Temporal evolution of left ventricular dyssynchrony after myocardial infarction: relation with changes in left ventricular systolic function

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Received 5 June 2011; revised 11 February 2012; accepted after revision 10 April 2012; online publish-ahead-of-print 7 May 2012

Aims
The relationship between temporal changes in left ventricular (LV) dyssynchrony and LV functional recovery after acute myocardial infarction (MI) remains unclear. Accordingly, the aim of the present study was to evaluate the temporal evolution of LV synchronicity after acute MI, and to explore the relationship between changes in LV systolic function and LV synchronicity.

Methods and results
In 193 patients with a first acute MI, LV dyssynchrony (SDI) and global systolic function were evaluated with real-time three-dimensional echocardiography 48 h after percutaneous coronary intervention and at 6 months follow-up. Changes in LV systolic function and synchronicity were evaluated at the follow-up and the relationship between these changes was explored. A total of 59 (40%) patients had an anterior acute MI. Median peak value of troponin T was 2.97 μg/L (1.41–6.06 μg/L). Mean LVEF was 47 ± 8% and mean SDI was 5.01 ± 2.10%, respectively. At 6 months follow-up, a significant improvement in LVEF (50 ± 9 vs. 47 ± 8%; P < 0.001) and SDI (4.52 ± 1.97 vs. 5.01 ± 2.10%; P = 0.003) was noted. A strong correlation was found between LVEF change and SDI change (β = −0.63; P < 0.001). At multivariate analysis, SDI change was an independent factor associated with changes in LVEF. Importantly, an addition of SDI change to the multivariate model significantly increased the R² from 0.41 to 0.57 (F change 49.0, P < 0.001).

Conclusion
A temporal evolution of LV synchronicity was observed after a first, mechanically reperfused, acute MI. The reduction in LV dyssynchrony independently influenced LV functional recovery in these patients.

Keywords
LV dyssynchrony • Acute myocardial infarction • Real-time 3-dimensional echocardiography

Introduction
Recently, impairment of the synchronicity of left ventricular (LV) contraction has been described in the acute phase of myocardial infarction (MI).1–4 In this setting, the presence of LV dyssynchrony has been shown to have a detrimental effect on haemodynamic function, mid-term LV remodelling, and long-term prognosis.1–4 However, scarce data are available regarding the temporal evolution of LV dyssynchrony during the follow-up. In addition, the relationship between temporal changes in LV dyssynchrony and LV functional recovery remains unclear. Accordingly, the aim of the present study was two-fold: first, to assess the temporal evolution of LV synchronicity after acute MI, and second, to explore the relationship between changes in LV systolic function and LV synchronicity.

Methods

Patient population
One-hundred ninety-three consecutive patients admitted with a first ST-segment elevation acute MI were selected from an ongoing registry.2 Patients with a QRS complex duration >120 ms were excluded from the study.
The diagnosis of acute MI was made on the basis of typical electrocardiographic changes and/or ischaemic chest pain associated with increased plasma levels of cardiac biomarkers. Immediate coronary angiography and primary percutaneous coronary intervention (PCI) of infarct-related artery were performed in all the patients. The infarct-related artery was identified by the site of coronary occlusion during coronary angiography and electrocardiographic criteria. Troponin T levels were determined at admission and at 6, 12, and 18 h of admission. Real-time three-dimensional echocardiography (RT3DE) was performed 48 h after PCI to assess global LV systolic function and LV dyssynchrony; in addition, the presence and grade of mitral regurgitation and diastolic dysfunction were evaluated with two-dimensional colour, pulsed, and continuous wave Doppler echocardiography. At 6 months follow-up, RT3DE was repeated and global LV systolic function and LV dyssynchrony were re-assessed. Accordingly, changes in LV systolic function and synchronicity were evaluated at follow-up and the relationship between these changes was explored. These echocardiographic examinations were performed as part of the routine, comprehensive assessment of patients presenting with acute MI in our clinic, and not purely for study purposes. Clinical, angiographic, and echocardiographic data were prospectively collected in the departmental cardiology information system (EPD-Vision) and retrospectively analysed.

