

# Coronary flow reserve in patients with chest pain and normal coronary arteries

Diana R Holdright, David C Lindsay, Debbie Clarke, Kim Fox, Philip A Poole-Wilson, Peter Collins

## Abstract

**Background**—Many studies have shown that coronary flow reserve is reduced in patients with chest pain and angiographically normal coronary arteries. The methods used to assess coronary blood flow have varied, but in nearly all reports dipyridamole has been used to bring about vasodilatation. This study was designed to assess whether the apparent impairment of coronary flow reserve seen with dipyridamole could be reproduced with either papaverine or adenosine, which induce maximum coronary blood flow by different mechanisms.

**Methods**—25 patients with chest pain and angiographically normal coronary arteries were studied with an intracoronary Doppler flow probe and quantitative angiography to determine epicardial coronary artery area, coronary blood flow velocity, coronary flow reserve, and coronary vascular resistance index (CVRI, the ratio of resistance after intervention to basal resistance). All patients received papaverine 8 mg. Eight patients with positive exercise tests received intracoronary papaverine (8 and 10 mg), intracoronary adenosine (6, 20, 60  $\mu$ g), and high-dose intravenous dipyridamole (0.84 mg/kg).

**Results**—The velocity ratio (peak after intervention: baseline) (mean (SEM)) after 8 mg papaverine was 3.3 (0.2) (n = 25) and the coronary flow reserve was 4.1 (0.3) (n = 25). There were no differences between patients with a positive (n = 16) or negative (n = 9) exercise test. In eight patients coronary flow reserve was measured after increasing doses of papaverine, adenosine, and dipyridamole. Coronary flow reserve was 4.5 (0.3) with papaverine, 4.8 (0.3) with adenosine, and 3.5 (0.4) with dipyridamole (p = 0.08 v papaverine and adenosine). CVRI was 0.22 (0.01) with papaverine, 0.21 (0.02) with adenosine, and 0.29 (0.03) with dipyridamole (p < 0.05 v papaverine, p = 0.09 v adenosine).

**Conclusions**—These results indicate that measurement of coronary flow reserve and CVRI in patients with chest pain and normal coronary arteries depends on the pharmacological stimulus. Normal values were obtained with papaverine in all patients, irrespective of the exercise test response. In patients with a positive exercise test significantly lower values

were obtained with dipyridamole than with papaverine, or adenosine. The reported impairment of coronary flow reserve in patients with angina and normal coronary arteries may reflect the variability in response to different pharmacological agents. The mechanism underlying this variability is unknown, but may involve an abnormality of adenosine metabolism in the myocardium.

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Up to one quarter of patients with chest pain referred for coronary angiography are subsequently found to have angiographically normal coronary arteries.<sup>1,2</sup> Further investigation shows a non-cardiac cause for symptoms in many patients, but in some patients abnormalities of coronary flow reserve have been demonstrated<sup>3-16</sup> that may account for their symptoms. Additional cardiac abnormalities have been documented, for example a positive exercise test,<sup>17</sup> altered left ventricular function,<sup>5,6</sup> and impaired endothelium-dependent vasodilatation.<sup>18</sup> The triad of chest pain, normal coronary arteries, and a positive exercise test has been called syndrome X.<sup>17</sup> Extracardiac manifestations such as abnormal oesophageal motility<sup>19</sup> and impaired forearm blood flow<sup>20</sup> have also been reported, suggesting a more generalised disorder rather than a specific cardiac problem.

A consistent finding has been an impairment of coronary flow reserve,<sup>3-16</sup> which is defined as the ability to reduce resistance acutely in the coronary vascular bed in response to a pharmacological or physiological stimulus. Because histological abnormalities of small vessels are not usually seen<sup>3,21</sup> a functional abnormality has been proposed<sup>22,23</sup> whereby a focal or regional increase in coronary resistance causes myocardial ischaemia. During exercise a steal phenomenon could result. This hypothesis fits well with the documented impairment of coronary flow reserve.

