Left Ventricular Remodeling After Primary Coronary Angioplasty

Patterns of Left Ventricular Dilation and Long-Term Prognostic Implications

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Background—We prospectively evaluated the prevalence, pattern, and prognostic impact of left ventricular (LV) remodeling after acute myocardial infarction (AMI) successfully treated with primary PTCA. The prevalence, course, and prognostic value of LV remodeling after primary PTCA are still to be clarified.

Methods and Results—In 284 consecutive patients with AMI treated with primary PTCA, serial echocardiographic and angiographic studies, within 24 hours (T1), at 1 (T2) and 6 months (T3) after AMI were performed. Long-term (61 ± 14 months) clinical follow-up data were collected for 98.6% patients enrolled in the study. Overall, 85 (30%) patients showed LV dilation (>20% end-diastolic volume increase) at T3 as compared with T1. Early (from T1 to T2), late (from T2 to T3), and progressive dilation patterns (from T1 to T2 to T3) were detected in 42 (15%), 41 (14%), and 36 (13%) patients, respectively. Cardiac death and combined events rate was significantly higher among patients with than among those without LV dilation (P = 0.005 and P = 0.025, respectively). The pattern of LV dilation during 6 months did not significantly affect survival. Cox survival analysis identified end-systolic volume at T1 and age as baseline predictors and end-systolic volume at T3 and age as 6-month predictors of cardiac death, respectively.

Conclusions—LV remodeling after successful PTCA occurs despite sustained patency of the infarct-related artery and preservation of regional and global LV function. LV dilation at 6 months after AMI but not the specific pattern of LV dilation is clearly associated with worse long-term clinical outcome. (Circulation. 2002;106:2351-2357.)

Key Words: myocardial infarction ■ angioplasty ■ remodeling ■ survival ■ prognosis

Left ventricular (LV) remodeling after acute myocardial infarction (AMI) is a precursor of the development of overt heart failure and is an important predictor of mortality.1,2 The benefits of primary PTCA have been ascribed to the achievement of early superior flow with significant larger myocardial salvage and improved survival compared with thrombolysis.3,4 However, the mechanism of benefit may be more complex and at least in part may be also due to sustained patency and flow in the infarct-related artery (IRA) that limits the remodeling process or at least attenuates its effects on LV shape and geometry improving prognosis.5

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However, data supporting this positive relation between IRA patency and preservation of LV geometry remain speculative. We hypothesized that LV remodeling would occur despite the persistent patency of the IRA and might influence prognosis even among patients with AMI successfully treated with primary PTCA. To test this hypothesis, we prospectively evaluated the prevalence and pattern of LV remodeling after AMI successfully treated with primary PTCA. In addition, we sought to assess early predictors of LV dilation in this subset of patients as well as its impact on long-term clinical outcome.

Methods

Patients and Study Protocol

We prospectively studied 352 patients with AMI among 421 patients consecutively referred to our catheterization laboratory for emergency PTCA between February 1995 and June 1997.

The study inclusion criteria were as follows: (1) confirmed AMI, (2) successful PTCA [defined as Thrombolysis in Myocardial Infarction trial (TIMI) flow grade 3 and residual stenosis of the IRA <30%] performed within 6 hours of the onset of symptoms or between 6 and 12 hours if there was the evidence of continuing...
ischemia, and (3) informed consent to perform echocardiography and coronary angiography at least at two prospectively defined points in time. No upper age limit was used.

Exclusion criteria were (1) IRA diameter stenosis <70% with TIMI grade 3 flow or inability to identify IRA, (2) clinical signs of congestive heart failure (CHF) or cardiogenic shock in the first week after infarction, (2) postinfarction angina, (3) significant other cardiac disease, and (4) life-limiting noncardiac disease.

Of the 352 patients initially selected for the study, 11 (3%) were excluded for death within the first month, 28 (7%) for inadequate echocardiographic image quality, and 28 patients (7%) did not adhere to follow-up protocol; 1 patient underwent heart transplantation. Two patients died within the first 6 months, but they performed an echocardiogram at 1 month and therefore were included in the study. Thus, 284 patients represent the final study group.

The study protocol was approved by the hospital’s ethics committee.

Data Analysis
Serial 2-dimensional echocardiographic examinations were performed in each patient within 24 hours at 1 and 6 months after the index infarction with commercially available machine (Aloka model SSD-830), using 2.5- and 3.5-MHz transducers.

