Late Cardiac Remodeling After Primary Percutaneous Coronary Intervention
– Five-Year Cardiac Magnetic Resonance Imaging Follow-up –
Tirza Springeling, MD; Sharon W. Kirschbaum, MD, PhD; Alexia Rossi, MD; Timo Baks, MD, PhD; Yusuf Karamermer, MD; Carl Schulz, MD, PhD; Mohammed Ouhlous, MD, PhD; Dirk J. Duncker, MD, PhD; Adriaan Moelker, MD, PhD; Gabriel P. Krestin, MD, PhD; Patrick W.J.C. Serruys, MD, PhD; Pim de Feyter, MD, PhD; Robert-Jan M. van Geuns, MD, PhD

Background: Primary percutaneous coronary intervention (PPCI) preserves function and improves survival. The late effects of PPCI on left ventricular remodeling, however, have not yet been investigated on cardiac magnetic resonance imaging (CMRI).

Methods and Results: Twenty-five patients with acute myocardial infarction (AMI) treated with PPCI underwent CMRI within 10 days, at 4 months and at 5 years. Left ventricular ejection fraction (LVEF), end-diastolic volume (EDV) and end-systolic volume were quantified on cine images. Infarct mass and transmural extent of infarction were quantified on contrast-enhanced imaging. In all patients EDV increased significantly in the early phase (192±40 ml to 211±49 ml, P≤0.01) and LVEF improved significantly (42±9% to 46±9%, P=0.02). In the late phase (>4 months) no significant changes were observed (LVEF 44±9%, P=0.07; EDV 216±68 ml, P=0.38). Three different groups could be identified. One-third (32%) had no dilatation at all; one-third (32%) had limited dilatation at 4 months without progression later; and 36% had progressive dilatation both at 4 months and at late follow-up. This third group had an average increase in EDV of 20% in the acute phase followed by an additional 13%. The strongest predictor for progressive dilatation was infarct mass.

Conclusions: Even in the era of PPCI for AMI followed by optimal medical therapy, one-third of patients had progressive dilatation, which was best predicted by infarct mass. (Circ J 2013; 77: 81–88)

Key Words: Acute myocardial infarction; Cardiac magnetic resonance imaging; Left ventricular function; Long-term follow-up; Primary percutaneous coronary intervention
Methods

The present study consisted of 40 patients presenting with an acute ST-segment elevation myocardial infarction (STEMI), who were prospectively studied. The patients were recruited between January 2002 and December 2006. The diagnosis of STEMI was based on clinical symptoms, ST-segment elevation on the electrocardiogram and angiographically demonstrated occlusion of one of the coronary arteries. The culprit lesion was successfully treated by PPCI and all patients received a drug-eluting stent within 12 h after onset of symptoms (mean 3 h). Successful PPCI was defined as stent implantation with a consent to the study protocol, which was approved by the medical ethics committee of the Erasmus MC, Rotterdam, the Netherlands.

Study Endpoints

The primary endpoint was the proportion of patients with progressive left ventricular dilatation between 4 months and 5 years after AMI despite successful PPCI. Secondary endpoints included global and regional function.

CMRI Protocol

CMRI was performed on a 1.5-Tesla clinical scanner (Signa CV/I, GE Medical systems, Milwaukee, WI, USA) using a dedicated 8-channel cardiac coil. Patients were positioned in the supine position. Repeated breath holds and gating by electrocardiogram were applied to minimize the influence of cardiac and respiratory motion on data collection.

Cine CMRI was performed using a steady-state free-precession technique (FIESTA, GE Medical System). Imaging parameters were as follows: 24 temporal phases per slice; field of view 36–40×28–36 cm; matrix size 160–192×128–192; repetition time 3.2–3.7 ms; number of average minimum of 0.50; time to echo 1.4 ms; flip angle 45°; 12 views per segment. To cover the entire left ventricle, 9–12 consecutive slices of 8.0 mm with a gap of 2.0 mm were planned in the short axis view perpendicular to the horizontal (4-chamber) and vertical long axis (2-chamber) of the left ventricle using standard techniques as described previously.4

First-pass perfusion imaging was performed at rest during 30–50 consecutive heartbeats immediately after injection of gadolinium DTPA (0.1 mmol/kg at 3 ml/s) into an antecubital vein followed by 15 ml of saline at 3 ml/s. A special presaturation scheme with a notched excitation followed by segmented gradient echo/echo planar readout was used, as described previously.4 Delayed enhancement imaging was performed with a gated breath hold T1-inversion recovery gradient-echo sequence with a minimum of 10 min after infusion of gadolinium DTPA (total of 0.2 mmol/kg i.v.) as described previously.4

