Different patterns of left ventricular enlargement and long-term prognosis after reperfused acute myocardial infarction

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KEYWORDS
Acute myocardial infarction; Left ventricular remodeling; Long-term prognosis

Summary
Background. — Dilation of end-systolic and end-diastolic volumes (ESV, EDV) has been used to define left ventricular remodelling after acute myocardial infarction (MI), but the prognostic significance of different enlargement patterns has not been evaluated fully.

Aim. — To analyse the evolution of left ventricular volumes and parameters of global and regional contractility and their correlations with long-term prognosis in patients treated by angioplasty in the acute phase of MI.

Methods. — Seventy-four patients (mean age 56 ± 13 years; 77% men), treated successfully by angioplasty in the acute phase of MI, were included prospectively. Significant enlargement of left ventricular volumes was defined as a greater than 20% increase between acute phase and 6-month control, assessed by contrast ventriculography. Clinical follow-up was obtained for all patients at 82 ± 19 months.

Results. — Four groups were identified based on volume evolution: Group I (n = 29, 39%; no volume enlargement); Group II (n = 8, 11%; isolated EDV enlargement); Group III (n = 10, 14%; isolated ESV enlargement); Group IV (n = 27, 36%; ESV plus EDV enlargement). Global left ventricular ejection fraction increased in Groups I (p = 0.001) and II (p = 0.037), but decreased

Abbreviations: EDV, end-diastolic volume; ESV, end-systolic volume; MI, myocardial infarction; LV, left ventricular; LVEF, left ventricular ejection fraction; RWMA, regional wall motion abnormalities.

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Introduction

Myocardial infarction (MI) remains a leading cause of mortality and morbidity in western countries. Patients who have had an MI have a 7- to 10-fold greater risk of developing heart failure compared with the normal population [1]. The development of clinically significant heart failure is frequently delayed, preceded by an asymptomatic phase during which LV volume enlargement is associated with changes in its shape [2]. The changes in ventricular topography, occurring both acutely and chronically after MI, were attributed to postinfarct remodelling in the 1990s and were identified as an important prognostic variable [3]. The prevention or reversal of LV remodelling has become one of the surrogate endpoints in the analysis of the efficacy of different therapeutic approaches, including reperfusion techniques in the acute phase of MI, pharmacological treatment or, more recently, cell replacement therapy in the subacute or ongoing MI confirmed by typical chest pain for more than 20 minutes associated with electrocardiogram changes (ST-segment elevation in at least two consecutive leads of greater than or equal to 1 mm in limb leads or 2 mm in precordial leads); admission within the first 12 hours after the onset of chest pain or within 24 hours if the pain persisted; successful angioplasty procedure defined as residual stenosis less than 30% and TIMI flow score 2 or 3; stable sinus rhythm; absence of bundle branch block;
long-term prognosis after left ventricular enlargement

Routine contrast digital ventriculography was performed immediately after the emergency angioplasty. According to the policy of our department, control coronary ventriculography was proposed at this stage to all patients treated by angioplasty in the acute phase of MI. The rationale for this approach was the search for occult restenosis of the culprit artery, which occurs frequently and can alter the functional recovery of partially infarcted myocardium [18]. Non-invasive tests for the detection of myocardial ischaemia produce disappointing results in this patient population [19,20]. This study was conducted according to the principles outlined in the Declaration of Helsinki and informed consent was obtained from all patients.

Acquisition and analysis of contrast digital ventriculograms

Contrast digital ventriculography was obtained in the acute phase and at 6-month control under the same technical conditions. A 30 mm steel sphere was placed on the lateral wall of the chest at the level of the “pig tail” catheter in the left lateral view and filmed in right oblique view at 30°. The non-ionic contrast dye was injected by a power injector (0.5 mL/kg of body mass at the rate of 10 mL/sec). Images were stored in digital form for offline analysis using dedicated software (Sanders Medical Data, San Francisco, CA, USA). The EDV and ESV were calculated using the area-length method and the RWMA index was calculated using the centerline method, as described by Sheehan et al. [21]. The software allows also the calculation of global LVEF and the contractility index in the wall opposite the necrosis. Significant enlargement of LV volume was defined as a greater than or equal to 20% increase between the acute phase and 6-month control, as proposed by Bolognese et al. [4].