All patients underwent coronary angiography at admission and 1 and 6 months after the index infarction. Details pertaining to acquisition and analyses of echocardiographic and angiographic data were reported elsewhere.

Definitions and Outcome Measures
LV dilation was defined as an increase in end-diastolic volume (EDV) ≥20%, based on repeated measurements in individual patients and on the upper 95% confidence limit of the intraobserver variability. According to the presence or absence of LV dilation at 6 months after infarction, patients were divided into an LV remodeling group and a no LV remodeling group, respectively.

According to the pattern of LV dilation over time, it was further classified as early (an increase of EDV ≥20% at 1-month without further increase at 6-month follow-up), late (an increase of EDV ≥20% between one and 6-month follow-up), and progressive (an increase of EDV ≥8% between baseline and 1 month, with further increase ≥8% between 1-month and 6-month follow-up). Major cardiac events were defined as cardiac death, nonfatal AMI, and hospitalization for CHF and combined events (all of the aforementioned). For purposes of survival analyses, only 1 event (the first which occurred) was tabulated for each patient. After hospital discharge, patients were referred to their private physician, who regulated therapy. No attempt was made to standardize therapy. All patients were asked to return to our outpatient clinic for evaluation by one of the investigators 6 months after discharge and annually thereafter. For those patients not returning to the clinic at the designated time, follow-up information was collected by telephone interview.

Statistical Analysis
Continuous data were expressed as mean±SD. Baseline data were compared by means of the χ² test for categoric variables and unpaired t test for continuous variables. ANOVA with the Tukey post hoc test was used to analyze repeated measures. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of different patterns of LV dilation during 6 months after infarction. Variables that were significant in univariate analyses were entered in the multivariate models.

Event-free survival curves for all major cardiac and combined events were constructed by use of the Kaplan-Meier method, and statistical differences between curves were assessed by log-rank test. A multivariate Cox proportional hazards regression model was used to identify baseline and 6-month predictors of major cardiac and combined events.

A value of P<0.05 was considered statistically significant. Statistical analyses were performed with Statistica 4.5 for Windows and SPSS 8.0 for Windows.

Results

Patient Characteristics
The clinical, angiographic, and echocardiographic characteristics of patients with (n=85) and without (n=199) LV remodeling are showed in Table 1. Patients with LV remodeling had larger enzymatic infarct size and more often had anterior infarcts and hypotension at admission. In addition, they had larger baseline end-systolic volume (ESV), higher infarct zone wall motion score index (IZWMSI), and lower ejection fraction (EF), and more frequently ACE inhibitor therapy was recommended at discharge.

Pattern of LV Remodeling
Overall, 85 patients showed LV dilation at 6 months. Early, late, and progressive dilation patterns were detected in 42 (15%), 41 (14%), and 36 (13%) patients, respectively. Baseline characteristics of patients with different patterns of LV dilation are presented in Table 2.

Angiographic Results
There was no significant difference in the percentage of stenting between patients with and those without LV remodeling (57% versus 49% respectively; P=NS) as well as among patients with different LV dilation patterns (early:
Independent predictors of different patterns of LV dilation during 6-month follow-up are listed in Table 3. Relatively small initial EDV and relatively high IZWMSI independently predicted early LV dilation. Independent predictors of late dilation were high peak creatine kinase (CK) value and the presence of multivessel coronary artery disease (CAD). Independent predictors of progressive dilation were again relatively small EDV and high IZWMSI, along with high peak CK values.

Finally, relatively small initial EDV, high IZWMSI, high peak CK value, and multivessel CAD were all independent predictors of LV remodeling at 6 months.

**Changes in LV Size and Regional and Global Functions Over Time**
Changes in EDV, ESV, EF, and IZWMSI in the total study population are shown in Figure 1 (a and b).

### Table 3. Independent Predictors of Different Patterns of LV Dilation During 6 Months and LV Remodeling at 6 Months After Myocardial Infarction

