INTERVENTIONAL CARDIOLOGY AND SURGERY

Non-invasive coronary flow reserve is correlated with microvascular integrity and myocardial viability after primary angioplasty in acute myocardial infarction

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Objective: To test whether preserved coronary flow reserve (CFR) two days after reperfused acute myocardial infarction (AMI) is associated with less microvascular dysfunction ('' no-reflow'' phenomenon) and is predictive of myocardial viability.

Design: 24 patients with anterior AMI underwent CFR assessment in the left anterior descending coronary artery (LAD) with transthoracic echocardiography and myocardial contrast echocardiography (MCE) 48 h after primary angioplasty in the LAD (mean 4 (SD 2) and 3 (1) days, respectively). Low-dose dobutamine echocardiography was performed 6 (3) days after AMI and follow-up echocardiography at three months.

Results: No-reflow extent was greater in patients with impaired CFR (< 2.5) than in those with preserved CFR (> 2.5) (55 (35)% *v* 11 (25)%, $p < 0.001$). MCE reflow was more common in patients with preserved CFR (8/12) than in those with reduced CFR (1/12, $p < 0.05$). Wall motion score index in the LAD territory (A-WMSI) was similar at the first echocardiography (2.14 (0.39) *v* 2.32 (0.47), NS), although it was better in patients with preserved CFR at dobutamine (1.38 (0.45) *v* 1.97 (0.67), $p < 0.05$) and follow-up echocardiography (1.36 (0.40) *v* 1.97 (0.64), $p < 0.05$). An inverse correlation was found between CFR and A-WMSI at dobutamine and follow-up echocardiography ($r = -0.49$, $p = 0.016$ and $r = -0.55$, $p = 0.005$) and between MCE and A-WMSI at dobutamine and follow-up echocardiography ($r = -0.75$, $p < 0.001$ and $r = -0.75$, $p < 0.001$). By multivariate analysis MCE reflow remained the only predictor of recovery at both dobutamine and follow-up echocardiography (odds ratio 1.06, 95% CI 1 to 1.1, $p = 0.009$).

Conclusion: CFR is inversely correlated with the extent of microvascular dysfunction at MCE two days after reperfused AMI. CFR and MCE reflow early after AMI are correlated with myocardial viability at follow up.

During acute myocardial infarction (AMI) early myocardial reperfusion is the target treatment to salvage ischaemic myocardium. As the optimal reperfusion therapy should restore not only epicardial patency and flow (TIMI (Thrombolysis in Myocardial Infarction) grade 3) but also myocardial tissue perfusion (reflow),[1 2] evaluation of coronary flow reserve (CFR) in patients with AMI has substantial importance in this context. Evaluation of CFR is the physiological approach to assess the severity of coronary stenosis and microvascular dysfunction.[1 3 4]

Previous studies showed that CFR and microvascular integrity are closely related[5 6] and that measurement of CFR immediately after recanalisation of the infarct-related coronary artery is predictive of myocardial viability.[5–11] In these studies, owing to the invasive nature of the interventional procedure, CFR was usually evaluated within minutes or a few hours after coronary recanalisation; in the clinical setting, however, it is not possible to study CFR invasively in all patients after primary percutaneous coronary intervention (PCI). Recently non-invasive analysis of CFR by transthoracic echocardiography has been successfully used to evaluate microvascular recovery after AMI.[12–14] Experimental studies have shown that microvascular damage is prolonged after reperfused AMI, and that such damage is progressive and reaches a peak 48 h after reperfusion.[15 16] CFR measurement more than 48 h later rather than very shortly after revascularisation may therefore be a more reliable indicator of microvascular damage and a better predictor of future left ventricular (LV) functional recovery. Although CFR and myocardial contrast echocardiography (MCE) have been used to evaluate the coronary microcirculation, little is known about their relationship 48 h after reperfusion therapy in AMI. The value of CFR in predicting LV functional recovery has not been fully studied.

