

Coronary haemodynamic effects of nifedipine *Comparison with glyceryl trinitrate*

DAVID L STONE,*† JOHN D STEPHENS, SEAMUS O BANIM

From the Department of Cardiology, St Bartholomew's Hospital, West Smithfield, London

SUMMARY The coronary haemodynamic effects of nifedipine and glyceryl trinitrate were compared in 22 patients undergoing investigations for suspected coronary artery disease. Myocardial blood flow was estimated by the coronary sinus thermodilution technique.

In sinus rhythm nifedipine increased mean coronary sinus flow from 135 ml/min to 152 ml/min, and reduced arterio-coronary sinus oxygen difference from 12.4 to 10.96 ml/100 ml without causing a significant change in coronary vascular resistance or in myocardial oxygen consumption. Glyceryl trinitrate reduced mean coronary sinus flow from 165 to 111 ml/min, myocardial oxygen consumption from 19.2 to 11.9 ml/min, and arterio-coronary sinus oxygen difference from 11.7 to 10.9 ml/100 ml. There was a rise in coronary vascular resistance from 54 355 to 74 364 dynes s cm⁻⁵.

During atrial pacing nifedipine reduced the arterio-coronary sinus oxygen difference from 11.99 to 11.0 ml/100 ml but had no significant effect on the other variables measured. Glyceryl trinitrate caused a fall in mean coronary sinus flow from 207 ml/min to 168 ml/min; myocardial oxygen consumption fell from 24 ml/min to 18 ml/min, while coronary vascular resistance rose from 41 714 to 51 234 dynes s cm⁻⁵. Direct comparison of the two drugs showed a significant difference in effects on coronary sinus flow and coronary vascular resistance in sinus rhythm. Both drugs appeared effective in relieving ischaemia as judged by a reduction of the incidence of pacing induced angina and an improvement in lactate status.

Nifedipine is a calcium antagonist which is widely used in the treatment of both exercise induced¹⁻³ and spontaneous⁴ angina. It reduces smooth muscle tone in coronary and peripheral resistance vessels⁵⁻⁷ and promotes collateral flow to the ischaemic myocardium.⁸ It also exerts a negative inotropic effect in vitro,^{9,10} which may account for the occasional deterioration when the drug is given to patients with heart failure or aortic stenosis, or to those who are on beta blocking agents.¹¹⁻¹⁶ The precise mechanism of its antianginal action has, however, not been defined conclusively.¹⁷ This study was performed to assess the coronary haemodynamic effects of nifedipine at rest and during haemodynamic stress, both by atrial pacing, and to compare its actions with the established antianginal agent, glyceryl trinitrate.

Patients and method

Twenty-two patients undergoing investigation for chest pain were studied at the time of cardiac catheterisation. Coronary arteriography and left ventriculography were performed by the Sones' technique from the right arm. At the end of the diagnostic procedure, a Ganz coronary sinus flow dilution catheter was advanced to the coronary sinus from a right antecubital vein. The arterial catheter used during the diagnostic procedure was left in the root of the aorta. Blood samples were taken via these two catheters. Standard lead II of the electrocardiogram was recorded. Systemic arterial pressure was recorded using a Bell and Howell transducer with a Mingo-graph 82 recorder.

Coronary sinus flow was recorded by the Ganz technique,¹⁸ the "down-stream" thermistor being placed close to the orifice of the coronary sinus and its position being ascertained by a small injection of contrast medium before each flow estimation. The Ganz

*Supported by a grant from Bayer (UK).

†Present address: Regional Cardiac Unit, Papworth Hospital, Nr Cambridge.

catheter was used for the collection of coronary sinus blood samples and for atrial pacing. Blood oxygen contents were measured spectrophotometrically (IL CO oximeter). Blood lactates were measured by an enzymatic technique. Coronary sinus and arterial samples were taken simultaneously.