**Real-time three-dimensional echocardiography**

Patients were imaged in the left lateral decubitus position with a commercially available system (Vivid 7, GE Healthcare, Horten, Norway) equipped with a 3V-phased array transducer (2.5 MHz). Apical full-volume three-dimensional data sets were acquired in harmonic mode, integrating, during a brief breath-hold, eight R-wave-triggered sub-volumes into a larger pyramidal volume (90° by 90°) with a complete capture of the LV. The 3D data sets were digitally stored and a dedicated software (4D LV-Analysis©; TomTec, Munich, Germany) was used for the offline analysis. The algorithm used by the software to calculate LV end-diastolic volume (EDV), LV end-systolic volume (ESV), and LVEF is described in detail elsewhere. Briefly, a semi-automated method for the detection of the apical four-chamber view and the 60° and 120° incremental views and for the tracing of the endocardial border in the entire 3D data set (including LV trabeculations and papillary muscles within the LV volume) is used. Subsequently, a final reconstruction of the LV model is generated and LV volumes and LVEF are obtained. Qualitative assessment of regional wall motion was performed according to the 16-segment model of the American Society of Echocardiography and the global wall motion score index (WMSI) was calculated for each patient. In addition, the same LV model was used for the assessment of LV dyssynchrony, as previously described. Briefly, the LV model was automatically divided in 16 pyramidal sub-volumes (six basal segments, six mid segments, and four apical segments) based around a non-fixed central point. For each volumetric segment, the time–volume curve for the entire cardiac cycle is derived and the time to minimum systolic volume (Tmvs) is calculated. The standard deviation (SD) of the 16 segments Tmvs expressed in percentage of cardiac cycle (the systolic dyssynchrony index, SDI) was then calculated as a marker of global LV dyssynchrony.

As previously reported, a normal control group value of SDI was 2.02 ± 0.70%; significant mechanical dyssynchrony was defined as an SDI > 3 SD above the mean for normal subjects (4.12%).

**Two-dimensional echocardiography**

Two-dimensional echocardiography was performed with the same commercially available system (Vivid 7 Dimension, GE Healthcare) equipped with a 3.5 MHz transducer. Standard Doppler and colour-Doppler data were acquired from parasternal and apical views (four-, two-, and three-chamber) and digitally stored in cine-loop format; analyses were subsequently performed offline using EchoPAC version 7.0.0 (GE Healthcare, Horten, Norway).

The severity of MR was quantitatively determined by integrating different echocardiographic parameters such as vena contracta width and regurgitant volume measured with the proximal isovelocity surface area method, as recommended. As previously described, transmural and pulmonary vein pulsed-wave Doppler tracings were used to classify diastolic function as (i) normal; (ii) diastolic dysfunction grade 1 (mild); (iii) diastolic dysfunction grade 2 (moderate); (iv) diastolic dysfunction grade 3 (severe).

**Statistical analysis**

Continuous variables are expressed as mean and standard deviation, when normally distributed, and as median and interquartile range, when not normally distributed. Categorical data are presented as absolute numbers and percentages.

Differences in continuous variables between baseline and 6 months follow-up were assessed using the paired t test or the Wilcoxon signed rank test, if appropriate. Differences in continuous variables between two different groups were assessed using the Student t-test or the Mann–Whitney U-test, if appropriate.

The relationship between the changes in LVEF (ΔLVEF) and in LVESV (ΔLVESV) and the change in LV dyssynchrony (ΔSDI) after 6 months follow-up was evaluated with the linear regression analysis. To evaluate the independent determinants of ΔLVEF at follow-up, univariate and multivariate linear regression analyses were performed. The following clinical and echocardiographic characteristics were included in the univariate model: age, gender, coronary risk factors, infarct location, multi-vessel disease, peak troponin T, symptoms onset to balloon time, baseline LVESV, baseline LVEF, baseline WMSI, presence of mitral regurgitation at baseline, presence of diastolic dysfunction at baseline, baseline SDI, and ΔSDI. Only significant variables at univariate analysis were entered as covariates in the multivariate model. Finally, in order to determine the potential incremental value of ΔSDI over the other variables, the R² of the multivariate model was compared with the R² of the same model without ΔSDI.

A two-tailed P value < 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software package (SPSS 15.0, Chicago, IL, USA).

**Results**

A total of 36 patients were excluded from the analysis because of suboptimal RT3DE image quality data; in addition, 10 patients were lost at follow-up. Consequently, a total of 147 patients were included in the final analysis.

**Characteristics of the patient population**

Baseline characteristics of the study population are summarized in Table 1. A total of 59 (40%) patients had an anterior acute MI; obstructive multi-vessel disease (i.e. more than 1 vessel with a luminal narrowing ≥70%) was present in 52 (35%) patients. The median peak value of troponin T was 2.97 μg/L (1.41–6.06 μg/L). Mean LVEF was 47 ± 8% and mean SDI was 3.01 ± 2.10%, respectively. A total of 87 (59%) AMI patients had an SDI higher than 4.12%, therefore having significant mechanical dyssynchrony.
Of note, anterior AMI patients had significantly worse SDI when compared with non-anterior AMI patients (6.06 ± 2.58 vs. 4.31 ± 1.32%; \( P < 0.001 \)). Conversely, no difference in SDI was observed between single-vessel and multi-vessel disease patients (4.83 ± 1.87 vs. 5.35 ± 2.46%; \( P = 0.19 \)).