Accordingly, this study was designed to test the hypothesis that preserved CFR in the infarcted-related coronary artery is associated with a greater extent of microvascular integrity two days after reperfused AMI and that the degree of microvascular integrity, as expressed by CFR and MCE reflow, is related to myocardial viability at low-dose dobutamine echocardiography and to LV function at follow up.

METHODS

Study population

Twenty four patients (19 men, mean age 54 (SD 7) years) with a first anterior AMI were prospectively enrolled into the

Abbreviations: AMI, acute myocardial infarction; A-WMSI, wall motion score index in the segments supplied by the left anterior descending coronary artery; CFR, coronary flow reserve; CK, creatine kinase; LAD, left anterior descending coronary artery; LV, left ventricular; MCE, myocardial contrast echocardiography; PCI, percutaneous coronary intervention; SPECT, single photon emission computed tomography; TIMI, Thrombolysis in Myocardial Infarction

study. AMI was diagnosed on the basis of (1) typical chest pain for more than 30 min; (2) ST elevation of more than 2 mm in two contiguous precordial leads; and (3) rise of serum creatine kinase concentrations to more than threefold the normal value. Coronary angiography and primary PCI were performed 3 (4) h after onset of chest pain by standard technique. CFR and MCE were evaluated at least two days after revascularisation. Patients with a previous anterior AMI, poor image quality, residual left anterior descending coronary artery (LAD) stenosis after intervention $> 20\%$, non-assessable MCE and lack of follow up were excluded.

Informed consent

All patients were informed about the objectives and the intended results of the study. Informed consent followed an enclosed protocol regarding the study design and international guidelines.

Two-dimensional echocardiography for evaluation of area at risk on admission

All echocardiographic studies were performed with an Agilent Sonos 5500 (Philips) or an Acuson Sequoia 512 (Siemens). The American Society of Echocardiography 16-segment model was used for analysis of LV wall motion. LV regional function was graded as normal, hypokinetic, akinetic or dyskinetic (score 1 to 4). Nine of the 16 segments were regarded to be supplied by the LAD, the whole anterior wall, the apical segment of inferior wall, mid- and basal segments of the anterior septum, apical and mid-segments of septum, and apical segment of the lateral wall.[17] The area at risk on admission was defined as dyssynergic myocardial segments in the LAD territory on two-dimensional echocardiography.[5 18] The wall motion score index in the segments supplied by the LAD (A-WMSI) was calculated.

Measurement of CFR

We used transthoracic contrast-enhanced harmonic Doppler echocardiography to assess CFR. We described this method in detail in our previous reports.[19 20] Briefly, a modified apical two-chamber view was applied to explore the flow in the distal portion of the LAD. Levovist (Schering AG, Berlin, Germany) was infused at a concentration of 300 mg/ml and at a rate of 0.5–1 ml/min to enhance the Doppler signal. Coronary blood flow velocity was evaluated in the distal LAD at baseline and after intravenous infusion of adenosine (140 μg/kg/min, lasting for 5 min). CFR was determined by dividing the maximum hyperaemic peak flow velocity by the resting flow velocity. Values of three cardiac cycles were averaged at baseline and during adenosine infusion for CFR measurement. A cut-off value of > 2.5 was regarded as normal or preserved CFR after primary PCI. Tracing of the LAD flow velocity profiles was reproducible, with very low interobserver and intraobserver measurement variability.[19]

Myocardial contrast echocardiography

Harmonic power Doppler with intermittent imaging mode (1:3 to 1:5 trigger rate at end systole) was performed with broadband transducers.[20] The mechanical index was set high (> 1.0). Focus was set at the two thirds depth of the image. Gain settings were maintained at $< 70\%$ to avoid a myocardial blooming artefact. Levovist was first administered intravenously as a small bolus (2 ml) and then as an infusion (8 ml, at a rate of 3 ml/min) to a concentration of 400 mg/ml. The left ventricle was divided into 16 segments as visualised in apical four-, two- and long-axis views. Two experienced cardiologists blinded to other data evaluated the MCE studies off line by visual grading. Myocardial perfusion was graded as full, patchy or absent. A segment was considered opacified if it was enhanced after contrast injection. A contrast defect was regarded as a relative decrease in contrast enhancement in one region compared with others in the same view. A myocardial segment was considered not assessable if shadowing, blooming or flashing artefacts existed. For evaluation of the extent of the perfusion defect, at least 50% of each segment had to show a pattern of poor or no opacification.