Measurements began 30 minutes after the diagnostic procedure. Heart rate, systemic arterial pressure, and coronary sinus flow were recorded. Coronary sinus and arterial blood were taken for lactate and oxygen content estimation. The heart rate was then increased by atrial pacing at increments of 10 beats a minute until a rate of approximately 30 beats a minute above sinus rate was reached (stage I). Measurements of arterial blood pressure and coronary sinus flow were repeated. Blood samples were taken to determine oxygen content. For those patients with obstructive coronary lesions the pacing rate was then increased at increments of 10 beats per minute until angina was induced, when blood samples were taken for lactate estimations (stage II). Pacing was then terminated. Then 20 mg sublingual nifedipine or 0.5 mg sublingual glyceryl trinitrate, randomly selected, were administered. Resting heart rate, blood pressure, and coronary sinus flow measurements were repeated after 10 minutes for glyceryl trinitrate and after 20 minutes for nifedipine. Heart rate was then increased by pacing to stage I and stage II levels where measurements were repeated.

DERIVED VARIABLES

$$\frac{\text{Coronary sinus flow (CSF)}}{(\text{ml/min})} = \frac{T_M - T_I}{T_B - T_M} \times K \times Q_I$$

T_M = temperature of mixture of blood and injectate, °C

T_I = temperature of injectate, °C

T_B = temperature of the blood, °C

K = a constant = 1.08

Q_I = rate of infusion of the injectate (35 ml/min).

$$\text{Myocardial oxygen consumption (MVO)}_2 = \text{CSF} \times \text{AV oxygen difference (ml/min)}$$

where AV oxygen difference (ml/100 ml) = coronary arteriovenous oxygen difference.

$$\text{Coronary vascular resistance (dynes s cm}^{-5}\text{)} =$$

$$\frac{\text{mean system arterial pressure} - \text{mean coronary sinus pressure} \times 80}{\text{mean coronary sinus flow}}$$

Statistical analysis was by paired Student's *t* test.

Results

Twelve patients received nifedipine and 10 glyceryl trinitrate, seven patients in each of these groups hav-

ing obstructive coronary lesions. The results are expressed as mean \pm standard error of the mean.

HEART RATE

Both nifedipine and glyceryl trinitrate had a significant effect on heart rate in sinus rhythm. Mean heart rate rose from 71 ± 2.8 bpm at rest to 76.33 ± 2.6 after nifedipine ($p < 0.02$) and from 71.5 ± 2.6 to 76.7 ± 3.3 after glyceryl trinitrate ($p < 0.01$).

SYSTEMIC ARTERIAL PRESSURE

There was no significant change in arterial pressure in sinus rhythm after nifedipine. During pacing at stage I mean arterial pressure fell from 99.75 ± 3.6 to 91.5 ± 3.6 ($p < 0.01$) after drug administration. Glyceryl trinitrate reduced mean arterial blood pressure from 97.3 ± 4.1 to 93.8 ± 3.9 mmHg in sinus rhythm and from 102.8 ± 4.9 to 98.5 ± 3.7 mmHg during atrial pacing at stage I, but neither of these changes was significant.

CORONARY HAEMODYNAMICS

Sinus rhythm

Mean coronary sinus flow rose after nifedipine from 135 ± 14 ml/min to 152 ± 19 ml/min (NS) (Fig. 1). There was little change in myocardial oxygen consumption, the mean value being 16.6 ± 1.8 ml/min

