Tissue viability by contrast echocardiography

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**KEYWORDS**

Contrast media; Microcirculation; Myocardial infarction; Tissue viability.

**Abstract**

Residual tissue viability within the infarct area is one of the major determinants of regional functional recovery after acute myocardial infarction, playing also a protective role against LV remodelling. However, viability and functional recovery are not synonymous: functional recovery is only one of the aspects of viability. Several studies have shown how important it is to maintain perfusion independently from functional recovery. In patients with an extensive endocardial necrosis and a preserved normal perfusion in the middle and epicardial myocardium layers, even though functional recovery does not occur, remodelling processes may be attenuated. Tissue viability may be detected using several different methods. Perfusion-based techniques (i.e. PET, SPECT, MRI and MCE) are more accurate in predicting global function and LV remodelling whereas inotropic reserve-based methods (i.e. DE) are more accurate in predicting functional recovery. Several studies support the hypothesis that either LV remodelling or the possibility of myocardial dysfunction to recover are strictly dependent on the extent of microvascular damage. To date, myocardial contrast echocardiography and magnetic resonance imaging have shown to be very effective techniques for assessing microvascular perfusion. Our initial experience showed a very close correlation between these two perfusional techniques. In particular by MCE, it has been demonstrated that the persistence of residual anterograde or retrograde blood flow within the infarct zone can maintain myocardial viability for a prolonged time span. The incidence of LV remodelling is significantly lower in dysfunctioning but still perfused segments than in non-perfused ones. Therefore MCE can be used to identify viable segments that may help to prevent infarct expansion and remodelling, and thus improve patient outcomes.

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**Introduction**

Despite improved clinical care, myocardial infarction and sudden death still remain the leading causes of death in western countries. Recent data from the CRUSADE trial\textsuperscript{1} aimed to assess the impact of congestive heart failure (CHF) after non ST-segment elevation myocardial infarction (NSTEMI) showed that CHF frequently occurs in these patients and is associated with less aggressive treatment and higher risk of mortality.

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Thus, there is a strong need for preventing post-ischemic left ventricular (LV) dysfunction and for new markers able to identify high risk patients after acute coronary syndromes.

Prevention of post-ischemic LV dysfunction

The best way to prevent LV dysfunction after acute myocardial infarction (AMI) is to reduce the time to treat. There is a general agreement based on several multicentre trials that independently of reperfusion strategies, time to reperfusion is the key determinant of myocardial salvage in patients with AMI. However, whereas primary percutaneous coronary intervention (PPCI) or fibrinolysis are equally recommended for patients presenting within 3h of symptom onset, PPCI is superior to lysis when reperfusion starts 3h after symptom onset. A recent survey showed that <25% of hospitals in the USA and <10% of European centres have the capability of performing emergency PCI, thus at present PPCI is only available on average for 15-20% of patients suffering from AMI in western countries. Therefore, fibrinolytic therapy is still the fastest and best accessible reperfusion treatment for the majority of STEMI patients. The appropriate management of patients timely treated with fibrinolytic therapy still remains under discussion. Despite successful infarct-related artery (IRA) reopening demonstrated by clinical signs of reperfusion, beneficial effects of fibrinolysis in terms of mortality can still be improved by complete coronary recanalization obtained by early elective angioplasty. Although convincing and consistently reproduced in several clinical trials, these results still have to find a pathophysiological explanation. We hypothesized that complete mechanical recanalization of IRA improves clinical benefits of thrombolysis as a result of more preserved and better perfused coronary microcirculation. To test this hypothesis we studied a selected ST-segment elevation acute myocardial infarction (STEMI) population presenting very early in our hospitals in whom successful IRA reperfusion was obtained by thrombolysis followed or not by elective PCI within 24 hours, and we compared these two groups with those who underwent primary PCI. Post-ischemic microvascular damage was assessed and quantitated by myocardial contrast echocardiography (MCE).

Our data suggest that early PCI after timely thrombolysis is more effective in preserving microvascular perfusion than lysis alone and may be a helpful alternative when emergency PCI is not available. Early thrombolysis with delayed aggressive management within 24 hours after admission is an effective reperfusion strategy when compared with primary PCI and may be an alternative strategy in the "real world" of acute coronary syndromes in large cities, where the time to balloon inflation is usually longer than recommended. This strategy could allow transferring the reperfused patients to perform PCI within 24h and not immediately, reducing the number and costs of urgent procedures. There is still a high proportion of patients for whom primary PCI is not available who could benefit if they first receive treatment with thrombolitics.

New markers for identifying high-risk patients after acute coronary syndromes

Clinical evidence shows that in patients with residual tissue viability after acute myocardial infarction the 1-year survival rate is about 50% in medically treated patients and about 80% in surgically treated patients as a consequence of a dramatically high ischemic event rate occurring in medically treated patients. These numbers indicate how crucial it is to carefully assess myocardial viability before revascularization to increase survival rate. The assessment of myocardial viability is a key point in patients with post-ischemic left ventricular (LV) dysfunction. Contrast echocardiography may help in detecting viability in different ways, as detailed in the following subsections.