Long-term clinical follow-up

Major cardiac adverse events were defined as cardiac death, heart transplantation and hospitalization for overt heart failure or life-threatening ventricular arrhythmias. After hospital discharge, patients were referred to their usual cardiologist and/or general practitioner. Follow-up data were collected by telephone interview with patients, their relatives and/or physicians.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Comparisons of numerical data within groups were carried out using Student’s t test for paired data. Comparisons between groups were performed using one-way analysis of variance and Newman-Keuls tests. Qualitative data were compared using the chi-square test with Yates’s correction or Fisher’s exact test. Event-free survival curves were constructed using the Kaplan-Meier method and statistical differences between curves were assessed by the log-rank test. All tests were two-tailed and a p-value less than 5% was considered to be significant. All computations were performed using the SAS statistical software package, release 8.02 (SAS Institute, Cary, NC, USA).

Results

Of the 90 patients included in this study, 11 (12%) were excluded because of insufficient quality of angiographic images and five (5.5%) refused control coronary angiography. The final study population consisted of 74 patients, who were predominantly men (77%) and relatively young (mean age 56 ± 13 years). Five patients had a history of previous MI and three had undergone another angioplasty procedure. The electrocardiogram location of the MI was anterior in 26 (35%) patients, inferior in 44 (59%) patients and lateral in four (6%) patients. Prehospital fibrinolysis was administered in seven (9%) patients and glycoprotein IIb/IIIa antagonists were used during or immediately after the angioplasty procedure in 12 (16%) patients. At hospital discharge, all patients received conventional treatment including aspirin and ticlopidine (100%), beta-blockers (93%), statins (57%) and angiotensin-converting enzyme inhibitors (42%).

The final study population of 74 patients were grouped as follows:

- absence of LV volume enlargement (n = 29, 39%; Group I);
- isolated enlargement of EDV (n = 8, 11%; Group II);
- isolated enlargement of ESV (n = 10, 14%; Group III);
- increase in both EDV and ESV (n = 27, 36%; Group IV).

All groups were similar in terms of their clinical variables except for the use of glycoprotein IIb/IIIa antagonists and the peak of creatine kinase release, which were borderline statistically significantly different (Table 1). Groups III and IV with ESV enlargement had a significantly higher peak creatine kinase release than Groups I and II without ESV enlargement (2995 ± 1760 IU/L vs 2032 ± 1440 IU/L, respectively; p = 0.009) and a lower use of glycoprotein IIb/IIIa inhibitors (9% vs 33%, respectively; p = 0.016).

Among the angiographic variables, total occlusion of infarct-related artery with TIMI flow grade 0–1 before angioplasty was seen more often in Groups III and IV with ESV dilation than in Groups I and II without ESV dilation (95% vs 76%, respectively; p < 0.05), while the difference in minimal lumen diameter was of borderline significance (0.05 ± 0.23 mm vs 0.18 ± 0.33 mm, respectively; p = 0.06). No difference was seen between angiographic variables immediately after angioplasty or at 6-month control except minimal luminal diameter of culprit lesion immediately after angioplasty, which was significantly higher in Group II compared with the other groups (p = 0.048; Table 2). The 6-month restenosis rate was 25% in Group I, 0% in Group II, 10% in Group III and 24% in Group IV (p = 0.50). All patients with restenosis greater than 50% were treated by another angioplasty during the control coronary angiography.

Evolution of LV volume and contractility between the acute phase and 6-month control

The evolution of LV volume and contractility between the acute phase and 6-month control is depicted in Fig. 1.
Table 1  Clinical characteristics of the patients.