Several different methods have been used to measure coronary blood flow and flow reserve. Most studies have used dipyridamole to elicit maximum coronary vasodilatation.<sup>3,7,9,11-16</sup> If coronary flow reserve is indeed reduced, this finding should be reproduced when vasodilatation is caused by other agents. We measured coronary flow reserve in response to intracoronary papaverine,<sup>24,25</sup> intracoronary

National Heart and Lung Institute, Dovehouse Street and Royal Brompton National Heart and Lung Hospital, London  
D R Holdright  
D C Lindsay  
D Clarke  
K Fox  
P A Poole-Wilson  
P Collins

Correspondence to:  
Dr D R Holdright, Royal Brompton National Heart and Lung Hospital, Sydney Street, London SW3 6NP.

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adenosine,<sup>26,27</sup> and intravenous dipyridamole.<sup>28</sup> These three agents have different biochemical mechanisms.

### Patients and methods

#### PATIENT CLASSIFICATION

We studied 25 patients with chest pain and angiographically normal coronary arteries. Patients were classified according to the ST segment response during standard treadmill exercise testing. A positive response was defined as  $\geq 1$  mm ST segment depression from baseline measured 80 ms after the J point. Sixteen patients (aged 31–65) including one man had a positive exercise test (range 1–2.5 mm ST segment depression). Nine patients aged 35–53, including two men, had a negative exercise test.

No patient had left bundle branch block on the electrocardiogram, either at rest or with exercise. In addition, no patient had evidence of diabetes mellitus, cardiomyopathy, hypertension or left ventricular hypertrophy, or other conditions associated with an altered coronary flow reserve detectable by clinical, electrocardiographic, radiographic, or echocardiographic criteria. Left ventricular mass was determined echocardiographically according to the Penn convention.<sup>29</sup>

All patients had been referred for diagnostic coronary arteriography, and prior written informed consent was obtained in accordance with guidelines established by the ethics committee of the Royal Brompton National Heart and Lung Hospital, which approved the study.

#### PROTOCOL

Antianginal therapy and other drugs that could affect measurement of coronary blood flow were discontinued at least 18 h before cardiac catheterisation. Caffeine-containing beverages and nicotine were forbidden for at least 12 h before the study. After standard coronary angiography from the femoral approach the coronary angiograms were reviewed to confirm patient classification and to determine the study vessel and appropriate angiographic view.

A bipolar temporary pacing wire was positioned in the right ventricle and set on demand at 10 beats/min less than the patient's resting heart rate. After full heparinisation, an 8F guiding catheter (Medtronic, Minneapolis, USA) was positioned in the coronary ostium and a 3F Schneider Doppler flow probe (Schneider, Zurich, Switzerland) was passed over a 0.014 inch guide wire into the coronary artery in its proximal or mid-portion. In one patient from each group a Wessex Doppler flow probe was used (Numed, Hopkington, NY, USA) and correction was made for the side-mounted crystal angle. The Doppler probe was connected to a Millar velocimeter (Millar Instruments, Texas, USA) for continuous recordings of mean and phasic coronary artery velocity onto a chart recorder (Lectromed, St Peter, Jersey). The catheter was calibrated on a 0–40 cm/s scale, and the position and range

gating adjusted to optimise the phasic velocity waveform and audio signal. The electrocardiogram, mean and phasic arterial pressure, and heart rate were measured continuously.

#### MEASUREMENT OF CORONARY FLOW RESERVE

Papaverine hydrochloride (Macarthy Medical, Romford) was diluted in sterile water to a concentration of 4 mg/ml, and was administered as a bolus of 8–10 mg over 5 s via the Doppler catheter selectively into the coronary artery. This dose has been shown previously to elicit maximum vasodilatation when injected selectively into the coronary artery.<sup>25</sup> Plasma potassium concentration and QT<sub>c</sub> were within normal limits before each study. Adenosine (Sigma Chemical, Poole) was diluted in 0.9% sodium chloride to concentrations of 6, 20, and 60  $\mu$ g in 2 ml volumes for intracoronary bolus injection through the Doppler probe. Dipyridamole 0.84 mg/kg (Boehringer Ingelheim, Germany) was given intravenously (0.56 mg/kg over 4 min, followed 4 min later by an additional 0.28 mg/kg over 2 min) using an infusion pump (Becton Dickenson, UK).

