Unfavourable Left Ventricular Remodelling in Patients with Dobutamine-Inducible Ischaemia after Acute Myocardial Infarction

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Aims: Aim of the study was to assess the role of early inducible ischaemia for determining left ventricular remodelling in patients with acute myocardial infarction.

Methods and Results: In 179 consecutive patients with first myocardial infarction the occurrence of new wall motion abnormalities during dobutamine stress echocardiography at discharge was related to the left ventricular volume changes at 6 months. Left ventricular end-diastolic and end-systolic index volumes (mL/m²) were echocardiographically detected at discharge and at 6 months and the relative changes were calculated. The study population consisted of 105 patients without and 74 patients with inducible ischaemia; of these, 46 patients had ≥4 ischaemic segments. At 6 months, the end-diastolic index volume increased in patients with inducible ischaemia compared to patients without (+7.5 ± 11.2 vs −0.1 ± 10.2 mL/m²; P=0.0049) and final mean end-diastolic volume was greater in patients with inducible ischaemia than without (70.8 ± 16.0 vs 61.1 ± 17.0 mL/m²; P=0.0012). The end-systolic volume increased at 6 months in patients with inducible ischaemia and it decreased in patients without (+2.8 ± 8.6 vs −1.4 ± 7.8 mL/m²; P=0.021). At the multivariate analysis, inducible ischaemia in ≥4 segments (odds ratio=6.43), the wall motion score index at the peak of dobutamine infusion (odds ratio=1.14) and the end-systolic index volume at discharge (odds ratio=1.06) were independent predictors of subsequent left ventricular end-diastolic index volume increase ≥15 mL/m².

Conclusion: In patients with first myocardial infarction the presence and the severity of inducible ischaemia, as detected by dobutamine stress echocardiography at discharge, indicates an unfavourable left ventricular remodelling.

Key Words: remodelling; inducible ischaemia; myocardial infarction; dobutamine.

Introduction

The development of left ventricular dilation following myocardial infarction is the main finding of the complex process named ventricular remodelling, and it is one of the major determinants of a bad outcome[1]. In previous studies, infarct size[2-3] and persistent occlusion of infarct-related artery[4-6] have been demonstrated to be the major determinants of remodelling. Moreover, the transmural extent of necrosis and the presence of surviving myocardium within the infarct area were found to be directly and inversely related to the post-infarction expansion process, respectively[7-9]. The favourable effect of infarct-zone viability, as detected by dobutamine infusion, on left ventricular enlargement has been demonstrated in a population with successful primary coronary angioplasty[10]. Conversely, left ventricular dilation has been found after myocardial infarction in patients with poor left ventricular function and exercise-inducible ischaemia[11], and a combined role of infarct-zone contractile reserve and inducible ischaemia on left ventricular remodelling has been suggested in preliminary reports[12,13]. However, definite data on the relation between presence and severity of early inducible ischaemia and left ventricular volume changes in patients with acute myocardial infarction are still lacking.
Dobutamine echocardiography is considered a first-choice stress test in patients with recent infarction, providing at the same time reliable information on left ventricular volumes and function, and it is an established tool for the detection and quantification of residual ischaemia\textsuperscript{[14,15]}. Indeed, the purpose of our study was to investigate the influence of early inducible ischaemia, as detected by dobutamine stress echocardiography, on left ventricular remodelling at 6 months in a general population with first, uncomplicated myocardial infarction.

**Methods**

**Patients and Protocol**

We prospectively considered 228 patients with first, acute myocardial infarction selected among 274 consecutive patients admitted to the intensive coronary care unit between January 1996 and December 1998. The study inclusion criteria were as follows: (1) typical chest pain lasting more than 30 min, ST-segment elevation in ≥2 leads, creatinine-kinasis elevation more than twice the upper normality level; (2) pre-discharge baseline and dobutamine stress echocardiography; (3) informed written consent to the study. Criteria of exclusion were age >75 years, Killip class III–IV at admission, pre-discharge angina or infarction extension, valvular heart disease, atrial fibrillation at the moment of echocardiographic examinations, life-limiting non-cardiac diseases, anticipated difficulties with the six-month outpatient evaluation.

Of the 228 patients selected for the study, 19 (8\%) were excluded because of inadequate image quality on the echocardiographic examination. Later, further exclusions in the interval time of the study were due to death (six patients), non-fatal reinfarction (six patients) and aorto-coronary by-pass surgical procedures (eight patients). Finally, 10 patients did not adhere to the follow-up protocol. Thus, 179 patients (150 men, 29 women; mean age: 58 ± 9 years, range 32 to 75 years) completed the study protocol. The research protocol was approved by the hospital’s Ethics Committee. Patients received conventional medical treatment according to individual needs on the decision of the attending physician.

