

Functional role of microvascular integrity in patients with infarct-related artery patency after acute myocardial infarction

S. Iliceto, L. Galiuto, A. Marchese, P. Colonna, S. Oliva and P. Rizzon

Institute of Cardiology, University Bari, Italy

Aims The study was set up to evaluate the functional role of post-infarct preserved microvascular integrity. Low dose dobutamine echocardiography and myocardial contrast echocardiography were used to study patients before hospital discharge who had suffered a recent myocardial infarction and had a patent infarct-related artery (TIMI flow grade 3).

Method In the dysfunctioning infarct area, the wall motion score index was calculated at baseline, during the dobutamine infusion and at the 3 month follow-up echocardiogram; contrast echocardiography was performed at the time of coronary angiography, before hospital discharge.

Results In patients with more than 50% of the dysfunctioning infarct area opacified at contrast echocardiography (group A), regional wall motion score index decreased, compared to baseline, during the dobutamine infusion (1.97 ± 0.78 vs 2.5 ± 0.35 at baseline; $P < 0.001$) and at

follow-up echocardiography (1.83 ± 0.63 vs 2.5 ± 0.35 at baseline; $P < 0.001$). In patients with less extensive microvascular integrity as revealed by contrast echocardiography (group B), regional wall motion score index did not decrease from baseline during either the dobutamine infusion (2.73 ± 0.21 vs 2.81 ± 0.20 at baseline; $P = \text{ns}$) or at follow-up (2.81 ± 0.20 vs 2.81 ± 0.20 at baseline; $P = \text{ns}$).

Conclusion In patients with post-infarct dysfunctioning myocardium but a patent infarct-related artery, microvascular integrity, as assessed by myocardial contrast echocardiography, is an indicator of myocardial viability in terms of preserved contractile reserve, as demonstrated by dobutamine infusion and functional recovery at follow-up. (*Eur Heart J* 1997; 18: 618–624)

Key Words: Myocardial contrast echocardiography, dobutamine echocardiography, myocardial viability, microvascular integrity

Introduction

In the acute phase of myocardial infarction, myocardial salvage can be achieved by reopening the infarct-related artery and re-establishing tissue-level perfusion within the jeopardised myocardium. Myocardial reperfusion limits infarct size and preserves left ventricular function^[1], improving early and late outcome after acute myocardial infarction^[2,3]. However, despite epicardial artery patency, myocardial tissue perfusion may be inadequate^[4,5]. This lack of intramyocardial reflow despite restoration of epicardial artery patency has been named the 'no-flow phenomenon' and is mainly related to extensive microcirculatory damage^[5,6].

Myocardial contrast echocardiography is a new diagnostic technique which delineates the spatial distribution of blood flow within the myocardium during

echocardiographic monitoring, allowing investigation of microcirculatory changes in the ischaemic myocardium^[7]. Myocardial salvage may reliably be assessed by exploring the contractile reserve of post-infarct dysfunctioning myocardium. Low dose dobutamine echocardiography, by beta-adrenergic inotropic stimulation, may elicit and detect this functional reserve^[8–10].

Microvascular integrity, as demonstrated by contrast echocardiography, can predict myocardial viability of post-infarct dysfunctioning myocardium. Thus it was decided to assess contractile reserve using dobutamine echocardiography, and functional recovery at follow-up, in patients with acute myocardial infarction and patent infarct-related arteries.

Method

Study population

From June 1994 to December 1995, 140 patients were admitted to the coronary care unit with acute

Revision submitted 9 October 1996, and accepted 16 October 1996.

Correspondence: Sabino Iliceto, MD, Istituto di Cardiologia, Università di Cagliari, via San Giorgio 12, Cagliari, Italy.