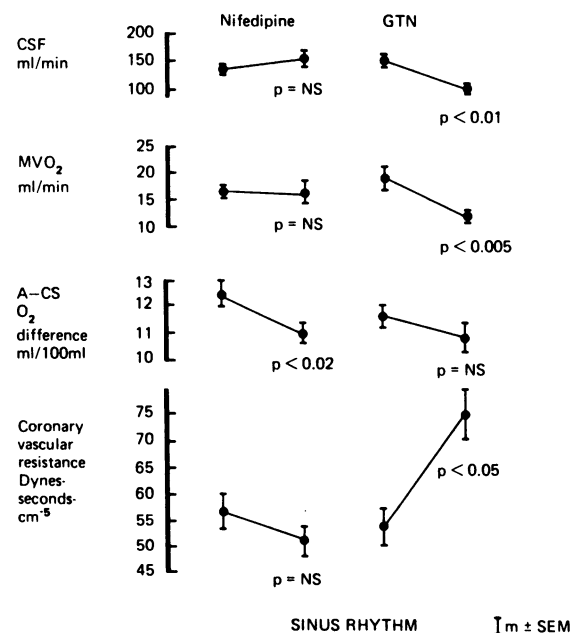


Fig. 1 Coronary haemodynamics at rest. CSF, coronary sinus flow; MVO₂, myocardial oxygen consumption; GTN, glyceryl trinitrate; A-CS O₂ difference, arterio-coronary oxygen difference.

before and 16.3 ± 2.02 ml/min after nifedipine. Mean arterio-coronary sinus oxygen difference fell from 12.4 ± 0.54 ml/100 ml to 10.96 ± 0.46 ml/100 ml after nifedipine ($p < 0.02$) and coronary vascular resistance fell from $56\,964 \pm 7191$ to $51\,400 \pm 5995$ dynes s cm^{-5} (NS).

Mean coronary sinus flow fell from 165 ± 20.97 ml/min before glyceryl trinitrate to 111 ± 14.0 ml/min after this drug ($p < 0.01$). Myocardial oxygen consumption fell from 19.2 ± 2.6 ml/min to 11.9 ± 1.7 ml/min ($p < 0.005$). Mean arterio-coronary sinus oxygen difference fell from 11.7 ± 6.39 ml/100 ml to 10.86 ± 0.54 , a change that was not significant. Coronary vascular resistance rose from $54\,355 \pm 7490$ dynes s cm^{-5} to $74\,364 \pm 10\,145$ ($p < 0.05$).

When a direct comparison of the percentage change induced by the two drugs on these variables was made, significant differences were found only in coronary sinus flow ($p < 0.001$) and coronary vascular resistance ($p < 0.005$).

Atrial pacing (stage I)

The effect of the two drugs on these variables during rapid atrial pacing is shown in Fig. 2.

After nifedipine coronary sinus flow fell from a mean of 167 ± 12.33 ml/min to a mean of 159 ± 20.9

ml/min (NS) and mean myocardial oxygen consumption from 19.3 ± 1.06 ml/min to 17.4 ± 2.38 ml/min (NS). Mean arterio-coronary sinus oxygen difference fell from 11.99 ± 0.64 ml/100 ml to 11.0 ± 0.5 ($p < 0.05$) and coronary vascular resistance rose from $48\,160 \pm 4938$ to $49\,905 \pm 6475$ dynes s cm^{-5} (NS).

Mean coronary sinus flow fell from 207 ± 21.5 ml/min to 168 ± 19.2 ml/min ($p < 0.025$) after glyceryl trinitrate. This was paralleled by a fall in myocardial oxygen consumption from a mean of 24 ± 2.8 ml/min before the drug to a mean of 18 ± 2.2 ml/min afterwards ($p < 0.05$). There was no significant change in arterio-coronary sinus oxygen difference after glyceryl trinitrate (mean 11.36 ± 0.52 ml/100 ml before the drug, 10.69 ± 0.48 afterwards). Coronary vascular resistance rose after glyceryl trinitrate from $41\,714 \pm 4819$ to $51\,234 \pm 5926$ dynes s cm^{-5} ($p < 0.05$).

There was no significant difference in any variable at this pacing level when percentage change induced by the two drugs was directly compared.

Pacing induced angina (stage II)

All 14 patients with significant coronary artery disease developed angina on rapid atrial pacing before drug administration. At pacing to the same rate after drug administration no patients who received glyceryl trinitrate developed chest pain and of the seven patients who received nifedipine two still developed chest pain.

