Long-term recovery of left ventricular function after primary angioplasty for acute myocardial infarction

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Aims To investigate changes in left ventricular function in the first 6 months after acute myocardial infarction treated with primary angioplasty. To assess clinical variables, associated with recovery of left ventricular function after acute myocardial infarction.

Methods Changes in left ventricular function were studied in 600 consecutive patients with acute myocardial infarction, all treated with primary angioplasty. Left ventricular ejection fraction was measured by radionuclide ventriculography in survivors at day 4 and after 6 months. Patients with a recurrent myocardial infarction within the 6 months were excluded.

Results Successful reperfusion (TIMI 3 flow) by primary angioplasty was achieved in 89% of patients. The mean ejection fraction at discharge was 43·7% ± 11·4, whereas the mean ejection fraction after 6 months was 46·3% ± 11·5 (P<0·01). During the 6 months, the mean relative improvement in left ventricular ejection fraction was 6%. An improvement in left ventricular function was observed in 48% of the patients; 25% of the patients had a decrease, whereas in the remaining patients there was no change.

After univariate and multivariate analysis, an anterior infarction location, an ejection fraction at discharge ≤40% and single-vessel disease were significant predictors of left ventricular improvement during the 6 months.

Conclusions After acute myocardial infarction treated with primary angioplasty there was a significant recovery of left ventricular function during the first 6 months after the infarction. An anterior myocardial infarction, single-vessel coronary artery disease, and an initially depressed left ventricular function were independently associated with recovery of left ventricular function. Multivessel disease was associated with absence of functional recovery. Additional studies, investigating complete revascularization are needed, as this approach may potentially improve long-term left ventricular function.

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Key Words: Acute myocardial infarction, primary angioplasty, left ventricular ejection fraction, stunning.

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Introduction

In survivors of acute myocardial infarction, left ventricular function is the most important predictor of long-term prognosis[1,2]. However, left ventricular function may change during the months after myocardial infarction, by mechanisms such as remodelling and gradual relief of stunning[3–7]. Determinants of a change in left ventricular function may have prognostic significance, give insight into the mechanisms of the changes in ventricular function, and may have important implications for the therapeutic approach. Data on changes of left ventricular function in the first 6 months after myocardial infarction, in patients treated with primary angioplasty are limited.

To identify predictors of left ventricular functional recovery, a large group of survivors of acute myocardial infarction, who were all treated with primary angioplasty, were studied. All patients had serial measurements of left ventricular ejection fraction by radionuclide ventriculography, both at day 4 and 6 months after the index infarction.
Methods

Patients

All patients were included prospectively from January 1994 to January 1998, with the inclusion and exclusion criteria as described previously for our primary angioplasty vs thrombolysis trial\(^8,9\). In short, they had symptoms of acute myocardial infarction and ST segment elevations, with presentation within 6 h after onset of symptoms (or between 6 and 24 h if there was evidence of continuing ischaemia). Both patients who presented at the emergency department of our own hospital and patients referred to our angioplasty centre from community hospitals were included. All patients were treated with primary angioplasty immediately after admission. From each patient, baseline characteristics, coronary anatomy and time to reperfusion were recorded. Only patients who died or had a recurrent infarction within 6 months were excluded in the present analysis. All patients received aspirin, nitroglycerin and heparin intravenously. Beta-blockers were given unless contraindications were present and ACE inhibitors were started in patients with clinical signs or symptoms of a large infarction and/or heart failure, in accordance with current guidelines of therapy of acute myocardial infarction.

Radionuclide ventriculography

Radionuclide ventriculography was performed, according to the study protocol, on day 4 or day 5 after myocardial infarction and at the 6 month follow-up. Measurements were performed by the multiple-gated equilibrium method after in vivo labelling of red blood cells with \(^{99m}\)Tc pertechnetate. A \(\gamma\)-camera (General Electric, Milwaukee, WI, U.S.A.) was used. The global left ventricular ejection fraction was calculated with the PAGE program (version 2.3). The standard deviation of the difference between repeat measurements obtained by this technique is 1-2%. A significant change in left ventricular ejection fraction was therefore defined as an increase or decrease of more than 2-4%. A left ventricular ejection fraction \(\leq 40\%\) was regarded as clinically significant depressed left ventricular function. Left ventricular ejection fraction difference was defined as \(\text{LVEF}_{\text{6 month}} - \text{LVEF}_{\text{discharge}} = \Delta \text{LVEF}\). A relative left ventricular ejection fraction difference was calculated: \(\Delta \text{LVEF}/\text{LVEF}_{\text{discharge}}\). This was used as the dependent variable in a multivariate model. By this method, the discharge left ventricular ejection fraction was taken into account in the analysis.