All patients underwent in-hospital baseline and dobutamine stress echocardiography at a mean of 8 days (range, 6 to 9) after admission. Moreover, a second echocardiographic examination was planned for all patients at a mean of 25 weeks (range, 23 to 26) after discharge.

Baseline and dobutamine echocardiograms were performed with a commercially available imaging system (Hewlett-Packard Sonos 1500 system; 2.5- and 3.5-MHz transducers). All patients underwent the echocardiographic examinations while taking the prescribed medications. Images (parasternal long- and short axis views, apical four-chamber and two-chamber views) were displayed in real time and recorded on a high-definition 0.5-in SVHS cassette recorder (Panasonic 7350 AG). Moreover, all baseline and stress images were digitally stored in a quad-screen format.

During continuous echocardiographic monitoring, an intravenous infusion of dobutamine (5 μg/kg per min) was started with an electronic infusion pump and continued for 3 min. Afterwards, dobutamine dosage was increased with 3 minutes interval steps (10, 20, 30, 40 μg/kg). In case of heart rate less than 85\% of age-predicted limit, 0.50–1 mg of atropine was administered and infusion of 40 μg/kg of dobutamine was maintained during 3 additional min. The criteria for stopping dobutamine infusion included a heart rate ≥85\% of age-predicted limit, the occurrence of hypotension (decrease of systolic or diastolic pressure ≥30 mmHg), hypertension (systolic pressure ≥220 mmHg, diastolic pressure ≥130 mmHg), intolerable angina, supraventricular tachycardia, ventricular tachycardia (more than three consecutive beats), significant ST-segment depression (≥3 mm) or ST-segment elevation (≥2 mm) in non-infarct leads. Two experienced investigators blinded to the clinical data interpreted all the DSE of the study. Discrepancies were resolved by consensus.

**Echocardiographic Measurements**

Left ventricular end-diastolic and end-systolic index volumes were calculated on the end-diastolic and end-systolic frames by use of the modified biplane Simpson’s rule algorithm from orthogonal apical long axis projections (four- and two-chamber views). The mean values of at least three measurements of the technically best cardiac cycles were taken from each examination and body surface index values (mL/m\(^2\)) were derived. End-diastolic and end-systolic index volumes at 6 months in comparison with the values assessed at discharge were considered to obtain the volume changes in mL/m\(^2\). Two expert observers calculated the left ventricular end-diastolic and end-systolic volumes at discharge and at 6 months in all patients. Moreover, thirty randomly selected echocardiographic studies were re-analysed to evaluate intra-observer and inter-observer variability in left ventricular volumes calculation.

The left ventricular ejection fraction was obtained by the following equation: end-diastolic volume – end-systolic volume/end-diastolic volume × 100. The wall motion analysis was performed according to a 16-segment model of the left ventricle\textsuperscript{[14]}, and particular attention was paid to the systolic thickening in the central portion of each segment. For each segment, wall motion was scored as 1 (normal), 2 (hypokinetic), 3 (akinetic) or 4 (dyskinetic). The left ventricular wall motion score index (wall motion score/16) was calculated at baseline, during dobutamine infusion and on the follow-up examination. The infarct-zone was identified by segments with resting dysfunction.

Inducible ischaemia was defined as any deterioration of segmental contractility ≥2 grades in at least one
segment or >1 grade in at least two segments during dobutamine infusion, either in the infarct zone or outside. Akinesis becoming dyskinesis during dobutamine infusion was not considered for inducible ischaemia.

### Statistical Analysis

Results are given as mean values ± 1 SD. Differences were compared using the $\chi^2$ for multway frequency tables for categorical variables and unpaired t-test for continuous variables. The left ventricular end-diastolic and end-systolic index volumes, the ejection fraction and the wall motion score index at baseline and at follow-up were compared in terms of mean values and changes over time using one-way repeated measures ANOVA, with time being the within-subjects variable. Among groups differences in the interval change of left ventricular volumes were analysed using the covariance method, adjusting each follow-up measurement for the baseline values. A value of $P<0.05$ was considered statistically significant.

