

## INTERVENTIONAL CARDIOLOGY AND SURGERY

# Prospective, randomised, controlled trial to study the effect of intracoronary injection of verapamil and adenosine on coronary blood flow during percutaneous coronary intervention in patients with acute coronary syndromes

K Vijayalakshmi, V J Whittaker, B Kunadian, J Graham, R A Wright, J A Hall, A Sutton, M A de Belder



Heart 2006;92:1278–1284. doi: 10.1136/hrt.2005.075077

See end of article for authors' affiliations

Correspondence to:  
Dr Mark A de Belder,  
Department of Cardiology,  
The James Cook University  
Hospital, Marton Road,  
Middlesbrough TS4 3BW,  
UK; mark.debelder@tees.  
nhs.uk

Accepted 17 January 2006  
Published Online First  
31 January 2006

**Objectives:** To study the impact of injection of verapamil and adenosine in the coronary arteries on TIMI (Thrombolysis in Myocardial Infarction) frame count (TFC) after percutaneous coronary intervention (PCI) in patients with an acute coronary syndrome (ACS).

**Methods:** Prospective, randomised, controlled study of the intracoronary administration of normal saline versus verapamil versus adenosine in patients undergoing PCI in the setting of an ACS, even when flow is visually established to be normal or near normal. Patients were randomised to receive verapamil (n = 49), adenosine (n = 51) or normal saline (n = 50) after PCI. Quantitative angiography, TIMI flow grade (TFG), TFC and myocardial blush grade were assessed before PCI, after PCI and after drugs were given. Wall motion index (WMI) was measured at days 1 and 30.

**Results:** 9 patients in the verapamil group developed transient heart block, not seen with adenosine (p ≤ 0.001). Compared with saline, coronary flow measured by TFC improved significantly and WMI improved slightly but insignificantly in both the verapamil (TFC: p = 0.02; mean difference in improvement in WMI: 0.09, 95% confidence interval (CI) 0.015 to 0.17, p = 0.02) and the adenosine groups (TFC: p = 0.002; mean difference in improvement in WMI: 0.08, 95% CI 0.004 to 0.16, p = 0.04). The improvements in TFC and WMI did not differ significantly between the verapamil and the adenosine groups (TFC: p = 0.2; mean difference in improvement in WMI: 0.01, 95% CI –0.055 to 0.08, p = 0.7, respectively).

**Conclusion:** Administration of verapamil or adenosine significantly improves coronary flow and WMI after PCI in the setting of an ACS. Flow and WMI did not differ significantly between verapamil and adenosine but verapamil was associated with the development of transient heart block.

Various factors influence blood flow through the coronary arteries. Slower than expected flow is also seen in some vessels without epicardial obstruction in patients with coronary artery disease.<sup>1–3</sup> This may be due to small vessel abnormalities such as neutrophil plugging, myocyte contracture, tissue oedema, microvascular spasm and endothelial blistering.<sup>4</sup> Administration of drugs such as verapamil<sup>5–8</sup> and adenosine<sup>9</sup> can increase blood flow through the arteries through various mechanisms.<sup>1 10–12</sup>

No studies have compared the impact of these drugs on coronary blood flow in the setting of an acute coronary syndrome (ACS). We studied the impact of injection of these drugs into the coronary arteries on the TIMI (Thrombolysis in Myocardial Infarction) frame count (TFC) and myocardial blush grade (MBG) after percutaneous coronary intervention (PCI) in patients with an ACS.

## METHODS

The local research ethics committee, the radiation protection adviser, and the research and development committee of our institution approved the study protocol. A patient information leaflet explaining the study as well as the benefits and potential risks of cardiac catheterisation and angioplasty was provided to all study patients. The potential advantages and the adverse effects of the drugs used in the study were clearly

explained to all patients. Written consent for participation in the study was obtained.

## Patient selection and exclusion

Patients who were listed for urgent coronary angiography (in the setting of an ACS) with a view to angioplasty were suitable for the study.

The following patients were excluded from the study: patients with asthma, renal impairment (creatinine concentration > 120 mmol), left main stem disease, blood pressure < 90 mm Hg, heart rate > 100 beats/min and known heart block.

## Cardiac catheterisation, PCI and randomisation

Eligible patients underwent cardiac catheterisation. PCI of the culprit artery was carried out. Glycoprotein IIb/IIIa inhibitor was used according to the departmental protocol. After the completion of the angioplasty procedure, coronary angiograms in the appropriate views<sup>13</sup> were taken after the

**Abbreviations:** ACS, acute coronary syndrome; MBG, myocardial blush grade; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; RCA, right coronary artery; STEMI, ST elevation myocardial infarction; TFC, TIMI frame count; TFG, TIMI flow grade; TIMI, Thrombolysis in Myocardial Infarction; WMI, wall motion index

administration of 200 µg of intracoronary nitrate. After this the study drugs were given and angiography in the same view was repeated.

All patients were randomly assigned to receive an intracoronary bolus of one of the study drugs after the completion of the angioplasty procedure. Verapamil (500 µg in 10 ml of heparinised saline) and heparinised saline (10 ml) were given slowly over a minute and a repeat angiogram was recorded after another minute. Adenosine (30 µg in 10 ml of heparinised saline) was given very quickly and a repeat angiogram of the relevant vessel was recorded within 10 s. In case of multivessel PCI, the study drug was given once only to one of the vessels and angiography was performed as mentioned above.

