Intravenous myocardial contrast echocardiography predicts regional and global left ventricular remodelling after acute myocardial infarction: comparison with low dose dobutamine stress echocardiography

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Objective: To assess the role of intravenous myocardial contrast echocardiography (MCE) in predicting functional recovery and regional or global left ventricular (LV) remodelling after acute myocardial infarction (AMI) compared with low dose dobutamine stress echocardiography (LDSE).

Methods: 21 patients with anterior AMI and successful primary angioplasty underwent MCE and LDSE during the subacute stage (2–4 weeks after AMI). Myocardial perfusion and contractile reserve were assessed in each segment (12 segment model) with MCE and LDSE. The 118 dysysynergic segments in the subacute stage were classified as recovered, unchanged, or remodelled according to wall motion at six months' follow up. Percentage increase in LV end diastolic volume (% ΔEDV) was also calculated.

Results: The presence of perfusion was less accurate than the presence of contractile reserve in predicting regional recovery (55% vs 81%, p < 0.0001). However, the absence of perfusion was more accurate than the absence of contractile reserve in predicting regional remodelling (83% vs 48%, p < 0.0001). The number of segments without perfusion was an independent predictor of % ΔEDV, whereas the number of segments without contractile reserve was not. The area under the receiver operating characteristic curve showed that the number of segments without perfusion predicted substantial LV dilatation (% ΔEDV > 20%) more accurately than did the number of segments without contractile reserve (0.88 vs 0.72).

Conclusion: In successfully revascularised patients with AMI, myocardial perfusion assessed by MCE is predictive of regional and global LV remodelling rather than of functional recovery, whereas contractile reserve assessed by LDSE is predictive of functional recovery rather than of LV remodelling.
failure or confirmed diagnosis of postinfarction angina during the six month follow up period; (7) significant restenosis (≥ 70%) in infarct related arteries on coronary angiography at six months’ follow up; and (8) inadequate echocardiographic image quality. Aspirin and either angiotensin converting enzyme inhibitors or angiotensin receptor blockers were routinely administered to all patients in the absence of contraindications or intolerance.

All patients underwent MCE and LDSE on the same day during the subacute stage and underwent quantitative coronary angiography and conventional echocardiography at six months’ follow up. Of the 31 patients selected for this study, three did not adhere to the follow up protocol. Furthermore, one had congestive heart failure, one had new permanent atrial fibrillation, and one had postinfarction angina due to restenosis in an infarct related artery and underwent revascularisation during the follow up period. Coronary angiography at the six month follow up showed that four additional patients had significant restenosis in infarct related arteries and they underwent target lesion revascularisation. Thus, the remaining 21 patients constituted the study group (15 men; mean (SD) age 68 (9) years). All echocardiograms were interpreted by two experienced echocardiographers who were blinded to the clinical information, and any disagreements were resolved by their consensus reading. The protocol was approved by the hospital ethics committee and all patients gave written informed consent.

Echocardiographic studies
All echocardiograms were performed with an HDI 5000 instrument (Philips Medical Systems, Bothell, Washington, USA) equipped with a broad band harmonic transducer. Images of all echocardiographic modalities were obtained from the apical two and four chamber views. The LV wall was divided into 12 segments (four segments each for basal, middle, and apical levels). Wall motion in each segment was scored with a five grade scale as follows: 4, dyskinesis; 3, akinesis; 2, severe hypokinesis; 1, hypokinesis; and 0, normokinesis or hyperkinesis. The wall motion score index (WMSI) was calculated as the average of the wall motion scores of those 12 segments. LV end diastolic volume, end systolic volume, and ejection fraction (EF) were calculated with the use of the modified Simpson’s rule.4