Statistical analysis

In the presentation of the data, continuous variables are given as mean \(\pm\text{SD}\), whereas discrete variables are given as absolute values and percents. A value of \(P<0.05\) was considered significant. Multivariate analysis was performed by fitting a linear regression model. In the multivariate analysis, adjustments were made for differences in age (continuous variable), gender, infarct location (anterior vs non-anterior), time from symptom-onset to first balloon inflation, previous infarction, multivessel disease and enzymatic infarct size.

Results

Study population

During the 4 year study period, 785 patients with acute myocardial infarction were treated with primary angioplasty in our centre. Within the 6-month follow-up period the mortality rate of this cohort was 5% (n=41 patients). Of the survivors, in 124 patients (15%) no paired measurements of left ventricular ejection fraction were performed. Most of these patients (n=111, 90%) were referred from other hospitals, and returned to the referring hospital immediately after primary PTCA, before left ventricular ejection fraction measurement was performed. Twenty patients (3%) had a recurrent infarction during the 6 months follow-up and were excluded. The remaining 600 patients were included in the final analysis. Their clinical characteristics are shown in Table 1. The median total ischaemic time was 200 min.

Left ventricular function at discharge

The mean left ventricular ejection fraction at discharge was 43-7% (SD 11%). Two hundred and fifteen patients (36%) had a LVEF\(_{\text{discharge}} \leq 40\%\). Patients with a low LVEF\(_{\text{discharge}}\) (\(\leq 40\%\)) were compared to those with a preserved LVEF\(_{\text{discharge}}\) (>40%). The clinical characteristics of these two groups are shown in Table 2. The mean left ventricular ejection fraction in the group with

Table 1 Clinical characteristics of 600 patients with myocardial infarction treated with primary angioplasty

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n or mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>600</td>
</tr>
<tr>
<td>Male</td>
<td>479 (80%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 (± 11)</td>
</tr>
<tr>
<td>Anterior infarct location</td>
<td>305 (51%)</td>
</tr>
<tr>
<td>Previous infarction</td>
<td>66 (11%)</td>
</tr>
<tr>
<td>Single vessel disease</td>
<td>286 (48%)</td>
</tr>
<tr>
<td>TIMI flow grade 3 after PTCA</td>
<td>515 (89%)</td>
</tr>
<tr>
<td>Enzymatic infarct size (LDH, U l(^{-1}))</td>
<td>1237 (± 1005)</td>
</tr>
<tr>
<td>ACE inhibitor at discharge</td>
<td>266 (44%)</td>
</tr>
</tbody>
</table>

TIMI=Thrombolysis In Myocardial Infarction; ACE=angiotensin converting enzyme; LDH=lactate dehydrogenase.
left ventricular ejection fraction ≤40% was 31.5%. Patients with an anterior infarct location had an increased risk of a low ejection fraction, relative risk 3.7 (95% confidence interval 2.7–4.9). Mean enzymatic infarct size was significantly higher in the group with a low ejection fraction. As expected, patients with a low left ventricular ejection fraction more often used an ACE inhibitor at discharge. Other clinical characteristics were comparable between the two groups.

**Left ventricular function after 6 months**

After 6 months, the mean left ventricular ejection fraction was 46.3% (SD 11.5), whereas 164 patients (27%) had an ejection fraction ≤40%. Again, patients with a low left ventricular ejection fraction (≤40%) were compared to those with a left ventricular ejection fraction higher than 40% (Table 3). Apart from the characteristics already found at discharge, single-vessel disease and TIMI flow 3 were significantly associated with a preserved left ventricular function after 6 months and after primary angioplasty, respectively.

**Changes in left ventricular function during the 6 months**

The mean left ventricular ejection fraction increased from 43.7% (SD 11.3) at discharge, to 46.3% (SD 11.5%) at 6 months (P<0.01). The mean relative improvement in the left ventricular ejection fraction was 6%. No significant change in left ventricular ejection fraction was observed in 164 patients (27%), an increase in left ventricular ejection fraction was found in almost half of the patients (289 patients, 48%), whereas in 147 patients (25%) there was a decrease in left ventricular ejection fraction. At discharge, 215 patients (36%) had a low left ventricular ejection fraction (≤40%) whereas after 6 months only 164 patients (27%) had a low left ventricular ejection fraction (Fig. 1, P<0.05).