myocardial infarction. Myocardial infarction was diagnosed if typical chest pain lasting more than 30 min was unresolved by nitroglycerin. In addition, ST segment elevation, on the initial electrocardiogram, had to be ≥ 0.1 mV in two or more limb leads or ≥ 0.2 mV in two or more contiguous precordial leads, and peak creatine kinase >2 SD above normal. Patients were prospectively selected for this study if they met the following inclusion criteria: (1) this was their first uncomplicated acute myocardial infarction; (2) a patent infarct-related coronary artery with complete anterograde perfusion (Thrombolysis in Myocardial Infarction trial [TIMI] flow grade 3)^[11] was evident at predischarge coronary angiography; (3) the echocardiogram was technically adequate. For 90 patients this was their first myocardial infarction and 75 of them underwent coronary angiography; 37 had a TIMI 3 infarct-related artery. Eleven patients were excluded because the echocardiogram was inadequate and six declined to participate in the study. The final study group comprised 20 patients. Within a week of admission, all patients underwent an echocardiogram while at rest and dobutamine echocardiography. Viability was assessed using a conventional protocol. Before hospital discharge, coronary angiography and selective intracoronary contrast echocardiography were performed in all patients. Within 3 months of the acute event echocardiographic follow-up was carried out in all patients. All patients gave informed consent and the Hospital Committee on Human Research approved the study protocol.

Low dose dobutamine echocardiography

Within 1 week of admission a low dose dobutamine protocol was chosen to assess viability in all patients undergoing echocardiographic monitoring. Two-dimensional echocardiography was performed before, during and after the dobutamine infusion, at a dose of $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 5 min and at $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for an additional 5 min^[8]. Commercial echocardiographic equipment (HP Sonos 1500) connected to a digital acquisition system (PreVue III, Nova Microsonics, U.S.A.) was used. Apical four- and two-chamber views, together with apical long and precordial short axis views at the level of the papillary muscles were digitally acquired at rest, at the end of the first and second stages of the dobutamine protocol and during recovery. Each tomographic plane was stored in a quad screen cine loop format. This simultaneously displayed the baseline, the first- and second-stage dobutamine protocol, and recovery to facilitate review and interpretation. Continuous monitoring of previously acquired digital cine loop images ensured comparability of the tomographic planes obtained throughout the dobutamine protocol. Review and interpretation of dobutamine studies were performed by two experienced observers unaware of the myocardial contrast echocardiography and angiographic results. During the dobutamine test, heart rate, blood pressure

and the electrocardiogram were continuously monitored. All studies were performed and completed without complication. None of the patients was on beta-blocker therapy.

Myocardial contrast echocardiography

Myocardial contrast echocardiography, obtained by manually injecting a small amount (2–3 cc) of sonicated contrast medium into both coronary arteries, was performed at the time of coronary angiography, and within 3 days of low dose dobutamine echocardiography. A commercially available sonicator (W-380 Heat Systems-Ultrasonics) with a 0.5 inch (1.27 cm) diameter horn was used to generate the microbubbles. The horn was placed at the bottom of a 50 cc truncated syringe containing 6 cc of Ioxaglate (Hexabrix '320' — Byk Gulden). Sonication lasted 15 s, producing microbubbles of 4–6 microns (light microscope observation). Left ventricular echocardiographic imaging was achieved using standard tomographic planes obtained from the precordial and apical approach. Multiple tomographic planes were acquired to obtain a complete image, during injection, of the post myocardial infarction dysfunctioning left ventricular segments. Particular attention was paid to the acquisition of tomographic planes corresponding to those obtained during low dose dobutamine echocardiography. During myocardial contrast echocardiography, heart rate, blood pressure and the electrocardiogram were continuously monitored.

Echocardiographic follow-up

Clinical and echocardiographic evaluation was performed in all patients within 3 months of hospital discharge. Eight patients received medical therapy; 12, with inducible residual ischaemia at the stress test, were successfully treated by percutaneous transluminal coronary angioplasty of the infarct-related artery. Revascularization was performed within 1 month of acute myocardial infarction.

Echocardiographic data analysis

Low dose dobutamine echocardiography, myocardial contrast echocardiography and follow-up echocardiographic data analysis were made using a 16 left-ventricular segment model. This study was confined to analysing dysfunctioning (dys- a-; hypokinetic) myocardial segments within the theoretical maximal risk area according to a previously described three-region scheme of coronary perfusion^[12]. A wall motion score index of the dysfunctioning infarct area at rest was obtained by assigning a semiquantitative score (1 = normo-, 2 = hypo-, 3 = a-, 4 = dys-kinesia) to all segments within this area and by dividing the sum of the individual segment scores by the number of segments. In each patient, the wall

motion score index within the dysfunctioning infarct area was calculated at baseline and within the same left ventricular area during the dobutamine infusion ($10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and at follow-up. Patients were considered positive if at dobutamine echocardiography and at follow-up, their function had improved in at least two contiguous myocardial segments by at least one wall motion score.

