangina and angina rates (Figure *c*). Nevertheless, it decreased progressively as the heart rate was increased to subangina and angina rates ($p < 0.01$). Myocardial oxygen extraction also decreased appreciably after nifedipine at baseline and subangina rates; at angina rates the decrease was less pronounced (Figure *d*). Myocardial oxygen consumption did not change significantly at baseline and subangina rates, but it was lower at angina rates after nifedipine (Figure *f*).

Discussion

That nifedipine is a potent coronary vasodilator and dilates epicardial coronary arteries and decreases coronary arterial tone has been suggested both in experimental animals and in humans.⁷⁻¹⁷ The present study shows that even in patients with atherosclerotic obstructive coronary artery disease nifedipine can cause vasodilatation of the coronary vascular bed. This was evident from the decreased mean coronary vascular resistance at rest and at subangina heart rates after nifedipine. After nifedipine, arterial pressure fell at all heart rates, and the double product decreased at subangina and angina rates; but the expected fall in coronary blood flow due to decreased myocardial

oxygen demand did not occur. Most importantly, coronary sinus oxygen content increased and myocardial oxygen extraction decreased consistently, suggesting that the global myocardial perfusion was in excess of that required to meet myocardial oxygen demand. Increased coronary sinus oxygen saturation and decreased myocardial oxygen extraction after nifedipine have been observed in other investigations.²¹ These findings suggest that nifedipine has the potential to increase coronary blood flow by primary coronary vasodilatation even in patients with obstructive coronary artery disease. From this study, however, the site of coronary vasodilatation—the epicardial coronary arteries or coronary arteriolar bed—cannot be determined.

Nevertheless, the present study also shows that nifedipine can induce angina at a lower angina threshold in many patients with atherosclerotic obstructive coronary artery disease. After nifedipine, double product—an index of myocardial oxygen demand—was not only lower at subangina but also at angina pacing rates in most of our patients. Although previous studies have suggested that the double product may not change,²¹ decreased angina threshold—evident from decreased double product and decreased myocardial oxygen consumption at angina rates after nifedipine—has not been found. In the study of Emanuelsson and Holmberg, however, in five of their 14 patients myocardial lactate production, indicating myocardial ischaemia, occurred at a lower double product after nifedipine.²¹ In three of their patients myocardial lactate production occurred at rest after nifedipine despite a significant fall in systolic blood pressure. Kaltenbach *et al* showed that the coronary vasodilatation produced by nifedipine is temporally dissociated from its antianginal effect.²²

Fig. Effects of nifedipine on (a) coronary sinus flow, (b) coronary vascular resistance, (c) coronary sinus oxygen content, (d) myocardial oxygen extraction, (e) double product, and (f) myocardial oxygen consumption at rest (baseline), and at subangina, and angina heart rates before (●) and after (○) nifedipine. Values are means (SEM) ($n = 11$). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Simonsen and Nitter-Hauge also reported that whereas nifedipine produces coronary vasodilatation at rest this effect becomes insignificant as the angina threshold is reached.²³ In contrast to these studies, Engle and Lichtlen suggested that during pacing induced myocardial stress nifedipine might enhance coronary blood flow to the poststenotic area.¹⁷ These investigators compared changes in regional myocardial blood flow, determined by xenon washout techniques, in normal and poststenotic areas after nifedipine. It is not clear, however, whether the heart rate was increased to angina rates after nifedipine in the study of Engle and Lichtlen.¹⁷ Furthermore, the increment in blood flow to the poststenotic area at prenifedipine angina heart rate was not statistically significant, whereas the flow to the normal areas decreased. Thus the difference in the changes in flow

to the normal and poststenotic areas became statistically significant. It is also noteworthy that in the study of Engle and Lichtlen¹⁷ the double product at the highest pacing rate after nifedipine was 22% lower than that before nifedipine, indicating no improvement but a decrement in angina threshold. Lack of improvement in angina threshold during pacing induced angina in patients with obstructive coronary artery disease is not only observed with nifedipine but also with other calcium entry blocking agents. Verapamil, which also possesses coronary vasodilating effects and has the potential to increase coronary blood flow, does not improve angina threshold or coronary reserve in patients with effort angina.²⁴ Prostacyclin, a vasodilating prostaglandin, also decreases coronary vascular resistance and increases coronary blood flow with concomitant reduction in