All patients received aspirin and unfractionated heparin before PCI. Where possible, patients were loaded with 300 mg of clopidogrel before angioplasty. For non-emergency procedures clopidogrel was given for 2–4 days before the patients were taken to the catheterisation laboratory. During intervention, the activated clotting time was maintained at 250–300 s.

### Quantitative coronary angiography and TFC

Coronary angiography was performed with a Philips DCI-SX Integris Monoplane system. Quantitative coronary angiography was performed with the Philips Inturis Suite R2.2 commercial software by the radiographer in charge of the case. Angiograms were recorded at 12.5 frames/s. Frame counts were determined by the method described previously by Gibson *et al.*<sup>14</sup> TFC was measured with a Philips Inturis Suite R2.2 by an independent observer blinded to the randomisation data (KV).

TFC,<sup>13 14</sup> TIMI flow grade (TFG)<sup>15</sup> and MBG<sup>16</sup> were determined on the angiograms that were taken before PCI, after PCI and after the administration of the drugs. For evaluation of myocardial blush, an extended angiographic film sequence of up to 16 s was acquired. The grading system introduced by van't Hof *et al.*<sup>16</sup> was used.

### TIMI flow grades

TFGs were described previously<sup>15</sup>: grade 0, no perfusion (no antegrade flow beyond the point of occlusion); grade 1, penetration without perfusion (contrast material passes beyond the area of obstruction but fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence); grade 2, partial perfusion (contrast material passes across the obstruction and opacifies the coronary artery distal to the obstruction—however, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) is perceptibly slower than its flow into or clearance from comparable areas not perfused by the previously occluded vessel (for example, the opposite coronary artery or the coronary bed proximal to the obstruction); and grade 3, complete perfusion (antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery).

### TIMI frame count

Frame counts were determined by the method described previously by Gibson *et al.*<sup>14</sup> The first frame in the TFC is defined by a column of contrast extending across > 70% of the arterial lumen with antegrade motion. The last frame counted is that in which contrast enters (but not necessarily fills) a distal landmark. These landmarks are as follows: the first branch of the posterolateral artery in the right coronary

artery (RCA); the distal branch of the lateral left ventricular wall artery furthest from the coronary ostium in the circumflex system; and the distal bifurcation known as the “moustache”, “pitch fork” or “whale’s tail” in the left anterior descending artery. In case of an occluded vessel, the TFC was set to a value of 100.<sup>17</sup> In general, the TFCs in the left anterior descending artery and the circumflex arteries were assessed in a right anterior oblique projection with caudal angulation (right anterior oblique caudal view) and TFCs in the RCA were assessed in a left anterior oblique projection with cranial angulation (left anterior oblique cranial view).

### Myocardial blush grade

MBGs were defined as previously described<sup>16</sup>: grade 0, no myocardial blush or contrast density; grade 1, minimal myocardial blush or contrast density; grade 2, moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery; and grade 3, normal myocardial blush or contrast density, comparable with that obtained during angiography of a contralateral or ipsilateral non-infarct-related coronary artery. When myocardial blush persisted (“staining”), this phenomenon suggested leakage of the contrast medium into the extravascular space and was graded 0.

### Other investigations

The 12-lead ECG was recorded on arrival, immediately after angioplasty and subsequently at 3, 6, 12, 24 and 48 h. Troponin T and creatine kinase concentrations were measured at 6 and 12 h after PCI. Transthoracic echocardiography was performed the day after angioplasty. Digital cine loops were stored in standard parasternal long axis, short axis, and apical two- and four-chamber views. Echocardiography was repeated at day 30. The left ventricular segmental score (wall motion index (WMI)) was calculated as follows: grade 1, normal; grade 2, hypokinetic; grade 3, akinetic; grade 4, dyskinetic; and grade 5, aneurysmal. An independent observer (KV) measured the wall motion score blinded to the angiographic data. Two observers (KV and JG) measured WMI in 25 randomly selected cases to study reproducibility.

### Standardisation of medical treatment and follow up

Standard medical care was offered to all patients after PCI. All patients were followed up for a minimum of six months. Clopidogrel was continued for one month after the procedure where non-drug-eluting stents were used. When a drug-eluting stent was used, clopidogrel was continued for up to six months at the discretion of the attending cardiologist.

**Table 1** Baseline characteristics of study patients

Characteristic	Verapamil group (n = 49)	Adenosine group (n = 51)	Normal saline group (n = 50)	p Value
Men	36 (73%)	39 (76%)	41 (82%)	0.5
Age (years)	58.3 (9.9)	59.6 (11.5)	61.7 (9.8)	0.3
Height (cm)	172 (8.4)	169.2 (11.7)	169.6 (9.5)	0.3
Weight (kg)	82.4 (13.9)	81.7 (20.1)	79.6 (17.3)	0.7
Diabetes	7 (14%)	5 (9.8%)	1 (2%)	0.09
Hypertension	21 (43%)	24 (47%)	23 (46%)	0.8
Previous MI	7 (14%)	8 (15.6%)	10 (20%)	0.7
Previous stroke	2 (4%)	1 (2%)	0	0.3
Current smoker	12 (24%)	14 (27%)	15 (30%)	0.8
Hypercholesterolaemia	27 (55%)	32 (63%)	26 (52%)	0.9
STEMI	7 (14%)	2 (4%)	9 (18%)	0.08

Data are presented as number (%) of mean (SD).

MI, myocardial infarction; STEMI, ST elevation myocardial infarction.