The myocardial echocardiographic pattern was evaluated in the area of the dysfunctioning infarct. A myocardial segment was considered opacified if, during myocardial contrast echocardiography, contrast enhancement of the myocardium was visually identified after intracoronary injection of sonicated contrast medium. Patients were considered positive if, at myocardial contrast echocardiography, more than 50% of dysfunctioning infarct segments were opacified during contrast injection.

Inter- and intra-observer variability

In order to assess inter- and intra-observer variability in interpreting myocardial contrast echocardiograms 30 left ventricular myocardial segments were independently reviewed by two observers and again 2 weeks later by one of them only. Agreement between the two observers was 85%, while in the same observer it was 95%. Similarly, 20 dobutamine echocardiography studies were evaluated by two observers and again 2 weeks later by one of them only. Inter-observer agreement in the rest echocardiograms was 89% and 84% in the dobutamine infusions; intra-observer agreement was 92% 'at rest' and 83% 'during dobutamine'. Disagreement was never more than one grade for a single segment.

Coronary angiography

Coronary angiography was performed in all patients using the Seldinger technique. TIMI flow grading of the infarct-related artery, a semiquantitative scale based on the visual impression of flow of contrast medium during injection into the coronary arteries, was identified, while percentage stenosis was calculated by digital electronic caliper.

Statistical analysis

All data are expressed as mean \pm SD. Statistical analysis of changes in the wall motion score index, in each group, from baseline to dobutamine echocardiography and follow-up was computed by one-way analysis of variance for repeated measures, with the implementation of Bonferroni's correction. Comparison between groups, in terms of clinical characteristics and wall motion score index, was obtained by unpaired Student's *t* test. Differences between comparisons were considered statistically significant with a two-sided *P* value <0.05 .

Results

Twenty patients with acute myocardial infarction and an infarcted vessel with TIMI flow grade 3 formed the study group. Eighteen were male and two female (mean age 55 ± 5 years); 15 received thrombolytic therapy with rt-PA within 4 h of onset (mean time to thrombolysis was 2.5 ± 1.2 h); five patients did not receive thrombolysis because of contraindications. The site of infarction was anterior in 11 patients and inferior in the remaining nine, with electrocardiographic evidence of pathological Q waves in 14 cases. No patient had angina or other cardiac complications during hospitalization. At pre-discharge coronary angiography, 11 patients had single-vessel disease (six left anterior descending, four right, one circumflex), five patients had two-vessel disease (left descending and right) and four had three-vessel disease. Mean residual stenosis of the infarct-related artery was $65 \pm 34\%$. Angiographic collateral circulation was detected in only one patient from group A, while it was absent in the remaining 19 (Table 1).

Myocardial contrast echocardiography

The study population was divided into two groups on the basis of the extent of microvascular integrity. This was demonstrated by echocardiographic contrast enhancement of dysfunctioning myocardial segments within the infarct area. Patients with more than 50% of the dysfunctioning infarct segments opacified at contrast echocardiography were defined as having well preserved microvascular integrity (group A) (Fig. 1), while patients with less than or 50% of dysfunctioning infarct segments opacified at contrast echocardiography, were considered to have poor microvascular integrity (group B) (Fig. 2). Eleven patients (55%) were included in group A and the remaining nine patients (45%) formed group B. The clinical characteristics of the two groups are listed in Table 1. No significant differences, in terms of clinical characteristics or angiographic results, were observed between the two groups. Peak creatine kinase values were higher in group B ($3040 \pm 2094 \text{ UI} \cdot \text{l}^{-1}$) than group A ($1081 \pm 868 \text{ UI} \cdot \text{l}^{-1}$; $P < 0.05$). In the 3-month follow-up period, none of the patients suffered from angina or re-infarction. Within 1 month of the acute event, 12 of the 20 patients (seven in group A and five in group B) underwent successful percutaneous transluminal coronary angioplasty of the infarct-related artery, because of inducible residual ischaemia at stress test.