Lactate estimations

An objective estimate of the effect of the drugs on myocardial ischaemia was provided by analysis of lactate levels in the arterial and coronary sinus blood. These results concern only those patients with obstructive coronary disease on whom technically satisfactory estimates were made (five for glyceryl trinitrate and six for nifedipine). Mean arterial coronary sinus lactate difference was $+0.21 \pm 0.51$ mmol/l before glyceryl trinitrate and -0.17 ± 0.35 mmol/l afterwards. For nifedipine the arterial coronary sinus lactate difference was -0.03 ± 0.2 mmol/l before the drug and -0.35 ± 0.7 afterwards. The arterial lactate levels were 1.4 ± 0.5 before glyceryl trinitrate and 1.4 ± 0.4 afterwards and 0.91 ± 0.3 mmol/l before nifedipine and 1.25 ± 0.5 mmol/l after this drug. The more negative values after drug administration may indicate an improvement in lactate status.

Discussion

Nifedipine and glyceryl trinitrate are both effective in relieving exercise induced^{1-3, 19} and spontaneous^{4, 20} angina. Glyceryl trinitrate has a major effect on venous capacitance vessels,²¹ causing a fall in venous

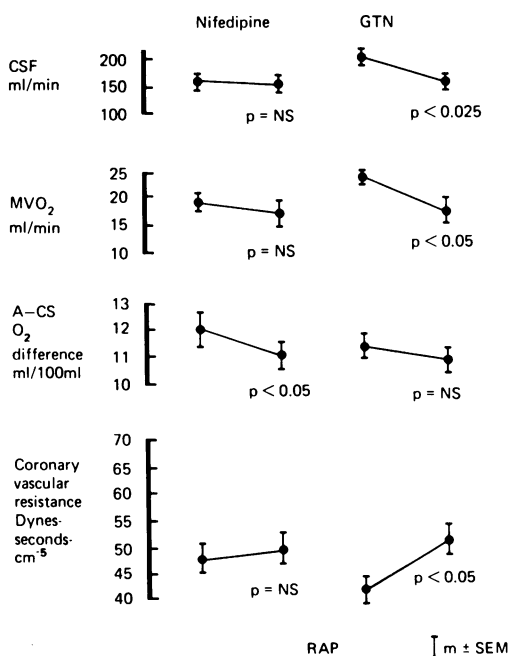


Fig. 2 Coronary haemodynamics during rapid atrial pacing (stage I). CSF, coronary sinus flow; MVO₂, myocardial oxygen consumption; GTN, glyceryl trinitrate; RAP, rapid atrial pacing (stage I); A-CS O₂ difference, arterio-coronary sinus oxygen difference.

return with a consequent drop in cardiac output and systemic arterial pressure. In this study we noted changes consistent with this action. There was a small fall in blood pressure both at rest, despite an increase in heart rate, and during atrial pacing. There was no change in systemic arterial pressure at rest after nifedipine but when the heart rate was fixed by atrial pacing a significant fall occurred. This could reflect the drug's cardiodepressant action or more likely its known action as a peripheral arteriolar vasodilator.²²

We concentrated on the coronary haemodynamics of both drugs using the coronary sinus flow technique originally developed by Ganz.¹⁸ Normally myocardial blood flow is controlled by an autoregulatory mechanism responsive to local metabolites.²³ Fluctuations in myocardial oxygen demand are associated with changes in myocardial blood flow but not in oxygen extraction.²⁴ A drug that has a direct coronary vasodilator or vasoconstrictor action may, however, override this autoregulatory mechanism and reduce oxygen extraction. Stephens *et al.*,²⁵ for example, have shown that sodium nitroprusside has a coronary vasodilator action only when oxygen consumption is held constant.

The two drugs considered in the present study had distinctly different effects on coronary haemodynamics. The predominant effect of glyceryl trinitrate was an overall reduction in myocardial oxygen consumption, presumably caused by its peripheral haemodynamic actions. This in turn leads to a significant fall in coronary sinus flow and a pronounced increase in coronary vascular resistance. Coronary arteriovenous oxygen difference did not alter significantly, which would suggest that under the circumstances of this study, glyceryl trinitrate did not have a coronary vasodilating action. Nifedipine, on the other hand, did not significantly alter myocardial oxygen consumption, coronary sinus flow, or coronary vascular resistance. It did, however, produce a significant fall in coronary arteriovenous oxygen difference, both in sinus rhythm and during atrial pacing, which points towards a direct coronary vasodilating action. Direct comparisons of the effects of the two drugs showed a significant difference in coronary sinus flow and coronary vascular resistance in sinus rhythm. These results suggest differing mechanisms of action for the two drugs, with nifedipine acting as a systemic and coronary arterial vasodilating agent while the effects of glyceryl trinitrate are predominantly venous. Similar results have been obtained by Gourgon *et al.*⁷