## End point

The primary end point was significant improvement in the TFC after the administration of the drugs.

Secondary end points were measured at 30 days and six months after the procedure. The secondary end points were left ventricular WMI at one day and at 30 days after the procedure. Ischaemic end points were recurrent ischaemic chest pain after angioplasty, recurrent chest pain with ECG changes, unplanned repeat cardiac catheterisation, unplanned repeat culprit artery angioplasty, and emergency coronary artery bypass grafting within the first 30 days and at six months.

## Statistical analysis

The SPSS statistical software package (V.10.1; SPSS Inc, Chicago, Illinois, USA) was used for all statistical calculations. A sample size of 35 patients in each group would allow evidence of a 25% reduction in corrected TFC with a power close to 0.9. Additional patients were recruited to allow for dropouts. A one-way analysis of variance was used to compare TFG, TFC and MBG between the three groups. A Kruskal–Wallis test was used to compare non-parametric data. A paired t test was used to compare the TFC after PCI and after the administration of drugs in the different groups. A Wilcoxon signed ranks test was used to compare non-parametric data. An independent samples t test was used to compare the difference in the WMI at days 1 and 30 and to compare TFC before and after drug administration between the three groups. The  $\chi^2$  test was used to compare categorical data. Fisher's exact test was used when  $\chi^2$  test was not applicable. Continuous variables are expressed as mean (SD) and the categorical variables are expressed as percentages. For all tests, a value of  $p < 0.05$  was considered significant.

## RESULTS

### Baseline characteristics

Baseline characteristics of the study patients did not differ significantly between the three groups, although only one patient in the normal saline group had diabetes and only two patients in the adenosine group had presented with ST elevation myocardial infarction (STEMI) (table 1).

Table 2 lists the drugs the study patients were taking on admission and on discharge. Medical treatment did not differ significantly between the three groups. As many of the patients were transferred from other cardiac units, usage of cardiac agents on admission was high, with subsequent titration before discharge. In total, 98% of patients were taking aspirin and 95% of patients were taking clopidogrel at the time of discharge; 85% of patients received glycoprotein IIb/IIIa inhibitor during PCI. The use of glycoprotein IIb/IIIa inhibitor did not differ significantly between the three groups (verapamil 43 (88%) *v* adenosine 42 (82%) *v* normal saline 40 (80%),  $p = 0.11$ ).

## Feasibility and safety of administration of intracoronary adenosine and verapamil

The injections of study drugs into the coronary arteries were well tolerated and free of side effects reported by the patients. All patients were in the same rhythm before and after the administration of adenosine and normal saline. In the verapamil group, however, nine patients developed transient heart block associated with a transient drop in blood pressure; the heart block lasted for up to 3 h.

Systolic blood pressure differed significantly after the administration of drugs. The difference was 13 (2.1) mm Hg (95% confidence interval (CI) 8.7 to 17.2,  $p \leq 0.0001$ ) between the verapamil and the adenosine groups and 11.2 (2) mm Hg (95% CI 7.1 to 15.3,  $p \leq 0.0001$ ) between the verapamil and saline groups. The change in systolic blood pressure did not differ significantly between the saline and the adenosine groups (1.7 (1.9), 95% CI -5.6 to 2.0,  $p = 0.4$ ).

## Angiographic results

Table 3 shows the angiographic characteristics. Angiographic characteristics did not differ significantly between the three groups before and after PCI. Post PCI there was evidence of angiographic slow flow/no reflow<sup>4</sup> in two patients in the verapamil group compared with three patients in the adenosine group and one patient in the saline group. After administration of drugs, none of the patients in the adenosine group had evidence of angiographic slow flow/no reflow compared with two in the verapamil group and one patient in the saline group.

MBG did not differ significantly between the three groups after the administration of drugs. In the verapamil group, five patients had MBG 2 after PCI. After the administration of verapamil three patients out of five had MBG 3. In the adenosine group, two patients had MBG 2 after PCI and one out of the two patients had MBG 3 after the administration of adenosine. Three patients with MBG 2 after PCI continued to have MBG 2 after the administration of saline. TFC improved significantly before (9.8 (6.6)) and after (8.6 (5.9)) the administration of verapamil ( $p = 0.02$ ) and adenosine (before, 10.3 (5.9) *v* after, 8.2 (5.1),  $p \leq 0.001$ ) but TFC did not improve significantly in the saline group (before, 10.2 (4.7) *v* after, 10.3 (5.5),  $p = 0.9$ ). The improvement in the TFC differed significantly between the verapamil and the saline groups ( $p = 0.02$ ), and the adenosine and saline groups ( $p = 0.002$ ). The improvement in the TFC did not differ significantly, however, between the verapamil and the adenosine groups ( $p = 0.2$ ).