Left ventricular function

In patients with more than 50% of the dysfunctioning infarct area opacified at contrast echocardiography (group A), the regional wall motion score index decreased from baseline to dobutamine echocardiography (from 2.5 ± 0.35 at baseline to 1.97 ± 0.78 at dobutamine echocardiography; $P < 0.001$); in the same

Table 1 Patient characteristics

PT	AMI	thr	IRA	Rest WMSI	DobWMSI	FU WMSI	MCE
1	anterior	no	LAD	2.8	2.6	2.6	positive
2	inferior	no	right	2.2	1.4	1.4	positive
3	inferior	yes	Right	2.7	2.7	2.7	positive
4	inferior	no	CX	2	1	1	positive
5	anterior	no	LAD	3	3	1	positive
6	inferior	yes	Right	2.5	2.1	1.9	positive
7	inferior	yes	Right	2.2	1	2.2	positive
8	anterior	yes	LAD	2.9	2.9	2	positive
9	inferior	yes	Right	2	1	1	positive
10	inferior	yes	Right	2.7	2	2.3	positive
11	inferior	yes	Right	2.5	2	2	positive
12	anterior	yes	LAD	3	3	3	negative
13	anterior	yes	LAD	2.8	2.7	2.8	negative
14	anterior	yes	LAD	3	3	3	negative
15	anterior	yes	LAD	2.8	2.7	2.8	negative
16	anterior	yes	LAD	2.7	2.5	2.7	negative
17	anterior	yes	LAD	2.9	2.9	2.9	negative
18	anterior	yes	LAD	2.7	2.7	2.7	negative
19	anterior	no	LAD	2.4	2.4	2.4	negative
20	inferior	yes	Right	3	2.7	3	negative

AMI=acute myocardial infarction; CX= circumflex artery; Dob=dobutamine, FU=follow-up; IRA=infarct-related artery; LAD=left anterior descending coronary; MCE=myocardial contrast echocardiography; PT=patient; Right=right coronary; Thr=thrombolysis, WMSI=wall motion score index.

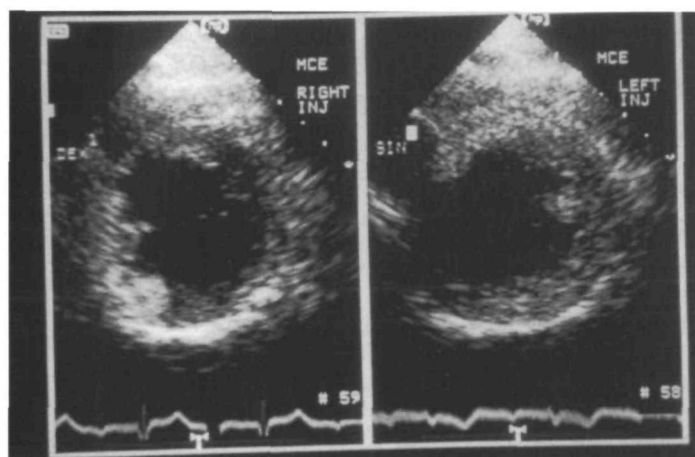


Figure 1 Myocardial contrast echocardiography study in the parasternal short axis view at the papillary muscle level of a patient with anterior myocardial infarction. Left panel, after injection of sonicated contrast medium in the right coronary artery (right inj), there is opacification of the corresponding perfusion bed. Right panel, after injection of contrast medium into the patent infarct-related left coronary artery (left inj). The anterior septum, anterior wall and lateral wall, dysfunctioning at rest, are entirely opacified; the anatomical integrity of the microvascular network is well preserved.

patient group, regional wall motion score index calculated at rest in the follow-up echocardiogram was significantly reduced compared to the baseline echocardiogram (from 2.5 ± 0.35 at baseline to 1.83 ± 0.63 at follow up; $P < 0.001$). This implied the presence of contractile reserve and spontaneous recovery of regional function at follow-up (Fig. 3). On the other hand, in

patients with less extensive microvascular integrity at contrast echocardiography (group B), the regional wall motion score index did not decrease from baseline, during either dobutamine infusion (from 2.81 ± 0.20 at baseline to 2.73 ± 0.21 at dobutamine echocardiography; $P = \text{ns}$) or at follow-up (from 2.81 ± 0.20 at baseline to 2.81 ± 0.20 at follow up; $P = \text{ns}$). In this subset of