myocardial oxygen extraction at rest; but it also does not increase angina threshold during atrial pacing.²⁵ It is apparent, therefore, that the pharmacological agents that can potentially increase coronary blood flow by primary coronary vasodilatation are unlikely to improve angina threshold in patients with fixed obstructive coronary artery disease. Indeed, potential exists for the reduction of angina threshold with potent coronary vasodilators. Clinical studies also suggest that in some patients angina may be precipitated after nifedipine.²⁶

The mechanism for this paradoxical response is not entirely clear. A reflex increase in myocardial contractile function or tachycardia and a possible increase in myocardial oxygen demand cannot be incriminated as the important cause since coronary sinus venous oxygen content was higher and global myocardial oxygen extraction lower at the time of angina.

One possible explanation is that nifedipine induced coronary vasodilatation increased blood flow to the non-ischaemic zone in excess of what was needed to meet the metabolic demand without increasing the flow to the potentially ischaemic zones. In the ischaemic zones the exhaustion of the autoregulatory reserve due to metabolically mediated reduction of coronary vascular resistance prevents further reduction of coronary vascular resistance. Diversion of blood flow from the ischaemic zones to the relatively non-ischaemic myocardial zones, as a potential cause for induction of myocardial ischaemia at rest or at a lower double product, cannot be entirely excluded. That the potent coronary vasodilators can cause such a diversion of flow from the ischaemic myocardial zones has been suggested in previous studies.^{27, 28}

In conclusion, the results of the present study suggest that nifedipine is a potent coronary vasodilator, and it decreases coronary vascular resistance even in patients with fixed obstructive coronary artery disease. In patients with significant obstructive coronary artery disease, however, it does not improve angina threshold. In some patients angina can occur at a lower myocardial oxygen demand.