Taking those who received verapamil or adenosine as a single group, TFC improved after the administration of the drug compared with saline when we studied patients with STEMI (8.5% *v* 0%) and non-STEMI (11% *v* 0%), and patients who were (24% *v* 16%) and were not (16% *v* -4%) taking calcium channel blockers. We obtained similar results when

**Table 2** Drug treatment on admission and discharge

Drug	On admission			On discharge		
	Verapamil (n = 49)	Adenosine (n = 51)	Saline (n = 50)	Verapamil (n = 49)	Adenosine (n = 51)	Saline (n = 50)
Aspirin	39 (80%)	38 (75%)	41 (80%)	49 (100%)	48 (94%)	50 (100%)
$\beta$ blocker	29 (59%)	36 (71%)	34 (67%)	43 (88%)	45 (88%)	45 (90%)
CCB	5 (10%)	8 (16%)	13 (26%)	4 (8%)	9 (18%)	13 (26%)
ACE inhibitor	32 (65%)	29 (57%)	32 (63%)	49 (100%)	46 (90%)	50 (100%)
Statin	37 (76%)	36 (71%)	37 (73%)	48 (98%)	47 (92%)	50 (100%)
Clopidogrel	34 (69%)	31 (61%)	30 (59%)	49 (100%)	44 (86%)	50 (100%)
Nitrate	6 (12%)	9 (18%)	10 (20%)	5 (10%)	7 (14%)	10 (20%)

ACE, angiotensin-converting enzyme; CCB, calcium channel blocker.

**Table 3** Angiographic characteristics

Angiographic feature	Verapamil group (n = 49)	Adenosine group (n = 51)	Normal saline group (n = 50)	p Value
LAD	19 (38.8%)	24 (47%)	24 (48%)	0.6
RCA	16 (32.7%)	17 (37%)	15 (30%)	0.9
Circumflex	14 (28.6%)	10 (19.6%)	10 (20%)	0.5
SVG	0	0	1 (2%)	0.3
<b>Before percutaneous coronary intervention</b>				
Stenosis (%)	78 (13.8)	74 (15.2)	72.3 (15.2)	0.1
MLD (mm)	0.83 (0.45)	0.93 (0.45)	0.9 (0.4)	0.4
RD (mm)	2.99 (0.54)	3.2 (0.59)	3.12 (0.75)	0.3
TFG	2.39 (1.2)	2.6 (0.9)	2.8 (0.7)	0.09
TFC	34.9 (33.4)	29.7 (26.9)	23.2 (22)	0.1
MBG	1.88 (1.2)	1.8 (1)	2.3 (0.9)	0.04
Slow flow/no reflow	5 (10.2%)	6 (11.7%)	2 (4%)	0.3
<b>After percutaneous coronary intervention</b>				
Stenosis (%)	4.1 (5.8)	3.5 (5.3)	4.1 (5.4)	0.8
MLD (mm)	3.26 (0.47)	3.32 (0.5)	3.19 (0.7)	0.5
RD (mm)	3.23 (0.47)	3.33 (0.5)	3.29 (0.6)	0.7
TFG	2.9 (0.1)	3 (0)	3 (0)	0.4
TFC	9.8 (6.6)	10.3 (5.9)	10.3 (4.7)	0.9
MBG	2.9 (0.3)	2.96 (0.2)	2.8 (0.6)	0.2
Slow flow/no reflow	2 (4%)	3 (5.8%)	1 (2%)	0.7
<b>After study drug</b>				
TFG	3 (0)	3 (0)	3 (0)	1
TFC	8.6 (5.9)	8.2 (5.1)	10.3 (5.5)	0.1
MBG	2.9 (0.2)	2.9 (0.1)	2.9 (0.2)	0.5
Slow flow/no reflow	2 (4%)	0	1 (2%)	0.4

Data are presented as number (%) or mean (SD).

LAD, left anterior descending artery; MBG, myocardial blush grade; MLD, minimum lumen diameter; RCA, right coronary artery; RD, reference diameter; SVG, saphenous vein graft; TFC, TIMI (Thrombolysis in Myocardial Infarction) frame count; TFG, TIMI flow grade.

we studied patients who did (19% v 0%) and did not (10% v 0%) receive glycoprotein IIb/IIIa inhibitors.

Troponin T (ng/ml) at 6 h was 1.2 (3.7), 0.4 (1) and 0.7 (2.1) ( $p = 0.9$ ; verapamil, adenosine and saline groups, respectively). Troponin T at 12 h was 1.9 (3.8), 0.4 (0.9) and 1.3 (2.7) ( $p = 0.5$ ; verapamil, adenosine and saline groups, respectively). Creatine kinase ( $\mu\text{g/l}$ ) at 6 h was 374.5 (992), 109.8 (134) and 234.4 (561.5) ( $p = 0.8$ ; verapamil, adenosine and saline groups, respectively). Creatine kinase at 12 h was 553.4 (1096), 117.5 (125) and 211.9 (468.8) ( $p = 0.4$ ; verapamil, adenosine and saline groups, respectively).

### Echocardiographic data

Table 4 shows the echocardiographic data. WMI measures did not differ significantly between the two observers (mean difference 0.04, 95% CI  $-0.01$  to  $0.09$ ,  $p = 0.1$ ).

WMI improved slightly but significantly between day 1 and day 30 in the verapamil and the adenosine groups. WMI did not improve significantly in the saline group. The mean difference in the improvement in WMI between the verapamil and the adenosine group was 0.01 (95% CI  $-0.055$  to  $0.08$ ,  $p = 0.7$ ). The mean difference in the improvement in WMI between the verapamil and saline groups was 0.09 (95% CI  $0.015$  to  $0.17$ ,  $p = 0.02$ ). The mean difference in the improvement in WMI between the adenosine and saline groups was 0.08 (95% CI  $0.004$  to  $0.16$ ,  $p = 0.04$ ).

**Table 4** Echocardiographic data

Group	WMI day 1	WMI day 30	p Value
Verapamil (n = 38)	1.17 (0.25)	1.11 (0.2)	0.03
Adenosine (n = 40)	1.09 (0.18)	1.03 (0.08)	0.03
Normal saline (n = 41)	1.06 (0.14)	1.09 (0.24)	0.5

Regional wall motion in the remaining patients was not assessed at 30 days because either the patient declined to attend for the study or the endocardial definition was inadequate.