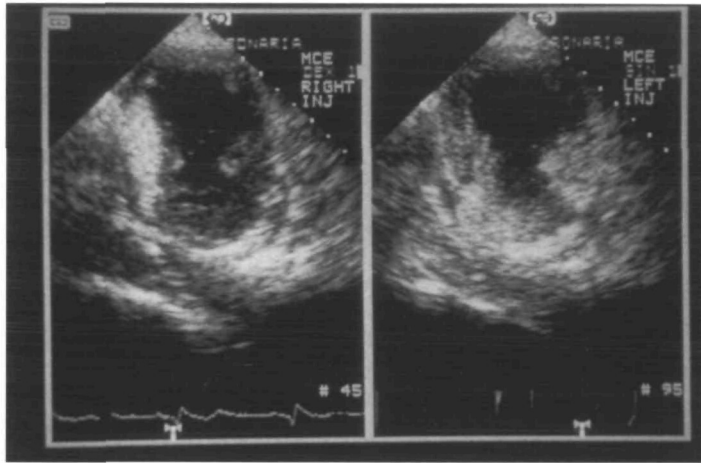


Figure 2 Myocardial contrast echocardiographic study of a patient with an anterior myocardial infarction and patent infarct related artery. Left panel, a normal right perfusion bed (right inj); right panel, after injection into the left coronary artery (left inj), a contrast perfusion defect is evident in the dysfunctioning anterior wall and anterior septum, due to lack of microvascular integrity.

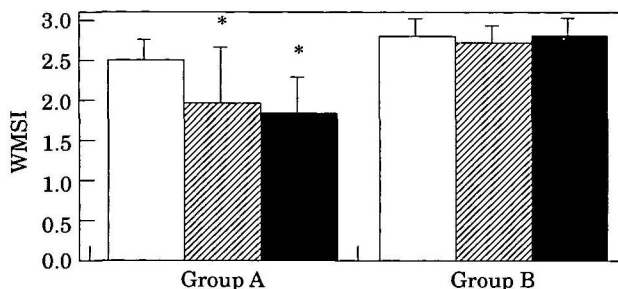


Figure 3 Wall motion score index (WMSI) of the dysfunctioning infarct area in baseline conditions (□) during low-dose dobutamine (▨) and at follow-up (■) (3 months after acute event) in group A and B patients (myocardial enhancement at myocardial contrast echocardiography >50% or ≤50% of dysfunctioning infarct area, respectively). While wall motion score index improved from baseline to dobutamine echocardiography and follow-up in group A, it did not change in group B. * $P < 0.001$.

patients, therefore, contractile reserve was absent and functional recovery not possible. Compared to group A, in the dysfunctioning infarct area of group B, wall motion score index was slightly higher at baseline (2.5 ± 0.35 in group A vs 2.81 ± 0.2 in group B; $P < 0.05$). The difference between the groups was even more evident at dobutamine echocardiography (1.97 ± 0.78 in group A vs 2.73 ± 0.21 in group B; $P < 0.05$) and at follow-up (1.83 ± 0.63 in group A vs 2.81 ± 0.2 in group B; $P < 0.001$) (Table 2). In six group A patients, dobutamine and contrast results were concordant and both positive. In five of them there was improvement at follow-up. In the remaining five group A patients, contrast echocardiography was positive, while the dobutamine infusion was negative. Three of them recovered at follow-up. In group B, seven patients were negative at both the dobutamine infusion and with contrast. One

had a negative dobutamine infusion and a positive contrast echocardiogram and one was positive during dobutamine and negative at contrast. None of them recovered at follow-up.

Discussion

After acute myocardial infarction, patients with infarct-related artery patency have a better clinical outcome^[13-14]. However, this angiographic condition does not identify an homogeneous group of patients; in fact, results of the TEAM-2 and TEAM-3 study state that only coronary arteries with brisk flow of contrast (TIMI flow grade 3) identify patients with better clinical outcome^[15,16] who may be considered to have undergone successful reperfusion after acute myocardial infarction.

Table 2 Group characteristics

MCE	Group A	Group B	P
Number	11	9	
Age (years)	57 ± 5	55 ± 5	ns
Male	10	8	ns
Thrombolysis	7	8	ns
Time to thrombolysis	2.4 ± 1.2	2.4 ± 1.3	ns
Q-wave infarcts	6	8	ns
CPK peak	1081 ± 868	3040 ± 2094	0.05
WMSI at baseline	2.5 ± 0.35	2.81 ± 0.2	0.05
WMSI at LDDE	1.97 ± 0.78	2.73 ± 0.21	0.05
WMSI at follow-up	1.83 ± 0.63	2.81 ± 0.2	0.001
%IRA stenosis	65 ± 34	65 ± 37	ns
Revascularized	7 (63%)	5 (55%)	ns

CPK=creatine phospho kinase; IRA=infarct related artery; LDDE=low dose dobutamine echocardiography; WMSI=wall motion score index.