CMRI Data Analysis and Definitions

All images were transferred to a Microsoft Windows™-based personal computer for analysis using the CAAS-MRV program (version 3.2.1; Pie Medical Imaging, Maastricht, The Netherlands). Cine, first-pass perfusion, and delayed enhancement images were acquired during the same imaging session and matched using the same slice position. Registration of follow-up and baseline cine and delayed enhancement images was achieved using anatomic landmarks such as papillary muscle and right ventricular insertion sites. Left ventricular volumes and left ventricular ejection fraction (LVEF) were analyzed using the additional information of the long axis to limit the extent of volume at the base and at the apex of the heart. Details of this analysis method have been given previously.14 Papillary muscle and trabeculation were considered as being part of the blood pool volume.

The patients were categorized according to the individual course of left ventricular end-diastolic dilatation (Figure 1). End-diastolic volume (EDV) dilatation was considered as progressive dilatation if the increase was >3%. If the EDV increased >3% on each subsequent CMRI the patient was assigned to the group with progressive dilatation. The second group, limited dilatation, consisted of patients in whom the EDV increased >3% until 4 months but without further increase thereafter. The third group, no dilatation, consisted of patients with <3% increase of the EDV until 4 months.

Segmental wall thickening (SWT) was calculated by sub-

---

Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M)</td>
<td>19 (76)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52±11</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>1.9±0.4</td>
</tr>
<tr>
<td>Time to balloon (min)</td>
<td>180±89</td>
</tr>
<tr>
<td>Creatinine kinase. (U/L)</td>
<td>3,947±1,965</td>
</tr>
<tr>
<td>Troponin T max.</td>
<td>8.47±5.5</td>
</tr>
</tbody>
</table>

Risk factors:
- Hypertension: 5 (20)
- Diabetes mellitus: 2 (8)
- Hypercholesterolemia: 6 (24)
- Smoking: 15 (60)
- Family history: 12 (48)

Medication at discharge:
- Aspirin: 25 (100)
- Clopidogrel: 25 (100)
- β-blockade: 23 (92)
- Statins: 24 (96)
- ACE inhibitors: 14 (56)
- AT-II antagonist: 5 (20)

Infarct location:
- Anterior: 19 (76)
- Lateral: 2 (8)
- Inferior: 4 (16)

Data given as mean±SD or n (%).

ACE, angiotensin-converting enzyme; AT-II, Angiotensin-2.
tracting end-diastolic wall thickness (EDWT) from end-systolic wall thickness and dividing by EDWT and multiplying by 100%. Myocardial segments were considered dysfunctional if SWT was <45%. The 17-segment model from the American Heart Association, excluding the apex, was used to analyze the myocardial wall in each patient.

Microvascular obstruction was evaluated on first-pass perfusion and scored as 1 for no microvascular obstruction (homogenous enhancement of myocardium) and 2 for presence of microvascular obstruction. Microvascular obstruction on first-pass perfusion was defined as early microvascular obstruction.

Infarct mass was determined on short axis delayed enhancement by quantitative analysis. For the hyperenhanced area the minimum and maximum signal intensity of the myocardium was used and a cut-off was visually detected for each patient, individually matching the hyperenhanced area visually estimated by the observer. Using this cut-off for hyperenhancement, contours were automatically traced. Manual correction was allowed especially to include the microvascular obstruction in the infarct mass. The hyperenhancement volume was multiplied by 1.05 g/ml to obtain infarct mass. Infarct size was expressed as a percentage of total left ventricular mass.

TEI was quantified by dividing the hyperenhanced area by the total area of the pre-defined segment and expressed as a percentage. Additionally a patient-based score was calculated, using the mean TEI score to determine the total transmurality of infarction. Mean TEI score was calculated for every initial examination by dividing the sum of TEI percentages per segment by the number of segments with any delayed enhancement.

On delayed enhancement images microvascular obstruction was defined as any region of hypoenhancement within the infarct core and was termed late microvascular obstruction. For segmental analysis only the slices with full circumferential myocardium were used.