WMI, wall motion index.

### Clinical outcome

All patients were alive at 30-day follow up and one patient in the saline group had died at six-month follow up. In the saline group, two patients had repeat PCI (one for subacute thrombosis in the culprit vessel, the other for stable angina), one patient had repeat left heart catheterisation and three patients had recurrent chest pain. None of the patients in the verapamil and the adenosine groups reached the secondary end points. The occurrence of death ( $p = 0.3$ ), recurrent chest pain ( $p = 0.3$ ), repeat PCI ( $p = 0.3$ ) and repeat angiography ( $p = 0.1$ ) did not differ significantly between the three groups.

### DISCUSSION

Intracoronary verapamil and adenosine exert their effect predominantly by dilating the resistance arterioles. Vasodilator drugs can be given before (either routinely or to selected patients) or after PCI. In practice, these drugs are considered in the setting of slow flow. A slow-flow phenomenon is not especially common and it is difficult to perform a randomised controlled trial specifically for this purpose. In a previous study, no reflow occurred in 26% of patients undergoing percutaneous transluminal coronary angioplasty (PTCA) for acute myocardial infarction<sup>12</sup> and in 2% of all patients undergoing PTCA.<sup>1</sup> In our study of patients with ACS, 9% of the total population had slow or no reflow before PCI. This reduced to 4% after PCI and reduced further to 2% after drug administration. All patients with slow flow/no reflow after PCI continued to have slow flow after the administration of verapamil and saline compared with none of the patients who received adenosine. It is clear from preliminary observations, however, that minor changes in flow are often not visually detected and not recognisable by TFG analysis. We therefore decided to perform this study after PCI, whether there was visible slow flow or not, to establish whether there was a microvascular effect that was modifiable by these drugs and, if so, to determine whether one agent was better than the other.



Several hypotheses<sup>10</sup> have been postulated on the mechanism of action of verapamil when used in the context of PCI for STEMI. Firstly, by lowering heart rate and arterial pressure, verapamil reduces global oxygen demand and may at least partially contribute to a reduction in the size of heart muscle damage. Secondly, verapamil may inhibit platelet aggregation and possibly clot formation in the coronary microvasculature, thereby reducing the obstruction to blood flow and the degree of ischaemia. Thirdly, verapamil has a vasodilatory effect on the microvasculature. Lastly, verapamil may have a direct effect on calcium flux across the sarcolemmal membrane or within intracellular compartments that may result in a protective action on reversibly injured myocytes.

The myocytes of coronary resistance vessels have an adenosine receptor (A<sub>2</sub>) on their cell membrane. When combined with adenosine, an endogenous purine nucleoside, the plasma membrane-bound receptor protein causes an increase in adenylate cyclase activity and a subsequent increase in intracellular cyclic AMP. Adenosine antagonises many of the biochemical and physiological mechanisms implicated in ischaemia-reperfusion injury and has been shown to reduce post-ischaemic ventricular dysfunction and myocyte necrosis and apoptosis.<sup>18, 19</sup> The exact mechanism of the cardioprotective effect of adenosine is not fully understood, although inhibition of neutrophil activation and prevention of endothelial damage seem to have a major role. The other effect of adenosine is presynaptic inhibition of norepinephrine release from sympathetic nerve terminals.<sup>11</sup> Three properties of adenosine have led to its extensive use in several studies. Firstly, intravenous or intracoronary adenosine can reliably increase coronary conductance to maximum levels (that is, at or exceeding a level produced by transient ischaemia). Secondly, the duration of action of adenosine is very brief (5–30 s). Thirdly, at high doses, adenosine produces transmural vasodilatation.

In a study of 40 patients with acute myocardial infarction, Taniyama *et al*<sup>10</sup> found that intracoronary administration of verapamil after primary PTCA significantly improved the TFC and wall motion score. Our findings in patients who presented with an ACS are comparable. Marzilli *et al*<sup>12</sup> studied 54 patients with acute myocardial infarction undergoing primary PCI. In their study, 4 mg of adenosine in 2 ml of saline was administered into the distal vascular bed after the balloon was inflated. They reported a reduction in the incidence of the no-reflow phenomenon and improved ventricular function in patients who received intracoronary adenosine. In our study, we have shown that the administration of both verapamil and adenosine was associated with a small but significant improvement in the wall motion abnormality between day 1 and day 30 after PCI.

In patients with evidence of no reflow, the administration of intracoronary verapamil (50–900 µg, total dose)<sup>1</sup> improved TFG in 89% and TFC also improved significantly. In our study, with only a small percentage of patients with evidence of slow flow/no reflow, we observed a significant improvement in the TFC and all patients had TFG 3 after the administration of study drugs. Overall, the uncorrected TFC improved significantly at the completion of the PCI procedure. The final TFC was lower than the mean value for normal or mildly diseased coronary arteries in our laboratory.<sup>13</sup> Our results clearly show that the addition of either verapamil or adenosine significantly improves epicardial coronary blood flow even when flow appears visually to be angiographically normal after PCI in the setting of an ACS. We observed this effect in patients with STEMI and non-STEMI, and in those who did and did not receive calcium channel blockers and glycoprotein IIb/IIIa inhibitors.