Even if complete angiographic perfusion is an important marker of successful reflow, intramyocardial perfusion needs to be investigated more accurately.

Myocardial contrast echocardiography, using a microvascular tracer that depicts the intramyocardial perfusion pattern^[17-21], is a safe and useful tool to evaluate the post-infarct microcirculation state^[7]. The clinical application of this technique increased our knowledge of the anatomical and functional consequences of an acute and prolonged ischaemic damage. Using contrast echocardiography, Ito *et al.*^[22,23] demonstrated that angiographically successful reflow cannot be used as an indicator of adequate myocardial reperfusion after acute myocardial infarction. A residual intramyocardial perfusion defect (no-reflow phenomenon), observed in 23% of their patients within the infarct area, was a predictor of poor functional recovery of dysfunctioning post-ischaemic myocardium. They also recently demonstrated that the no-reflow phenomenon has real prognostic value after acute myocardial infarction^[24].

Microvascular integrity and myocellular viability

In animal models of acute myocardial infarction, myocellular necrosis has been associated with loss of microvasculature^[25-30]. In a previous study, we investigated the relationship between microvascular integrity using contrast echocardiography and contractile reserve using dobutamine echocardiography in the dysfunctioning post-infarct viable myocardium^[31]. The results of this study have shown that, after acute ischaemic damage, only the preserved anatomical integrity of the microvascular network can guarantee myocyte viability. If the microcirculation has been destroyed by a severe and prolonged absence of flow, the myocardium is irreversibly necrotic and gains no benefit from subsequent reopening of the epicardial vessel. Thus, microvascular integrity at contrast echocardiography may be considered a fundamental prerequisite for preserving contractile reserve and functional recovery^[31].

In the present study, patients with acute myocardial infarction and angiographically patent infarct-related artery were stratified according to the presence and extent of the intramyocardial flow at contrast echocardiography within the dysfunctioning infarct area. Patients with comparable baseline clinical and angiographic characteristics and more than 50% of the infarct area with microvascular integrity intact, indicated myocardial viability of the infarcted area. On the other hand, if the microvascular network was mostly damaged, viable myocardium was unlikely to occur. Thus, salvaged myocardium is strictly dependent on the extent of microvascular integrity.

In a similar study, Agati *et al.*^[32] demonstrated the key role of microvascular integrity within the post-infarct dysfunctioning myocardium. Improvement in regional and global function was found only in patients

with residual contrast perfusion in the infarct zone. The importance of assessing myocardial tissue perfusion in patients with acute myocardial infarction and patent infarct-related arteries has also been addressed by Maes *et al.*^[33] using positron emission tomography. In more than one third of their patient population, an important perfusion defect was seen in the infarct area after successful thrombolysis (TIMI flow grade 3 of the infarct-related artery). In these patients, functional recovery was not observed at follow-up. On the other hand, the presence of adequate myocardial tissue perfusion was clearly associated with functional recovery at follow-up. Our data are comparable to those observed in this study in which positron emission tomography was used. These showed that functional recovery of post-infarct reperfused myocardium is possible only when adequate tissue flow is restored within a preserved microvascular network.

Study limitations

Only patients with a precise clinical indication on the basis of inducible residual ischaemia at stress test were revascularized. However, non-revascularized patients were uniformly distributed among the two groups. Coronary angiography was not performed at follow-up and thus, although all patients were in a stable clinical condition, lack of functional recovery may have theoretically been due, in some patients, to late asymptomatic coronary reocclusion. Myocardial contrast echocardiographic results were not analysed quantitatively, but qualitatively by visual assessment of myocardial contrast enhancement. However, the importance of quantitative parameters of intramyocardial reflow after acute myocardial infarction is still far from being fully clarified.