Assessment of LV volumes, regional wall motion and ejection fraction

Analysis of regional wall motion and ejection fraction is characterized by considerable inter-observer variability even using high quality imaging modalities. Hoffmann et al. in a very elegant study recently showed that inter-observer agreement on regional wall motion analysis and accuracy in detecting wall motion abnormalities is good using contrast echocardiography and significantly improved compared to unenhanced echocardiogram. Further this study showed that the accuracy of enhanced echo is quite similar to magnetic resonance imaging. Thus image quality is dramatically increased by using contrast echo. New softwares have been implemented in echo machines for clear delineation of endocardial border and with addition of contrast this tool represents a perfect method for assessing LV function (Fig. 1). Image quality may be increased also using live 3D. This new important improvement really needs contrast. Inferior wall usually is not very well depicted. With contrast there could be
Fig. 1. New software is used to identify and track the endocardial border during contraction. The illustration shows the endocardial contours at end-diastole and the arrows the excursion during systole.

Fig. 2. Live 3D. Left ventricular opacification for endocardial border enhancement. By using Tomtec software, endocardial surface is automatically recognized and a 3D reconstruction of LV volume is obtained. Upper panel: two perpendicular long-axis views. Lower panel: (left) short axis, (right) 3D reconstruction of LV volume.

an improvement in the definition of all cavities and borders (Fig. 2).

To increase the diagnostic capability of echocardiography we do not need fast but non-diagnostic procedures in our echo labs. We absolutely need to spend some more time to produce good and diagnostic images and this is now feasible with contrast.

Assessment of myocardial infarction and residual ischemia after AMI

Two recent studies showed in a large series of patients the additional value of myocardial contrast echo in the diagnosis of acute coronary syndrome. In the first study, the authors hypothesized that regional function and myocardial perfusion may
be superior to the TIMI score for diagnosis and prognosis in patients presenting to the emergency department with chest pain and a non-diagnostic electrocardiogram. They were able to show that myocardial contrast echo can rapidly and accurately provide short-, intermediate- and long-term prognostic information in patients presenting to the emergency department with suspected cardiac chest pain even before serum cardiac markers are known. The second study showed that in patients with regional wall motion abnormalities, the contemporary presence of abnormal perfusion increases the likelihood of adverse events in the follow-up.

In the first large study in patients undergoing dobutamine stress for detecting residual ischemia after acute myocardial infarction, the additional role of myocardial perfusion over wall motion in identifying the amount of myocardium at risk has been clearly demonstrated. Patients with normal perfusion have a better outcome than patients with normal wall motion.

The explanation for the additional prognostic value of myocardial contrast perfusion echocardiography is related to the way in which bubbles behave: during hyperaemia all bubbles arrive quickly in the ROI and at 2 frames after the flash there is complete replenishment of the bubbles into the myocardium; if there is a stenosis, bubbles arrive more slowly and at 1-2 frames after flash it is not possible to see a complete replenishment of ROI but only after 4-8 frames. The majority of inducible perfusion abnormalities occur at an intermediate phase of stress, without wall motion abnormalities, thus explaining the higher sensitivity of perfusion imaging over wall motion. Myocardial contrast echo may be of great help in identifying residual area of ischemia into the infarction area or surrounding area.

Assessment of microvascular perfusion within the infarct area (true infarct size)

Tissue viability is the main determinant of functional recovery after acute myocardial infarction. However, myocyte viability and functional recovery are not synonymous, but the latter has to be considered as one aspect of the former. Tissue viability is also very important to prevent post-ischemic LV remodelling. In patients with extensive subendocardial necrosis but preserved normal perfusion in mid wall and epicardium, even though functional recovery is not observed, attenuation of the LV remodelling process may occur. Thus, all the efforts to assess and maintain tissue viability are strongly justified.

Several techniques have been developed to identify dysfunctional but viable myocardium. Perfusion-based techniques (i.e. PET, SPECT, MRI and MCE) are more accurate in predicting global function recovery and LV remodelling whereas inotropic reserve-based methods (i.e. dobutamine stress echo) are more accurate in predicting regional functional recovery. Dobutamine stress is the best method to assess regional functional recovery. Several studies agree that dobutamine has a high positive predictive accuracy for predicting functional recovery whereas thallium has high negative predictive value in predicting functional recovery, as have MCE or MRI. Therefore nuclear imaging is highly sensible for cell viability but it overestimates functional recovery. Dobutamine echocardiography is highly specific but it underestimates the amount of viability; MCE and MRI are the only techniques able to evaluate microvascular integrity which is a "conditio sine qua non" for cell viability and later functional improvement.