**Statistical Analysis**
Continuous data are expressed as mean±SD, whereas dichotomous data are expressed as numbers and percentages. To test the difference in demographic variables, clinical characteristics and baseline CMRI findings between all groups, 1-way ANOVA was used for continuous variables and chi-square test for categorical variables. To test the significant changes of
variables over time within each group, 1-way ANOVA for repeated measurements was used, and if significant, multiple comparison procedures were performed. P-value was adjusted with Bonferroni correction. To select the strongest predictor(s) for progressive dilatation at 5 years follow-up all variables were subjected to multivariate discriminant analysis based on the forward stepwise addition of variables. Due to the small sample size only 3 parameters could be included in the analysis. The 3 most significant parameters at univariate analysis were included in the model. Analyzed variables included age, hypertension, smoking, hypercholesterolemia, family history, diabetic mellitus, infarct-related artery, baseline EDV, baseline end-systolic volume (ESV), baseline LVEF, change of EDV between baseline and 4 months follow-up (delta EDV), ESV between baseline and 4 months follow-up (delta ESV) and LVEF between baseline and 4 months follow-up (delta LVEF), baseline infarct mass, baseline infarct size and microvascular obstruction. Statistical significance was assumed for P<0.05. All tests were 2-sided. All analysis was done with SPSS 15.0 (SPSS Inc, Chicago, IL, USA, 2006).

**Results**

**Subjects**
The subject group consisted of 25 patients, of whom 19 patients had an anterior infarction. Mean peak creatinine kinase was 3,947±1,965 U/L (range, 643–7,641 U/L). More patient characteristics are listed in **Table 1**. Between baseline and 4 months follow-up LVEF improved (from 42±9% to 46±9%, P=0.02), EDV increased (from 192±40ml to 211±49ml, P=0.01)
Late Cardiac Remodeling After Primary PCI

and ESV did not change (from 112±33 ml to 116±40 ml; P=0.46). At 5 years follow-up no significant changes in LVEF, EDV and ESV had taken place compared to 4 months (LVEF 44±9%, P=0.07; EDV 216±68 ml, P=0.38; ESV 124±56 ml, P=0.09).

Differences in Global Dilatation

In the present patients there were different patterns of left ventricular dilatation between baseline and 4 months and 5 years. Of these patients, 32% (8/25) had no left ventricular dilatation, 32% (8/25) had limited dilatation and 36% (9/25) had progressive dilatation after treated AMI. Between the groups, according to baseline characteristics there were significantly fewer men in the no dilatation group (no dilatation, 38%; limited dilatation, 88%; and progressive dilatation, 100%; P=0.01). Body mass index was significantly different between the groups (no dilatation, 1.6±0.3 kg/m²; limited dilatation, 1.9±0.3 kg/m²; and progressive dilatation, 2.2±0.4 kg/m²; P=0.01). In addition, maximum creatinine kinase was significantly different (no dilatation, 2,693±1,685 U/L; limited dilatation, 3,439±1,412 U/L; and progressive dilatation, 5,514±1,666 U/L; P<0.01). No other significant differences were seen between the groups for baseline characteristics. In particular, there was no significant difference between anterior and non-anterior infarctions (P=0.10).

CMRI parameters are listed according to group in Table 2. There was no significant difference in baseline EDV, although the EDV in the progressive dilatation group tended to be increased. ESV was significantly increased in the progressive dilatation group compared to the no dilatation group. Furthermore, LVEF was significantly decreased in patients with progressive dilatation compared to patients with no dilatation. Infarct mass was significantly larger in the progressive dilatation group compared to the limited or no dilatation groups. There was no difference between groups in early microvascular obstruction, but late microvascular obstruction was significantly more present in patients with progressive dilatation.

The time course of left ventricular volumes and LVEF is given in Figure 2. In patients with progressive dilatation EDV increased 20% between baseline and 4 months (P<0.01) and another 13% between 4 months and 5 years (P<0.01). In patients with limited dilatation, EDV increased 13% between baseline and 4 months (P<0.01), with no further change between 4 months and 5 years. In patients with no dilatation there was no change in EDV between baseline and 4 months, but EDV decreased 7% between 4 months and 5 years (P=0.03). In patients with progressive dilatation ESV increased 17% between baseline and 4 months (P=0.04) and another 19% between 4 months and 5 years (P=0.01). No change was seen in patients with limited or no dilatation. In patients with progressive dilatation there was no change in LVEF throughout the study. In patients with limited dilatation LVEF increased 17% between baseline and 4 months (P=0.01), but there was no further change between 4 months and 5 years. There was no change in LVEF in patients with no dilatation throughout the study.

