Haemodynamic and radionuclide effects of amlodipine in coronary artery disease

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- 1 The haemodynamic and radionuclide effects of a new long-acting slow-calcium channel blocking agent, amlodipine, were evaluated in 32 patients with coronary artery disease.
- 2 Haemodynamic measurements in 24 patients were made at rest and 10 to 15 min after 20 mg i.v. amlodipine. Amlodipine significantly reduced systemic arterial blood pressure and vascular resistance index with an increased heart rate and augmented cardiac index. Cardiac stroke volume index rose and stroke work fell without change in pulmonary artery occluded pressure (PAOP).
- 3 The exercise effects were determined by comparison of measurements during 4 min of supine bicycle exercise at a fixed workload before and after drug treatment. During dynamic exercise, amlodipine reduced systemic arterial pressure and vascular resistance index. Exercise cardiac index, stroke volume index and heart rate were higher. The left ventricular filling pressure was significantly reduced.
- 4 Radionuclide parameters were studied in 16 patients at rest and on exercise; ejection fraction was unaltered following amlodipine.
- 5 Pre-therapy haemodynamic values correlated with response following amlodipine for resting mean blood pressure, systemic vascular resistance and exercise PAOP.
- 6 Thus, the immediate impact of amlodipine in stable coronary artery disease was to reduce left ventricular afterload and thereby improve cardiac pumping performance.

Keywords amlodipine haemodynamics dose-response effects

Introduction

Membrane slow-calcium channel blocking drugs have been found to be of haemodynamic and symptomatic benefit in angina pectoris (Atterhog *et al.*, 1975; Moskowitz *et al.*, 1979). Administered acutely, they reduce systemic vascular resistance and left ventricular afterload (Singh, 1982; Stone *et al.*, 1980). This is usually accompanied by an increased cardiac output with reduced left ventricular volume and filling pressure (Kieval *et al.*, 1982; Silke *et al.*, 1984a,b, 1985a, 1986). The clinical consequences include reduction in symptomatic and objective measures

of myocardial ischaemia with prolongation of exercise time (Rousseau *et al.*, 1984a,b; Scheidt *et al.*, 1985; Visser *et al.*, 1985). Drugs of this group are prescribed twice or three times daily in angina pectoris (Opie, 1980) due to their short half-life and consequent limited duration of action. Amlodipine is a new calcium channel blocking compound with a half-life of approximately 45 h (Beresford *et al.*, 1985; Faulkner *et al.*, 1986). When given as monotherapy it increased exercise treadmill time by 25% in patients with chronic stable angina pectoris (Jackson *et al.*,

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1985). We have described the immediate haemodynamic dose-response effects of amlodipine (2.5–20 mg i.v.); pharmacodynamic activity was demonstrated after 10 mg and 20 mg (Frais *et al.*, 1986). The present study extends these observations, evaluates the relationship between baseline haemodynamics and response to amlodipine; the actions of amlodipine on radio-nuclide markers of cardiac performance in coronary disease are described.

Methods

Patients

Thirty-two men with chronic stable angina were studied. Twenty-four were evaluated during right heart catheterization as part of their work-up for coronary artery bypass grafting ($n = 21$) or at assessment 3 to 6 months following myocardial infarction ($n = 3$). These patients were aged 54 ± 2 years (range 38–64) and all had a normal radiographic cardiothoracic ratio (0.47 ± 0.01 ; range 0.39–0.56). Nineteen of these 24 patients had sustained a previous myocardial infarction > 3 months prior to study. Those who underwent angiography ($n = 21$) had significant coronary stenosis (> 70% diameter narrowing) in the major coronary vessels (single in 6, double in 7 and triple vessel in 8). The angiographically calculated resting left ventricular ejection fraction was $47\% \pm 2$ (range 22–68%). The average workload maintained during 4 min supine bicycle exercise was 77 ± 9 watt (range 20–150). Sixteen patients (including eight of the previous group) were studied on a separate occasion with a radio-nuclide assessment of amlodipine. These patients had a background of chronic stable angina or previous myocardial infarction; they had a resting ejection fraction of $46\% \pm 3$ (30–74%) which fell to $36\% \pm 2$ (26–56%) at an average supine bicycle workload (4 min) of 82 ± 10 watts (20–150). Informed consent was given by all patients and the studies were approved by the Hospital Ethics Committee.