Intravenous myocardial contrast echocardiography
MCE was performed during the subacute stage with intermittent harmonic power Doppler imaging in the harmonic mode for transmitting and receiving at mean frequencies of 1.6 and 3.2 MHz, respectively. The emission power was set at the highest level (mechanical index of 1.3) and to attenuate wall motion artefacts. The images were obtained by triggering at end systole. Pulsing intervals were altered from one to eight cardiac cycles. The focus was set at the level of the mitral annulus. Levovist (Schering, Berlin, Germany), used as a contrast agent, was prepared in the standard manner at a concentration of 300 mg/ml and was infused intravenously at a rate of 450–600 mg/min with an infusion device. During the initial two minutes of the infusion, we adjusted the gain, scan plane, and infusion rate to optimise myocardial opacification. Image acquisition began two minutes after the start of the infusion. The transmission power, overall gain, repetition frequency, and image depth were held constant during image acquisition in each patient. Myocardial perfusion in each segment was scored according to contrast opacification as follows: 2, homogeneous; 1, partial or patchy; and 0, none even with long pulsing intervals. The presence of perfusion was defined as a perfusion score of 1–2 and the absence of perfusion (perfusion defect) was defined as a perfusion score of 0.

Low dose dobutamine stress echocardiography
LDSE was performed during the subacute stage according to a previously described procedure.4 After a baseline study, we began an intravenous infusion of dobutamine at the rate of 5 µg/kg/min for four minutes, then 10 µg/kg/min for the next four minutes. We recorded the ECG, heart rate, and blood pressure during the test. Two dimensional recordings were made at the end of each stage with second harmonic imaging. A wall motion score in each segment was assessed at each stage in LDSE. Myocardial contractile reserve in each dysynergic segment was defined as improvement in wall motion score of at least one grade during stress compared with rest.

Follow up evaluation
Conventional echocardiography was performed at six months’ follow up and dysynergic segments in the subacute stage were classified as recovered, unchanged, or remodelled according to changes in wall motion compared with the subacute stage. Recovered wall motion was defined as a decrease in wall motion score of at least one grade. Remodelled was defined as an increase in wall motion score of at least one grade or a persistent wall motion score of 4 (dyskinesia). Unchanged wall motion was defined as a persistent wall motion score of 1–3 with no change. Global LV dilatation was assessed as the percentage increase in LV end diastolic volume (%ΔEDV) from the subacute stage to the six month follow up in each patient, and significant global LV remodelling was defined as a %ΔEDV > 20%.

Table 1  Clinical characteristics and LV volumes and function

<table>
<thead>
<tr>
<th>All patients (n = 21)</th>
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<td>Age (years)</td>
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<td>Men</td>
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<td>Risk factors</td>
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<td>Stenting</td>
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<td>Biochemical parameters</td>
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<td>Peak creatine kinase (IU/l)</td>
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<td>Peak creatine kinase MB (IU/l)</td>
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<td>LV volumes and function</td>
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<td>Subacute stage</td>
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<td>LV EDV (ml)</td>
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<td>LV ESV (ml)</td>
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<td>LV ESV (ml)</td>
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<td>LV EF (%)</td>
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<td>WMSI</td>
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Data are presented as mean (SD) or number (% of patients).

*p<0.05 versus subacute stage.

EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume; LV, left ventricular; WMSI, wall motion score index.
Statistical analysis

Data are presented as absolute values, absolute values (percentages), or mean (SD) as appropriate. Differences in continuous variables between the subacute stage and the six month follow up were assessed by the Wilcoxon signed rank test. Sensitivities, specificities, and accuracy were calculated according to standard definitions. McNemar’s test for paired data was used to compare the sensitivities, specificities, and accuracy of MCE and LDSE for the prediction of changes in regional wall motion.

We constructed a 3 × 3 table to study the relation between changes in regional wall motion and three combinations between perfusion and contractile reserve (that is, concordant positive results, discordant results, and concordant negative results). We used κ statistics to determine the concordance between them: κ values > 0.4, > 0.6, and > 0.8 indicated fair, good, and excellent agreement, respectively.