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Early Dilation (n=42)</th>
<th>Late Dilation (n=41)</th>
<th>Progressive Dilation (n=36)</th>
<th>LV Remodeling at 6 mo (n=85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV at baseline</td>
<td>−0.27, 0.973 (0.962–0.987), &lt;0.0001</td>
<td>...</td>
<td>−0.02, 0.977 (0.964–0.990), 0.0007</td>
<td>−0.01, 0.987 (0.978–0.995), 0.003</td>
</tr>
<tr>
<td>IZWMSI at baseline</td>
<td>1.05, 2.85 (1.12–7.26), 0.028</td>
<td>...</td>
<td>1.34, 3.828 (1.17–12.47), 0.026</td>
<td>1.16, 3.18 (1.35–7.50), 0.008</td>
</tr>
<tr>
<td>Peak CK value</td>
<td>...</td>
<td>0.0002, 1.0002 (1.0001–1.0003), 0.006</td>
<td>0.0002, 1.0002 (1.0001–1.0004), 0.002</td>
<td>0.0003, 1.0003 (1.0001–1.0004), 0.001</td>
</tr>
<tr>
<td>Extent of the CAD</td>
<td>...</td>
<td>0.70, 1.730 (1.150–2.603), 0.008</td>
<td>...</td>
<td>0.41, 1.502 (1.034–2.182), 0.033</td>
</tr>
</tbody>
</table>

Variables included in multivariate models are age, history of diabetes and hypertension, infarct location, peak CK value, extent of coronary artery disease and the presence of significant collateral circulation on initial angiogram, symptoms-to-balloon time and door-to-balloon time, and baseline EDV, IZWMSI, and EF.

Data in cells are presented as B value, relative risk with 95% confidence interval, and P value, respectively.
During 6 months after infarction, EDV and EF increased (from 124±36 to 130±46 mL, P<0.0055, and from 43±10 to 51±13%, P<0.0001, respectively), whereas ESV and IZWMSI decreased (from 71±28 to 67±40 mL, P=0.023 and from 2.3±0.5 to 1.8±0.7, P<0.0001, respectively).

Changes of the same parameters of LV function in patients with different patterns of LV dilation are shown in Figure 2 (a through d).

Initial EDV was similar in patients with early and progressive dilation and for both groups was lower as compared with the late dilation group. At 6 months, EDV was higher as compared with baseline values within all groups, and patients with progressive dilation had the highest EDV, followed by those with late and early dilation, respectively.

Initial ESV was the smallest in patients with early dilation, followed by progressive and late dilation groups. Six-month ESV in the early and late dilation groups was similar to baseline values.

Baseline EF was lower in patients with progressive dilation as compared with the two other groups. It increased from baseline to 1 month only in the late dilation group. No change of EF was noted within early and progressive dilation groups. Six-month EF was lower in the progressive dilation group than in the other two groups.

Baseline IZWMSI was higher in patients with progressive dilation than in the other two groups. It decreased at 1 month in all groups and remained unchanged thereafter. The highest 6-month IZWMSI was observed in the progressive dilation group.

LV Dilation and Long-Term Clinical Outcome
Clinical follow-up data were collected for all but 4 patients (98.6%) enrolled in the study. The mean length of clinical follow-up was 61±14 months (range 2 to 81). During this period, 15 (5%) patients had nonfatal AMI, 13 (5%) were hospitalized for overt CHF, and 36 (13%) died. Of the deaths, 22 (8%) were cardiac. Overall, there were 49 (17%) major cardiac events (cardiac death, nonfatal AMI, or hospitalization for CHF). Additional revascularization procedures were performed in 47 (17%) patients.

Overall, cardiac death and hospitalization for CHF were significantly higher in patients with LV remodeling as compared with those without (Table 4). According to the Kaplan-Meier method, patients with LV remodeling at 6 months had a higher 5-year cardiac mortality rate (14% versus 5%, P=0.005, by log rank) and cumulative 5-year combined event-rate (18% versus 10%, P=0.025, by log-rank) than those without (Figure 3).

Major cardiac event rate was not significantly different among groups with different patterns of LV dilation (Table 4). According to the Kaplan-Meier method, the pattern of LV dilation did not significantly affect the cardiac mortality rate (P=0.60, by log rank) as well as combined event rate (P=0.66, by log rank) (Figure 4).

At Cox analysis baseline ESV and age were identified as baseline predictors for cardiac death (P=0.02; relative risk
The major findings of the present study are the following: (1) LV dilation occurs after primary PTCA in patients with AMI despite the persistence of patency of the IRA; (2) post-AMI LV dilation still retains its prognostic significance in this setting; (3) the remodeling process is heterogeneous, but the specific pattern of LV dilation does not affect independently the clinical outcome; and (4) as for the thrombolytic setting, LV remodeling after primary PTCA can be predicted by simple demographic and echocardiographic variables.

