CHAPTER 4

Does left ventricular dyssynchrony immediately after acute myocardial infarction result in left ventricular dilatation?

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ABSTRACT

Background
Reverse remodeling of the left ventricle (LV) is one of the advantageous mechanisms of cardiac resynchronization therapy (CRT). Substantial LV dyssynchrony seems mandatory for echocardiographic response to CRT. Conversely, LV dyssynchrony early after acute myocardial infarction may result in LV dilatation during follow-up.

Objective
The purpose of this study was to evaluate the relation between LV dyssynchrony early after acute myocardial infarction and the occurrence of long-term LV dilatation.

Methods
A total of 124 consecutive patients presenting with acute myocardial infarction who underwent primary percutaneous coronary intervention were included. Within 48 hours of intervention, 2D echocardiography was performed to assess LV volumes, LV ejection fraction (LVEF) and wall motion score index (WMSI). LV dyssynchrony was quantified using color-coded tissue Doppler imaging (TDI). At 6 months follow-up, LV volumes and LVEF were reassessed.

Results
Patients with substantial LV dyssynchrony (≥ 65 ms) at baseline (18%) had comparable baseline characteristics to patients without substantial LV dyssynchrony (82%), except for a higher prevalence of multi-vessel coronary artery disease (p = .019), higher WMSI (p = .042), and higher peak levels of creatine phosphokinase (p = .021). During 6 months follow-up, 91% of the patients with substantial LV dyssynchrony at baseline developed LV remodeling, compared to 2% in the patients without substantial LV dyssynchrony. LV dyssynchrony at baseline was strongly related to the extent of long-term LV dilatation at 6 months follow-up.

Conclusion
Most patients with substantial LV dyssynchrony immediately after acute myocardial infarction develop LV dilatation during 6 months follow-up.
INTRODUCTION

Nowadays, a substantial proportion of patients with moderate to severe ischemic heart failure, despite optimal medical therapy, is treated with cardiac resynchronization therapy (CRT).(1-5) The presence of left ventricular (LV) dyssynchrony seems to be of considerable importance for response and prognosis after CRT.(6-8) Importantly, reverse remodeling of the left ventricle more frequently occurs in those patients with substantial LV dyssynchrony at baseline. In addition, patients with LV reverse remodeling after CRT have a better prognosis than those without LV reverse remodeling.(6-8)

Presumably, LV dyssynchrony after acute myocardial infarction results in LV dilatation. However, no study thus far has systematically examined this potential relationship. Tissue Doppler imaging (TDI) is established for the assessment of myocardial velocities and the detection of LV dyssynchrony, and has been used in patients who had a myocardial infarction.(9) This study evaluates the relation between LV dyssynchrony at baseline, assessed with TDI, and the occurrence of long-term LV dilatation in patients following acute myocardial infarction.

METHODS

Patients
A total of 135 consecutive patients, admitted with an acute myocardial infarction, were screened. Patients who were treated conservatively (n = 4) or who underwent thrombolysis (n = 3) or coronary artery bypass grafting (n = 1) in the acute setting were excluded from the study in order to obtain a homogenous study group. Three patients died during follow-up and therefore did not have the follow-up assessment. These patients were excluded from the study. The final study population comprised 124 patients who all underwent primary percutaneous coronary intervention.

Protocol
Two-dimensional echocardiography was performed within 48 hours of admission (baseline) and at 6 months follow-up. At baseline, conventional echocardiography was used to assess LV volumes, LV ejection fraction (LVEF) and wall motion score index (WMSI). LV dyssynchrony was quantified using color-coded tissue Doppler imaging (TDI). LV volumes and LVEF were reassessed at 6 months follow-up.(10)
The study was approved by the institutional ethics committee, and informed consent was obtained from all patients.

**Echocardiography**

Patients were imaged in the left lateral decubitus position using a commercially available system (Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin, USA). Standard images were obtained using a 3.5-MHz transducer, at a depth of 16 cm in the parasternal (long- and short-axis) and apical (2- and 4-chamber) views. Standard 2-dimensional and color Doppler data, triggered to the QRS complex, were saved in cine-loop format. LV volumes (end-systolic and end-diastolic) and LVEF were calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson’s technique. LV remodeling at 6 months follow-up was defined as an increase in LV end-systolic volume (LVESV) ≥15%. LV was divided into 16 segments. A semiquantitative scoring system (1, normal; 2, hypokinesia; 3, akinesia; 4, dyskinesia) was used to analyze each study. Global WMSI was calculated by the standard formula: sum of the segment scores divided by the number of segments scored.