All patients received intracoronary papaverine. The effects of increasing doses of intracoronary papaverine, intracoronary adenosine, and intravenous dipyridamole on coronary blood flow and coronary vascular resistance were compared in eight patients in whom the exercise test was positive.

#### QUANTITATIVE CORONARY ANGIOGRAPHY

Single plane angiograms were taken under basal conditions and at peak velocity change after drug administration. At least 20 minutes elapsed after diagnostic angiography and before the study. All angiograms (including those for diagnostic catheterisation) were performed with non-ionic contrast media (Omnipaque, Nycomed, Oslo, Norway) with an iodine concentration of 350 mg/ml and at an injection rate of 5–8 ml/s. The view that best displayed the artery segment in the isocentre was selected, and the position of the x-ray gantry was maintained for the study. A 5–10 mm length of vessel was measured in up to three consecutive end diastolic frames at the tip of the Doppler probe and the results were averaged.

In seven patients, angiograms were acquired on 35 mm cinefilm (Kodak CFE) at 25 frames/s (dose rate 20  $\mu$ R/frame) with a 17 cm nominal input field and a 0.8 mm<sup>2</sup> focal spot. The films were developed to produce an average gradient of 1.4. End diastolic frames were analysed on a Cardio 500 workstation (Kontron Elektronik, Munich, Germany) by means of a computer-assisted automatic edge detection algorithm (micro-Mipron software) of the digitised image (512  $\times$  512 matrix, 8 bit depth) from an IGE Cap 35B cine projector. In the remaining patients angiographic data were acquired digitally in a 512  $\times$  512 matrix with 10 bit depth on a real-time image acquisition and analysis system (Digitron III VACI, Siemens, Munich, Germany) at 12.5 frames/s (dose

rate 25  $\mu$ R/frame) with gap filling, a 17 cm nominal input field, and 0.8 mm<sup>2</sup> focal spot. A low-lag, 1249 line progressive scan video camera (Videomed C) was directly coupled to the image intensifier. The analogue output of the video camera was digitised in real time by a linear lookup table relating radiographic density to gray level, with parallel transfer via a solid state buffer, and stored on 4  $\times$  740 Winchester hard disks.

Calibration was determined from the guiding catheter to correct for geometric magnification. The diameter of each guiding catheter was measured with hand-held micrometer calipers. Both algorithms for automatic edge detection of digital data (directly acquired or from the digitised film image) used the weighted sum of the first and second derivatives to detect the vessel edge. In one patient the digital data were analysed on the videotape image of the digital data.

#### Validation

To validate the methods of data acquisition and analysis we used contrast-filled Perspex phantoms of cylindrical wells (diameter 1.5–4.0 mm). The mean difference between the measured and the true diameter (accuracy) and the pooled standard deviation of the differences (precision) were assessed from images acquired on 35 mm cinefilm and analysed on the Kontron workstation and from images acquired on the Digitron and analysed both on the Siemens workstation and on the Kontron workstation. The accuracy of the measurements was  $-70 \mu\text{m}$ ,  $-220 \mu\text{m}$ , and  $50 \mu\text{m}$ , and the precision was  $40 \mu\text{m}$ ,  $80 \mu\text{m}$ , and  $110 \mu\text{m}$  for each system respectively.

#### AREA, VELOCITY AND FLOW MEASUREMENTS

Epicardial coronary artery cross sectional area measured at the site of velocity recording was calculated from the mean luminal diameter on the assumption that the artery is circular in cross section. The velocity ratio was expressed as the ratio of peak mean velocity (cm/s) after drug administration to baseline velocity immediately before drug injection. Estimates of coronary flow (velocity area index) were derived from the product of velocity and cross sectional area at baseline and at peak response. Coronary flow reserve was defined as the ratio of peak flow (after drug administration) to baseline flow (just before drug injection). The change in coronary vascular resistance with each intervention, or coronary vascular resistance index (CVRI), was calculated as the quotient of mean aortic pressure at peak flow velocity (mmHg)/peak coronary blood flow (ml/s) and mean aortic pressure at resting flow velocity (mmHg)/resting coronary blood flow (ml/s).