The role of contrast echocardiography and magnetic resonance in predicting wall motion recovery and LV remodelling in patients with previous MI has been elucidated by several studies. In particular, MRI may be considered as the reference method to detect scar tissue in post-ischemic LV dysfunction. Late gadolinium enhancement (LGE) is inversely related to recovery of systolic thickening. There is a >7-fold increase in major adverse coronary events in patients with late enhancement, finally there is a close correlation between LGE and life-threatening arrhythmias. Thus, the extent of scar tissue can be considered as a new marker for identifying patients at high risk of sudden cardiac death caused by ventricular dysrhythmia and who could be candidates for ICD implantation.

Similar data has been obtained by MCE, as depicted in Figs. 3 and 4. Balcels et al. showed a close correlation between contrast score at 3 days after MI and wall motion score at 4 weeks. Lepper et al. and Badano et al. demonstrated that the best predictor of left ventricular recovery is the extent of perfusion defect.

In our study we showed a closer correlation between contrast defect at day 1 and wall motion abnormalities at follow-up than between the initial and final extent of wall motion abnormalities (Fig. 5). In other words, the status of microvascular perfusion after reperfusion is the most powerful predictor of EF and definitive extent of infarct size at follow-up.
Fig. 3. Patient with acute apical myocardial infarction treated with primary angioplasty within 3 hours from symptom onset. No late enhancement or residual contrast defect is detected by either (A) magnetic resonance imaging or (B) myocardial contrast echo.

Fig. 4. Patient with acute apical myocardial infarction treated with primary angioplasty within 3 hours from symptom onset. Similar extent of late enhancement and residual contrast defect is detected both by (A) magnetic resonance imaging and (B) myocardial contrast echo.

Fig. 5. Linear regression analysis shows a closer correlation between contrast defect at day 1 (CD%-T1) and wall motion abnormalities at follow up (WMA%-T3) (left panel) than between the initial (WMRA-T1) and final (WMA%-T3) extent of wall motion abnormalities (right panel).
Assessment of left ventricular remodelling

After acute myocardial infarction, aging and time to treat are the major determinants of subsequent LV dysfunction, thus of the initial extent of wall motion abnormalities (WMA) and end-diastolic LV volume (EDV). All these parameters play a major role in inducing LV remodelling. However, the initial extent of regional wall motion abnormalities provides indirect measures of infarct size whereas myocardial contrast echocardiography by assessing the extent of microvascular perfusion defect represents a direct measure of true infarct size.

For these reasons, patients with similar extent of WMA and EDV soon after reperfusion may have different LV remodelling. The missing link is the microvascular damage, which explains why for similar volumes, ejection fraction and extent of regional wall motion abnormalities, LV remodelling can be different. LV remodelling may occur from 24-48 hours after reperfusion to pre-discharge (early LV remodelling) or from pre-discharge to 6 months (late LV remodelling). Different parameters may predict early and late remodelling. According to the GISSI 3 echo sub-study, EDV and the extent of WMA are important for predicting early remodelling; however for late remodelling prediction, EDV is not always so specific. Late remodelling is associated with progressive deterioration of global ventricular function over time: patients with extensive WMA and not significantly enlarged ventricular volume before discharge are at higher risk for progressive dilation and LV dysfunction. Nicolau et al. pointed out for the first time the importance of microvascular perfusion, showing that the presence of ST-segment resolution after MI precludes the occurrence of remodelling. Similar conclusions were drawn by Bolognese et al. demonstrating the correlation between microvascular dysfunction within the risk area and LV remodelling and survival at follow-up.

Our data obtained during a multicentre Acute Myocardial Infarction Imaging (A.M.I.C.I) study conducted at 4 institutions in Italy on 120 patients with first acute ST-elevation acute myocardial infarction undergoing different reperfusion strategies within 6 hours from symptom onset, further confirm the key role of MCE in predicting LV remodelling. From multivariate analysis using Cox regression, the most important echo parameters for predicting LV remodelling at day 1 after reperfusion are contrast defect (CD) and WMA extent and ejection fraction. However from analysis of ROC curves the most powerful predictor of LV remodelling with the best sensitivity/specificity ratio is the CD extent (Fig. 6). Considering all clinical, echocardiographic and angiographic parameters together (i.e. ST-segment reduction, all echo and angio parameters) the CD extent, TIMI post and ejection fraction are the most important parameters to predict remodelling.
Therefore, contrast defect as compared to ST-segment reduction after reperfusion more strongly reflects the efficacy of reperfusion and it should be used routinely for assessing different reperfusion strategies. In the subset of patients reaching TIMI 3 score after reperfusion, multivariate analysis shows CD extent is the only independent parameter for LV remodelling (Table 1).

**Conclusions**

Microvascular damage is the missing link between LV remodelling infarct size and LV volumes.

After acute myocardial infarction, MCE or MRI are the ideal methods for (1) assessing residual tissue viability, (2) following perfusional changes, and (3) evaluating the efficacy of treatment.

The extent of scar tissue as detected by MRI or MCE can be considered as a new marker for identifying patients at high risk for sudden cardiac death caused by ventricular dysrythmia, and it may be used for a better selection of patients as candidates for ICD implantation.

**References**


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