Myocardial blood volume and the amount of viable myocardium early after mechanical reperfusion of acute myocardial infarction: prospective study using venous contrast echocardiography

P Andrassy, M Zielinska, R Busch, A Schömig, C Firschke

Heart 2002;87:350-355

See end of article for authors' affiliations

Correspondence to:
Dr C Firschke, Deutsches
Herzzentrum München,
Lazarettstraße 36,
D-80636 Munich,
Germany

Accepted
11 December 2001

Background: Myocardial capillary perfusion is a prerequisite of myocellular viability after reperfusion of acute myocardial infarction. It was hypothesised that the magnitude of myocardial capillary perfusion, assessed by transmural signal intensity in venous contrast echocardiography as a corollary of the blood volume of myocardial capillaries, and the amount of viable myocardium, represented by differential levels of contractile function two weeks after reperfusion, are correlated.

Objectives: To evaluate the role of venous contrast echocardiography for the identification of viable myocardium in patients with acute myocardial infarction early after successful mechanical reperfusion.

Methods: 60 patients with a first acute myocardial infarction underwent venous contrast echocardiography several hours after successful mechanical reperfusion (median time interval 190 min.). The relative transmural videointensity (median (25th, 75th percentiles)) of akinetic segments was determined. After two weeks, contractile function was re-evaluated at rest and during dobutamine infusion if segments without functional recovery were present.

Results: Relative videointensity early after reperfusion differed significantly between functional groups after two weeks: normokinesia (88% (77%, 100%)), hypokinesia (74% (54%, 99%)), and akinesia with (61% (48%, 76%)) and without contractile reserve (31% (22%, 46%)). Relative videointensity and contractile function were significantly correlated ($r = -0.67$). The diagnostic accuracy of relative videointensity $> 50\%$ for prediction of contractility of initially akinetic segments at rest or during dobutamine was 82% ($\chi^2 = 76.2$, $p < 0.001$).

Conclusions: Early after successful mechanical reperfusion of acute myocardial infarction, the magnitude of capillary perfusion in the perfusion territory of an infarct related artery is correlated with the amount of viable myocardium. Quantitative venous contrast echocardiography can be used for accurate identification of viable myocardium.

The aim of mechanical reperfusion in patients with acute myocardial infarction is to restore blood flow through the infarct related artery to limit myocellular necrosis and ultimately preserve myocardial contractile function, which is the most powerful predictor of survival after acute myocardial infarction.¹ The success of reperfusion, however, is indicated by perfusion of myocardial capillaries rather than simply patency of the infarct related artery.²⁻³ Myocardial contrast echocardiography can be used to assess myocardial capillary perfusion.⁴⁻⁵ The signal from the myocardium following an intravenous injection of microbubbles has been shown to be a corollary of the blood volume of myocardial capillaries and thus functional capillary integrity.⁶ Identification of viable myocardium after reperfusion following acute myocardial infarction, through contrast enhancement after intracoronary injection of microbubbles, was, however, limited in most studies by low specificity for the binary prediction of recovery of resting contractile function.⁷⁻⁹ We expected that the more physiological intramyocardial distribution of the contrast agent after venous administration would result in a precise image of differential degrees of myocardial microvascular damage. We therefore hypothesised that measuring the transmural contrast signal from the myocardium would correlate with the extent of myocardial viability and functional recovery after mechanical reperfusion of acute myocardial infarction. Since endocardial necrosis may not be associated with recovery of resting contractile function,¹⁰ we assessed myocardial viability by measuring contractile function during do-

butamine infusion in patients without functional recovery. Furthermore, because reactive hyperaemia may mask the degree of capillary damage immediately after reperfusion,¹¹ we measured contrast intensity several hours following reperfusion when the hyperaemic response had abated.