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 29)</th>
<th>Group II (n = 8)</th>
<th>Group III (n = 10)</th>
<th>Group IV (n = 27)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)a</td>
<td>56.0 ± 13.4</td>
<td>53.1 ± 12.6</td>
<td>57.2 ± 10.2</td>
<td>58.0 ± 16.6</td>
<td>0.81</td>
</tr>
<tr>
<td>Men (%)</td>
<td>76</td>
<td>75</td>
<td>90</td>
<td>74</td>
<td>0.81</td>
</tr>
<tr>
<td>Location of myocardial infarction (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>34.4</td>
<td>37.5</td>
<td>30.0</td>
<td>37.0</td>
<td>0.96</td>
</tr>
<tr>
<td>Inferior</td>
<td>55.2</td>
<td>62.5</td>
<td>70.0</td>
<td>59.3</td>
<td></td>
</tr>
<tr>
<td>Lateral</td>
<td>10.3</td>
<td>0</td>
<td>0</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>Previous myocardial infarction (%)</td>
<td>0</td>
<td>12.5</td>
<td>0</td>
<td>11.1</td>
<td>0.14</td>
</tr>
<tr>
<td>Unstable angina (%)b</td>
<td>51.7</td>
<td>50.0</td>
<td>10.0</td>
<td>8.3</td>
<td>0.057</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa antagonists (%)</td>
<td>40.0</td>
<td>14.3</td>
<td>10.0</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>Fibrinolysis (%)</td>
<td>15.0</td>
<td>0</td>
<td>0</td>
<td>14.8</td>
<td>0.58</td>
</tr>
<tr>
<td>Peak of creatine kinase release (IU/L)a</td>
<td>1860 ± 1248</td>
<td>2459 ± 2117</td>
<td>2883 ± 1410</td>
<td>3037 ± 1896</td>
<td>0.054</td>
</tr>
</tbody>
</table>

a Mean ± standard deviation.
b Present in the 48 hours before index hospitalization.

When Groups I and II without ESV dilation were compared with Groups III and IV with ESV dilation, there was a borderline difference in EDV in the acute phase (122 ± 30 mL vs 108 ± 28 mL, respectively; p = 0.045), while at 6-month control this ratio was reversed, with a larger difference (124 ± 30 mL vs 148 ± 39 mL, respectively; p = 0.005).

Global LVEF increased in Group I (from 57 ± 11% to 62 ± 8%; p = 0.001) and in Group II (from 49 ± 13% to 63 ± 9%; p = 0.037), but decreased in Group III (from 65 ± 11% to 52 ± 9%; p = 0.0002) and in Group IV (from 55 ± 12% to 49 ± 11%; p = 0.019). Similar differences were observed when groups with and without ESV enlargement were compared.

RWMA indexes were similar in all groups in the acute phase. In contrast, at 6-month control, a significant recovery of RWMA was observed in Group I (from —2.90 ± 1.42

Table 2  Angiographic data during acute phase and 6-month control contrast coronary angiography.

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 29)</th>
<th>Group II (n = 8)</th>
<th>Group III (n = 10)</th>
<th>Group IV (n = 27)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before PTCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>2.97 ± 0.62</td>
<td>2.84 ± 0.65</td>
<td>2.92 ± 0.58</td>
<td>2.96 ± 0.62</td>
<td>0.97</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>0.18 ± 0.28</td>
<td>0.22 ± 0.57</td>
<td>0.00 ± 0.00</td>
<td>0.07 ± 0.27</td>
<td>0.26</td>
</tr>
<tr>
<td>Total occlusion (%)</td>
<td>66.0</td>
<td>75.0</td>
<td>100</td>
<td>85.0</td>
<td>0.09</td>
</tr>
<tr>
<td>TIMI flow (%)</td>
<td>0—1</td>
<td>72.4</td>
<td>87.5</td>
<td>100</td>
<td>0.096</td>
</tr>
<tr>
<td>Rentrop classa (%)</td>
<td>2—3</td>
<td>27.6</td>
<td>12.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>TIMI 2—3 and/or Rentrop 2—3 (%)</td>
<td>21.0</td>
<td>13.0</td>
<td>20.0</td>
<td>7.0</td>
<td>0.49</td>
</tr>
<tr>
<td>After PTCA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>3.04 ± 0.54</td>
<td>3.54 ± 0.21</td>
<td>3.15 ± 0.47</td>
<td>3.11 ± 0.65</td>
<td>0.22</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>2.45 ± 0.75</td>
<td>3.20 ± 0.33</td>
<td>2.60 ± 0.41</td>
<td>2.56 ± 0.57</td>
<td>0.048</td>
</tr>
<tr>
<td>Residual stenosis (%)</td>
<td>18.97 ± 19.2</td>
<td>9.39 ± 8.88</td>
<td>16.75 ± 7.95</td>
<td>17.0 ± 12.30</td>
<td>0.51</td>
</tr>
<tr>
<td>TIMI flow (%)</td>
<td>0—1</td>
<td>3.4</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rentrop classa (%)</td>
<td>2—3</td>
<td>96.6</td>
<td>100</td>
<td>100</td>
<td>1.00</td>
</tr>
<tr>
<td>6-month control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>2.85 ± 0.61</td>
<td>3.18 ± 0.31</td>
<td>3.06 ± 0.51</td>
<td>3.18 ± 0.68</td>
<td>0.24</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>1.85 ± 0.70</td>
<td>2.42 ± 0.75</td>
<td>2.11 ± 0.61</td>
<td>1.91 ± 0.92</td>
<td>0.33</td>
</tr>
<tr>
<td>Stenosis (%)</td>
<td>36.0 ± 19.15</td>
<td>25.0 ± 16.73</td>
<td>31.2 ± 15.46</td>
<td>40.4 ± 25.27</td>
<td>0.32</td>
</tr>
<tr>
<td>50% restenosis rate (%)</td>
<td>25.0</td>
<td>0</td>
<td>10.0</td>
<td>24.0</td>
<td>0.50</td>
</tr>
<tr>
<td>Total reocclusion rate (%)</td>
<td>0</td>
<td>0</td>
<td>7.0</td>
<td>0.56</td>
<td></td>
</tr>
</tbody>
</table>