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**Table 2** Differences between patients with low (LVEF ≤40%) and those with preserved (LVEF >40%) left ventricular function at discharge

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LVEF_{discharge} ≤40% n=215</th>
<th>LVEF_{discharge} &gt;40% n=385</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>174 (81%)</td>
<td>305 (79%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 (± 11)</td>
<td>58 (± 12)</td>
</tr>
<tr>
<td>Anterior infarct location</td>
<td>170 (80%)</td>
<td>135 (35%)</td>
</tr>
<tr>
<td>Previous infarction</td>
<td>23 (11%)</td>
<td>43 (11%)</td>
</tr>
<tr>
<td>Single vessel disease</td>
<td>103 (48%)</td>
<td>203 (47%)</td>
</tr>
<tr>
<td>TIMI flow grade 3 after PTCA</td>
<td>173 (85%)</td>
<td>342 (91%)</td>
</tr>
<tr>
<td>Median ischaemic time (min)</td>
<td>195</td>
<td>208</td>
</tr>
<tr>
<td>Enzymatic infarct size (LDHQ72, U . l$^{-1}$)</td>
<td>1898 (± 1141)</td>
<td>859 (± 672)*</td>
</tr>
<tr>
<td>ACE inhibitor at discharge</td>
<td>174 (81%)</td>
<td>92 (24%)*</td>
</tr>
</tbody>
</table>

LVEF=left ventricular ejection fraction; TIMI=Thrombolysis In Myocardial Infarction; ACE=angiotensin converting enzyme; LDHQ72=cumulative release of lactate dehydrogenase.

**Table 3** Differences between patients with low (LVEF ≤40%) and those with preserved (LVEF >40%) left ventricular function 6 months after myocardial infarction

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LVEF_{6 months} ≤40% n=164</th>
<th>LVEF_{6 months} &gt;40% n=436</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>135 (82%)</td>
<td>344 (79%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58 (± 11)</td>
<td>58 (± 12)</td>
</tr>
<tr>
<td>Anterior infarct location</td>
<td>120 (73%)</td>
<td>185 (42%)*</td>
</tr>
<tr>
<td>Previous infarction</td>
<td>24 (15%)</td>
<td>42 (10%)</td>
</tr>
<tr>
<td>Single vessel disease</td>
<td>66 (40%)</td>
<td>220 (51%)†</td>
</tr>
<tr>
<td>TIMI flow grade 3 after PTCA</td>
<td>128 (78%)</td>
<td>387 (89%)*</td>
</tr>
<tr>
<td>Median ischaemic time (min)</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Enzymatic infarct size (LDHQ72, U . l$^{-1}$)</td>
<td>2040 (± 1201)</td>
<td>924 (± 692)*</td>
</tr>
<tr>
<td>ACE inhibitor at discharge</td>
<td>126 (77%)</td>
<td>140 (32%)*</td>
</tr>
</tbody>
</table>

LVEF=left ventricular ejection fraction; TIMI=Thrombolysis In Myocardial Infarction; ACE=angiotensin converting enzyme.

*P<0.01, †P<0.05.
Separate analysis for patients with LVEF
\(\leq 40\%\) showed that in these patients only single-vessel
disease remained significantly associated with an
improvement in left ventricular function after multivariate
analysis. In the 103 patients with LVEF
\(\leq 40\%\) and single-vessel disease, the relative increase in left
ventricular ejection fraction was 20\%. In patients with
LVEF
\(>40\%\), single-vessel disease (relative left
ventricular ejection fraction increase 4-9\%) and an
anterior location (relative left ventricular ejection fraction
increase 6-2\%) were significantly associated with an
increase in left ventricular ejection fraction after
multivariate analysis.

There was no significant difference in the relative
increase of left ventricular ejection fraction between
patients with ischaemic time \(<6\ h\ (6-1)\) and patients with
ischaemic time \(>6\ h\ (5-2)\).

**Discussion**

In our study of patients who were treated with primary
angioplasty for acute myocardial infarction, almost 50%
had a significant improvement in left ventricular func-
tion after 6 months. The mean left ventricular ejection
fraction increased from 43.7\% at discharge, to 46-3\% at
6 months \((P<0.01)\). This improvement is in contrast to a
study assessing systolic left ventricular function after
thrombolytic therapy\(^{10}\). An anterior infarction,
single-vessel disease and a low \((\leq 40\%)\) LVEF
\(\text{discharge}\) were independent predictors of improvement of left
ventricular function in our study population.