Previous investigators have found that primary coronary vasodilators may increase myocardial ischaemia caused by a coronary "steal" effect^{26 27} and that the extremely potent vasodilator dipyridamole could produce a detrimental effect on poststenotic

flow in chronically underperfused areas of the myocardium. In this investigation both drugs relieved pacing induced angina, and analysis of lactate levels suggested an improvement in ischaemic status. These findings imply, though not conclusively, that an important coronary "steal" effect does not occur with nifedipine. Failure to show a significant difference between glyceryl trinitrate and nifedipine in terms of arterio-coronary sinus oxygen difference suggests that the vasodilator effect of nifedipine is not of such a degree that it would rival dipyridamole. These findings are supported by the work of Lichtlen *et al.*²⁸ who showed, by using a Xenon washout technique, that dipyridamole might reduce flow distal to coronary stenosis whereas nifedipine increased it, and Engel *et al.*²² who had shown an increase in blood flow to ischaemic myocardium after nifedipine resulting in a reduction of inhomogeneity of flow between normal and ischaemic areas.

In summary, these results suggest differing actions for glyceryl trinitrate and nifedipine, with the latter having a primary coronary vasodilator action which is not of a sufficient degree to promote a coronary "steal" phenomenon.

References

- 1 Moskowitz RM, Piccini PA, Nacarelli GV, Zelis R. Nifedipine therapy for stable angina pectoris: preliminary results of effects on angina frequency and treadmill exercise response. *Am J Cardiol* 1979; 44: 811-6.
- 2 Kobayashi T, Ito Y, Tawara I. Clinical experiences with a new coronary-active substance (BAYI1040). *Arzneim Forsch* 1972; 22: 380-9.
- 3 Ekelund LG, Atterhög JH, Melin AL. Effect of nifedipine on exercise tolerance in patients with angina pectoris. In: Hashimoto K, Kimura E, Kobayashi T, eds. *1st nifedipine symposium*. Tokyo: Tokyo Press, 1975: 144-9.
- 4 Antman E, Muller J, Goldberg S, *et al.* Nifedipine for coronary artery spasm. Experience in 127 patients. *N Engl J Med* 1980; 302: 1269-73.
- 5 Vater W, Kroneberg G, Hoffmeister F, *et al.* Zur Pharmakologie von (4-(2'-Nitrophenyl)-2, 6, dimethyl-1, 4-dihydropyridin-3, 5-dicarbonsäuredimethylester Nifedipine) Bay a 1040. *Arzneim Forsch* 1972; 22: 1-14.
- 6 Vandenbrand M, Reem EWJ, Maester GT, Tiggelaar-de Widt I, de Ruite RR, Hugenholtz PG. Changes in right and left ventricular haemodynamics in angina pectoris following Adalat administration. In: Jatene AD, Lichtlen P, eds. *New therapy of ischaemic heart disease. Proceedings of the 3rd International Adalat symposium*. Amsterdam: Excerpta Medica: 1976: 69-75.
- 7 Gourgon R, Merillon JP, Zygelman M, Morgan TC, Patart O, Prasquier R. In: Lichtlen PR, Kimura E, Taira N, eds. *International Adalat Panel Discussion, Tokyo*. London: Excerpta Medica, 1979: 96-101.
- 8 Henry PD, Schuchleib R, Clark RE, Perez JE. Effect of nifedipine on myocardial ischemia: analysis of collateral