METHODS

Patient population

This prospective study enrolled patients with first acute myocardial infarction admitted to the hospital within 24 hours after onset of chest pain. Acute myocardial infarction was diagnosed in the presence of two of the following criteria: typical anginal chest pain lasting ≥ 20 minutes; presumed new ST elevation of ≥ 0.1 mV in two or more contiguous limb ECG leads or ≥ 0.2 mV in two or more contiguous precordial leads; and increased creatine kinase to two or more times the upper reference limit with a concomitant rise in creatine kinase MB isoenzyme. Exclusion criteria were inability to give informed consent, cardiogenic shock, and inadequate echocardiographic window for assessment of wall thickening in any segment of the apical four and two chamber views. All patients underwent successful mechanical reperfusion, which was defined as the presence of TIMI (thrombolysis in myocardial infarction) grade 3 flow immediately and two weeks after the intervention.

Study protocol

Two dimensional and venous myocardial contrast echocardiography were performed approximately three hours after

Table 1 Patient characteristics

Age, median years (25th, 75th centiles)	58 (51, 64)
Women, n (%)	9 (15)
Mechanical reperfusion, n (%)	
Stent	46 (77)
Percutaneous transluminal coronary angioplasty	14 (23)
Time from symptom onset to reperfusion, median hours (25th, 75th centiles)	8 (3, 17)
Peak creatine kinase, median IU (25th, 75th centiles)	825 (426, 1410)
Infarct related artery, n (%)	
Left anterior descending coronary artery	29 (48)
Right coronary artery	25 (42)
Left circumflex coronary artery	6 (10)
Multivessel disease, n (%)	36 (60)
Q wave infarction, n (%)	49 (82)
Arterial hypertension, n (%)	34 (57)
Hypercholesterolaemia, n (%)	39 (65)
Diabetes mellitus, n (%)	10 (17)
Smoking, n (%)	39 (65)
β Blocker medication at follow up, n (%)	57 (95)

mechanical reperfusion (median (25th, 75th centiles) 190 minutes (160 minutes, 242 minutes)). At follow up after two weeks, coronary angiography and both echocardiographic studies were repeated. Patients with akinetic segments at follow up underwent dobutamine stress echocardiography. The study protocol was approved by our institutional review board and patients gave written informed consent.

Venous myocardial contrast echocardiography

Three milliliters of Optison (Mallinckrodt Medical Imaging, Dublin, Ireland) was diluted with 27 ml 0.9% sodium chloride. A volumetric pump (Perfusor fm, Braun Melsungen, Melsungen, Germany) was used for intravenous infusion at 200 ml/h and adequate mixing of the solution was maintained by careful shaking of the pump. A phased array echocardiographic system (Sonos 5500, Agilent Technologies, Palo Alto, California, USA) was used. Harmonic (1.8/3.6 MHz) and intermittent imaging (every seventh cardiac cycle, ECG triggered to end systole) were applied.^{12,13} The maximum power output and dynamic range of the system (60 dB) were used and the most linear postprocessing mode (A) was selected. A dual focus was used and placed in the upper and lower third of the imaging sector. Overall gains and time gain compensation were adjusted to minimise myocardial tissue noise but still to allow myocardial contours to be seen. Machine settings were adjusted before each study and kept constant throughout. Imaging was performed using apical four and two chamber views and all images were recorded on S-VHS videotape. Contrast images were digitally processed off line as previously described.⁶ Mean videointensity was measured in each of the

six segments in the apical four and two chamber views. To account for differences in echogeneity between patients, the relative videointensity of a segment was calculated as the ratio between the videointensity of the segment and the brightest normokinetic segment of the same view. This parameter has been recently clinically validated with quantitative radionuclide single photon emission computed tomography data.¹⁴ Variability of relative videointensity of normokinetic segments early after reperfusion was 9% (1%, 13%). Intraobserver and interobserver variability of relative videointensity of segments were 5% (1.5%, 8.5%) and 7.5% (1.5%, 15%), respectively. Quantitative venous myocardial contrast echocardiography was performed by experienced investigators blinded to all clinical, echocardiographic, and angiographic data.