Study design

a) Haemodynamics The haemodynamic effects of amlodipine were examined without pre-medication in fasting patients; studies were undertaken on the day prior to coronary angiography. After a brief warm-up exercise to ensure stability of haemodynamic variables (Verma *et al.*, 1984), resting measurements, after 10 ml i.v. dextrose-saline as control, were made during four consecutive 5 min periods (Figure 1). Haemodynamic variables were recorded in the last 2 min of each 5 min control period. Amlodipine 20 mg was then given over 5 min into the pulmonary artery via the thermodilution catheter and further haemodynamic measurements commenced 10 min following end of the injection. The effects of amlodipine on haemodynamics during 4 min constant load supine bicycle exercise were compared with pre-treatment exercise.

Haemodynamic techniques

Heart rate was measured from the electrocardiogram (CM5) and systemic arterial pressure through a brachial artery catheter. Pulmonary vascular pressures were measured through a balloon-tipped thermodilution catheter positioned so that inflation of the balloon resulted in replacement of the pulmonary artery pressure record by a typical pulmonary wedge tracing (pulmonary artery occluded pressure—PAOP). Pressures were externally transduced using strain gauges (zero reference being at mid-chest level) and recorded together with heart rate (EMI 6300). Mean pressures were integrated over at least two respiratory cycles. Thermodilution cardiac output was measured using a gas-operated constant speed injector (OMP Model 3700) with 10 ml of dextrose-saline at 0°C as indicator. Cardiac output estimates were made in triplicate and each set of determinations followed an initial injection of dextrose-saline to overcome catheter warming errors. The cardiac output was automatically computed (Gould Statham SP 1435 Computer/SP 2009 Recorder). This system is

Figure 1 Study design, ■ haemodynamic measurements, X amlodipine 20 mg i.v., S saline control.

linear *in vitro*, with a variance of < 6% in patients at rest and < 7% during supine constant load bicycle exercise. Systemic and pulmonary vascular resistance and stroke volume were calculated using the following formulae and corrected for body surface area:

systemic vascular resistance index (SVRI)
= mean systemic artery pressure (MAP)
× 80/cardiac index

stroke volume index (SVI)
= cardiac index/heart rate

stroke work index (SWI)
= (mean arterial pressure—PAOP)
× SVI × 0.0136

The left ventricular ejection fraction was averaged from three planimetric integrations of the left ventricular angiogram performed in the right anterior oblique projection. The average variability of this technique between two blinded observers was less than 5%.

b) Effect on left ventricular ejection fraction
Sixteen patients were studied 10–15 min following i.v. 10 mg ($n = 8$) or 20 mg ($n = 8$) amlodipine. Four sets of control radionuclide ejection fraction estimates were obtained at 5 min intervals and measurements repeated after dosing. Exercise measurements were obtained during each of 4 min supine bicycle exercise at fixed workload (load-limited by symptoms for each individual) and compared with control data obtained at an identical workload.

Radionuclide methods

The radionuclide studies were undertaken with an ECG-triggered, microprocessor based, non-imaging nuclear probe (Nuclear Stethoscope, Bios Inc., Valhalla, New York), using previously described techniques (Strashun *et al.*, 1981; Wagner, 1982). Patients were injected with 15 mg of stannous pyrophosphate (TechneScan PYP kit, Mallinckrodt Diagnostic Products) and 30 min later with red blood cells labelled *in vitro* with 99m-technetium (15 mCi). For each study, the nuclear stethoscope was positioned parallel to the catheter table 90 cm from the sternal angle midpoint. The degree of obliquity and caudal tilt for optimum assessment was individually determined and thereafter fixed (usually 20–35 degree LAO with a 10–20 degree caudal tilt). To maintain the same position the probe circumference was marked on the chest and rest and exercise studies used techniques which minimise chest movement. The area of maximal left ventricular count activity

and level of background activity were determined before each study using the microprocessor algorithm incorporated in the nuclear probe. Data were acquired in the ECG-gated mode for between 30 and 60 s, to a minimum of 10,000 counts. The left ventricular ejection fraction was determined from the displayed background subtracted left ventricular time-activity curves. Repeatability was previously examined in 20 patients. The coefficient of variation for resting ejection fraction measured 10 times at 2 min intervals in 10 cases was 3.5% (range 0.9–5.7%) and 4.6% (1.0–11.2) over six determinations during steady state supine bicycle exercise in a further ten.

Statistical analysis

Statistical analysis of the haemodynamic data compared control and post-drug data by analysis of variance of repeated measurements (B.M.D.P., 1979). Tukey's Studentised Range Test (Winer, 1977) was then used to generate the single value by which difference between control and post-drug values was tested. Variation of measurements during the control studies was determined by the coefficient of variation which expresses standard deviation as a percentage of the mean.