Clinical implications

Among patients with infarct-related artery patency and post-infarct dysfunction, microvascular integrity is fundamental in discriminating those with salvaged, and thus viable, myocardium. The importance of therapeutic strategies aimed at preserving microcirculation during ischaemia and in the reperfusion phase is, therefore, obvious. Preliminary data have shown the potential of calcium antagonists in this context^[34-36]. This potential, of course, needs to be further verified in an appropriate clinical setting.

Conclusions

In the acute as well as in the subacute phase of myocardial infarction, in patients with patent infarct-related artery, evaluation of microvasculature is fundamental when planning therapeutic strategies and for assessing long-term prognosis.

References

- [1] Braunwald E. The path to myocardial salvage by thrombolytic therapy. *Circulation* 1987; 76 (Suppl II): II-2-II-7.
- [2] White HD, Norris RM, Brown MA, Brandt WT, Whitlock RML, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 1987; 76: 44-51.
- [3] Cerqueira MD, Manard C, Ritchie JL, Davis KB, Kennedy JW. Long-term survival in 618 patients from the Western Washington Streptokinase in Myocardial Infarction trials. *J Am Coll Cardiol* 1992; 20: 1452-9.
- [4] Krug A, deRochemont WM, Korb G. Blood supply of the myocardium after temporary coronary occlusion. *Circ Res* 1966; 19: 57-62.
- [5] Kloner RA, Ganote CE, Jennings RB. The 'no reflow' phenomenon after temporary coronary occlusion in dogs. *J Clin Invest* 1974; 54: 1496-1508.
- [6] Willerson JT, Watson JT, Templeton GH, Fixler DE. Reduced myocardial reflow and increased coronary vascular resistance following prolonged myocardial ischemia in the dog. *Circ Res* 1975; 36: 771-81.
- [7] Iliceto S, Marangelli V, Marchese A, Amico A, Galiuto L, Rizzon P. Myocardial contrast echocardiography in acute myocardial infarction: pathophysiological background and clinical applications. *Eur Heart J* 1996; 17: 344-53.
- [8] Pierard LA, De Landsheere C, Berthe C, Rigo P, Kulbertus H. Identification of viable myocardium by echocardiography during dobutamine infusion in patients with myocardial infarction after thrombolytic therapy: comparison with positron emission tomography. *J Am Coll Cardiol* 1990; 15: 1021-31.
- [9] Barilla F, Gheorghide M, Alam M, Khaja F, Goldstein S. Low-dose dobutamine in patients with acute myocardial infarction identifies viable but not contractile myocardium and predicts the magnitude of improvement in wall motion abnormalities in response to coronary revascularization. *Am Heart J* 1991; 122: 1522-31.
- [10] Smart SC, Sawada S, Ryan T *et al.* Low-dose dobutamine echocardiography detects reversible dysfunction after thrombolytic therapy of acute myocardial infarction. *Circulation* 1993; 88: 405-15.
- [11] The TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial: phase I findings. *N Engl J Med* 1985; 312: 932-6.
- [12] Sawada SG, Segar DS, Ryan T *et al.* Echocardiographic detection of coronary artery disease during dobutamine infusion. *Circulation* 1991; 83: 1605-14.
- [13] Kim CB, Braunwald E. Potential benefits of late reperfusion of infarcted myocardium. The open artery hypothesis. *Circulation* 1993; 88: 2426-36.
- [14] Maroko PR, Libby P, Ginks WR *et al.* Coronary artery reperfusion. I: early effects on local myocardial function and the extent of myocardial necrosis. *J Clin Invest* 1972; 51: 2710-16.
- [15] Karagounis L, Sorensen SG, Menlove RL, Moreno F, Anderson JL. Does thrombolysis in myocardial infarction (TIMI) perfusion grade 2 represent a mostly patent artery or a mostly occluded artery? Enzymatic and electrocardiographic evidence from the TEAM-2 Study. *J Am Coll Cardiol* 1992; 19: 1-10.
- [16] Anderson JL, Karagounis LA, Becker LC, Sorensen SG, Menlove RL, for the TEAM-3 investigators. TIMI perfusion grade 3 but not grade 2 results in improved outcome after thrombolysis for myocardial infarction. Ventriculographic, enzymatic, and electrocardiographic evidence from the TEAM-3 study. *Circulation* 1993; 87: 1829-39.