A multivariate regression analysis was performed to assess the influence of selected clinical variables, baseline echocardiographic and dobutamine stress test results on a left ventricular end-diastolic volume increase ≥15 mL/m² at 6 months (value approaching to the mean end-diastolic volume increase in the overall population ± 1 SD). In particular, the considered variables were: age (continuous variable), male gender (yes/no), anterior infarction (yes/no), thrombolysis (yes/no), ACE-inhibition at discharge (yes/no), peak creatine-kinase activity values (continuous variable), baseline end-diastolic index volume (continuous variable), baseline end-systolic index volume (continuous variable), baseline ejection fraction (continuous variable), baseline wall motion score index (continuous variable), inducible ischaemia during dobutamine infusion (yes/no), inducible ischaemia in at least four segments (yes/no), wall motion score index at the peak of dobutamine infusion (continuous variable). Statistical analysis was performed using SPSS for Windows, Version 8.0 (SPSS Inc, Chicago, Illinois).

### Results

### Patient Characteristics and DSE Response

The study population was divided on the basis of dobutamine stress test response. One hundred and five patients showed absence of inducible ischaemia and were classified as having negative stress test. Seventy-four patients showed wall motion deterioration during dobutamine infusion and were classified as having positive stress test. In 46 of 74 patients with inducible ischaemia (62%) the ischaemic response involved ≥4 segments (large ischaemic area). In 56 patients (76%) the inducible ischaemia was inside the infarct zone, whereas in 15 patients (20%) the ischaemic response involved both the infarct zone and wall segments outside the infarct zone. Finally, in three patients (4%) inducible ischaemia was detected outside the infarct zone.

In Table 1 the main clinical characteristics of the patient population are reported: there were no significant differences in age, infarct location, thrombolysis, peak creatine-kinase activity, ACE-inhibition and beta-blockers therapy at discharge between patients with and without inducible ischaemia. Male gender was slightly more frequent among patients with inducible ischaemia ($P=0.022$).

Physicians were not blinded to the results of dobutamine stress test, and during the first 6 months after admission a re-vascularization procedure by coronary angioplasty was performed in a higher proportion of patients with inducible ischaemia (18 of 74, 24% vs 12 of 105, 11%; $P=0.035$). Twelve of 46 patients (26%) with a large ischaemic area underwent coronary angioplasty. Altogether, the revascularization procedures were performed at a mean of 6 ± 5 weeks from hospital discharge (range: 2–23).

### Mean Left Ventricular Volumes (Table 2, Fig. 1)

At the first evaluation the left ventricular end-diastolic and end-systolic index volumes were comparable in patients with and without inducible ischaemia, and in the subgroup of patients with ≥4 ischaemic segments.

At 6 months, mean end-diastolic index volume was greater in patients with inducible ischaemia than patients without ($P=0.0012$), and the mean end-systolic index volume was slightly but not significantly greater in patients with inducible ischaemia ($P=0.056$). Both the subgroups of patients with large (≥4 segments) and limited (<4 segments) ischaemic area showed greater end-diastolic volumes at 6 months compared to patients with a negative stress test response ($P=0.0018$ and $P=0.0043$, respectively), whereas mean end-systolic volume at 6 months was greater only in patients with a large ischaemic area ($P=0.044$).

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**Table 1.** Baseline clinical characteristics of all patients and of the two patient groups.

<table>
<thead>
<tr>
<th></th>
<th>IS − (n=105)</th>
<th>IS + (n=74)</th>
<th>All patients (n=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>58.0 ± 8.4</td>
<td>58.6 ± 8.9</td>
<td>58.4 ± 9.0</td>
</tr>
<tr>
<td>Male, %</td>
<td>78</td>
<td>92</td>
<td>84</td>
</tr>
<tr>
<td>Anterior MI, %</td>
<td>49</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>Thrombolysis, %</td>
<td>56</td>
<td>68</td>
<td>61</td>
</tr>
<tr>
<td>Peak CK, U/L</td>
<td>2256 ± 1935</td>
<td>2238 ± 1674</td>
<td>2248 ± 1745</td>
</tr>
<tr>
<td>CE-inhibition, %</td>
<td>48</td>
<td>53</td>
<td>50</td>
</tr>
<tr>
<td>Beta-blockers, %</td>
<td>47</td>
<td>46</td>
<td>47</td>
</tr>
</tbody>
</table>

IS: inducible ischaemia; MI: myocardial infarction; CK: serum creatine kinase.

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Changes of Left Ventricular Volumes

In the overall population of the study, the left ventricular end-diastolic index volume increased at 6 months (P=0.042), whereas end-systolic index volume was unmodified (P=0.32).

At 6 months, the end-diastolic index volume increased in patients with inducible ischaemia but it was unmodified in patients without (P=0.0049). The end-systolic index volume increased in patients with inducible ischaemia and decreased in patients without (P=0.0021).
In the subgroup of patients with a large ischaemic area both end-diastolic and end-systolic volumes increased at 6 months and these changes were significantly different compared to patients without inducible ischaemia (P = 0.0002 and P = 0.0016, respectively). By contrast, end-diastolic and end-systolic volume changes observed in patients with less than four ischaemic segments were intermediate between those observed in patients without inducible ischaemia (P = 0.061) and patients with ≥4 ischaemic segments (P = 0.11).