#### STATISTICAL ANALYSIS

All data are expressed as mean (SEM). For statistical analysis we used analysis of variance and the Wilcoxon matched pairs signed rank sum test for paired data and the Mann-Whitney test for unpaired data.

## Results

### EFFECTS OF INTRACORONARY PAPAVERINE

#### (8 mg)

All patients received intracoronary papaverine 8 mg delivered as a bolus through the intracoronary Doppler flow probe selectively into the coronary artery. Patients classified on the basis of the exercise test were similar in all respects including age, blood pressure, blood glucose, and lipid profile (table 1). Exercise thallium scintigraphy was performed in 10 patients and showed a reversible perfusion defect in one case. No patient had evidence of left ventricular hypertrophy on the electrocardiogram. In echogenic subjects (20) left ventricular mass was determined and was within the normal range in all cases. Because coronary flow reserve is similar in vessels supplying the right and left ventricles<sup>30</sup> the coronary artery selected for study depended on the ability to obtain suitable angiographic views without overlap and foreshortening. Non-dominant coronary arteries were not selected. No rhythm change was seen after papaverine injection but transient ST-T changes and QT<sub>c</sub> prolongation were observed in most patients.

Intracoronary papaverine (8 mg) increased

Table 1 Characteristics of patients (mean (SEM))

Variable	Positive ETT	Negative ETT
Number	16	9
Females	15	7
Mean age (yr) (range)	49.5 (31–65)	45.8 (35–53)
Glucose (mmol/l)	5.3 (0.3)	5.1 (0.3)
Cholesterol (mmol/l)	6.2 (0.4)	6.1 (0.4)
HDL-C (mmol/l)	1.4 (0.1)	1.1 (0.1)
Triglycerides (mmol/l)	1.3 (0.2)	1.6 (0.4)
Systolic BP (mm Hg)	129 (6)	118 (2)
Diastolic BP (mm Hg)	77 (2)	71 (2)
LVEDP (mm Hg)	13 (2)	11 (2)

ETT, exercise treadmill test; BP, blood pressure; HDL-C, high density lipoprotein cholesterol; LVEDP, left ventricular end diastolic pressure.

Table 2 Velocity ratios and coronary flow reserve with papaverine 8 mg

Patient	CA	ETT	VR	CFR
1	LAD	+	2.7	3.0
2	LAD	+	3.4	7.4
3	RCA	+	3.5	4.1
4	LAD	+	3.8	5.5
5	Cx	+	1.9	3.5
6	RCA	+	3.3	4.2
7	Cx	+	2.0	2.4
8	RCA	+	1.6	1.7
9	RCA	+	6.0	6.4
10	Cx	+	3.4	3.6
11	RCA	+	4.5	5.3
12	LAD	+	3.6	4.1
13	Cx	+	3.1	5.6
14	LAD	+	3.0	4.0
15	LAD	+	2.6	3.1
16	Cx	+	4.6	5.0
17	Cx	–	2.4	3.0
18	Cx	–	5.8	5.6
19	RCA	–	4.9	3.3
20	RCA	–	2.3	2.6
21	LAD	–	2.1	2.6
22	Cx	–	3.1	4.1
23	RCA	–	3.9	4.9
24	RCA	–	3.5	4.2
25	RCA	–	2.2	2.3

CA, coronary artery studied (LAD, left anterior descending; RCA, right coronary artery; Cx, circumflex); VR, velocity ratio; CFR, coronary flow ratio.

the epicardial coronary artery area from 7.0 (1.1) mm<sup>2</sup> to 9.1 (1.4) mm<sup>2</sup> ( $p = 0.003$  *v* baseline). The velocity ratio with papaverine (table 2) was 3.3 (0.2) and the coronary flow reserve was 4.1 (0.3) ( $n = 25$ ). There was no difference in response between patients according to the exercise test result.