In our study we administered 0.5 mg of verapamil. This dose was previously shown to improve TFC and wall motion

score in patients with acute myocardial infarction.<sup>10</sup> However, a significant number of patients in our study developed transient heart block that lasted up to 3 h and was associated with a significant drop in the systolic blood pressure. Although this was not life threatening, these patients were monitored for up to 12 h in the cardiology wards. Of the nine patients who developed heart block, seven patients had PCI to the RCA (six RCA dominance, one mixed dominance), one patient had circumflex artery PCI (RCA dominance) and the other underwent PCI to the left anterior descending artery (RCA dominance). None of these patients were taking a calcium channel blocker. Five patients were taking a β blocker, of whom four had PCI to the RCA and one had circumflex PCI.

In a different study population,<sup>6</sup> the peak effect on the left coronary system was reached with an intracoronary dose of 1.0 mg verapamil. The authors did not report a further increase in coronary blood flow with larger doses of verapamil. Their study consisted of 20 patients (normal angiograms in three patients, mild lumen irregularities in 11 patients and > 50% diameter stenosis in six patients) who underwent only routine coronary angiography. Patients admitted with unstable angina or myocardial infarctions in the preceding three months were excluded. Our study suggests that in patients with an ACS, a balance has to be struck between the potential benefits of verapamil and the risk of complications. On the basis that the microvasculature in this setting may make it more sensitive to treatment, a much lower dose than we used (for example, 50–100 µg) may possibly achieve appropriate microvascular vasodilatation without the complications seen with 0.5 mg. Alternatively, a dose higher than 0.5 mg might have achieved a greater downstream effect but might have resulted in more complications. Our study was not a dose-ranging study and the optimal dose of verapamil to use in this setting is uncertain. We based the dose in our study on that used by Taniyama and colleagues.<sup>10</sup>

In a previous study of 31 patients who had atypical chest pain with normal or mildly stenotic coronary arteries (< 50% diameter stenosis) by Wilson *et al*,<sup>11</sup> 12 µg of intracoronary adenosine achieved maximum hyperaemia in the RCA and 16 µg of intracoronary adenosine achieved maximum hyperaemia in the left coronary system. In our study, we injected 30 µg of intracoronary adenosine into both the right and the left coronary arteries. This was not associated with any significant change in heart rate or in the ECG. Patients did not often complain of chest pain during the injection, which, if present, was mild and resolved within seconds. In contrast to the above study, we chose a larger dose of 30 µg of adenosine because it was easy to prepare 30 µg of adenosine from a 3 mg vial. Intracoronary adenosine injection may be followed by transient atrioventricular block, but this was not seen in our study.

MBG is a strong angiographic predictor of death in patients with TIMI 3 flow after angioplasty.<sup>16, 20</sup> Although our study was not designed to detect improvements in myocardial perfusion by using the MBG method, we have not observed any significant differences in the MBGs between the three groups after the administration of study drugs. Only a few patients in the current study had STEMI. The MBG improved after PCI to such an extent that there was little room for further improvement. Whether verapamil or adenosine improves the MBG in patients with only MBG grades 1 or 2 after PCI is not known, but this was not the purpose of our study.

### Limitations

There are a number of caveats to this study. Firstly, the study was not blinded. Because of differences in the doses and preparation methods, we used an open-label strategy.

We measured coronary flow by the TFC method. We did not use a Doppler coronary flow wire. However, other workers have previously reported the correlation between these two methods that, in effect, measure the same thing.<sup>21–22</sup> The TFC method is validated and robust, and we believe that the results of our study are clinically valid.<sup>13</sup> Indeed, the TFC method can be used to determine the coronary flow velocity reserve (frame count reserve). Most catheterisation laboratories do not have access to a flow wire, whereas the TFC method is universally applicable.

Randomisation in small studies often results in an apparent numerical difference between groups that is, nonetheless, not statistically different on analysis. In our study relatively few patients in the saline group had diabetes and only two patients presented with STEMI in the adenosine group. Overall, the number of patients with diabetes is consistent with other PCI studies. It is possible that different subgroups of patients (for example, patients with diabetes, undergoing saphenous vein graft intervention, presenting with STEMI as opposed to non-STEMI or with differing degrees of left ventricular dysfunction) have differing responses to the study drugs, but our study was not designed to evaluate this. Because we felt that verapamil and adenosine would exert their effects predominantly on the distal vascular bed we did not exclude patients undergoing vein graft PCI. Moreover, these patients are more likely than patients undergoing native vessel PCI to experience a slow-flow phenomenon (possibly for different reasons). Although we acknowledge that such subgroups may differ, in reality we enrolled only one patient with a vein graft procedure. Excluding the patient made no difference to the results.

Our study population had received extensive medical treatment before going to the catheterisation laboratory. The impact of concurrent drugs on the effect of intracoronary vasodilators cannot be ascertained from our study, but the use of drugs of various classes did not differ between the study groups. Despite these oral drugs being taken, both verapamil and adenosine were shown to have an impact on flow, and heart block occurred with verapamil whether or not patients were taking drugs that have an effect on the atrioventricular node. In reality, slow flow occurs in patients regardless of their oral drugs; the results of our study suggest that adenosine may be a preferable agent to use, and this may especially be the case for patients already taking a  $\beta$  blocker, digoxin or a rate-modifying calcium channel blocker.