MLD: minimal luminal diameter; PTCA: percutaneous transluminal coronary angioplasty; TIMI: thrombolysis in myocardial infarction.
a Collateral circulation assessment using Rentrop classification.
S.D. to $-1.32 \pm 1.25 \text{ S.D.}; p \leq 0.0001$) and Group II (from $-3.39 \pm 0.59 \text{ S.D. to } -1.03 \pm 0.93 \text{ S.D.; } p = 0.0002$) but not in Group III (from $-3.39 \pm 1.04 \text{ S.D. to } -2.67 \pm 1.03 \text{ S.D.; } p = 0.25$) and Group IV ($-3.01 \pm 1.14 \text{ S.D. to } -2.92 \pm 1.02 \text{ S.D.; } p = 0.68$). Compensatory hyperkinesis in the myocardial region opposite the infarction was statistically more important in the acute phase in Groups III and IV ($2.45 \pm 1.08 \text{ S.D. and } 2.06 \pm 1.47 \text{ S.D., respectively}$) compared with Groups I and II ($1.15 \pm 1.43 \text{ S.D. and } 0.87 \pm 1.23 \text{ S.D., respectively}; p = 0.001$ between groups). This difference disappeared at 6-month control.

**Long-term follow-up**

Clinical follow-up was obtained for all patients at $82 \pm 19$ months. The overall six-year clinical event rate was 30%. The total ischaemia-driven revascularization rate at 6-month control was 13.5% (14%, 13%, 0% and 15% in Groups I—IV, respectively; $p = 0.8$). Three patients died from cancer during long-term follow-up (one each in Groups I, III and IV).

During long-term follow-up, eight (11%) patients experienced a predefined major adverse cardiac event. Four patients died from cardiac causes (three from progressive heart failure and one from sudden cardiac death); all...
presented with simultaneous enlargement of ESV and EDV at six months (Group IV). Another two patients from this group presented with ventricular arrhythmias and were implanted with an implantable defibrillator. Two patients from Group III were hospitalized for worsening of dyspnoea (New York Heart Association class IV); one was treated further by heart transplantation. At six years, the major adverse cardiac event-free survival rate was significantly better in Groups I and II (100%) than in Groups III and IV (80 and 78%, respectively, \( p = 0.0039 \) vs Groups I and II). The difference in event-free survival between groups became statistically significant after three years of follow-up (Fig. 2).