Regional Left Ventricular Function

A total of 271 myocardial segments were available for analysis, of which 183 (68%) were dysfunctional at baseline. At baseline 149 segments (55%) had a pattern of hyperenhancement. Presence of dysfunctional segments at baseline increased with TEI; 62% of segments with 1–25% TEI, 85% of segments with 26–75% TEI and 94% of segments with 76–100% TEI were dysfunctional. Figure 3 shows the observed changes in wall thickening in segments within the 4 different TEI groups. There was an inverse correlation between TEI and SWT. At 4 months follow-up there was an increase in SWT of all seg-

**Figure 3.** Changes in segmental wall thickening. Remote myocardium and dysfunctional segmental wall thickening at (orange) baseline, (blue) 4 months follow-up and (red) 5 years follow-up vs. transmural extent of infarction at baseline. *P<0.05 compared to baseline.
ments compared to baseline independent of TEI with no further change at 5 years. Figure 4 shows the observed changes in EDWT in segments with different TEI. At 4 months follow-up there was a decrease in EDWT of all infarcted segments compared to baseline independent of TEI. At 5 years follow-up there was a decrease in EDWT in segments with TEI >25%, although not significant in the transmural infarction. The remote myocardium did not change between 4 months and 5 years, although there was a significant decrease in the first 4 months.

**Predictors of Progressive Left Ventricular Dilatation**

Table 3 lists the variables selected on univariate and multivariate linear regression according to decreasing significance

| Table 3. Predictors of Progressive Left Ventricular Dilatation |
|---------------------------------|------------|------------|---|
| **Univariate analysis**          | B         | 95%CI      | P-value |
| Infarct mass                     | 0.14      | 1.03–1.29  | 0.02    |
| Delta EDV                        | 0.12      | 1.02–1.23  | 0.02    |
| ESV baseline                     | 0.05      | 1.01–1.09  | 0.02    |
| Infarct size                     | 0.10      | 1.01–1.21  | 0.03    |
| Delta ESV                        | 0.07      | 1.01–1.13  | 0.03    |
| LVEF baseline                    | –0.16     | 0.74–0.99  | 0.03    |
| EDV baseline                     | 0.03      | 1.00–1.05  | 0.05    |
| Mean TEI                         | 0.04      | 0.97–1.11  | 0.27    |
| Smoking                          | 0.74      | 0.56–7.79  | 0.28    |
| Hypercholesterolemia             | –1.29     | 0.03–2.83  | 0.28    |
| Delta LVEF                       | –0.02     | 0.94–1.02  | 0.37    |
| Infarct related artery           | –0.57     | 0.16–2.05  | 0.39    |
| Hypertension                     | –0.98     | 0.35–4.00  | 0.42    |
| Age                              | –0.28     | 0.90–1.05  | 0.49    |
| Family history                   | 0.47      | 0.31–8.32  | 0.57    |
| Diabetes mellitus                | –20.76    | 0.00–       | 0.99    |
| **Multivariate analysis**        |           |            |         |
| Infarct mass                     | 0.14      | 1.03–1.29  | 0.02    |

CI, confidence interval. Other abbreviations as in Table 2.
for the prediction of progressive left ventricular dilatation. Infarct mass, delta EDV and ESV at baseline were the most significant predictors for progressive dilatation at follow-up. Stepwise multivariate analysis showed that infarct mass at baseline was the only independent predictor of progressive left ventricular dilatation.

Discussion

PPCI restores coronary flow in AMI and allows viable ischemic tissue to recover, thus limiting necrosis and thereby increasing survival.\(^7\) At long-term follow-up event-free survival is approximately 61–75%.\(^{14,15}\) To our knowledge the present study is the longest follow-up of the course of CMRI parameters of systolic function in patients with AMI treated by PPCI. We conducted this study to determine whether left ventricular dilatation occurs and continues beyond 4 months after AMI despite PPCI. The major findings of the present study are (1) ventricular dilatation occurs after restoration of coronary perfusion by PPCI; (2) the left ventricular remodeling process is highly variable among patients; and (3) the best predictor for progressive dilatation is infarct mass at baseline.

Global Function

The extent of dilatation provides important prognostic information. Left ventricular volume is a powerful functional predictor of survival in patients with coronary heart disease.\(^{16}\) The present results show that ventricular dilatation is not necessarily progressive after 4 months. Thus, 68% of patients had left ventricular dilatation between baseline and 4 months but only 32% had progressive dilatation between 4 months and 5 years. This difference in dilatation was also observed in the clinical study by Gaudron et al.\(^{7}\) The present study contained more patients with limited (32% vs. 26%) and progressive dilatation (36% vs. 20%), although comparison is difficult due to the fact that they used echocardiography and therefore a different cut-off point for the EDV. For categorization of the Gaudron et al. patients, they used increase of EDV >8%. Next to this their study population had a overall smaller infarct size compared to the present population.