We have shown a small but significant improvement in the WMI in the verapamil and the adenosine groups. This result should be interpreted with caution, as the current study was not sufficiently powered to detect this benefit. Moreover, the difference is small and of uncertain clinical significance. Although the result can be considered surprising, in that a single injection of intracoronary verapamil or adenosine may not be expected to have a significant effect on myocardial function, relatively small microvascular changes immediately after PCI may possibly have a beneficial effect on myocardial recovery in the setting of an ACS. Larger, sufficiently powered studies are required to find out whether vasodilator treatment affecting the distal coronary bed does have a beneficial effect.

We did not record echocardiograms before PCI. It was not logistically feasible to have all of our patients undergo echocardiography before their procedures, especially as many were transferred from other hospitals at a time linked to the planned catheterisation laboratory procedure. We believe, however, that the randomisation process would have made the pre-PCI WMI likely to be similar between groups, but we cannot confirm this. On this basis, we believe that any differences seen between the patients receiving study drugs

and those receiving saline would most probably be associated with the study drugs. We do not routinely perform left ventricular angiography in these patients.

Lastly, we did not measure pre-PCI creatine kinase or troponin T concentrations. As the majority of patients were transferred from another hospital, we did not have access to all of the troponin T or creatine kinase concentrations of these patients before the procedure, and the different hospitals that refer patients to us have different protocols and different assays for these markers. We did not take our own samples just before PCI. One can argue that randomisation should have resulted in matched groups, and on that basis the troponin T and creatine kinase results that we measured at 6 and 12 h after the angioplasty in part reflect preprocedural concentrations.

## Conclusion

Administration of bolus doses of intracoronary verapamil or adenosine significantly improves coronary flow and WMI after PCI in the setting of an ACS. The beneficial effects of verapamil and adenosine are not significantly different. Verapamil was, however, significantly associated with transient heart block compared with adenosine, and this side effect may make adenosine the preferred agent for routine clinical use.

## Authors' affiliations

**K Vijayalakshmi, B Kunadian, J Graham, R A Wright, J A Hall, A Sutton, M A de Belder**, Department of Cardiology, The James Cook University Hospital, Middlesbrough, UK  
**V J Whittaker**, School of Health and Social Care, University of Teesside, Middlesbrough, UK

Competing interests: None declared.

## REFERENCES

- 1 **Piani R**, Palik G, Moscucci M, *et al*. Incidence and treatment of 'no-reflow' after percutaneous coronary intervention. *Circulation* 1994;**89**:2514–8.
- 2 **Bates E**, Krell M, Dean E, *et al*. Demonstration of no-reflow phenomenon by digital coronary arteriography. *Am J Cardiol* 1986;**57**:177–8.
- 3 **Feld H**, Lichstein E, Schachter J, *et al*. Early and late angiographic findings of the no-reflow phenomenon following direct angioplasty as primary treatment for acute myocardial infarction. *Am Heart J* 1992;**123**:782–4.
- 4 **Kloner R**, Ganote C. The no-reflow phenomenon after temporary occlusion in the dog. *J Clin Invest* 1974;**54**:1508.
- 5 **Werner G**, Lang K, Kuehnert H, *et al*. Intracoronary verapamil for reversal of no-reflow during coronary angioplasty for acute myocardial infarction. *Catheter Cardiovasc Interv* 2002;**57**:444–51.
- 6 **Oldenburg O**, Eggerbrecht H, Herrmann J, *et al*. Dose-dependent effects of intracoronary verapamil on systemic and coronary hemodynamics. *Cardiovasc Drugs Ther* 2000;**14**:651–5.
- 7 **Kaplan B**, Benzuly K, Kinn J, *et al*. Treatment of no-reflow in degenerated saphenous vein graft interventions: comparison of intracoronary verapamil and nitroglycerin. *Catheter Cardiovasc Interv* 1996;**39**:113–8.
- 8 **Michaels A**, Appleby M, Otten M, *et al*. Pretreatment with intragraft verapamil prior to percutaneous coronary intervention of saphenous vein graft lesions: results of the randomised, controlled vasodilator prevention on no-reflow (VAPOR) trial. *J Invasive Cardiol* 2002;**14**:299–302.
- 9 **Lim S**, Bae E, Jeong M, *et al*. Effect of combined intracoronary adenosine and nicorandil on no-reflow phenomenon during percutaneous coronary intervention. *Circ J* 2004;**68**:928–32.
- 10 **Taniyama Y**, Ito H, Iwakura K. Beneficial effects of intracoronary verapamil on microvascular and myocardial salvage in patients with acute myocardial infarction. *J Am Coll Cardiol* 1997;**30**:1193–9.
- 11 **Wilson R**, Wyche K, Christensen B, *et al*. Effects of adenosine on human coronary arterial circulation. *Circulation* 1990;**82**:1595–606.
- 12 **Marzilli M**, Orsini E, Marracini P, *et al*. Beneficial effects of intracoronary adenosine as adjunct to primary angioplasty in acute myocardial infarction. *Circulation* 2000;**101**:2154–9.
- 13 **Vijayalakshmi K**, Ashton V, Wright R, *et al*. Corrected TIMI frame count (cTFC): applicability in modern digital catheter laboratories when different frame acquisition rates are used. *Catheter Cardiovasc Interv* 2004;**63**:426–32.
- 14 **Gibson MC**, Cannon CP, Daley WL, *et al*. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation* 1996;**93**:879–88.
- 15 **The TIMI Study Group**. Thrombolysis in myocardial infarction (TIMI) trial. *N Engl J Med* 1985;**312**:932–6.