All echocardiographic measurements were obtained by two independent observers without knowledge of the clinical status of the patient. Inter- and intra-observer agreement for assessment of LV volumes were 90% and 93% for LVESV, and 92% and 93% for LVEDV, respectively.

**Tissue Doppler imaging**

Color Doppler frame rates were >80 and pulse repetition frequencies were between 500 Hz and 1 KHz, resulting in aliasing velocities between 16 and 32 cm/s. TDI parameters were measured from color images of three consecutive heart beats by offline analysis. Data were analyzed using commercial software (Echopac 6.01, General Electric-Vingmed). To determine LV dyssynchrony, the sample volume (6 x 6 mm) was placed in the LV basal portions of the anterior, inferior, septal and lateral walls (using the two- and four-chamber views) and, per region, the time interval between the onset of the QRS complex and the peak systolic velocity was obtained. LV dyssynchrony was defined as the maximum delay between peak systolic velocities among these four LV regions. LV dyssynchrony was defined as LV dyssynchrony ≥65 ms. Inter- and intra-observer agreement for assessment of LV dyssynchrony were reported previously (90% and 96%, respectively).
Statistical analysis

Most continuous variables were not normally distributed (as evaluated by Kolmogorov-Smirnov tests). For reasons of uniformity, summary statistics for all continuous variables are therefore presented as medians together with the 25th and 75th percentiles. Categorical data are summarized as frequencies and percentages.

Differences in baseline characteristics between patients who demonstrated substantial LV dyssynchrony versus those who did not were analyzed using Wilcoxon-Mann-Whitney tests, Chi-square tests with Yates’ correction or Fisher’s exact tests, as appropriate. Linear regression analysis was used to evaluate the relations between baseline variables and the change in LVESV during follow-up. All statistical tests were two-sided. Unless otherwise specified, a p value <.05 was considered statistically significant.

RESULTS

Baseline data of the study population

In the present study 124 patients were included (99 men and 25 women, median age 61 (53, 71) years). During primary percutaneous coronary intervention TIMI-III flow was achieved in all but 6 (5%) patients. Multi-vessel disease was observed in 67 (54%) patients. Median creatine phosphokinase (CPK) levels were 2469 (1023, 3702) U/L. Median WMSI was 1.50 (1.31, 1.63). Seven (6%) patients had a previous myocardial infarction. At baseline, median LVESV and LVEDV were 65 (54, 83) ml and 129 (106, 151) ml, respectively, whereas the median LVEF was 48% (42%, 53%). Median LV dyssynchrony as measured by TDI was 10 (0, 40) ms.

Six months follow-up

In the entire patient population, the mean LVESV remained unchanged at 6 months follow-up (64 (51, 84) ml versus 65 (54, 83) ml at baseline, p = .11). LVEDV increased significantly during follow-up (130 (110, 155) ml versus 129 (106, 151) ml at baseline, p = .007). LVEF remained unchanged (49%(43%, 56%) versus 48 (42, 53) % at baseline, p = .31).

LV dilatation in patients with baseline LV dyssynchrony

Patients were subsequently divided into patients with substantial LV dyssynchrony (n = 22, 18%) and without LV dyssynchrony (n = 102, 82%) at baseline. Patients in the group with substantial LV dyssynchrony had a median dyssynchrony of 85 (80,
100) ms, whereas median dyssynchrony among those without substantial LV dyssynchrony was 10 (0, 20) ms (p < .0001, by definition). Clinical and echocardiographic patient characteristics of the 2 groups are summarized in Table 1 and 2, respectively. Various baseline variables differed significantly between patients with and without substantial LV dyssynchrony at baseline. Patients with LV dyssynchrony more often had multi-vessel coronary artery disease. WMSI (as a reflector for infarct size) was higher among those patients with LV dyssynchrony. In addition, peak levels of CPK (reflecting enzymatic infarct size) were higher in the patients with LV dyssynchrony.

Baseline LV volumes and LVEF were similar between patients with and without LV dyssynchrony at baseline. However, at 6 months follow-up LVESV and LVEDV were