- [17] Armstrong WF. Assessment of myocardial perfusion with contrast enhanced echocardiography. *Echocardiography* 1986; 3: 355-70.
- [18] Feinstein SB. Assessment of myocardial perfusion using contrast echocardiography. *Echocardiography* 1989; 6: 17-25.
- [19] Armstrong WF, Mueller TM, Kinney EL, Tickner EG, Dillon JC, Feigenbaum H. Assessment of myocardial perfusion abnormalities with contrast-enhanced two-dimensional echocardiography. *Circulation* 1982; 66: 166-73.
- [20] Kaul S, Kelly P, Oliner JD, Glasheen WP, Keller MW, Watson DD. Assessment of regional blood flow with myocardial contrast two-dimensional echocardiography. *J Am Coll Cardiol* 1989; 13: 468-82.
- [21] Feinstein SB, Lang RM, Dick C *et al.* Contrast echocardiography during coronary arteriography in humans: perfusion and anatomic studies. *J Am Coll Cardiol* 1988; 11: 59-65.
- [22] Ito H, Tomooka T, Sakai N *et al.* Lack of myocardial perfusion immediately after successful thrombolysis. A predictor of poor recovery of left ventricular function in anterior myocardial infarction. *Circulation* 1992; 85: 1699-1705.
- [23] Ito H, Tomooka T, Sakai N *et al.* Time course of functional improvement in stunned myocardium in risk area in patients with reperfused anterior infarction. *Circulation* 1993; 87: 355-62.
- [24] Ito H, Maruyama A, Iwakura K *et al.* Clinical implications of the 'no reflow' phenomenon. A predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. *Circulation* 1996; 93: 223-8.
- [25] Kloner RA, Rude RE, Carlson N, Maroko PR, Deboer LWV, Braunwald E. Ultrastructural evidence of microvascular damage and myocardial cell injury after coronary artery occlusion: which come first? *Circulation* 1980; 62: 945-52.
- [26] Willerson JT, Watson JT, Templeton GH, Fixler DE. Reduced myocardial reflow and increased coronary vascular resistance following prolonged myocardial ischemia in the dog. *Circ Res* 1975; 36: 771-81.
- [27] Krug A, deRochemont W, Korb G. Blood supply of the myocardium after temporary coronary occlusion. *Circ Res* 1966; 19: 57-62.
- [28] West PN, Connors JP, Clark RE *et al.* Compromised microvascular integrity in ischemic myocardium. *Lab Invest* 1978; 38: 677-84.
- [29] Kloner RA, Ellis SG, Lange R, Braunwald E. Studies of experimental coronary artery reperfusion: effects on infarct size, myocardial function, biochemistry, ultrastructure, and microvascular damage. *Circulation* 1983; 68 (Suppl I): 1-8-115.
- [30] Kloner RA, Ganote CE, Jennings RB. The 'no reflow' phenomenon after temporary coronary occlusion in dogs. *J Clin Invest* 1974; 54: 1496-1508.
- [31] Iliceto S, Galuto L, Machese A *et al.* Microvascular integrity, contractile reserve and myocardial viability after acute myocardial infarction. *Am J Cardiol* 1996; 77: 441-5.
- [32] Agati L, Voci P, Bilotta F *et al.* Influence of residual perfusion within the infarct zone on the natural history of left ventricular dysfunction after acute myocardial infarction: a myocardial contrast echocardiography study. *J Am Coll Cardiol* 1994; 24: 336-42.
- [33] Maes A, Van de Werf F, Nuyts J, Bormans G, Desmet W, Mortelmans V. Impaired myocardial tissue perfusion early after successful thrombolysis. Impact on myocardial flow, metabolism, and function at late follow-up. *Circulation* 1995; 92: 2071-8.
- [34] Villari B, Ambrosio G, Golino P *et al.* The effects of calcium channel antagonist treatment and oxygen radical scavenging on infarct size and the no-reflow phenomenon in reperfused hearts. *Am Heart J* 1993; 125: 11-23.
- [35] Piana RA, Paik GY, Moscucci M *et al.* Incidence and treatment of 'no-reflow' after percutaneous coronary intervention. *Circulation* 1994; 89: 2514-18.
- [36] Taniyama Y, Ito H, Iwakura K, Takiuchi S, Masuyama A, Fujii K. Effects of intracoronary injection of Verapamil and Nicorandil on microcirculation and left ventricular function in patients with reperfused myocardial infarction (Abstr). *Circulation* 1995; 92: 1-77.