- 16 **Van't Hof A**, Liem A, Suryapranata H, et al. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. *Circulation* 1998;**97**:2302-6.
- 17 **Gibson C**, Murphy S, Rizzo M. Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. *Circulation* 1999;**99**:1945-50.
- 18 **Olafsson B**, Forman M, Puett D, et al. Reduction of reperfusion injury in the canine preparation by intracoronary adenosine. *Circulation* 1987;**76**:1135-45.
- 19 **Van der Heide R**, Reimer K. Effects of adenosine therapy at reperfusion on myocardial infarct size in dogs. *Cardiovasc Res* 1996;**31**:711-8.
- 20 **Henriques J**, Zijlstra F, van't Hof A, et al. Angiographic assessment of reperfusion in acute myocardial infarction. *Circulation* 2003;**107**:2115-9.
- 21 **Stoel M**, Zijlstra F, Visser C. Frame count reserve. *Circulation* 2003;**107**:3034-9.
- 22 **Manginas AM**, Gatzov PM, Chasikidis CM, et al. Estimation of coronary flow reserve using the thrombolysis in myocardial infarction (TIMI) frame count method. *Am J Cardiol* 1999;**83**:1562-5.

## IMAGES IN CARDIOLOGY.....

doi: 10.1136/hrt.2005.082701

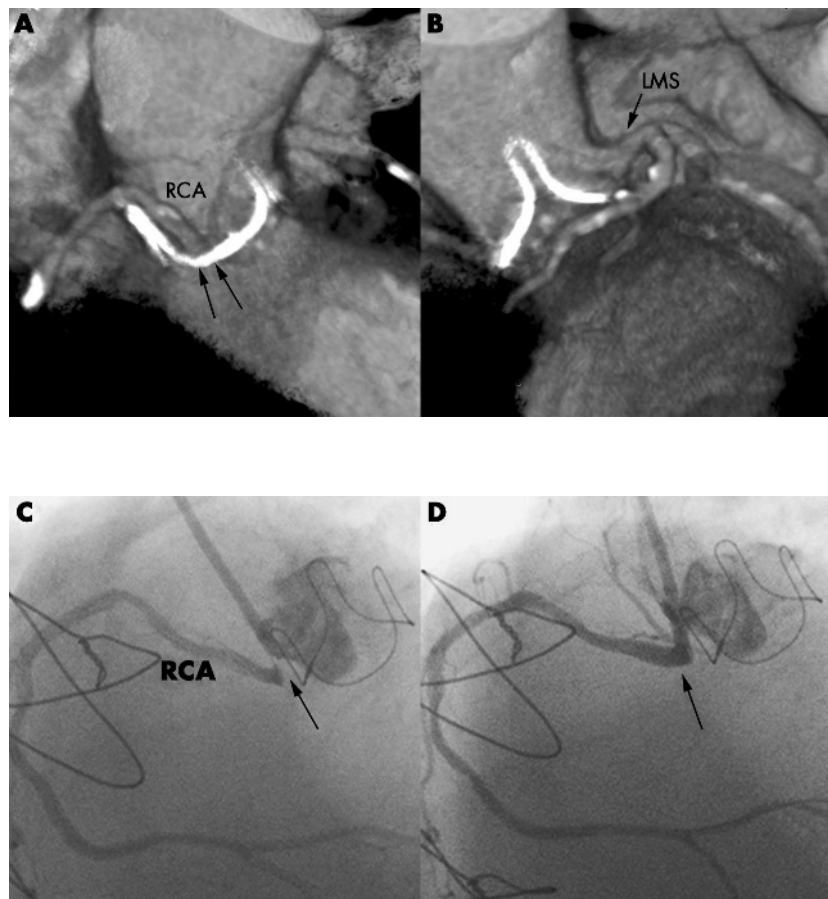
### Angioplasty and stenting to correct ostial right coronary artery obstruction by a prosthetic aortic valve

**A** 76-year-old woman underwent aortic valve replacement with a 23 mm Carpentier Edwards bioprosthesis for aortic stenosis. Preoperative coronary angiograms were normal. Within three months she developed exertional angina. A multislice computed tomographic (CT) angiogram indicated that part of the valve stent encroached upon the right coronary ostium (panel A, compared to left main stem (LMS), panel B).

At angiography the right coronary ostium was engaged around the stent strut, showing a slit-like lumen (panel C). This was crossed with a Pilot 50 guide wire and progressively predilated up to 2.5 mm. A 2.75 × 16 mm Taxus stent was deployed and postdilated to 3.5 mm (panel D). An aortogram confirmed normal prosthetic valve function. Her symptoms improved immediately and routine angiography after seven weeks showed no restenosis.

Iatrogenic ostial coronary stenosis is a rarely reported complication of aortic valve replacement, usually presenting after two to six months and resulting from fibrous intimal proliferation, thought to be caused by trauma to the ostia during cannulation of the coronaries for direct cardioplegia.

Very rarely the stenosis is caused by direct obstruction by the prosthetic stent, reported in less than 0.2% of aortic valve replacements. This may be due to oversizing of the aortic prosthesis or abnormally low ostia. Such obstruction will usually be noticed following the procedure, and the prosthetic valve will be resected or replaced, sometimes with enlargement of the aortic annulus and relocation of the coronary ostia. This is the first reported case of percutaneous intervention to non-atherosclerotic coronary ostial obstruction caused by a prosthetic aortic valve.



**P Das**  
**I Meredith**  
 paul.das@med.monash.edu.au