Two dimensional and dobutamine stress echocardiography

Tissue harmonic imaging (2.1/4.2 MHz) was used to assess wall thickening at rest and during dobutamine stress echocardiography (incremental doses of intravenous dobutamine were 5, 10, 20, 30, and 40 g/kg/min at three minute intervals). Single systoles obtained at rest and before each dobutamine increment from the apical four and two chamber views were stored digitally for review in a quad screen format. The entire study was also continuously recorded on S-VHS videotape. Wall thickening was assessed by two experienced readers blinded to clinical, angiographic, and contrast echo data. In cases of disagreement, the wall motion score was resolved by consensus of opinion. Each of the same segments used for videointensity measurements was assigned a score (1 = normokinesia, 2 = hypokinesia, 3 = akinesia, 4 = dyskinesia). Recovery of contractile function of a formerly dyskinetic or akinetic segment was defined as an improvement to at least hypokinesia at rest. Contractile reserve was defined as improvement to at least hypokinesia during dobutamine infusion. Wall motion score index was defined as the mean score of the 12 segments of a patient.

Statistical analysis

Nominal variables are expressed as counts and percentages. Differences between groups were assessed with a two sided χ^2 test. Continuous variables are presented as median (with the 25th and 75th centiles) and, as appropriate, Kruskal-Wallis and Mann-Whitney tests were applied for group comparisons. α Correction using the method of Marcus and colleagues¹⁵ was used. Spearman correlation coefficient (r) is given. Sensitivity and specificity of relative videointensities for prediction of functional status at the two week follow up was calculated. Areas under the resulting receiver operator characteristic curves were compared with the Wilcoxon signed rank test. The Youden index (sensitivity + specificity – 100%) was derived to assess the optimal cut off value. Differences between groups

Figure 1 Segmental wall thickening early after reperfusion and after two weeks at rest and during dobutamine infusion. In seven patients (18 akinetic segments at follow up), dobutamine was not infused for clinical reasons. Thick frame: either recovery of contractile function or presence of contractile reserve; thin frame: neither recovery of contractile function nor presence of contractile reserve.

Figure 2 Relative videointensity of akinetic segments early after reperfusion is significantly different between differential functional groups as observed at two weeks' follow up.

were considered significant at $p < 0.05$. SPSS 10.0 (SPSS Inc, Chicago, Illinois, USA) was used as the statistical software package.

RESULTS

Patient characteristics

Seventy four patients were enrolled in the study. In six patients, inadequate image quality prevented quantification of contrast echocardiography. Six patients could not be followed up (one died, three underwent emergency coronary artery bypass grafting, and two refused to participate). The infarct related artery did not show TIMI 3 flow at follow up in two patients. Table 1 lists the demographic, clinical, and angiographic characteristics of the remaining 60 patients. In seven patients, dobutamine stress echocardiography was not performed at two week follow up for clinical reasons (congestive heart failure in two, ventricular tachycardia in one, atrial flutter in one, chest pain in one, and by patient request in two).

Relation between relative videointensity early after reperfusion and differential levels of contractile function at follow up

The vast majority of myocardial segments (211 of 720) in the territory of the infarct related artery were akinetic at the time of postreperfusion echocardiography. Fig 1 summarises

sequential changes in contractile function of initially akinetic segments at rest and during dobutamine at the two week follow up.

We specifically looked at the relation between relative videointensity of initially akinetic segments and contractile function after two weeks. Relative videointensity was higher (83% (66%, 99%)) in segments with functional recovery (normokinesia, $n = 39$; hypokinesia, $n = 63$) than in those that remained akinetic or dyskinetic (relative videointensity 40% (28%, 57%), $p < 0.0001$). In the functional recovery group, relative videointensity was significantly different between segments with recovery to normokinesia and those with recovery to hypokinesia (88% (77%, 100%) v 74% (54%, 99%), respectively, $p < 0.001$; fig 2). In segments without functional recovery, relative videointensity was significantly higher in those with contractile reserve ($n = 33$) than in segments without contractile reserve ($n = 58$; 61% (48%, 76%) v 31% (22%, 46%), respectively, $p < 0.001$; fig 2). Relative videointensity of segments with functional recovery to hypokinesia was significantly higher than that of segments without functional recovery but with a contractile reserve present ($p < 0.001$). Relative videointensity early after reperfusion and contractile function at the two week follow up were significantly correlated ($r = -0.67$).