LV Dilation After Successful Primary PTCA

The favorable effects of early and sustained IRA patency on LV remodeling are suggested by several studies,4.10,11 even if the magnitude of its impact on late death is less clear.3 In light of these results, one could expect a low prevalence of remodeling process after mechanical reperfusion. Conversely, the present study showed that a significant LV dilation occurred in a relevant proportion (30%) of patients with AMI successfully treated with primary PTCA, very close to the 34% observed in thrombolysed patients.12 The finding is even more striking since our series represents a relatively low-risk population treated with a high late IRA patency rate. These results highlight once more that the concept of optimal reperfusion must include not only early and sustained epicardial patency but also optimal microvascular flow and tissue reperfusion.13,14 Furthermore, other factors different from infarct size and IRA patency may play a role in triggering post-MI LV remodeling.

We found that similar to previous studies on thrombolysed patients,12 LV remodeling after AMI treated with primary PTCA occurs despite spontaneous recovery of regional and global LV function and is particularly evident in larger infarcts. Finally, we found a wide heterogeneity of the remodeling process with different time courses and specific patterns that can be easily identified by serial echocardiographic examinations. Interestingly, the prevalence of severe early or late LV dilation was very similar to that observed in thrombolysed patients (14% versus 19%, and 13% versus 16%, respectively).12 Thus, it appears that the patterns of post-AMI LV dilation are independent of which reperfusion strategy has been used.

Prediction of LV Dilation and Heterogeneity of Post-MI LV Remodeling: Mechanistic Insights

Early identification of patients at risk of LV dilation may have important therapeutic implications. Infarct size,15,16 anterior infarct location,17 perfusional status of the IRA,18 CHF on admission,19 and restrictive pattern of LV filling8,20,21 have been identified as major predictors of LV dilation after AMI. Our data revealed that after successful PTCA, early but also progressive dilation can be expected in patients with large infarction but relatively small initial EDV.

The analysis of serial changes in LV volumes and function as well as of predictors of different patterns of LV dilation provides some speculative mechanistic insights. Both base-
line relatively small EDV and high IZWMSI were the only independent predictors of severe early dilation, which would be then expected to occur in patients with large functional infarct size that initially does not significantly compromise the overall cavity dimensions and function. These patients showed the smallest ventricular enlargement, associated with favorable changes of other parameters of LV function over time, confirming the adaptive compensatory nature of early remodeling that is not necessarily progressive.

Patients with progressive dilation did not show improvement of EF throughout follow-up, being the lowest as compared with the two other groups, and they reached the highest ventricular volumes at 6 months. In addition, although a slight improvement of IZWMSI was noted at 1 month, it remained the highest among the 3 groups, indicating the most severe myocardial damage that acts as a continuous stimulus for remodeling.

Interestingly, late dilation was predicted by high peak CK values and multivessel CAD and occurred despite a significant improvement of LV function over time. These findings suggest that late dilation may be triggered by factors different from initial infarct size, such as progressive ischemia.

LV Remodeling After Primary PTCA and Long-Term Clinical Outcome
We used two methods of analyzing prognostic implications of LV dilation: first, by looking at the occurrence of significant (>20%) LV dilation in a binary fashion, and second, by looking at the potential prognostic implications of different patterns of LV dilation observed during 6 months after infarction.

Patients with significant LV dilation at 6 months after infarction had a worse long-term clinical outcome. On the other hand, no significant interaction between specific patterns of LV dilation and clinical outcome was found. Therefore, it appears that LV dilation at 6 months after successful PTCA indicates poor prognosis regardless of the specific remodeling pattern observed.

Finally, in agreement with pioneering studies performed in the prerereperfusion era, age and initial ESV still retain the early and late prognostic significance even in patients successfully treated with PTCA.

Clinical Implications
There are some important clinical implications of this study. First, patients successfully treated with primary PTCA and relatively small initial EDV should not be considered at low risk for LV remodeling. These patients should be carefully evaluated, and therapeutic measures aimed to prevent LV remodeling should not be neglected or postponed.

Second, the simple observation that the LV is significantly dilated or not at 6 months after the index AMI carries almost all prognostic power in this patient population. Although progressive dilation appears to be associated with the largest ventricle size and with the most severe deterioration of LV function, long-term prognosis of these patients does not differ from patients with early or late dilation of comparable extent. Thus, assessment of specific patterns of LV dilation is less important for risk stratification in individual patients than simple measuring of LV volumes at baseline and after 6 months.

Finally, as for thrombolysed patients, simple demographic and echocardiographic variables can be used to identify patients treated with primary PTCA at risk for postinfarction LV remodeling.

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