Linear regression analysis was applied to study the correlation between %ΔEDV and variables. To determine independent predictors of %ΔEDV, stepwise multivariate linear regression analysis was performed. All variables with p < 0.10 between baseline characteristics and echocardiographic parameters at the subacute stage were included in the multivariate model.

To analyse the predictive value of variables for global LV remodelling, we constructed receiver operating characteristic curves. We considered that the variable with the larger area under the curve had the better predictive value and determined the most suitable cut off point where the sum of the sensitivity and specificity was highest. A probability value of p < 0.05 was considered significant.

RESULTS

The 21 patients in the study underwent MCE and LDSE 19 (4) days after AMI. Table 1 shows clinical characteristics and LV volumes and function at the subacute stage and six months’ follow up. Mean LV end diastolic volume, LV end systolic volume, LV EF, and WMSI at the subacute stage were 95 (26) ml, 53 (22) ml, 45 (11)%, and 1.13 (0.96), respectively. During the follow up period LV volumes and WMSI did not change significantly but LV EF increased significantly (p < 0.05).

Prediction of changes in regional wall motion

Of the 252 segments in the 21 patients, 146 (58%) were dysynergic in the subacute stage. Of the 146 dysynergic segments in the subacute stage, 28 segments were excluded because of inadequate MCE image quality. Thus, 118 dysynergic segments were assessed in the final analysis. Of the 118 dysynergic segments in the subacute stage, 41 (35%) were classified as recovered, 59 (50%) as unchanged, and 18 (15%) as remodelled at six months’ follow up.

Table 2 shows results of perfusion scoring and contractile reserve assessment in comparison with changes in regional wall motion in the 118 segments. Myocardial perfusion was present (perfusion score of 1–2) in 40 (98%) of the 41 recovered segments, 46 (78%) of the 59 unchanged segments, and six (33%) of the 18 remodelled segments. Contractile reserve was present in 30 (73%) of the 41 recovered segments, 10 (17%) of the 59 unchanged segments, and one (6%) of the 18 remodelled segments.

Table 3 gives the sensitivities, specificities, and accuracy of perfusion assessed by MCE and contractile reserve by LDSE for identifying recovered segments. The sensitivity of perfusion assessed by MCE was significantly higher than the sensitivity of contractile reserve assessed by LDSE (98% vs 73%, p = 0.004) in all dysynergic segments. The specificity and accuracy of perfusion were significantly lower than contractile reserve (32% vs 86%, 55% vs 81%, respectively, both p < 0.0001). Significantly lower specificity and accuracy of
perfusion than of contractile reserve for identifying recovered segments were also seen in akinetic or dyskinetic segments (wall motion score of 3–4) and in hypokinetic segments (including severe hypokinesis; wall motion score of 1–2).

The specificity and accuracy of a perfusion defect for identifying remodelled segments were significantly higher than those of the absence of contractile reserve (86% v 40%, 83% v 48%, respectively, both p < 0.0001), as table 4 shows. Significantly higher specificity and accuracy of perfusion than of contractile reserve for identifying remodelled segments were also seen in akinetic or dyskinetic segments and in hypokinetic segments.

**Combined assessment of perfusion and contractile reserve for predicting changes in regional wall motion**

Table 5 shows the relation between perfusion assessed by MCE and contractile reserve by LDSE. Concordant positive results, discordant results, and concordant negative results between perfusion and contractile reserve were seen in 40 (34%), 53 (45%), and 25 (21%) segments, respectively. Table 6 shows combined assessment of perfusion and contractile reserve in comparison with changes in regional wall motion. The χ value of the concordance between changes in regional wall motion and three combinations of perfusion and contractile reserve was 0.44, which indicated fair agreement.

**Prediction of changes in global LV volume**

The mean %∆EDV was 1 (22)% (range −30% to 47%). Six (29%) of the 21 patients had global LV remodelling, defined as %∆EDV > 20%.