Prediction of segmental contractile function with contrast echocardiography

Fig 3 depicts examples of differential relative videointensities within akinetic myocardium of patients early after successful mechanical reperfusion of a first acute myocardial infarction. Fig 4A (curve A) depicts the receiver operator characteristic curve for contrast echocardiographic prediction of myocardial segments with recovery of resting contractile function or presence of contractile reserve at the two week follow up. Curve B depicts the receiver operator characteristic curve for prediction of recovery of resting contractile function alone. The curves differ only slightly, albeit significantly ($p < 0.001$). Fig 4B shows the Youden index derived from curve A, which plateaus between 42% and 62%. In light of intraobserver and interobserver variabilities of relative myocardial videointensity of 5% and 7.5%, respectively, a cut off of 50% relative videointensity for prediction of recovery of contractile function or presence of contractile reserve by contrast echocardiography was determined. The power of this criterion for early discrimination between segments with and those without

Figure 3 Relative videointensity of akinetic segments of three patients in the two chamber view early after reperfusion (A) with functional recovery at rest at two weeks' follow up, (B) without functional recovery at rest but presence of contractile reserve at two weeks' follow up, and (C) with neither functional recovery at rest nor presence of contractile reserve at two weeks' follow up.

Figure 4 Receiver operator characteristic curves for identification of functional recovery or presence of contractile reserve (curve A) or functional recovery alone (curve B) by contrast echocardiography. (B) The Youden index (sensitivity + specificity – 100) of different relative videointensities for the prediction of functional recovery or presence of contractile reserve at two weeks' follow up.

contractility at rest or during dobutamine infusion at two weeks' follow up is characterised by a $\chi^2 = 76.2$ (df = 1, $p < 0.001$). Diagnostic accuracy was 82% (sensitivity 83%, specificity 81%).

Prediction of recovery of global left ventricular function with contrast echocardiography

We then compared the wall motion score index of two groups of patients early after reperfusion and at the two week follow up: $\geq 50\%$ (group 1, $n = 23$) and $< 50\%$ (group 2, $n = 37$) of initially akinetic segments contrast positive (relative videointensity $\geq 50\%$). Clinical and angiographic characteristics were not different between group 1 and 2 except for the presence of non-Q wave acute myocardial infarction (nine in group 1 *v* none in group 2, $p < 0.01$). Early after reperfusion, the wall motion score index was not different between group 1 and group 2 (1.5 (1.3, 1.9) *v* 1.8 (1.3, 2.0), respectively). At follow up, the wall motion score index was significantly lower in group 1 than in group 2 (1.3 (1.1, 1.5) *v* 1.5 (1.3, 1.8), respectively, $p = 0.002$). Improvement of the wall motion score index between early postreperfusion and follow up was significant only in group 1 ($p < 0.0001$, fig 5).

Relative videointensity early after reperfusion and at two weeks' follow up

No significant difference was found between relative videointensity early after reperfusion (60% (35%, 87%)) and at two weeks' follow up (73% (37%, 91%)).

Figure 5 Wall motion score index early after reperfusion and at follow up in patients with $\geq 50\%$ (group 1) and $< 50\%$ (group 2) contrast positive (relative videointensity $\geq 50\%$) segments of initially akinetic myocardium.

DISCUSSION

The present study had two main findings in patients with a first acute myocardial infarction, early after successful mechanical reperfusion once reactive hyperaemia has abated. Firstly, there is a correlation between the blood volume of myocardial capillaries, as assessed by transmural signal in venous contrast echocardiography, and the amount of viable myocardium within the perfusion territory of the infarct related artery. Secondly, quantitative venous contrast echocardiography can be used early after reperfusion to predict accurately not only recovery of contractile function at rest but also the presence of contractile reserve without functional recovery.

Pathophysiology of myocardial perfusion and contractile function early after reperfusion of acute myocardial infarction

Structural capillary damage accompanying myocellular necrosis,¹⁶ complex cellular interactions including release of inflammatory and vasoconstrictive mediators from ischaemic myocardium and blood cells triggering endothelial adhesion and aggregation of neutrophils¹⁷ and platelets,¹⁸ and distal embolisation of platelet aggregates from the infarct causing ruptured atherosclerotic plaque¹⁹ are thought to contribute to myocardial "no reflow" after reperfusion of a previously occluded coronary artery. Measuring reduced blood volume of myocardial capillaries, associated with "no reflow", throughout the thickness of a myocardial segment as in the present study can account for transmural heterogeneity of these processes and therefore can accurately quantify capillary perfusion of a myocardial segment.