Results

The studies were completed without incident in any patient. None developed hypotension, bradycardia, cardiac conduction abnormalities or other unwanted effects. Flushing or a warm sensation was noted in six.

Stability of control observations

During the control period with repeated saline injections, the baseline variability in circulatory variables was small (Verma *et al.*, 1984). The coefficient of variation average values and their range were: systolic blood pressure 1.8% (range 0.4–4.0), diastolic blood pressure 2.3% (0.6–5.5), mean arterial pressure 1.9% (0.5–5.7), heart rate 2.7% (0–6.3), pulmonary artery occluded pressure 7.4% (0–22.2), cardiac index 3.5% (1.3–8.3) and ejection fraction 3.2% (0.9–6.2). Since the repeated measures procedure revealed no trends during the control period these data were averaged.

Effects at rest (Table 1)

Amlodipine significantly reduced all components of the systemic arterial blood pressure ($P <$

Table 1 Haemodynamic effects of amlodipine (20 mg i.v.) in coronary artery disease (mean $\pm$ s.e. mean)

	Control	Rest Drug	Difference	Control	Exercise Drug	Difference
Systolic blood pressure (mm Hg)	145 $\pm$ 5	130 $\pm$ 4	-15**	181 $\pm$ 6	173 $\pm$ 6	-8**
Diastolic blood pressure (mm Hg)	80 $\pm$ 2	72 $\pm$ 2	-8**	89 $\pm$ 2	85 $\pm$ 3	-4**
Mean blood pressure (mm Hg)	105 $\pm$ 3	94 $\pm$ 3	-10**	121 $\pm$ 4	115 $\pm$ 4	-6**
Heart rate (beats min ⁻¹)	66 $\pm$ 3	75 $\pm$ 3	+9**	101 $\pm$ 4	106 $\pm$ 4	+5**
Pulmonary artery occluded pressure (mm Hg)	12.8 $\pm$ 0.6	14.2 $\pm$ 0.8	+1.4	27.7 $\pm$ 1.6	23.4 $\pm$ 2.0	-4.3**
Cardiac index (l min ⁻¹ m ⁻²)	3.2 $\pm$ 0.1	3.9 $\pm$ 0.1	+0.7**	5.7 $\pm$ 0.3	6.2 $\pm$ 0.3	+0.5**
Stroke volume index (ml m ⁻²)	49 $\pm$ 2	53 $\pm$ 2	+3**	57 $\pm$ 2	59 $\pm$ 2	+2*
Systemic vascular resistance index (dyn cm s ⁻⁵ m ²)	2684 $\pm$ 98	1986 $\pm$ 66	-698**	1768 $\pm$ 89	1549 $\pm$ 79	-220**

Difference from control (ANOVA) * P < 0.05, ** P < 0.01.

Figure 2 Haemodynamic effects (mean $\pm$ s.e. mean) of intravenous amlodipine (20 mg) on exercise in stable coronary artery disease. Statistics related to comparison with control. ** P < 0.01.

0.01), vascular resistance index (-698 dyn cm s⁻⁵ m²; 26%: P < 0.01) and stroke work index (-4 g m m⁻²; 7%: P < 0.01). Heart rate ($+9$ beats min⁻¹; P < 0.01) and cardiac index increased ($+0.7$ l min⁻¹ m⁻²; 21%: P < 0.01). Cardiac stroke volume index was augmented ($+3$ ml m⁻²; 6%: P < 0.01), resting PAOP was unchanged.

Effects during dynamic exercise (Table 1, Figure 2)

The fall in systemic arterial pressure and vascular resistance index (-219 dyn cm s⁻⁵ m²; 12%: P < 0.01) was augmented after amlodipine treatment compared with pre-drug measurements. The cardiac index and heart rate increased ($+0.5$ l min⁻¹ m⁻²; 9%: $+5$ beats min⁻¹; P < 0.01). The

cardiac stroke volume index increased (+2 ml m⁻²; 4%; $P < 0.01$) and the PAOP fell (-4 mm Hg; 16%; $P < 0.01$) after amlodipine. Cardiac stroke work was unaltered.

Effects on left ventricular ejection fraction (Table 2, Figure 3)

Dose-related effects on radionuclide parameters were evident. The left ventricular ejection fraction was unaltered after amlodipine either at rest or during exercise. The 20 mg dosage significantly increased rest and exercise heart rate and cardiac index; there was an accompanying reduction in left ventricular ejection (-75 ms: $P < 0.05$) and filling times (-113 ms: $P < 0.01$) and an increased ejection (+42 ml m⁻¹: $P < 0.01$) and filling rates (+38 ml m⁻¹: $P < 0.01$). The exercise ejection time was reduced (-30 ms: $P < 0.01$).