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References

- Maseri A, L'Abbate A, Chierchia S, *et al.* Significance of spasm in the pathogenesis of ischemic heart disease. *Am J Cardiol* 1979; 44: 788-92.
- Parodi O, Maseri A, Simonetti I. Management of unstable angina at rest by verapamil: a double-blind crossover study in coronary care unit. *Br Heart J* 1979; 41: 167-74.
- Goldberg S, Reichel N, Wilson J, Hirshfeld JW Jr, Muller J, Kastor JA. Nifedipine in the treatment of Prinzmetal's (variant) angina. *Am J Cardiol* 1979; 44: 804-10.
- Muller JE, Gunther SJ. Nifedipine therapy for Prinzmetal's angina. *Circulation* 1978; 57: 137-9.
- Johnson SM, Mauritsen DR, Willerson JT, Hillis LD. Comparison of verapamil and nifedipine in the treatment of variant angina pectoris: preliminary observations in ten patients. *Am J Cardiol* 1981; 47: 1295-300.
- Rouleau J-L, Chatterjee K, Ports TA, Parmley W. Coronary reserve angina threshold in patients with fixed obstructive coronary artery disease: alterations in coronary vascular tone do not play a significant role [Abstract]. *J Am Coll Cardiol* 1983; 1: 672.
- Imai S. Effects of nifedipine on heart and coronary circulation. In: Hashimoto K, Kimura E, Kobayashi T, eds. *New therapy of ischemic heart disease*. Tokyo: University of Tokyo Press, 1975: 23.
- Fleckenstein A, Grun G, Byon KY, Doring HJ, Tritthart H. The basic Ca antagonist actions of nifedipine on cardiac energy metabolism and vascular smooth muscle tone. In: Hashimoto K, Kimura E, Kobayashi T, eds. *New therapy of ischemic heart disease*. Tokyo: University of Tokyo Press, 1975: 31.
- Naylor WG, Ferrari R, Williams A. Protective effect of pretreatment with verapamil, nifedipine and propranolol on mitochondrial function in the ischemic and reperfused myocardium. *Am J Cardiol* 1980; 46: 242-8.
- Henry PD, Clark RE. Protection of ischemic myocardium by treatment with nifedipine. In: Winbury MM, Abiko Y, eds. *Ischemic myocardium and antianginal drugs*. New York: Raven Press, 1979: 143.
- Henry PD, Schuchleib 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.
- Gunther S, Green L, Muller JE, Mudge GH Jr, Grossman W. Inappropriate coronary vasoconstriction in patients with coronary artery disease: a role for nifedipine? *Am J Cardiol* 1979; 44: 793-7.
- Stone PH, Antman EM, Muller JE, Braunwald E. Calcium channel blocking agents in the treatment of cardiovascular disorders. Part 2: Hemodynamic effects and clinical applications. *Ann Intern Med* 1980; 93: 886-904.
- Henry PD. Comparative pharmacology of calcium antagonists: nifedipine, verapamil and diltiazem. *Am J Cardiol* 1980; 46: 1047-58.
- Sobel BE. Mechanisms of action and clinical implications of calcium antagonists. *Practical Cardiology* 1981; 7: 31.
- Bertrand ME, Lablancche JM, Tilmant PY. Treatment of spasm of the coronary artery with nifedipine. *Eur Heart J* 1980; suppl B: 65.
- Engle H-J, Lichtlen PR. Beneficial enhancement of coronary blood flow by nifedipine. Comparison with nitroglycerin and beta blocking agents. *Am J Med* 1981; 71: 658-66.
- Mathey DG, Chatterjee K, Tyberg JV, Lekven J, Brundage BH, Parmley WW. Coronary sinus reflux: a source of error in the measurement of thermodilution coronary sinus flow. *Circulation* 1978; 57: 778-86.
- Ganz W, Tamura K, Marcus HS, Donoso RR, Yoshida S, Swan HJC. Measurement of coronary sinus blood flow

- by continuous thermodilution in man. *Circulation* 1971; 44: 181-95.
- 20 Dixon WJ. *BMDP statistical software 1981*. Berkeley: University of California Press, 1981.
- 21 Emanuelsson H, Holmberg S. Mechanisms of angina relief after nifedipine: a hemodynamic and myocardial metabolic study. *Circulation* 1983; 68: 124-30.
- 22 Kaltenbach M, Schultz W, Kober G. Effects of nifedipine after intravenous and intracoronary administration. *Am J Cardiol* 1979; 44: 832-8.
- 23 Simonsen S, Nitter-Hauge S. Effect of nifedipine (adalat) on coronary haemodynamics in patients with coronary arteriosclerotic disease. *Acta Med Scand* 1978; 204: 179-84.
- 24 Rouleau J-L, Chatterjee K, Ports TA, Doyle MB, Hiramatsu B, Parmley WW. Mechanism of relief of pacing-induced angina with oral verapamil: reduced oxygen demand. *Circulation* 1983; 67: 94-100.
- 25 Bergman G, Daly K, Atkinson L, et al. Prostacyclin: haemodynamic and metabolic effects in patients with coronary artery disease. *Lancet* 1981; i: 569-72.
- 26 Jariwalla AG, Anderson EG. Production of ischaemic cardiac pain by nifedipine. *Br Med J* 1978; i: 1181-3.
- 27 Mann T, Cohn PF, Holman BL, Green LH, Markis JE, Phillips DA. Effect of nitroprusside on regional myocardial blood flow in coronary artery disease. Results in 25 patients and comparison with nitroglycerin. *Circulation* 1978; 57: 732-8.
- 28 Arrotti J, Gunnar RM, Ward J, Loeb HS. Comparative effect of intravenous dipyridamole and sublingual nitroglycerin on coronary hemodynamics and myocardial metabolism at rest and during atrial pacing in patients with coronary artery disease. *Clin Cardiol* 1980; 3: 365-70.