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 124)</th>
<th>No LV Dyssynchrony (n = 102)</th>
<th>LV Dyssynchrony (n = 22)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>61 (53, 71)</td>
<td>61 (53, 71)</td>
<td>64 (56, 71)</td>
<td>0.50</td>
</tr>
<tr>
<td>Gender (M/F, %)</td>
<td>99/25 (80/20)</td>
<td>81/21 (79/21)</td>
<td>18/4 (82/18)</td>
<td>1.00</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>7 (6)</td>
<td>7 (7)</td>
<td>0</td>
<td>0.35</td>
</tr>
<tr>
<td>QRS duration baseline (ms)</td>
<td>94 (88, 104)</td>
<td>94 (90, 104)</td>
<td>95 (82, 106)</td>
<td>0.78</td>
</tr>
<tr>
<td>Wide QRS (≥120 ms, %)</td>
<td>6 (5)</td>
<td>5 (5)</td>
<td>1 (5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Risk factors for CAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>11 (9)</td>
<td>10 (10)</td>
<td>1 (5)</td>
<td>0.69</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>37 (30)</td>
<td>29 (28)</td>
<td>8 (36)</td>
<td>0.54</td>
</tr>
<tr>
<td>Hyperlipidemia (%)</td>
<td>25 (20)</td>
<td>22 (22)</td>
<td>3 (14)</td>
<td>0.56</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>59 (48)</td>
<td>50 (49)</td>
<td>9 (41)</td>
<td>0.48</td>
</tr>
<tr>
<td>Peak CPK (U/L)</td>
<td>2469 (1063, 3681)</td>
<td>2167 (946, 3395)</td>
<td>3703 (1584, 5616)</td>
<td>0.021</td>
</tr>
<tr>
<td>Multi-vessel disease (%)</td>
<td>67 (54)</td>
<td>50 (49)</td>
<td>17 (77)</td>
<td>0.019</td>
</tr>
<tr>
<td>Medication at 6 months follow-up</td>
<td></td>
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<td></td>
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<tr>
<td>Beta-blockers (%)</td>
<td>112 (90)</td>
<td>92 (90)</td>
<td>20 (91)</td>
<td>0.52</td>
</tr>
<tr>
<td>ACE-inhibitors/ARBs (%)</td>
<td>122 (98)</td>
<td>100 (98)</td>
<td>22 (100)</td>
<td>0.11</td>
</tr>
<tr>
<td>Anti-coagulants (%)</td>
<td>124 (100)</td>
<td>102 (100)</td>
<td>22 (100)</td>
<td>1.00</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>122 (98)</td>
<td>100 (98)</td>
<td>22 (100)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Table 1. Baseline clinical characteristics of patients without versus with left ventricular dyssynchrony. ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CAD: coronary artery disease; CPK: creatine phosphokinase; MI: myocardial infarction.

* Patients with versus without LV dyssynchrony
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### Table 2.
Echocardiographic data of patients without versus with left ventricular dyssynchrony.
Data in parentheses are 25th and 75th percentiles.
LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; WMSI: wall motion score index.
* Patients with versus without LV dyssynchrony

<table>
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<th>LV Dyssynchrony (n = 22)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>LV dyssynchrony (ms)</td>
<td>10 (0, 40)</td>
<td>10 (0, 20)</td>
<td>85 (80, 100)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>WMSI</td>
<td>1.50 (1.31, 1.63)</td>
<td>1.50 (1.25, 1.63)</td>
<td>1.56 (1.38, 1.69)</td>
<td>0.042</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>65 (54, 82)</td>
<td>65 (52, 79)</td>
<td>70 (54, 88)</td>
<td>0.55</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>129 (106, 151)</td>
<td>129 (108, 149)</td>
<td>131 (101, 158)</td>
<td>0.82</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>48 (42, 53)</td>
<td>48 (42, 53)</td>
<td>47 (43, 51)</td>
<td>0.88</td>
</tr>
<tr>
<td><strong>6-Months follow-up</strong></td>
<td></td>
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<tr>
<td>LVESV (ml)</td>
<td>64 (51, 83)</td>
<td>62 (50, 78)</td>
<td>96 (64, 122)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>130 (110, 155)</td>
<td>129 (109, 148)</td>
<td>147 (115, 184)</td>
<td>0.048</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>49 (43, 56)</td>
<td>50 (44, 56)</td>
<td>41 (35, 44)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

**Figure 1.**
LV dyssynchrony acutely after MI was demonstrated to be strongly related to change in LVESV during 6 months follow-up.
significantly larger in the patients with LV dyssynchrony. Moreover, the LVEF was significantly lower in the patients with LV dyssynchrony. Importantly, LV remodeling at 6 months follow-up was demonstrated in 91% of patients with substantial LV dyssynchrony, whereas only 2% of patients without substantial LV dyssynchrony had LV remodeling.

Baseline variables and relation with LV dilatation
No significant relation was found between WMSI and the extent of LV dilatation at 6 months follow-up. A modest relation was noted between the peak plasma levels of CPK \( y = -5.25 + 0.003x, n = 124, r = 0.34, p <.001 \) and the extent of LV dilatation at 6 months follow-up. A strong relation was observed between the severity of LV dyssynchrony and the extent of LV dilatation \( y = -7.52 + 0.35x, n = 124, r = 0.73, p <.0001 \); Figure 1).