Relationship of baseline function to response (Figure 4)

Comparison of initial rest or exercise haemodynamic parameters and the response to amlodipine demonstrated significant relationships for resting systemic mean blood pressure ($r = -0.62$; $P = 0.001$), vascular resistance index ($r = -0.59$; $P = 0.002$), and exercise PAOP ($r = -0.53$; $P = 0.007$).

Figure 3 Effect of i.v. amlodipine (10 mg or 20 mg) on left ventricular ejection fraction. ● control, ○ drug. Statistics are differences from control (ANOVA). ** $P < 0.01$.

Table 2 Haemodynamic effects of amlodipine in coronary artery disease (mean $\pm$ s.e. mean)

	Rest	Low dose (10 mg i.v.) Difference	Exercise	Difference	Rest	High dose (20 mg i.v.) Difference	Exercise	Difference
Heart rate (beats min ⁻¹)	76 $\pm$ 5	+3	108 $\pm$ 4	+2	71 $\pm$ 5	+8**	97 $\pm$ 6	+9*
Ejection fraction (%)	44 $\pm$ 3	0	37 $\pm$ 3	+1	48 $\pm$ 4	0	37 $\pm$ 5	+1
Ejection rate (ml min ⁻¹)	278 $\pm$ 19	+12	432 $\pm$ 34	-4	280 $\pm$ 20	+42**	362 $\pm$ 21	+34
Ejection time (ms)	357 $\pm$ 14	-11	286 $\pm$ 10	-6	320 $\pm$ 30	-75*	308 $\pm$ 16	-30*
Peak ejection rate (ml min ⁻¹)	475 $\pm$ 34	-5	710 $\pm$ 66	+9	492 $\pm$ 31	+32*	672 $\pm$ 54	+94
Cardiac index (l min ⁻¹ m ⁻²)	3.7 $\pm$ 0.2	+0.2	6.8 $\pm$ 0.4	0	3.6 $\pm$ 0.2	+0.6**	5.6 $\pm$ 0.3	+0.6**
Filling rate (ml min ⁻¹)	212 $\pm$ 13	+11	508 $\pm$ 37	-26	192 $\pm$ 12	+38**	369 $\pm$ 17	+24
Filling time (ms)	453 $\pm$ 31	-24	240 $\pm$ 20	+2	508 $\pm$ 45	-112.5**	304 $\pm$ 24	+26
Time to peak filling time (ms)	164 $\pm$ 10	-10	111 $\pm$ 13	-1	118 $\pm$ 7	-5	130 $\pm$ 9.8	0
Peak filling rate (ml min ⁻¹)	417 $\pm$ 15	-12	857 $\pm$ 52	+45	522 $\pm$ 44	+64	669 $\pm$ 51	-20

Difference from control * $P < 0.05$, ** $P < 0.01$.

Figure 4 Change in exercise pulmonary artery occluded pressure after amlodipine related to initial value in 24 coronary patients.

Discussion

This study described the haemodynamic effects of amlodipine in patients with stable coronary artery disease. The haemodynamic effects of the drug were investigated following a period of control exercise to ensure a phase of relative haemodynamic stability (Verma *et al.*, 1984); that this was achieved was evident from the relatively small coefficient of variation of the haemodynamic variables over the saline period. The study design was based on an earlier haemodynamic dose-response study which defined the pharmacodynamically active dose range for i.v. amlodipine (Frais *et al.*, 1986); the latter study did not however examine the impact of amlodipine on global left ventricle ejection fraction nor did it examine the relationship between response and pre-therapy parameters.

Our data suggest that amlodipine produces systemic arterial vasodilation which lowers total vascular resistance. The blood pressure drop reflexly increases heart rate and the reduction of afterload improves left ventricular emptying and augments cardiac stroke volume index. No significant change occurred in left ventricular filling pressure (PAOP) at rest suggesting lack of appreciable action on capacitance vessels. The improved cardiac stroke volume index suggests that any negative inotropic actions of amlodipine are offset by reflex sympathetic activation as previously described with nicardipine (Amlie & Landmark, 1978; Pouleur *et al.*, 1984). Similarly, during constant load sub-maximal supine bicycle exercise, vascular resistance was lower and cardiac stroke volume index higher during

amlodipine treatment. The exercise induced increase in left ventricular filling pressure (PAOP) was less following amlodipine and probably reflects a reduced LV afterload.