#### COMPARISON OF 8 mg AND 10 mg PAPAVERINE

The effects of the two doses of papaverine were compared in eight patients who all had positive exercise tests. Both doses produced similar increases in coronary artery area (41.4 (14.3)% with 8 mg ( $n = 8$ ) and 22.0 (7.4)% with 10 mg). Velocity ratios were 3.8(0.4) and 4.2 (0.3) ( $p = \text{NS}$ ) and coronary flow reserve was 4.6 (0.4) and 4.5 (0.3) ( $p = \text{NS}$ ) respectively. Analysis of variance showed that neither the coronary artery studied nor the dose of papaverine influenced the response to papaverine.

#### WITHIN-PATIENT COMPARISON OF PAPAVERINE, ADENOSINE, AND DIPYRIDAMOLE

A within-patient comparison of the effects of papaverine, adenosine, and dipyridamole on coronary blood flow and coronary vascular index (CVRI) was performed in eight patients, all of whom had a positive exercise test. Intracoronary papaverine (8 and 10 mg bolus) and adenosine (6, 20, and 60  $\mu\text{g}$  bolus) were given in random order but in

increasing order of concentration. Dipyridamole was always given last because of its long duration of action. Six patients received 0.84 mg/kg dipyridamole which was infused intravenously as 0.56 mg/kg over 4 min, followed 4 min later by 0.28 mg/kg over 2 min. Two patients received only 0.56 mg/kg dipyridamole because of flushing and headache. At the end of the study 100–200 mg aminophylline was given by slow intravenous injection to reverse the effects of dipyridamole. There was an interval of 3 to 5 min between each drug administration. This was extended if any measured haemodynamic variable had not returned to baseline. Coronary angiography was performed before drug administration and at peak change in velocity. All the drugs were well tolerated: dipyridamole caused flushing and headache in two patients.

#### Haemodynamic responses (fig 1)

Heart rate did not change with either intracoronary papaverine or adenosine ( $-0.3$  (2.5) and  $-1.3$  (2.2) beats/min respectively). Intravenous dipyridamole increased heart rate ( $+25.5$  (3.9) beats/min,  $p < 0.0005$ ) more than papaverine ( $p = 0.002$ ) or adenosine ( $p = 0.002$ ). There was a small fall of arterial pressure with all three drugs ( $-3.8$  (2.2) mm Hg with papaverine,  $-1.4$  (2.2) mm Hg with adenosine,  $-5.4$  (3.4) mm Hg with dipyridamole).

#### Coronary artery dimensions and velocity ratios

Coronary artery area measured at the Doppler probe tip increased with papaverine (22.0 (7.4)%,  $p = 0.02$  *v* baseline) dipyridamole (16.7 (8.1)%,  $p = 0.08$ ), and adenosine (5.4 (2.6)%,  $p = 0.08$ ). Velocity ratios (table 3) were less with dipyridamole than with either papaverine or adenosine. Maximum velocity ratios were 4.2 (0.3) papaverine, 4.6 (0.3) adenosine, and 3.0 (0.2) dipyridamole ( $p = 0.04$  *v* papaverine,  $p = 0.04$  *v* adenosine).

#### Coronary flow reserve and coronary vascular resistance index (CVRI) (fig 2)

Analysis of variance revealed a difference between the values for coronary flow reserve with the three drugs ( $p = 0.046$ ). Values for coronary flow reserve with papaverine and