The microvascular dysfunction region (''no-reflow'' region) was defined as a contrast defect in the risk area. No-reflow extent was defined as the percentage ratio of segments not opacified to segments in the risk area. MCE reflow was considered if $> 50\%$ of segments within the risk area was fully opacified.[5 18 22]

Low-dose dobutamine and follow-up echocardiography

Low-dose dobutamine echocardiography was performed with a standard protocol. Dobutamine was infused at a maximum dosage of 10 μg/kg/min.[23] Recovery was considered to be functional at low-dose dobutamine or at three-month follow-up echocardiography if the patient's wall motion improved in at least two contiguous dysfunctional segments by > 1 grade. During follow up, no patients developed new symptoms of ischaemia.

Statistical analysis

Data are expressed as mean (SD). Continuous variables were analysed with paired (within group) or unpaired (between groups) Student's t test. Two-sided p values are reported. Linear regression analysis was used to assess the relationship between CFR, MCE and wall motion score index in the segments supplied by the LAD (A-WMSI) at admission, low-dose dobutamine and three-month follow-up echocardiography. Categorical data were compared by a χ^2 analysis. A value of $p < 0.05$ was considered to be significant. To identify independent predictors of recovery of function (both at low-dose dobutamine results and at follow up), multivariate logistic regression analysis with a forward- and backward-stepping algorithm was used (SPSS software V.12.0; SPSS Inc, Chicago, Illinois, USA). Variables included in this

Table 1 Clinical and angiographic characteristics in patients with preserved and impaired CFR

	Impaired CFR (n = 12)	Preserved CFR (n = 12)	p Value
Age (years)	56 (11)	53 (7)	0.474
Men	9	10	1.0
Cigarette smoking	9	8	1.0
Hypertension	6	8	0.679
Diabetes mellitus	4	6	0.679
Hypercholesterolaemia	7	4	0.413
Drug treatment			
Nitrates	11	11	1.0
β blockers	10	6	0.194
ACE inhibitors	6	9	0.399
Heparin	12	12	1.0
Peak CK (U/l)	4842 (4638)	1270 (1078)	0.001
Peak CK-MB (U/l)	391 (303)	168 (193)	0.001
LV ejection fraction (%)	49 (11)	48 (9)	0.918
Thrombolytic agent	2	1	1.0
Time interval from onset of chest pain to angioplasty (h)	3 (5)	3 (3)	0.556
LAD stenosis (%)	89 (17)	93 (10)	0.470
Multivessel disease	6	7	1.0
No of diseased vessels	1.5 (0.5)	1.9 (0.9)	0.182
TIMI grade 3 flow before PCI	5	11	0.030

Data are mean (SD) or number.
ACE, angiotensin converting enzyme; CFR, coronary flow reserve; CK, creatine kinase; LAD, left anterior descending coronary artery; LV, left ventricular; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