Despite these haemodynamic benefits of amlodipine no short-term change in left ventricular ejection fraction was seen. This is unlikely to have a methodological explanation. Several groups have validated the nuclear ejection fraction method (Bacharach *et al.*, 1977; Berger *et al.*, 1981; Strashun *et al.*, 1981); it correlated closely with the standard gamma camera technique in normal volunteers (Lahiri *et al.*, 1984) and repeatability in our laboratory is good (coefficient of variation of < 4% at rest and < 6% on exercise). In many reports on the exercise effects of slow-calcium channel blockade in angina, ST segment depression developed during the control exercise; thus an improved ejection fraction consequent on an anti-ischaemic effect of the drug could be anticipated. Our studies using supine bicycle exercise, with fixed workload and duration of exercise insufficient to induce ischaemia (i.e. ST segment depression), would in contrast show an augmented ejection fraction only due to vasodilator or 'unloading' effects of the drug. However using the same technique, diltiazem (0.5 mg kg⁻¹) did not alter rest or exercise ejection fraction (Silke *et al.*, 1987b) but the peripherally selective dihydropyridine, nisoldipine (4–8 µg kg⁻¹) tended to increase rest (+18%) and exercise (+13%) ejection fraction and nicardipine (20 mg i.v.) significantly increased exercise (+25%) ejection fraction in coronary patients (Silke *et al.*, 1985a,b). These investigations and those of other workers on diltiazem (Anderson *et al.*, 1984; Hung *et al.*, 1983; Josephson *et al.*, 1985) and verapamil (Klein *et al.* 1983) suggest variable effects on rest ejection fraction but reversal of exercise-induced ischaemia has usually augmented exercise ejection fraction. With long-term vasodilation, remodelling and improved geometry may further optimise cardiac performance (Franciosa, 1986).

The relationship between baseline haemodynamic status and response to amlodipine is of interest. Patients with greatest depression of left ventricular function (highest resting SVRI) would theoretically derive greatest haemodynamic benefit from the vasodilator actions of amlodipine but be at highest risk for negative inotropic actions. At rest those with highest SVRI demonstrated clear haemodynamic improvement but these effects were lost during exercise. Presumably exercise had resulted in near maximal vasodilatation during the control period and the small additional fall following amlodipine had little impact on exercise cardiac pumping. The

resting left ventricular filling pressure (PAOP) predicted haemodynamic response to diltiazem in ischaemic patients with exercise abnormality (PAOP < 20 mm Hg) of cardiac pumping (Hossack *et al.*, 1982). In our study the fall in LV filling pressure after amlodipine was similarly proportional to the degree of abnormality induced by the control exercise.

Our haemodynamic data on amlodipine are in agreement with animal studies (Burges *et al.*, 1985). Comparing amlodipine with other slow-calcium channel blocking agents (Silke *et al.*, 1987a), its haemodynamic profile appears similar to the peripherally selective arteriolar vasodilator calcium channel blockers, nicardipine and nisoldipine, but different from verapamil. Thus, in terms of effects on left ventricular function, at rest and during exercise, the reduction in mean arterial blood pressure increased heart rate and cardiac index. The haemodynamic profile of amlodipine is also in keeping with other reports of dihydropyridine calcium channel blocking agents in clinical practice. Nifedipine has been shown to reduce peripheral vascular resistance and increase heart rate and cardiac output (Guazzi *et al.*, 1977; Murakami *et al.*, 1972; Simonsen & Nitter-Hauge, 1978). Similar profiles for nicardipine have been shown by Rousseau *et al.* (1984b), Visser *et al.* (1985) and Lambert *et al.* (1985) and for nisoldipine by Vogt *et al.*

(1980, 1983). In contrast verapamil and diltiazem appear to reduce left ventricular afterload without improvement in cardiac performance (Chew *et al.*, 1981; Legrand *et al.*, 1984; Seabra-Gomes *et al.*, 1976; Singh & Roche, 1977). Such differences can be explained on the basis of the relative selectivity of the dihydropyridines for vascular smooth muscle and lack of the cardiac (dromotropic) effects of verapamil and diltiazem.

In pharmacodynamic terms the circulatory profile of amlodipine is consistent with it being a relatively peripherally acting slow-calcium channel blocker. Confirmation of arteriolar selectivity without cardiodepression will need more detailed investigations. The present study cannot exclude electrophysiological or negative inotropic actions, although the overall circulatory pattern suggests that these would be unlikely to be a frequent clinical problem. The data confirm that i.v. amlodipine was well tolerated and possesses circulatory actions which are likely to be of therapeutic benefit in cardiovascular disease.

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