**Predictors and potential mechanisms of left
ventricular improvement**

After acute myocardial infarction, the earliest change is
expansion of the infarcted zone. In the period thereafter,
compensatory hypertrophy of the non-infarcted seg-
ments leads to stable enlargement of the ventricle\(^{11-14}\).
The main factor affecting this remodelling process is
infarct size\(^{15,16}\). In patients treated with reperfusion
therapy (either thrombolytic therapy or angioplasty),
infarct size is reduced when patency is achieved within
the period of myocardial salvage, in particular if patency
is also complete and sustained\(^{17-19}\). Reperfusion not
only limits infarct size\(^{17}\), but also preserves viable
myocardium in the infarct zone\(^{18,20}\). However, in this
potentially viable myocardium, despite restoration of
perfusion, myocardial function can be depressed for a
long period (stunning)\(^{17,21}\). This reversible impairment of
left ventricular function has been demonstrated, in
particular, in patients with anterior infarction\(^{22}\). This is
in agreement with our findings, that an anterior infar-
ction lent itself to an improvement in left ventricular
function during the months after the infarction.
Hibernation is another cause of reversible left ventricular dysfunction. Revascularization or optimal antiischaemic pharmacotherapy may cause a reversal of hibernation, and consequently an improvement in left ventricular ejection fraction. In our study, all patients were treated with primary angioplasty, which achieves early and complete patency in a large number of patients. Furthermore, the majority of patients were treated within the time window of myocardial salvage. The relatively high percentage of patients with an increase in left ventricular function between day 4 and 6 months could, in part, be a reflection of this rapid and complete reperfusion.

A low left ventricular ejection fraction at discharge was a significant predictor of left ventricular ejection fraction improvement in our study. Possibly, stunning is prolonged in larger infarctions, while in smaller infarctions this has already (partially) resolved when left ventricular ejection fraction measurement at day 4 is performed.

The presence of single-vessel disease was also a strong predictor of left ventricular improvement in our analysis, in particular in patients with a low left ventricular ejection fraction at discharge. Patients with multivessel disease have more extensive coronary artery disease and probably a limited collateral blood flow. This may be associated with prolonged or profound myocardial ischaemia, causing more severe hibernation. Studies investigating the influence of complete revascularization are therefore needed to demonstrate whether revascularization of potentially ischaemic myocardium distant from the infarct size is of clinical benefit.

There was only a non-significant association between a shorter ischaemic time and better recovery of left ventricular function.

**Deterioration of left ventricular function**

There was deterioration of left ventricular function between day 4 and 6 months in 25% of patients. This may be due to hyperkinesia of the non-infarcted area in the acute phase, further loss of myocardial function during the 6 months, or a combination of these mechanisms. To distinguish between these two causes, regional wall motion analyses or simultaneous measurements of flow and function should be performed. Silent restenosis of the infarct-related artery during the 6 months follow-up period could have been a cause of deterioration of left ventricular function, although the incidence of restenosis after primary angioplasty is not very high. However, since we did not perform coronary angiography after 6 months routinely in our study population, we cannot rule out that restenosis or new stenosis had occurred.

**Study limitations**

In our study early left ventricular function was measured 4 days after primary angioplasty, whereas no routine assessment of left ventricular function was undertaken before or immediately after angioplasty. Since an improvement in left ventricular function may have occurred during the first 4 days, the observed improvement in left ventricular ejection fraction may have under-estimated the true benefit.

In our study population, we measured only serial left ventricular ejection fraction. We had no data on diastolic left ventricular dysfunction, or left ventricular dimensions, including end-diastolic or end-systolic volumes. This could have provided additional information on the remodelling process. Furthermore, follow-up left ventricular ejection fraction was performed at 6 months, and some reports have demonstrated ongoing remodeling beyond this period. Moreover, we had no data on the extent of stunned but functionally viable myocardium in the infarct zone, as can be estimated by dobutamine stress echocardiography. Also we did not study the possible influence of collaterals on recovery of left ventricular function.

It was not possible to evaluate the exact role of drugs, in particular ACE inhibitors, in our analysis. ACE inhibitors were given mainly to patients with poor left ventricular ejection fraction at discharge, introducing selection bias. Randomized trials have demonstrated the beneficial role of ACE inhibitors, and it is indeed possible that the significant increase in left ventricular ejection fraction in patients with low left ventricular ejection fraction at discharge was, in part, a result of use of ACE inhibitors.

Since we had no follow-up data after 6 months, it was not possible to evaluate whether a change in left ventricular function is also associated with a change in prognosis. Future follow-up studies should be performed to evaluate this.

**Conclusions and clinical implications**

Recovery of left ventricular function is seen in almost half the patients with acute myocardial infarction treated with primary angioplasty, whereas in 25% a deterioration is observed. Anterior infarct location, low left ventricular ejection fraction at discharge and single-vessel disease are associated with left ventricular functional recovery. In particular, patients with a poor left ventricular function at discharge and single-vessel disease have pronounced ventricular function recovery after 6 months. Multivessel disease with the potential of additional myocardial ischaemia, is associated with a decrease in left ventricular ejection fraction. As patients with coronary artery disease and left ventricular dysfunction with non-revascularized viable myocardium may benefit from revascularization, a trial with a more aggressive approach to myocardial ischaemia, by complete revascularization in the first months after myocardial infarction, is needed.
References