In 18 patients (24%) ischaemia was inducible outside the infarct zone. Changes of end-diastolic and end-systolic index volumes in patients with remote inducible ischaemia were comparable with those observed in patients with infarct zone inducible ischaemia (P = 0.234).

**Ejection Fraction and Wall Motion Score Index**

Mean ejection fraction and wall motion score index were comparable at baseline and at 6 months in patients with and without inducible ischaemia. Final wall motion score index appeared unchanged in patients with inducible ischaemia but it decreased at 6 months in patients with a negative stress test (P = 0.012, Table 3). In patients with ≥4 ischaemic segments the wall motion score index worsened at 6 months, whereas it improved in patients with less than four ischaemic segments (P = 0.0001, Table 3).

**Multivariate Regression Analysis**

At the multivariate regression analysis, inducible ischaemia in ≥4 segments during dobutamine stress echocardiography (odds ratio: 6.43; 95% confidence interval, 1.68–33.10), the wall motion score index at dobutamine peak infusion (odds ratio: 1.14, 95% confidence interval, 1.01–1.29) and the end-systolic index volume at discharge (odds ratio: 1.06; 95% confidence interval 0.99–1.15) were the variables independently predictive of a subsequent ≥15 mL/m² end-diastolic index volume increase.

**Heart Rate and Blood Pressure**

Mean heart rate at discharge was comparable with that observed at six-months (67 ± 12 vs 69 ± 13 bpm; P = ns). Both systolic and diastolic blood pressure values were comparable in the two time-interval observations (114 ± 18 vs 117 ± 19 and 79 ± 9 vs 80 ± 10 mmHg respectively; P = ns).

**Reproducibility of Data Analysis**

There was low variability (in per cent difference values) between left ventricular volume measurements made by a single observer at two time points (intra-observer variability) for left ventricular end-diastolic (3.6 ± 4.0%) and end-systolic (4.4 ± 3.8%) index volume calculation. When measurements were made by two independent observers (inter-observer variability), analogous per cent values of variability were obtained for left ventricular end-diastolic (4.2 ± 4.4%) and end-systolic (4.8 ± 5.1%) index volume calculation.

**Discussion**

This prospective study demonstrates that left ventricular dilation occurs at 6 months in patients with first, uncomplicated myocardial infarction and residual inducible ischaemia by pre-discharge dobutamine stress echocardiography. Moreover, a large ischaemic area and the dyssnergy score at the dobutamine peak infusion appeared independently predictive of subsequent end-diastolic volume increase ≥15 mL/m². The contractility index improved at 6 months only in patients without

inducible ischaemia and in the subgroup of patients with less than four ischaemic segments, whereas ejection fraction similarly increased in patients with- and without inducible ischaemia. Of note, left ventricular volumes, left ventricular function indexes and ACE-inhibition at discharge were comparable in patients with- and without inducible ischaemia, thus their influence on the results of this study should have been negligible.

Determinants of Remodelling

Left ventricular remodelling is a complex process characterized by changes of shape and global dimension of the cavity as a consequence of the disproportionate response to post-infarction expansion and subsequent, chronic elevation of filling pressure. Infarct size[4,5], perfusional status of the infarct-related artery[4,5], microvascular integrity[17] and a restrictive diastolic filling pattern[18,19] play an important role in determining infarct expansion and remodelling[20]. Conversely, the protective effect of the therapy with ACE-inhibitors against post-infarction left ventricle dilation has been demonstrated in case of delayed[21,22] or early administration[23], with clinical benefits in terms of survival, heart failure prevention and ischaemic events occurrence[24]. The effectiveness of ACE-inhibition in patients with large myocardial infarction and impaired left ventricular function is indisputable [22]; however, benefits of ACE-inhibition have also been demonstrated in case of preserved function and limited infarct areas[25,26]. Accordingly, several physiopathological mechanisms seem to interfere with the left ventricular remodelling process, and their determination could help for a more efficacious intervention strategy after acute myocardial infarction.

Previous Studies

The role of infarct-zone myocardial viability has been demonstrated by Bolognese et al.[10] in a population with early reperfusion by primary angioplasty. In their patients the presence of contractile reserve during low-dose dobutamine infusion identified a lower probability of diastolic and systolic left ventricular dilation at the 1 and 6 months assessment, and the protection against subsequent dilation was unrelated to the infarct area. In another study absent or reduced contractile reserve has been found to be related with left ventricular dilation, and a significant recruitment of regional wall motion during dobutamine stress test was present in patients without post-infarction remodelling[27].