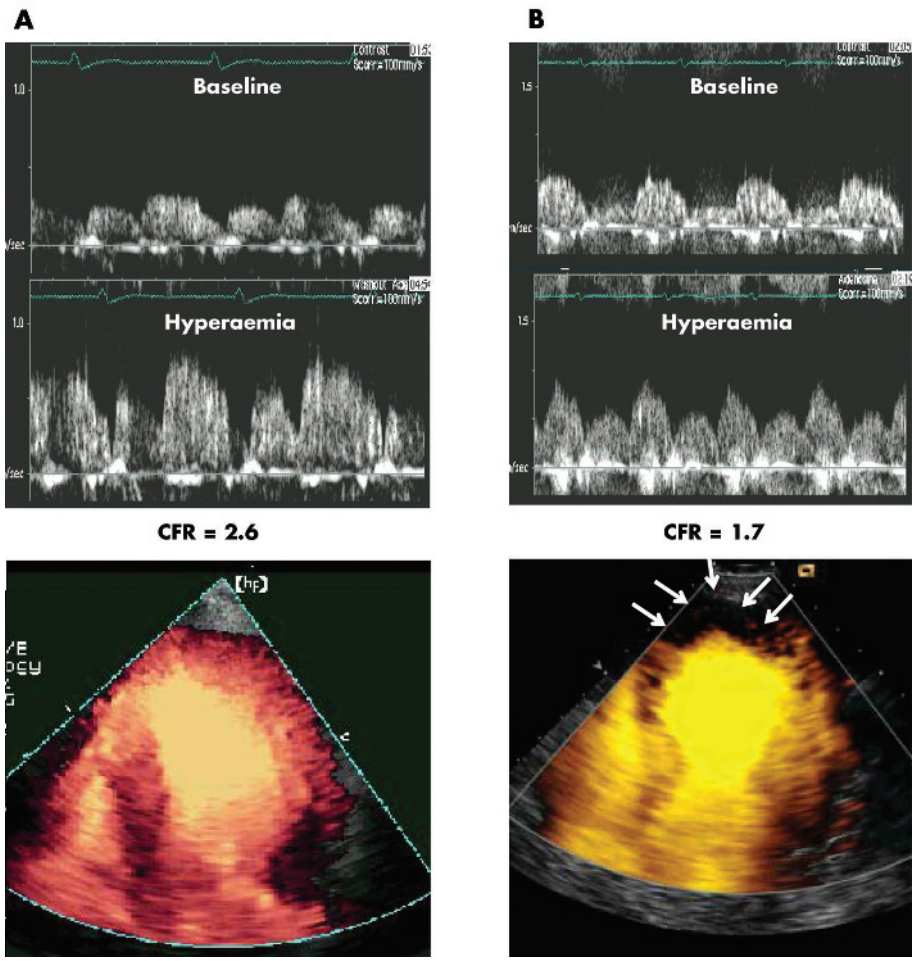

Figure 1 (A) Examples of echocardiographic images obtained in a patient with preserved coronary flow reserve (CFR) in the left anterior descending artery (LAD) after stent deployment. Apical four-chamber view shows homogeneous normal myocardial perfusion after revascularisation (lower panel). (B) Examples of echocardiographic images obtained in a patient with impaired CFR in the LAD after stent deployment. Apical four-chamber view shows a perfusion defect in the apex (arrows) (lower panel).

analysis were sex, age, hypercholesterolaemia, diabetes, history of preinfarction angina, history of hypertension, history of smoking, concentrations of creatine kinase (CK) and CK-MB, precoronary time, CFR and MCE results.

RESULTS

Patient characteristics

In the 24 patients studied, coronary angioplasty and stent implantation were successful in the LAD 3 (4) h after onset of chest pain. Three patients received thrombolysis (recombinant tissue-type plasminogen activator) on admission. CFR, MCE and low-dose dobutamine echocardiography were performed 4 (2), 3 (1) and 6 (3) days after interventional revascularisation. Follow-up echocardiograms were assessed at a mean time of three months (99 (31) days). All patients underwent the examinations in the research protocol and no side effects occurred during these procedures. Of the 216 segments supplied by the LAD, 16 (7%) were not assessable at MCE because of artefacts. Clinical and angiographic characteristics were similar in the two groups, with the exception of higher creatine kinase concentration and less TIMI grade 3 flow in patients with impaired CFR (table 1).