The pathophysiology of myocardial contractile function after mechanical reperfusion in acute myocardial infarction is heterogeneous and may, in addition to myocardial stunning, include various amounts of myocardial necrosis or recurrent ischaemia. Early after reperfusion, conventional echocardiographic measures of contractile function cannot be used to differentiate the underlying pathophysiology of akinetic myocardium. Later, once stunning has abated, myocardium with only minor transmural extent of necrosis will show functional recovery. The persistence of akinesia, however, is not synonymous with transmural myocardial necrosis. Evaluation of myocardial contractile function at rest allows evaluation of only the inner (endocardial) third of the myocardium: if there is no or only minor necrosis the myocardium is normokinetic or hypokinetic but subendocardial necrosis results in akinesia.¹⁰ Akinesia, therefore, occurs irrespective of the amount of vital tissue in the mid and epicardial portions of the myocardium. Although these portions contribute little to contraction at rest, they can be recruited to produce contractile reserve of akinetic myocardium during dobutamine

stimulation.²⁰ The four functional classes differentiated at the two week follow up in the present study can therefore be regarded as functional corollaries of differential degrees of transmural myocardial necrosis.

Contractile reserve of akinetic myocardium is clinically relevant because it has been shown to protect against ventricular dilatation and development of heart failure.²¹ Our data indicate that the continuum between myocardial “no reflow” and “reflow”, imaged with venous contrast echocardiography and quantified with its transmural signal intensity, gives an estimate of the extent of necrosis in a myocardial segment as soon as three hours after reperfusion. This result is in line with the findings of previous animal studies comparing the extent of myocardial contrast enhancement after venous contrast injection with myocardial necrosis by using triphenyltetraacolum chloride staining.^{22–23} With respect to the relevance of the spatial extent of contrast enhancement for subsequent recovery of global left ventricular function, our findings confirm the results of Porter and colleagues²⁴ and Lepper and associates.²⁵ These first two studies of the use of venous contrast echocardiography in patients after reperfusion of acute myocardial infarction used a semiquantitative score for the assessment of myocardial contrast enhancement in the risk area 48²⁴ and 24 hours²⁵ after reperfusion.

Prediction of functional recovery or presence of contractile reserve with venous contrast echocardiography early after reperfusion

This is the first study to define a quantitative signal threshold for the prediction of myocardial contractile function in venous contrast echocardiography early after mechanical reperfusion of acute myocardial infarction. Several investigators have attempted to predict recovery of contractile function early after reperfusion treatment in acute myocardial infarction using semiquantitative assessment of myocardial contrast enhancement with intracoronary injection of microbubbles. Depending on the strictness of criteria for the positive contrast effect, sensitivities for prediction of subsequent functional recovery were found between 66%⁷ and 100%.⁸ Specificity, however, was only between 18%⁹ and 60%⁷ in most studies. We found higher diagnostic accuracy of venous contrast echocardiography for prediction of recovery of contractile function or the presence of contractile reserve after acute myocardial infarction. This finding cannot be attributed solely to our consideration of contractile reserve, in distinction to previous studies with intracoronary contrast injection, because our receiver operator curves using functional recovery alone (fig 4A, curve B) or both variables (curve A) differ only slightly.

Several additional factors may contribute to the improved diagnostic accuracy. Firstly, intracoronary bolus injection with a hand held syringe used in previous studies may force contrast material into the dependent microvasculature. Therefore, lack of opacification may be observed only in the myocardium with the most seriously damaged microvessels, whereas it may still be seen in areas with moderate microvascular damage. Venous infusion, in distinction, may result in more physiological myocardial distribution of microbubbles and provide a better representation of differential degrees of microvascular damage. Secondly, the diagnostic accuracy of the prediction of functional recovery depends on the definition of the threshold for positive contrast effect. It is difficult to quantify the magnitude of the contrast effect after poorly standardised intracoronary bolus injection of sonicated radio-opaque dye. Therefore, semiquantitative assessment has been used in most intracoronary studies. However, defining a threshold is less accurate with a framework of only a few scores than with the quantitative approach used in the present study. Thirdly, myocardial contrast enhancement was evaluated 10–16 minutes after successful reperfusion in previous intracoronary studies while reactive hyperaemia might have

been present, likely causing an overestimation of contrast effect within the infarct bed.¹¹ Venous contrast echocardiography was performed later (approximately three hours after reperfusion) in the present study and relative videointensity was even slightly higher after two weeks. It is therefore unlikely that relative videointensity measurements were affected by reactive hyperaemia. Our data therefore favour a time interval of approximately three hours between mechanical reperfusion of acute myocardial infarction and contrast echocardiographic assessment of myocardial viability.