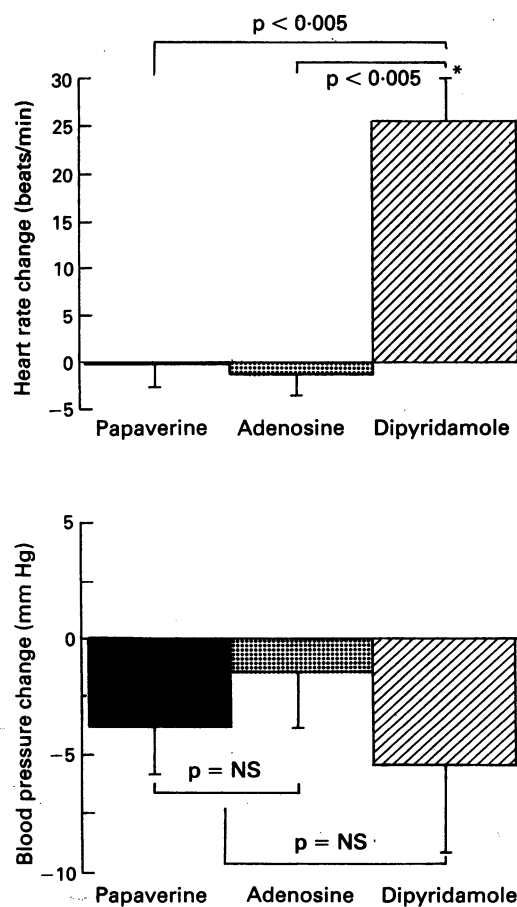


Figure 1 Changes in heart rate and blood pressure in response to papaverine, adenosine, and dipyridamole. \* $p < 0.0005$  *v* baseline.

Table 3 Velocity ratios with papaverine, adenosine, and dipyridamole

	Papaverine (mg)		Adenosine ( $\mu\text{g}$ )			Dip
	8	10	6	20	60	
	6.0	4.9	3.7	4.4	4.9	3.1
	3.4	3.3	2.9	3.6	3.6	2.4
	4.5	5.6	4.1	4.8	4.8	2.9
	3.6	3.9	4.1	3.9	4.0	3.0*
	3.1	3.9	3.3	3.7	4.5	3.9*
	3.0	4.0	3.5	4.0	6.2	2.1
	2.6	3.2	1.5	3.0	3.9	3.1
	4.6	4.8	2.4	4.4	4.6	3.3
Mean (SEM)	3.8 (0.4)	4.2 (0.3)	3.2 (0.3)†	4.0 (0.2)	4.6 (0.3)	3.0 (0.2)‡

Dip, dipyridamole 0.84 mg/kg, except \*0.56 mg/kg. † $p < 0.05$  *v* adenosine 20  $\mu\text{g}$ ,  $p < 0.01$  *v* adenosine 60  $\mu\text{g}$ . ‡ $p = 0.005$  *v* adenosine 60  $\mu\text{g}$ ,  $p = 0.008$  *v* papaverine 10  $\mu\text{g}$ .

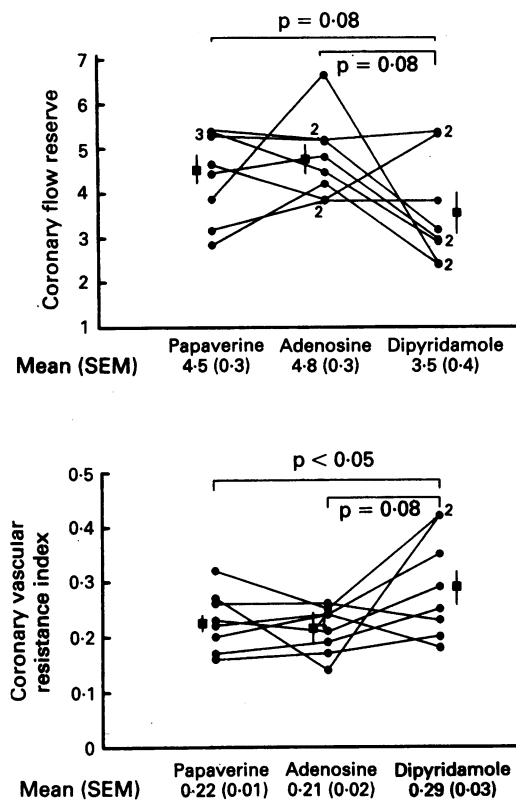


Figure 2 Coronary flow reserve and coronary vascular resistance index (CVRI) with papaverine, adenosine, and dipyridamole. Each patient is represented as a single point. Mean (SEM) is also indicated.