Relationship between CFR and no-reflow extent

CFR was significantly higher in patients with preserved CFR than in patients with impaired CFR (3.1 (0.6) *v* 1.7 (0.5), $p < 0.001$). Patients with preserved CFR had a smaller no-reflow region in the risk area at MCE than did patients with impaired CFR (11 (25)% *v* 55 (35)%, $p < 0.001$). MCE reflow in the segments supplied by the LAD was more common in patients with preserved CFR (8/12 (67%)) than in the group with reduced CFR (1/12 (8%), $p = 0.011$). Linear regression showed a moderate inverse correlation between CFR and the extent of no reflow in the LAD territory ($y = -0.014 \times 2.60$, $r = -0.59$, $p = 0.003$). Figure 1 displays examples of CFR and MCE perfusion.

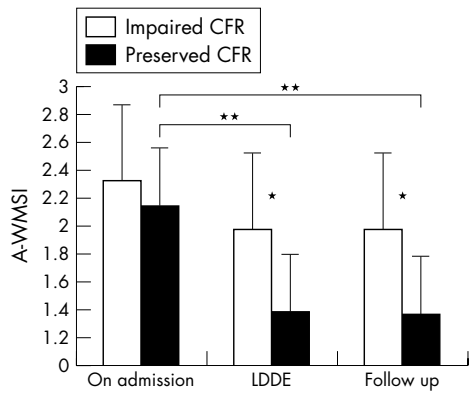

Figure 2 Wall motion score index in the segments supplied by the left anterior descending coronary artery (A-WMSI) on admission, at low-dose dobutamine echocardiography (LDDE) and at three-month follow-up echocardiography.*$p < 0.05$; **$p < 0.001$. CFR, coronary flow reserve.

Relationship between CFR, MCE reflow and myocardial viability

A-WMSI was similar on admission in the two groups. Wall motion improved significantly in patients with preserved CFR, with A-WMSI decreasing from 2.14 (0.39) on admission to 1.38 (0.45) at low-dose dobutamine echocardiography ($p < 0.001$) and to 1.36 (0.40) at the three-month follow up ($p < 0.001$). On the contrary, wall motion did not improve significantly in patients with impaired CFR, with A-WMSI changing from 2.32 (0.47) on admission to 1.97 (0.67) at low-dose dobutamine echocardiography ($p = 0.052$) and to 1.97 (0.64) at follow up ($p = 0.060$) (fig 2). Thus, viable myocardium was more commonly present in patients with normal CFR than in patients with impaired CFR. CFR measured 4 (2)days after LAD stenting was not correlated with A-WMSI on admission ($r = -0.21$, $p = 0.317$). CFR was, however, inversely correlated with A-WMSI at low-dose dobutamine echocardiography ($r = -0.49$, $p = 0.016$) and at three-month follow up ($r = -0.55$, $p = 0.005$) (fig 3). Also, MCE reflow was inversely correlated with A-WMSI at low-dose dobutamine echocardiography ($r = -0.75$, $p = 0.0001$) and three-month follow up echocardiography ($r = -0.75$, $p = 0.0001$). At univariate analysis predictors of functional recovery at low-dose dobutamine echocardiography and at three-month follow up were CK-MB concentration ($p < 0.05$), CFR ($p < 0.005$) and MCE reflow ($p < 0.005$). At multivariate analysis the only significant predictor of recovery was MCE reflow (odds ratio 1.06, 95% confidence interval 1 to 1.1, $p = 0.009$).

DISCUSSION

We investigated the relationship between CFR and microvascular dysfunction 48 h after successful primary PCI for anterior AMI when no further major progression of microvascular obstruction and reactive hyperaemia is expected. Recently, others have pointed out the importance of non-invasive analysis of coronary flow and its derivatives (deceleration time of the diastolic phase) and CFR in predicting myocardial viability after coronary reperfusion in AMI.[11–14 24] Our study showed that CFR was inversely correlated with the ratio of no-reflow region to risk area and was predictive of LV myocardial viability, as shown by low-dose dobutamine echocardiography and three-month follow-up echocardiography. CFR measured non-invasively two days after reperfused AMI therefore seems to be an indicator of microvascular integrity and of myocardial viability.