Swinburn and colleagues²⁶ recently reported a sensitivity of 62% of venous contrast echocardiography scores obtained approximately five days after acute myocardial infarction for binary prediction of recovery of resting contractile function of myocardial segments. Apart from differences in methods and the sole consideration of functional recovery at rest, however, undefined coronary anatomy at the time of contrast echocardiography and at follow up may have prevented unequivocal interpretation of the association between an early contrast score and contractile function at follow up in their study.²⁶

Study limitations

Because of anisotropy, heterogeneous beam profile, and attenuation, the contrast signal intensity of differential myocardial segments is subject to variability independent of the volume of myocardial microvasculature (9% (1%, 13%) in normokinetic segments in the present study), which might have prevented a closer correlation between relative myocardial videointensity early after reperfusion and the amount of viable myocardium. A slight divergence of imaging planes between initial and follow up studies may have attenuated this correlation as well. Although imaging planes were carefully chosen, this typical source of inaccuracy of serial echocardiography cannot be completely eliminated.

Advantages of intermittent harmonic imaging, used in the present study, are a broad dynamic range and high signal amplitude caused by microbubble disruption with high mechanical index imaging. On the other hand, off line image processing is mandatory because the tissue component of the harmonic signal is considerable. Recent advances in this technique including multiple pulse transmission, reduction of myocardial tissue signal by modified transmit and receive frequencies, and colour coding of raw image data may, however, obviate the need for time consuming off line processing in the future. Recently developed autocorrelation based imaging technology offers alternative echocardiographic modalities (power Doppler, pulse inversion, or power modulation technique) for venous contrast echocardiography. Image analysis is facilitated by on line background subtraction, and real time venous myocardial contrast echocardiography has become available. The range of myocardial blood volumes detectable with these techniques, characterised by a narrow dynamic range compared with harmonic imaging, however, needs to be defined.

We used a measure of myocardial blood volume to characterise myocardial perfusion. There are first reports that myocardial blood flow velocity assessed by analysis of increasing pulsing intervals may be a more robust parameter for the quantitative analysis of venous myocardial contrast echocardiography.⁶

Diagnostic accuracy found for prediction of contractile myocardium by venous myocardial contrast echocardiography in the present study may be too optimistic since the underlying contrast intensity cut off value was determined in the same patient population.

Although raw signal intensity data were not used in the present study, despite theoretical superiority, the validity of videodensitometric data was shown in a head to head comparison with digital raw data.²⁷

The contractile response to dobutamine could have been attenuated by β blocker treatment, which was not discontinued in the present study. Therefore, although we used high

doses of dobutamine, we may have incorrectly classified patients as having no contractile reserve.

Clinical implications and perspective

Our data imply that myocardial capillary perfusion characterised by venous contrast echocardiography is a sensitive and meaningful marker for the evaluation of the success of reperfusion treatment in patients with acute myocardial infarction. Determination of TIMI myocardial perfusion grade,³ Doppler flow wire,^{25,28} nuclear myocardial perfusion imaging,²⁹ and magnetic resonance imaging³⁰ have been used to assess myocardial microvasculature after acute myocardial infarction. Each of these techniques has its specific strengths and limitations, but none of them has been implemented in routine diagnostic investigation of patients with acute myocardial infarction because they are either invasive or not readily available in most hospitals. Venous myocardial contrast echocardiography used in the present study, in distinction, is a bedside technique and has the potential to be widely available. Furthermore, the application of pharmacological stress, so far needed for echocardiographic assessment of myocardial viability, is not required. In light of increasing numbers of reperfusion strategies for patients with acute coronary syndromes and existing highly effective treatment modalities, a versatile tool for rational and cost effective comparison of efficacy differences between them is important and may guide the planning for large scale clinical mortality trials.