adenosine were similar (4.5 (0.3) and 4.8 (0.3) respectively) whereas coronary flow reserve with dipyridamole was lower (3.5 (0.4),  $p = 0.08$  *v* papaverine and adenosine). CVRI was similar with papaverine and adenosine (0.22 (0.01) and 0.21 (0.02) respectively), but higher with dipyridamole (0.29 (0.03),  $p = 0.04$  *v* papaverine,  $p = 0.08$  *v* adenosine) and was  $>0.30$  in three patients (0.35, 0.42, 0.42), all of whom received high dose dipyridamole (0.84 mg/kg).

### Discussion

Patients with chest pain and angiographically normal coronary arteries pose an important clinical problem. Up to a quarter of all patients referred with chest pain for coronary angiography are subsequently found to have angiographically normal coronary arteries.<sup>1,2</sup> Though a normal coronary angiogram may be reassuring for the patient's physician, many patients derive little or no benefit from the knowledge of a normal study. A significant number of patients continue to experience chest pain, take antianginal drugs, and require readmission to hospital for severe symptoms.<sup>31,32</sup> In some patients this outcome may reflect a lack of diagnosis and the pain may have a non-cardiac cause. In others, further cardiac investigations show abnormalities that could account for the patient's symptoms.

The term syndrome X was introduced in 1973 by Kemp to describe patients with the

triad of anginal-type chest pain, a positive exercise test, and angiographically normal coronary arteries.<sup>17</sup> Since that time the term has been used rather loosely to include patients not strictly fulfilling the criteria of Kemp and new terms have been introduced to describe patients with chest pain and normal coronary arteries. In several studies comparisons have been made between patients with a positive exercise test and controls with chest pain and a normal exercise test response. Some would argue that any patient with chest pain cannot, by definition, form part of a control group irrespective of the exercise test result. Instead, patients with chest pain are subdivided into two or more groups by statistical analysis of the patients' responses to one or more intervention. For example, patients have been categorised according to their response to atrial pacing after ergonovine,<sup>10</sup> the coronary blood flow response to dipyridamole,<sup>33</sup> or the result of thallium scintigraphy.<sup>34</sup> Consequently, direct comparisons between studies are often difficult, if not impossible.

One of the most consistent abnormalities in patients with chest pain and angiographically normal coronary arteries is an impairment of coronary flow reserve<sup>3-16</sup> which, in the absence of structural vascular abnormalities,<sup>3,21</sup> may be due to a functional abnormality of the resistance vessels.<sup>22,23</sup> Our results show that coronary flow reserve in response to papaverine is normal in patients with chest pain and normal coronary arteries, irrespective of the exercise test result. In the only other published report in which papaverine was used to assess coronary flow reserve in syndrome X<sup>35</sup> normal values similar to our results were obtained.

The possibility that the measurement of coronary flow reserve in patients with chest pain might depend upon the pharmacological agent used led us to compare the effects of three different vasodilators. Dipyridamole, a widely used drug for assessing coronary flow reserve, inhibits adenosine uptake by erythrocytes and other cells, resulting in a higher intravascular concentration of adenosine.<sup>28</sup> Adenosine binds to A<sub>2</sub> purinoceptors on the vascular smooth muscle cell membrane of the coronary resistance vessels, stimulating adenylate cyclase and increasing intracellular cyclic AMP.<sup>27</sup> Smooth muscle relaxation results and vascular resistance falls. Papaverine, an opiate alkaloid, is a non-specific smooth muscle relaxant that is thought to act predominantly by inhibiting cyclic AMP phosphodiesterase.<sup>36</sup> Because we recognised the difficulties in obtaining a control group for comparison we elected to compare the three agents within individual patients. We purposely undertook this study in patients with a positive exercise test because a positive exercise test is a highly sensitive marker for patients with an impaired coronary flow reserve to dipyridamole.<sup>33,37</sup>