Early ventricular dilatation after AMI has been associated with improvement in stroke volume and reduction in ventricular filling pressure.\(^{17}\) Late ventricular dilatation involves both infarcted and non-infarcted segments. Late ventricular dilatation is probably initiated by an increased EDV, causing increased diastolic wall stress and resulting in eccentric hypertrophy.\(^{18}\) This was also observed in the present patients. None of the patients in the no dilatation group had an increase in EDV during the complete period. Deterioration of left ventricular volume increases the risk of developing heart failure and constitutes a poor prognosis.\(^{7}\) Notwithstanding the relatively small number of patients in the present study, we observed a clear correlation between progressive dilatation and baseline ESV, delta EDV and infarct mass. Infarct mass proved to be the strongest predictor for progressive dilatation on multivariate linear regression. Previous studies with short term follow-up until 4 months have also found infarct mass to be the most important predictor for global function at follow-up,\(^{4,19}\) although we must take into account that this study also included lateral and inferior infarction, which are supposed to result in smaller infarct size. In total there were 6 non-anterior infarctions, which were distributed throughout the groups, resulting in 88% anterior infarction in the no dilatation group, 63% in the limited dilatation group and 78% in the progressive dilatation group (P=0.10). Subgroups analysis was not possible due to the small number of patients with a non-anterior infarction. Taken together these observations indicate that the substantial loss of myocardium due to necrosis and progressive dilatation are closely related. Importantly, there was no relationship between mean TEI and progressive dilatation, suggesting that the total mass of myocardium that is lost is more important than TEI. We must be careful with this statement, however, due to the fact that necrosis develops in 2 directions: transmural and circumferential.\(^{20}\)

Regional Wall Function and Recovery

An overall inverse correlation was found between TEI at baseline and EDWT and SWT at baseline, 4 months and 5 years follow-up. SWT improved in the first 4 months after PPCI. This suggests stunning at baseline due to the ischemia. There were no further changes between 4 months and 5 years follow-up. This suggests that there was no further deterioration of function at a segmental level. There was a trend toward decrease in EDWT as TEI increases. The combination of reabsorption of edema and the loss of viable myocardium leads to the loss in wall thickness in the first 4 months.

Adjuvant Pharmacotherapy

To further reduce mortality and morbidity it is important to reduce the remodeling process. PCI for reperfusion therapy along with adjuvant pharmacotherapy is associated with improved clinical short- and long-term survival. Treatment with \(\beta\)-blockers reduces morbidity and mortality, as has been demonstrated before and after the introduction of PPCI and thrombolysis.\(^{31,22}\) This is partly due to the lower rate of sudden cardiac death. In heart failure patients, however, it is known that irrespectively of the origin of heart failure, \(\beta\)-blockers can improve LVEF, ESV and EDV.\(^{23}\) Just like \(\beta\)-blockers, angiotensin-converting enzyme (ACE) inhibitors also have been shown to reduce morbidity and mortality.\(^{24,25}\) The treatment effect of ACE inhibitors includes a cardioprotective as well as a vasculo-protective effect. The reduction in morbidity and mortality is probably mostly due to the vascular protective effect of ACE inhibitors and not the cardioprotective effect. A meta-analysis showed that there was no difference in left ventricular dilatation between patients taking ACE inhibitors or placebo in patients treated with thrombolysis.\(^{26}\) Hence none of these studies looked at the different dilatation patterns, and also these studies used echocardiography and not CMRI. The latter is considered to be the gold-standard for functional imaging and is able to accurately visualize the extent of infarct mass. Also the combination of both drugs reduces mortality and morbidity in patients treated with PPCI for AMI. In the present patients all groups received both therapies, but it is unclear what the influence on the remodeling process may have been.

Conclusion

A total of 68% of patients with AMI treated with PPCI had left ventricular dilatation between baseline and 4 months, and only 36% had progressive dilatation beyond 4 months. The infarct mass proved to be the best predictor for progressive dilatation. In addition, we observed that between 4 months and 5 years of follow-up there was no additional improvement of SWT compared to the first 4 months in patients with acute STEMI treated by PPCI.

Study Limitations

Sample size in the present study group was relatively small so...
further trials need to be performed to verify the generalizability of the present conclusions. Furthermore, a possible selection bias could have been present in this study because 15 patients were unable or refused to undergo a third CMRI. Importantly, none of these patients dropped out due to cardiac death and none of the patients had clinical evidence of recurrent myocardial ischemia. Most of the present patients had an anterior infarction, therefore due to the small group it was not possible to perform additional analysis for patients with non-anterior infarction. Patients with non-anterior infarction, however, were represented in all groups. Functional follow-up was assessed at 4 months and 5 years. Unfortunately, we did not have additional time points; therefore precise timing of dilatation is not possible.

Disclosures
Conflicts of Interest: None. Financial Disclosures: None.

References