Relationship between CFR and no-reflow phenomenon

Previous studies showed that, despite successful recanalisation after AMI, CFR of the infarct-related coronary artery was usually reduced immediately after reperfusion. The time course of CFR, however, varies greatly between reports.[24 25] Lastly, epicardial stenosis before and after angioplasty have been proved to be important factors influencing CFR measurement.[26] Patients in our study did not differ in terms of stenosis severity before revascularisation, nor did they have significant residual stenosis (> 20%) after revascularisation, so impaired CFR in our study may have been caused by impaired microvascular structure or function, due to the ischaemic and reperfusion injury. In fact at revascularisation time, TIMI grade 3 flow was less common in patients with reduced CFR than in patients with preserved CFR, suggesting that more prolonged and severe myocardial ischaemia causes more severe microvascular dysfunction.[27]

Our results extended the previous findings[5 6] by showing a close inverse relation between CFR and the no-reflow phenomenon, when it is used to assess microvascular integrity. Lepper *et al*[5] found a significant CFR improvement

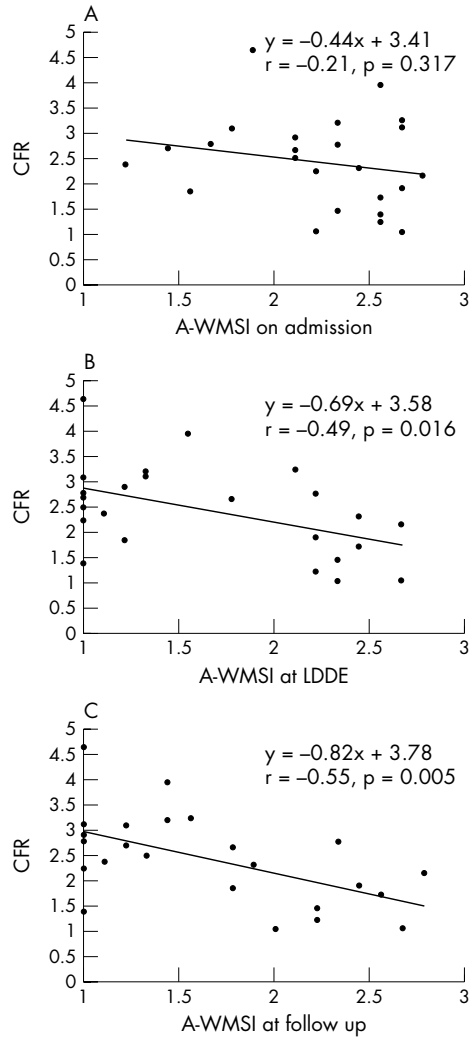

Figure 3 Correlations between coronary flow reserve (CFR) and wall motion score index in the segments supplied by the left anterior descending coronary artery (A-WMSI) (A) on admission, (B) at low-dose dobutamine echocardiography (LDDE), and (C) at three-month follow-up echocardiography.

at 24 h after reperfused AMI relative to immediately after primary PCI, and that CFR measurements matched the myocardial perfusion score at MCE. In their study, however, CFR and MCE analysis may still have been in the evolving phase, when microvascular damage or oedema are still progressing. In fact, Rochitte *et al*[15] showed, by using MCE and magnetic resonance imaging, that microvascular damage develops progressively up to 48 h after reperfusion and stabilises after two days. They found that the ratio of microvascular obstruction to infarct size at 48 h was significantly higher than when measured at 2 and 6 h. Conversely, our study evaluated CFR and MCE at least two days later, when the microvascular damage after infarction and reperfusion was stable.[15]