The role of residual, exertional ischaemia for determining left ventricular remodelling has been already demonstrated in patients with anterior myocardial infarction and poor left ventricular function[11]. More recently, the relative influence of contractile reserve, inducible ischaemia and of their combination has been evaluated in patients with first, uncomplicated myocardial infarction[12,13]. In these studies the four possible dobutamine echocardiography responses (scar, contractile reserve, inducible ischaemia, biphasic) were considered, and a significant increase of diastolic and systolic left ventricular volumes was demonstrated in patients with biphasic response and in patients with inducible ischaemia. Similarly to the residual exertional ischaemia, these modalities of dobutamine stress test response indicate the presence of hypoperfused but still viable myocardium, where a progressive loss of viable myocytes can occur through the time, determining delayed infarct expansion and consequent long-term left ventricular dilation[15]. Recently, absence of left ventricular remodelling has been demonstrated after re-vascularization of a totally occluded infarct-related artery, whereas significant cavity dilation occurred in patients with patent, though stenosed infarct-related artery[28].

Present Study

In our study, the severity of inducible ischaemia was also considered. A greater end-systolic volume dilation has been detected in the subgroup of patients with large ischaemic area, and this result significantly distinguished these patients from those in whom residual ischaemia was ruled out by dobutamine stress test. The multivariate analysis confirmed the independent role of a large ischaemic area for determining a major end-diastolic dilation at 6 months. The wall motion score index at the peak of dobutamine infusion and the baseline end-systolic volume at discharge were the other independent predictors of significant left ventricular enlargement, indicating that infarct size, left ventricular function and residual ischaemia are main determinants of the remodelling process after myocardial infarction.

Inducible Ischaemia and Function Indexes

In a previous report the different change of diastolic- and systolic volumes over the time determined higher ejection fraction values at 1 and 6 months in patients with contractile reserve[10]. In our study, a slight increase of ejection fraction during the interval time was observed independently from the presence and the severity of inducible ischaemia. Conversely, the wall motion score index change was strictly dependent from the presence and severity of inducible ischaemia.

Limitations of the Study

This study should be considered in light of some methodological limitations. Infarct-related coronary flow status is considered one of the major determinants of post-infarction remodelling, and the long-term...
Persistence of perfusion in the infarct zone is related to the presence of hibernating or non-ischaemic myocardium depending on the entity of flow. In our study we did not perform coronary angiography as a rule because the population was representative of a wide range of clinical situations, comprehensive of small, uncomplicated myocardial infarction. In these patients a systematic pre-discharge and 6-months coronary angiography procedure would have been unethical and expensive. The purpose of the study was to evaluate the role of pre-discharge indoluble ischaemia and of its severity as detected by non-invasive methods, and dobutamine stress echocardiography has been demonstrated to be a safe and accurate diagnostic tool in this set of patients, reliably discriminating the presence of residual ischaemia after myocardial infarction[29].

The referring physician was not blinded to the dobutamine stress test result, so that a higher proportion of patients with residual ischaemia has been referred for coronary angiography and revascularization procedures by angioplasty during the interval time. This interfered with the results of the study, probably reducing the entity of left ventricular dilation in patients with restored infarct-related coronary blood flow. In spite of this limitation, a left ventricular dilation has been detected in patients with inducible ischaemia in <4 segments (IS+) and in patients with inducible ischaemia in ≥4 segments (IS++) by dobutamine stress echocardiography. See text for details.

Finally, we considered both patients with anterior and infero-posterior myocardial infarction. This could be a limitation because a greater remodelling process has been reported in patients with anterior infarction[22,23]. However, enlargement of the left ventricle also occurs in patients with infero-posterior infarction[6,9]. In our study the infarct location was considered at the multivariate analysis, but no relation with a major end-diastolic volume increase was found.

### Conclusions

After a first, uncomplicated myocardial infarction the absence of inducible ischaemia during pre-discharge dobutamine stress echocardiography indicates stable left ventricular volumes at 6 months, whereas an ischaemic response identifies patients with left ventricular diastolic and systolic remodelling. Thus, by using a rather simple diagnostic tool such as dobutamine stress test, one is able to assess the individual risk of subsequent left ventricular enlargement. This appears to be a relevant clinical information in patients with small or medium myocardial infarction, in whom a tailored anti-ischaemic and remodelling-preventing approach, either conservative or aggressive, can be planned on the basis of clinical data and dobutamine stress test response.

### References