**Discussion**

LV remodelling can be considered to be both an adaptive and a maladaptive process, with the adaptive component enabling the heart to maintain function in response to myocardial insult in the acute phase of cardiac injury. To date, however, there are no data to indicate when the transition from possible adaptive to maladaptive remodelling occurs or how this might be evaluated in patients [22]. Our results suggest that visualization of isolated EDV enlargement between the acute phase and six months after a reperfusion could serve as an indicator of such an adaptive mechanism. In our study, patients with isolated EDV enlargement and those with no volume enlargement had a similar evolution pattern with regard to RWMA, contractility in the opposite wall to the infarction and global LVEF; patients with this pattern had small enzymatic infarct size and normalized global LVEF at six months, associated with the recovery of RWMA in the infarct territory. Similar findings with magnetic resonance imaging have been reported by Fieno et al. [23] in an animal model of MI and by Kramer et al. [17] in a clinical study of patients treated by angioplasty in the acute phase of MI. We have also shown that a relatively small initial EDV is predictive of further remodelling — a finding that has been observed previously in larger studies [4,15]. However, in contrast to these two studies, we did not find a difference in the RWMA index in the acute phase between groups with and without remodelling; this could be related to the use of different techniques for its assessment (the semiquantitative score obtained by echocardiography and the quantitative centerline method used in our work).

More importantly, the long-term prognosis of patients with isolated EDV enlargement was excellent in our study. One explanation might be that the LV volume overload that occurs after MI increases end-diastolic stress which causes the laying down of new sarcomeres at the end of individual myocytes. Longer myocardial fibres result in increased LV end-diastolic chamber size. The resulting larger EDV can accommodate the volume overload with a smaller (or no) increase in end-diastolic pressure [24]. Unfortunately, only a few patients in our study (11%) showed such an isolated EDV enlargement. In contrast, ESV enlargement (isolated or associated with EDV enlargement), which was observed in 50% of patients in this study, is associated with a completely different evolution of regional and global LV contractility. ESV enlargement is associated at six months with a fall in global LVEF, absence of recovery of RWMA and a dramatic decrease in compensatory hyperkinesis in the opposite wall, particularly if both volumes dilate. The event-free survival at six years is significantly worse than in patients without ESV enlargement. ESV has been shown to be the variable that is most predictive of long-term prognosis, both in patients in the prereperfusion era [9] and in those treated by reperfusion therapy [4]. Moreover, significant ESV enlargement impedes functional recovery after bypass surgery, even in the presence of a substantial amount of viable myocardium [25]. A lack of recovery gives those patients a poor long-term prognosis [26]. Taken together, all these data indicate that ESV rather than EDV evolution should be used as a marker of ischaemic heart disease evolution and eventually serve as a surrogate endpoint for the comparison of different therapeutic approaches.

Despite the predominant inferior infarct location in this study, the observed LV volume enlargement rate is one of the highest compared with data published previously [4,12,15,16]. This observation can be explained in part by the low rate of prescription of angiotensin-converting enzyme inhibitors at discharge from initial hospitalization in these supposedly low-risk patients. The 36% rate of simultaneous EDV and ESV enlargement is very similar to that observed in the echo substudy of the third Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico study (GISSI-3) (19% for early dilation and 16% for late dilation), where the angiotensin-converting enzyme inhibitor lisinopril was used in 50% of patients. Additionally, our results suggest that LV remodelling should also be evaluated in patients with non-anterior infarct location.

**Study limitations**

The main limitation of our study was the small sample size, so our results need to be confirmed by a larger-scale study. Furthermore, functional patient assessment was not done during long-term follow-up, which could have given additional insights into their evolution. We did not perform a serial assessment of LV volumes and contractility, unlike Bolognese et al. [4] and Giannuzzi et al. [15]. Contrary to these two studies, in which echographic assessment of LV function was performed, our analysis was based on contrast ventriculography, which cannot be repeated serially due to its invasive character. Another limitation of our study was the use of contrast angiography for LV volume assessment. A magnetic resonance imaging approach would have been more precise but this technique was not at our disposal during the inclusion period of our study. Finally, the LV end-diastolic pressure was not recorded systematically during
the acute phase intervention, so we were unable to analyse the eventual predictive character of this variable.

**Conclusions**

Our study stresses the long-term clinical impact of ESV dilation after acute MI. ESV enlargement of 20% or greater corresponds better to the definition of LV remodelling than EDV enlargement. EDV dilation can accompany ESV dilation or be a compensatory mechanism associated with the recovery of global and regional LV contractility.

**Conflicts of interest**

None.

**References**