The relationship between CFR and MCE, as shown by our study and others, can be explained by the common pathophysiological basis in the microcirculation after reperfused AMI. After re-establishment of epicardial patency and flow, complex anatomical and functional changes occur, such as neutrophil infiltration, tissue oedema, endothelial dysfunction, inflammatory responses, platelet microemboli and microvascular stunning.[2] Recent advances in ultrasound instrumentation and contrast media have made it possible

to use intravenous MCE as an alternative technique to evaluate myocardial perfusion.[21 22 28 29] Previous studies have shown that up to several hours after infarction, the spatial distribution of MCE perfusion defects during reflow underestimates the degree of necrosis because of hyperaemia in the risk area.[25] In conjunction with coronary vasodilators, MCE can accurately predict infarct size early after reperfusion by unmasking abnormalities in flow reserve within the infarct zone, and CFR can be used as an indicator of the integrity of the myocardial microvasculature.[30] We used intravenous MCE 3 (1) days after reperfusion to evaluate the extent of myocardial perfusion defects. Eight patients (67%) in the normal CFR group and one (8%) in the impaired CFR group had MCE reflow ($p < 0.05$), indicating that preserved CFR was associated with a greater extent of microvascular integrity.

CFR, MCE reflow and myocardial viability

Previous studies,[5 7–11 13 14] by using different modalities including single photon emission computed tomography (SPECT), LV angiogram and echocardiography, have proved that CFR after AMI predicts viable myocardium, the ultimate recovery of LV function and late LV remodelling. Accordingly, in this study the extent of microvascular integrity was greater in patients with normal CFR than in patients with impaired CFR, in correspondence with MCE perfusion. In our study we confirmed the same relationship of non-invasively assessed CFR, evaluated 48 h after primary PCI, with myocardial viability assessed with dobutamine stress echocardiography and LV function assessed at follow up echocardiography. When compared with dobutamine-stimulated myocardial contractile reserve and LV function at three-month follow up, LV function as expressed by a significant decrease of A-WMSI improved in patients with normal CFR after reperfused AMI.

Furthermore, there was a negative correlation between CFR and A-WMSI at dobutamine and at follow-up echocardiography; conversely, no correlation was found on admission (fig 3). It seems difficult to give a precise cut-off value at a given time to predict LV functional recovery, however, because the relationship between CFR and contractile reserve in myocardium with reversible contractile dysfunction is not entirely clear, and because CFR can vary greatly over time after AMI, as CFR determined in the clinical setting usually is only a single time point in the natural course of CFR. This can explain why, in the current as well as in other studies of patients with improved LV function after revascularisation, CFR values in the infarct-related coronary artery were different both before and immediately after PCI.[8] Lastly, at multivariate analysis only MCE reflow was predictive of LV functional recovery, confirming the important role of coronary microcirculation integrity in preserving myocardial viability, as already shown by previous studies.[5 18 25 29] In fact, CFR and MCE reflect different aspects of microvascular function: MCE reflow is a direct dependent marker of microvascular integrity, whereas CFR is related to several factors apart from microvascular integrity.

Study limitations

Transthoracic echocardiography can visualise blood flow better in the LAD, thus restricting its application in other coronary arteries. We used MCE to determine myocardial perfusion; we did not use a reference standard such as SPECT or contrast cardiac magnetic resonance imaging. Previous studies that used harmonic power Doppler imaging technology[28] have shown, however, that myocardial perfusion at MCE closely correlated with SPECT findings on a segment by segment basis. We assessed perfusion by visual scoring; quantitative analysis may be more accurate to distinguish normal perfusion for mild defects. Owing to intermittent triggering, we could not observe myocardial perfusion throughout the cardiac cycle. Recent use of a real-time low mechanical index provided a new approach to assess myocardial perfusion,[29] whose potential needs to be further explored in the clinical context. Flashing artefacts caused by wall motion, attenuation in the far field and blooming are disturbing factors that affect the accurate interpretation of myocardial perfusion. In this study, segments with artefacts were excluded, and only 16 segments (7%) supplied by the LAD were not assessable at MCE. We used dobutamine-induced contractility and wall motion recovery at three-month follow-up echocardiography as indicators of myocardial viability. This approach has some limitations when compared with positron emission tomography or contrast cardiac magnetic resonance assessment of myocardial perfusion and viability.