Based on the present data, it also appears reasonable to evaluate the role of venous contrast echocardiography for risk stratification after acute myocardial infarction in future studies.

Analysis of time intensity curves based on signals from incremental imaging intervals or real time registration of signals using low mechanical index imaging has the potential for evaluating myocardial microvascular flow velocity and blood flow.⁶ This may provide further insight in to the process of recovery of myocardial microvascular and contractile function after reperfusion of acute myocardial infarction.

ACKNOWLEDGEMENTS

We are indebted to Kevin Wei MD and Donald Hall MD for thoughtful critique of the manuscript. We gratefully acknowledge the invaluable contribution of the staff of the coronary care units and catheterisation laboratories.

Authors' affiliations

P Andrassy, M Zielinska, A Schömig, C Firschke, Deutsches Herzzentrum München, Lazarettstraße 36, D-80636 Munich, Germany
R Busch, Institut für Medizinische Statistik und Epidemiologie, Technische Universität München, Ismaninger Straße 22, 81675 Munich, Germany

Presented in part at the 73rd Annual Scientific Sessions of the American Heart Association, New Orleans, Louisiana, USA.

Dr Andrassy was supported by a fellowship training grant from Deutsche Gesellschaft für Kardiologie, Düsseldorf, Germany.

Dr Zielinska was supported by grants from Dietmar-Zumpf-Stiftung, Forstern-Preisendorf, Germany, and Deutscher Akademischer Austauschdienst, Bonn, Germany.