DISCUSSION

The main findings of the present study can be summarized as follows: 1) substantial LV dyssynchrony was present in 18% of patients early after acute myocardial infarction treated with primary percutaneous coronary intervention; 2) patients with substantial LV dyssynchrony more often had multi-vessel coronary artery disease, higher WMSI and higher peak levels of CPK at baseline; 3) 91% of patients with substantial LV dyssynchrony developed long-term LV remodeling; and 4) LV dyssynchrony at baseline was strongly related to the extent of long-term LV dilatation.

In the present study, 18% of the patients demonstrated substantial LV dyssynchrony early after myocardial infarction followed by successful primary percutaneous coronary intervention (TIMI-III flow was achieved in all but 6 patients during the procedure). Zhang et al. investigated 47 patients after first acute myocardial infarction.(17) The majority of patients were treated with thrombolytic therapy. The authors observed that almost 70% of patients had LV dyssynchrony. This large difference in prevalence can (partially) be explained by differences in mean infarct size between both studies, as infarct size correlates with LV dyssynchrony.(17) However, no adequate comparison regarding infarct size can be made due to differences in assessment of infarct size (contrast-enhanced magnetic resonance imaging versus echocardiographic wall motion score index in the current study). Fahmy et al. demonstrated LV dyssynchrony in 77.5% of 155 patients.(18) Mean WMSI, as a reflector
of infarct size, was higher in their study population compared to the population in the current study (1.78 versus 1.47, respectively).

In addition to differences in infarct size, the definition of LV dyssynchrony may be of importance to explain the difference in prevalence of LV dyssynchrony after myocardial infarction. Both Zhang et al. and Fahmy et al. used the assessment of the standard deviation of time to peak systolic velocity (Ts-SD) as expression for LV dyssynchrony, though different cut-off values based on measurements in control patients were used (Ts-SD >32 ms versus >22.14 ms, respectively).(17,18) In the present study, LV dyssynchrony was defined as the maximum delay between peak systolic velocities among the anterior, inferior, septal and lateral walls and a predefined cutoff of ≥65 ms was used.(6) Of note, assessment of LV dyssynchrony using TDI may become jeopardized when basal segments are akinetic, although assessment of LV dyssynchrony was feasible in all patients in the present study.

Both Zhang et al. and Fahmy et al. described the significant impact of infarct size on LV dyssynchrony.(17,18) They demonstrated that the degree of LV dyssynchrony is mainly determined by the infarct size. In the present study, patients with substantial LV dyssynchrony more often had multi-vessel coronary artery disease, higher WMSI (reflector for infarct size) and higher peak levels of CPK (reflector for enzymatic infarct size) at baseline. These observations seem in concordance with the theory that infarct size strongly influences the extent of LV dyssynchrony.

The relation between LV dyssynchrony early after myocardial infarction and the occurrence of LV dilatation still remains unclear. No study thus far has systematically examined this presumed relationship. The clinical importance of LV dilatation was emphasized by White et al., who demonstrated that patients who died during follow-up after myocardial infarction had significantly higher LV volumes and lower LV ejection fractions than survivors.(12) Furthermore, the authors indicated LVEF as the primary predictor of survival after myocardial infarction. As a consequence, early identification of patients with substantial LV dilatation after acute myocardial infarction is of vital importance.

Observations from patients treated with CRT have demonstrated that patients with substantial LV dyssynchrony before implantation more often respond to CRT than patients without substantial LV dyssynchrony.(6-8) Patients who did respond to CRT demonstrated an increase in LV ejection fraction and a decrease in LV volumes, a process referred to as reverse remodeling. Therefore, a relation between LV dyssynchrony and LV dilatation after myocardial infarction is presumed.

In the present study, LV dyssynchrony at baseline was strongly related to the extent of long-term LV dilatation. More than 90% of the patients with substantial LV dyssyn-
chrony at baseline developed long-term LV remodeling during 6 months follow-up. In contrast, no significant relation was found between WMSI, which reflects infarct size, and LV dilatation. Only a modest relation was noted between peak CPK level, which reflects enzymatic infarct size, and LV dilatation.

Still, at this stage it remains uncertain what mainly determines / predicts LV dilatation; the current data suggest that LV dyssynchrony plays a role, but a causal relation cannot be concluded yet and further studies are needed.

**CONCLUSION**

LV dyssynchrony after acute myocardial infarction is strongly related to LV dilatation and most patients with substantial LV dyssynchrony immediately after acute myocardial infarction develop LV dilatation during 6 months follow-up. Further large studies are needed to confirm these findings.
REFERENCES