Clinical implications

Non-invasive measurement of CFR and intravenous MCE provide a totally non-invasive evaluation of microvascular integrity in patients after reperfused AMI. Non-invasive measurement of CFR and MCE at two days after AMI has the potential to predict myocardial viability and LV functional recovery at follow up and can provide insight into the pathophysiological changes of microcirculatory function after AMI and reperfusion. This finding is relevant for selected patients after primary angioplasty who may benefit from adjunctive treatments aimed at improving recovery of LV function and reducing remodelling of the post-ischaemic heart.

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IMAGES IN CARDIOLOGY

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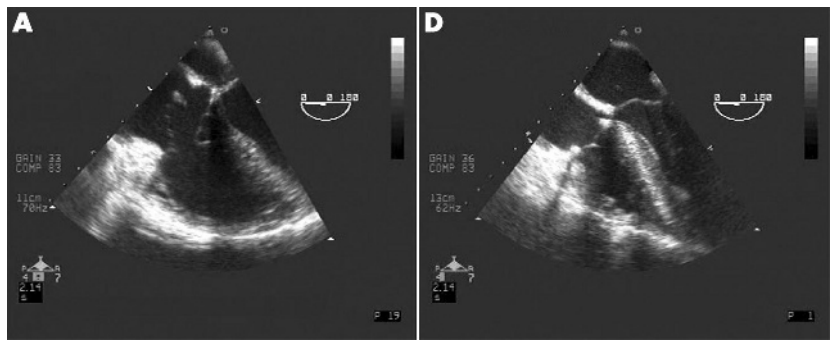
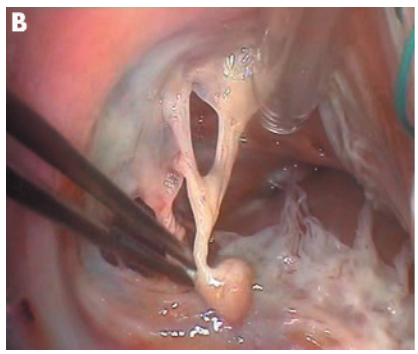
Traumatic tricuspid insufficiency

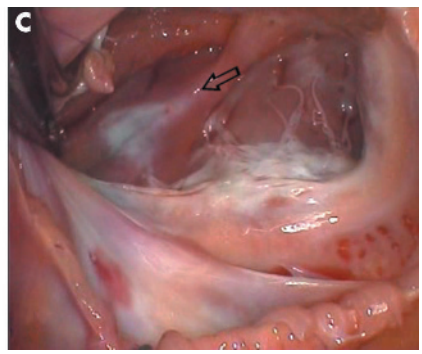
A 19 year old man sustained a blunt thoracic trauma in a high velocity accident. Initial examination revealed severe thoracic injuries with bilateral haemopneumothorax, pulmonary contusion and postero-inferior mediastinal haematoma without oesophageal perforation. An ECG demonstrated right bundle branch block. Transoesophageal echocardiography revealed severe tricuspid valve insufficiency with complete prolapse of the anterior valve leaflet in the right atrium (panel A). Because of good haemodynamic tolerance, surgical correction was deferred until resolution of associated thoracic injuries.

The patient was operated on six weeks later, and a complete transection of the base of the anterior papillary muscle was demonstrated (panel B). In addition significant annular dilatation had developed. No leaflet or chordal lesions were noted. Surgical correction was performed by papillary muscle reimplantation, which was facilitated by the existence of a fibrotic scar marking the native implantation site on the anterior wall of the right ventricle (panel C, arrow). Annular dilatation was corrected by implantation of an annuloplasty ring.

Postoperative transoesophageal echocardiography showed satisfactory leaflet coaptation and only trivial residual valvular regurgitation (panel D). Subsequent patient recovery was uneventful.







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