- flow, pulsatile heart and regional muscle shortening. *Am J Cardiol* 1979; **44**: 817-24.
- 9 Fleckenstein A, Doring HH, Janke J, Byon YK. Basic actions of ions and drugs on myocardial high energy phosphate metabolism and contractility. In: Schmier J, Eichler E, eds. *Handbook of experimental pharmacology*. Berlin: Springer-Verlag, 1975: 345-405.
 - 10 Fleckenstein A. Specific pharmacology of calcium in myocardium, cardiac pacemakers and vascular smooth muscle. *Annu Rev Pharmacol Toxicol* 1977; **17**: 149-66.
 - 11 Polese A, Fiorentini C, Olivari MT, Guazzi M. Clinical use of a calcium antagonist agent (nifedipine) in acute pulmonary oedema. *Am J Med* 1979; **66**: 825-30.
 - 12 Klugmann S, Salvi A, Camerini F. Haemodynamic effects of nifedipine in heart failure. *Br Heart J* 1980; **43**: 440-6.
 - 13 Brooks N, Cattell M, Pidgeon J, Balcon R. Unpredictable response to nifedipine in severe heart failure. *Br Med J* 1980; **281**: 1324.
 - 14 Anastassiades CJ. Nifedipine and beta blocker drugs. *Br Med J* 1980; **281**: 1251-2.
 - 15 Robson RH, Vishwanath MC. Nifedipine and beta blockade as a cause of cardiac failure. *Br Med J* 1982; **284**: 104.
 - 16 Gillmer DJ, Kark P. Pulmonary oedema precipitated by nifedipine. *Br Med J* 1980; **280**: 1420-1.
 - 17 Lown B. Introduction: Symposium on nifedipine and calcium flux inhibition in the treatment of coronary arterial spasm and myocardial ischaemia. *Am J Cardiol* 1979; **44**: 780-2.
 - 18 Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC. Measurement of coronary sinus blood flow by continuous thermodilution in man. *Circulation* 1971; **44**: 181-95.
 - 19 Epstein SE, Redwood DR, Goldstein RE. Angina pectoris: pathophysiology evaluation and treatment. *Ann Intern Med* 1971; **75**: 263-96.
 - 20 Hillis LD, Braunwald E. Coronary-artery spasm. *N Engl J Med* 1978; **299**: 695-702.
 - 21 Mason DT, Braunwald E. Effects of nitroglycerin and amyl nitrite on arteriolar and venous tone in the human forearm. *Circulation* 1965; **32**: 755-66.
 - 22 Engel HJ, Wolf R, Hundeshagen H, Lichtlen PR. Different effects of nitroglycerin and nifedipine on regional myocardial blood flow during pacing induced angina pectoris. *Eur Heart J* 1980; **1** (suppl B): 53-8.
 - 23 Berne RM. Regulation of coronary blood flow. *Physiol Rev* 1964; **44**: 1-29.
 - 24 Katz LN, Feinberg H. The relation of cardiac effort to myocardial oxygen consumption and coronary flow. *Circ Res* 1958; **6**: 656-69.
 - 25 Stephens JD, Hayward RP, Dymond DS, Ead H, Adams L, Spurrell RAJ. Effects of sodium nitroprusside and phenylephrine on coronary dynamics in patients with normal left ventricular function. *Br Heart J* 1979; **41**: 456-62.
 - 26 Sharma GVRK, Kumar R, Molokhia K, Miesser JV. 'Coronary steal'. Regional myocardial blood flow studies during isoprotenerol infusion in acute and healing myocardial infarction (abstract). *Clin Res* 1971; **19**: 339.
 - 27 da Luz PL, Forrester JS, Wyatt HL, et al. Hemodynamic and metabolic effects of sodium nitroprusside on the performance and metabolism of regional ischemic myocardium. *Circulation* 1975; **52**: 400-7.
 - 28 Lichtlen PR, Engel HJ, Hundeshagen H. Regional myocardial blood flow in normal and poststenotic areas after nitroglycerine, -blockade (atenolol), coronary dilatation (dipyridamole) and calcium antagonism (nifedipine). *Herz* 1977; **2**: 81-6.

Requests for reprints to Dr David L Stone, Regional Cardiac Unit, Papworth Hospital, Papworth Everard, Cambridge CB3 8RE.