We found that measured responses to dipyridamole were impaired, as in many earlier studies,<sup>3,7,9,11-16</sup> but the responses to

papaverine and adenosine were normal. If these results are not the result of inadequate or non-equivalent drug dosing schedules, the different responses to the three agents may shed light on the mechanism(s) underlying the cause of chest pain in patients with normal coronary arteries. The reduced response to dipyridamole might have been caused by an inadequate dose of the drug. This is unlikely because others have shown that intracoronary papaverine and intravenous dipyridamole in doses similar to our study produce changes in coronary blood flow and vascular resistance within the expected normal range.<sup>25-38</sup> In a study of 10 patients with atypical chest pain, normal coronary arteries, and a negative exercise test, Wilson and White used an intracoronary Doppler probe to measure coronary blood flow velocity in response to incremental doses of papaverine injected into the coronary ostium and in response to intravenous dipyridamole 0.56 mg/kg.<sup>25</sup> Coronary flow reserve with papaverine was 4.8 (0.4) and CVRI fell to 0.21 (0.01), which is the same as our results. Whereas we found reduced responses to dipyridamole in patients with a positive exercise test, Wilson and White showed that the response to dipyridamole in patients with a negative exercise test was normal, and identical to the papaverine response. In addition, to minimise the likelihood of an inadequate dose of dipyridamole we used a high-dose regimen (0.84 mg/kg) rather than the more commonly used dose of 0.56 mg/kg, even though available data indicate that the low dose is probably adequate.<sup>25-38</sup> Most studies in patients with normal coronary arteries have used doses in the range 0.4–0.6 mg/kg.<sup>2,6,10-14</sup>

Other mechanisms for the reduced response to dipyridamole need to be considered. Because dipyridamole, adenosine, and papaverine act differently within the cell, the impaired response with dipyridamole could result from an abnormality of adenosine metabolism. Interventions such as exercise, atrial pacing, and dipyridamole, which all increase intravascular adenosine concentration, produce submaximal increases in coronary flow in patients with chest pain and normal coronary arteries.<sup>3,4,6-16</sup> With intracoronary adenosine, coronary flow reserve and CVRI were within the normal range, like other data,<sup>39</sup> suggesting that adenosine receptor ( $A_2$ ) function is normal. Adenosine production might be impaired in these patients, which would explain not only why dipyridamole was a less effective vasodilator than exogenously administered adenosine but also why exercise and atrial pacing caused submaximal increases in coronary blood flow. Locally produced adenosine is an important physiological regulator of coronary vascular resistance.<sup>40</sup> If adenosine production from myocardial and endothelial cells is impaired the effects of dipyridamole, which depend on adenosine production, would be reduced.

#### Limitations

Coronary flow reserve is underestimated if

resting coronary flow is not truly basal. Geltman *et al*<sup>13</sup> and Galassi *et al*<sup>14</sup> have described patients with increased basal coronary flow. Coronary flow reserve will be lower whether or not maximum blood flow is reduced. Our patients were studied at the same time of day when patients were not taking cardiac drugs. Alterations in factors such as heart rate and blood pressure could affect coronary blood flow. We do not believe that the lower coronary flow reserve with dipyridamole was due to a change in haemodynamics with drug administration because baseline heart rate and blood pressure, two variables that alter baseline but not peak blood flow,<sup>41</sup> remained stable throughout the study. Dipyridamole was purposely administered at the end of the study to avoid alterations in baseline velocity.

The Doppler probe has been extensively validated in *in vitro* and *in vivo* models.<sup>42</sup> Coronary artery diameter has to be measured in order that coronary blood flow can be calculated from blood flow velocity. To assume that the cross sectional area of the artery is circular, though not physiologically exact, is reasonable, particularly as we considered relative changes rather than absolute values. Changes in flow were expressed as flow ratios because the Doppler sampling volume may not have been aligned with the area of maximum velocity.

The results of this study show that coronary flow reserve and CVRI measured after administration of papaverine or adenosine were not impaired in patients with chest pain and angiographically normal coronary arteries. The frequently documented abnormality of coronary flow reserve seen with dipyridamole may be caused by an abnormality of adenosine metabolism within the coronary bed.

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