REFERENCES

- Volpi A, De Vita C, Franzosi MG, *et al*. Determinants of 6-month mortality in survivors of myocardial infarction after thrombolysis: results of the GISSI-2 data base. The ad hoc working group of the GISSI-2 data base. *Circulation* 1993;**88**:416–29.
- Ito H, Tomooka T, Sakai N, *et al*. Lack of myocardial perfusion immediately after successful thrombolysis. *Circulation* 1992;**85**:1699–705.
- Gibson CM, Cannon CP, Murphy SA, *et al*. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation* 2000;**101**:125–30.
- Keller MW, Segal SS, Kaul S, *et al*. The behavior of sonicated albumin microbubbles within the microcirculation: a basis for their use during myocardial contrast echocardiography. *Circ Res* 1989;**65**:458–67.
- Kaul S, Kelly P, Oliner JD, *et al*. Assessment of regional myocardial blood flow with myocardial contrast two-dimensional echocardiography. *J Am Coll Cardiol* 1989;**13**:468–82.
- Wei K, Jayaweera AR, Firoozan S, *et al*. Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered as a constant venous infusion. *Circulation* 1998;**97**:473–83.
- Brochet E, Czitró D, Karila-Cohen D, *et al*. Early changes in myocardial perfusion patterns after myocardial infarction: relation with contractile reserve and functional recovery. *J Am Coll Cardiol* 1998;**32**:2011–7.
- Lecleq F, Messner-Pellenc P, Descours Q, *et al*. Combined assessment of reflow and collateral blood flow by myocardial contrast echocardiography after acute reperfused myocardial infarction. *Heart* 1999;**82**:62–7.
- Bolognese L, Antoniucci D, Rovai D, *et al*. Myocardial contrast echocardiography versus dobutamine echocardiography for predicting functional recovery after acute myocardial infarction treated with primary coronary angioplasty. *J Am Coll Cardiol* 1996;**28**:1677–83.
- Lieberman AN, Weiss JL, Judgutt BL, *et al*. Two-dimensional echocardiography and infarct size: relationship of regional wall motion and thickening to the extent of myocardial infarction in dog. *Circulation* 1981;**63**:739–46.
- Villanueva FS, Camarano G, Ismail S, *et al*. Coronary reserve abnormalities in the infarcted myocardium. *Circulation* 1996;**94**:748–54.
- Porter TR, Xie F. Transient myocardial contrast after initial exposure to diagnostic ultrasound pressures with minute doses of intravenously injected microbubbles. *Circulation* 1995;**92**:2391–5.
- Firschke C, Lindner JR, Goodman NC, *et al*. Myocardial contrast echocardiography in acute myocardial infarction using aortic root injections of microbubbles in conjunction with harmonic imaging: potential application in the cardiac catheterization laboratory. *J Am Coll Cardiol* 1997;**29**:207–16.
- Lindner JR, Villanueva FS, Dent JM, *et al*. Assessment of resting perfusion with myocardial contrast echocardiography: theoretical and practical considerations. *Am Heart J* 2000;**139**:231–40.
- Marcus R, Peritz E, Gabriel KR, *et al*. On closed testing procedures with special reference to ordered analysis of variance. *Biometrika* 1976;**63**:655–60.
- Kloner RA, Ganote CE, Jennings RB. The no-reflow phenomenon after temporary coronary occlusion in the dog. *J Clin Invest* 1974;**54**:1496–508.
- Engler RL, Schmid-Schonbein GW, Pavelec RS. Leukocyte capillary plugging in myocardial ischemia and reperfusion in the dog. *Am J Pathol* 1983;**111**:98–111.
- Massberg S, Enders G, Matos FC, *et al*. Fibrinogen deposition at the postischemic vessel wall promotes platelet adhesion during ischemia-reperfusion in vivo. *Blood* 1999;**94**:3829–38.
- Gavin JB, Maxwell L, Edgar SG. Microvascular involvement in cardiac pathology. *J Mol Cell Cardiol* 1998;**30**:2531–40.
- Sklenar J, Ismail S, Villanueva FS, *et al*. Dobutamine echocardiography for determining the extent of myocardial salvage after reperfusion. *Circulation* 1994;**90**:1502–12.
- Bolognese L, Cerisano G, Buomaci P, *et al*. Influence of infarct-zone viability on left ventricular remodeling after acute myocardial infarction. *Circulation* 1997;**96**:3353–9.
- Grayburn PA, Erickson JM, Escobar J, *et al*. Peripheral intravenous myocardial contrast echocardiography using a 2% dodecafluoropentane emulsion: identification of myocardial risk area and infarct size in the canine model of ischemia. *J Am Coll Cardiol* 1995;**26**:1340–7.
- Firschke C, Lindner JR, Wei K, *et al*. Myocardial perfusion imaging in the setting of coronary artery stenosis and acute myocardial infarction using venous injection of a second-generation echocardiographic contrast agent. *Circulation* 1997;**96**:959–67.
- Porter TR, Li S, Oster R, *et al*. The clinical implications of no reflow demonstrated with intravenous perfluorocarbon containing microbubbles following restoration of thrombolysis in myocardial infarction (TIMI) 3 flow in patients with acute myocardial infarction. *Am J Cardiol* 1998;**82**:1173–7.
- Lepper W, Hoffmann R, Kamp O, *et al*. Assessment of myocardial reperfusion by intravenous myocardial contrast echocardiography and coronary flow reserve after primary percutaneous transluminal coronary angioplasty in patients with acute myocardial infarction. *Circulation* 2000;**101**:2368–74.
- Swinburn JMA, Lahiri A, Senior R. Intravenous myocardial contrast echocardiography predicts recovery of dysynergic myocardium early after acute myocardial infarction. *J Am Coll Cardiol* 2001;**38**:19–25.
- Ismail S, Jayaweera AR, Skyba DM, *et al*. Integrated backscatter and digital acquisition during myocardial contrast echocardiography: is there an advantage over conventional echocardiography for intracoronary injections? *J Am Soc Echocardiogr* 1995;**8**:453–64.
- Neumann FJ, Blasini R, Schmitt C, *et al*. Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. *Circulation* 1998;**98**:2695–701.
- Neumann FJ, Kosa I, Dickfeld T, *et al*. Recovery of myocardial perfusion in acute myocardial infarction after successful balloon angioplasty and stent placement in the infarct-related coronary artery. *J Am Coll Cardiol* 1997;**30**:1270–6.
- Rogers WJ Jr, Kramer CM, Geskin G, *et al*. Early contrast-enhanced MRI predicts late functional recovery after reperfused myocardial infarction. *Circulation* 1999;**99**:744–50.