The %∆EDV was significantly associated with the number of segments without perfusion and the number of segments without contractile reserve in univariate analysis ($r = 0.64$, $p = 0.002$ and $r = 0.44$, $p = 0.04$, respectively) (fig 1). Among a variety of other factors, diabetes mellitus and Q wave infarction were associated ($p < 0.10$) with %∆EDV in univariate analysis ($r = 0.40$, $p = 0.07$ and $r = 0.37$, $p = 0.096$, respectively). In stepwise multivariate linear regression analysis including these four parameters in the model, only the number of segments without perfusion was an independent predictor of %∆EDV ($F = 13.2$, $p = 0.002$), whereas the number of segments without contractile reserve was not ($F = 0.4$).

Figure 2 shows the receiver operating characteristic curves for predicting global LV remodelling. The area under the curve of the number of segments without perfusion was larger than the area under the curve of the number of segments without contractile reserve (0.88 v 0.72). The highest sum of the sensitivity and the specificity for predicting global LV remodelling was seen when the threshold value was taken as two or more segments without perfusion by MCE (sensitivity 83%, specificity 87%).

**DISCUSSION**

Our results show that myocardial perfusion defects assessed by MCE predict the deterioration of regional wall motion and LV dilatation, implying regional and global LV remodelling respectively. The predictive value of MCE was better than that of contractile reserve assessed by LDSE. In contrast, our results also show that regional functional recovery can be predicted by contractile reserve better than by myocardial perfusion.

**Prediction of regional functional recovery and regional LV remodelling**

Previous studies have attempted to compare intracoronary or intravenous myocardial contrast echocardiography with LDSE for predicting changes in regional wall motion after AMI, and have shown that myocardial contrast echocardiography has a lower specificity than LDSE, resulting in poorer accuracy in predicting regional functional recovery. Our results agree with these previous studies. These previous findings strongly suggest that preservation of the microvasculature is necessary but not sufficient for functional recovery. In the present study, we attempted to clarify the differences between the two modalities by analysing both the recovery and deterioration of regional function.
regional remodelling) than does the absence of contractile reserve assessed by LDSE. This finding indicates that preservation of the microvasculature is sufficient as well as necessary to prevent regional remodelling after AMI.

A possible explanation for our segmental results is that the transmural extent of necrosis may determine the development of functional recovery or remodelling. Previous studies have shown that contractile reserve and functional recovery predominantly reflect the function of the subendocardium, but the development of LV remodelling depends on the function of the subepicardium. The infarcted myocardium with subepicardial viability should not contribute to contractile reserve and functional recovery but prevents remodelling. Residual perfusion in such viable subepicardium can be detected by MCE. In contrast, transmural necrosis that leads to a cascade of LV remodelling and further deterioration of regional wall motion towards dyskinesis, implying regional LV remodelling, may be represented by the entire perfusion defect delineated by MCE.

Some previous studies have shown that the combined assessment of perfusion by MCE and contractile reserve by LDSE enhances the diagnostic accuracy of predicting regional functional recovery after AMI by excluding discordant results between perfusion and contractile reserve. In contrast, we attempted to study the diagnostic accuracy of the combined assessment of perfusion and contractile reserve without excluding their discordant results because one of the key issues of this study was to clarify the differences in clinical significance between MCE and LDSE. The present study showed that most of the discordant results consisted of the presence of perfusion and the absence of contractile reserve (52 of 53 segments (98%)) and that there was a fair agreement between changes in regional wall motion and three combinations of perfusion and contractile reserve with \( \kappa = 0.44 \). Contractile reserve should lead to regional functional recovery, while perfusion should lead to prevention of regional remodelling. Accordingly, a combination of the presence of perfusion and the absence of contractile reserve should keep regional wall motion unchanged. In our additional analysis by \( \kappa \) statistics, changes in regional wall motion agreed more weakly with the independent assessment of MCE by a three grade perfusion score as shown in table 1 (\( \kappa = 0.22 \)). Including this finding, all of our segmental results indicate that assessing both MCE and LDSE should be clinically useful, which have different roles for predicting three types of change in regional wall motion after AMI (that is, recovered, unchanged, or remodelled).

It should also be noted that hypokinetic segments gave us similar segmental results to akinetic or dyskinetic segments. In a previous study several (17%) hypokinetic segments without changes at one month’s follow up after AMI deteriorated to akinetic or dyskinetic by six months’ follow up. The present study also showed that several (13%) hypokinetic segments in the subacute stage deteriorated by six months’ follow up. Thus, we believe it is important to predict regional LV remodelling in hypokinetic segments as well as akinetic segments.

Prediction of global LV remodelling

Some previous studies have shown that LDSE is useful for predicting global LV remodelling after AMI. Other studies have shown that intracoronary or intravenous myocardial contrast echocardiography is useful for the prediction of global LV remodelling after AMI. Both LDSE and MCE have been shown to be useful for predicting LV remodelling. However, the differences between LDSE and MCE in predicting LV remodelling have not been fully elucidated. In the present study, the extent of a perfusion defect was an independent predictor of an increase in LV volume, whereas the extent of a contractile reserve defect was not. Thus, for predicting global LV remodelling after AMI, assessing residual perfusion by MCE is more suitable than assessing contractile reserve by LDSE as also seen in our segment by segment analysis.

Limitations

Several limitations should be acknowledged. The number of patients studied was relatively small. Prospective studies with larger numbers of patients are required to clarify the differences between MCE and LDSE in the assessment of functional recovery and LV remodelling.

We did not perform MCE in the acute phase of AMI. A previous study has shown that LV remodelling influences prognosis with no difference in the pattern of LV dilatation between early (<1 month) and late (1–6 months) follow up among patients with AMI treated successfully with primary coronary angioplasty. Thus, it is very important to predict both early and late LV remodelling after AMI. Furthermore, other studies suggested that one day after primary revascularisation was the optimal time to estimate microvascular integrity for predicting LV viability and remodelling after AMI. According to these findings, it may be better to perform MCE for predicting LV viability and remodelling early after AMI than during the subacute stage, when MCE was performed in the present study. In Japan, however, Levovist is the only commercially available contrast agent for MCE and is contraindicated within two weeks after AMI. Thus, we had to wait for two weeks after the onset of AMI to perform MCE with Levovist.

We did not analyse MCE and LDSE quantitatively. The differences between the two modalities seen in the present study might have been caused by different thresholds between myocardial perfusion and contractile reserve that we could recognise visually with each modality. Thus, quantitative evaluation with MCE and LDSE may be more suitable to clarify differences between these two modalities. However, one of the major limitations of MCE is non-uniformity of the ultrasound field in the scan plane, preventing the accurate quantification of myocardial perfusion. Thus, we compared MCE and LDSE by visual and qualitative analysis, as is done in routine practice.
Harmonic power Doppler imaging is suitable for visual recognition of myocardial perfusion due to its excellent discrimination between microbubble signals and tissue signals. It does, however, have some limitations such as the susceptibility to motion artefacts and lower resolution. Although the discordant results between myocardial perfusion and contractile reserve may result from a shift in the transmural distribution of myocardial perfusion towards the epicardium, we observed few segments (only two of the 53 segments with discordant results) with MCE with obvious differences between epicardial opacification and endocardial opacification. A shift in the transmural distribution of myocardial perfusion may be shown by indistinct partial opacification with harmonic power Doppler imaging due to its lower resolution. For the distinct identification of an altered distribution of transmural myocardial perfusion, an MCE procedure with higher resolution may be required.

Conclusions
In successfully revascularised patients with AMI, the assessment of myocardial perfusion by MCE is predictive of regional and global LV remodelling rather than of functional recovery. Contractile reserve detected by LDSE is predictive of functional recovery rather than of LV remodelling.

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