**Evolution of LV volumes, systolic function, and LV dyssynchrony**

At follow-up, a slight increase in LVEDV was observed (105 ± 27 vs. 109 ± 32 mL; \( P = 0.094 \)), whereas LVESV remained unchanged (56 ± 18 vs. 55 ± 24 mL; \( P = 0.48 \)); however, a total of 34 (23%) patients showed adverse LV remodelling (defined as an increase \( \geq 15\% \) of LVESV)\(^{12,13} \) at 6 months follow-up.

A significant improvement in LVEF (47 ± 8 vs. 50 ± 9%; \( P < 0.001 \)) and SDI (5.01 ± 2.10 vs. 4.52 ± 1.97%; \( P = 0.003 \)) was also noted (Figure 1). A total of 72 (49%) AMI patients remained with an SDI higher than 4.12%, therefore still having significant mechanical dyssynchrony at 6 months follow-up.

Of note, patients with anterior AMI improved in SDI to a larger extent when compared with non-anterior AMI patients (\( \Delta SDI: 2.10 ± 2.32 \) vs. \( 0.53 ± 1.55\% \); \( P < 0.001 \)). Conversely, no difference in \( \Delta SDI \) was observed between patients with single-vessel and multi-vessel disease (\( -0.55 ± 1.85 \) vs. \( -0.39 ± 2.27\% \); \( P = 0.66 \)).

A strong correlation was found between \( \Delta LVEF \) and \( \Delta SDI \) (\( \beta = -0.63; P < 0.001 \)); importantly, patients having an improvement in LV synchronicity showed also an improvement in LVEF, while worsening in SDI was associated to a further decline in LVEF (Figure 2). A significant but weak correlation was observed also between \( \Delta LVESV \) and \( \Delta SDI \) (\( \beta = 0.33; P < 0.001 \)).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of acute MI patients</th>
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<tr>
<td><strong>Acute MI patients</strong> ( (n = 147) )</td>
<td><strong>Baseline characteristics</strong></td>
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<tr>
<td>Age (years)</td>
<td>58 ± 11</td>
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<tr>
<td>Male gender</td>
<td>116 (79%)</td>
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<tr>
<td>Diabetes</td>
<td>15 (10%)</td>
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<tr>
<td>Family history of CAD</td>
<td>59 (40%)</td>
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<tr>
<td>Hypercholesterolaemia</td>
<td>23 (16%)</td>
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<tr>
<td>Hypertension</td>
<td>50 (34%)</td>
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<tr>
<td>Current or previous smoking</td>
<td>87 (59%)</td>
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<tr>
<td>Anterior myocardial infarction</td>
<td>59 (40%)</td>
</tr>
<tr>
<td>Infarct-related artery</td>
<td></td>
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<tr>
<td>Left anterior descending coronary artery</td>
<td>59 (40%)</td>
</tr>
<tr>
<td>Left circumflex coronary artery</td>
<td>25 (17%)</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>63 (43%)</td>
</tr>
<tr>
<td>Multi-vessel disease</td>
<td>52 (35%)</td>
</tr>
<tr>
<td>Peak troponin T (( \mu G/L ))</td>
<td>2.97 (1.41–6.06)</td>
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<tr>
<td>Symptom onset to balloon time (min)</td>
<td>192 ± 100</td>
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**ACE**, angiotensin-converting enzyme; **ARBs**, angiotensin receptor blockers; **CAD**, coronary artery disease; **EF**, ejection fraction; **EDV**, end-diastolic volume; **ESV**, end-systolic volume; **LV**, left ventricular; **MI**, myocardial infarction; **SDI**, systolic dyssynchrony index; **WMSI**, wall motion score index.
Correlates of change in LV systolic function (LVEF) at 6 months follow-up

Table 2 shows the results of the univariate and multivariate regression analysis performed to determine the factors related to ΔLVEF between baseline and 6 months follow-up. At univariate analysis, several variables were significantly related to ΔLVEF: hypercholesterolaemia, hypertension, anterior location of acute MI, peak troponin T, baseline LVEF, and ΔSDI. At multivariate analysis, hypercholesterolaemia, peak troponin T, baseline LVEF, and ΔSDI were independent factors associated with ΔLVEF. More importantly, the addition of ΔSDI to the multivariate model significantly increased the $R^2$ from 0.41 to 0.57 ($F$ change 49.0, $P < 0.001$). This underscores the strong and independent relationship between these two parameters of LV mechanical performance (LVEF and SDI).

Discussion

The present study demonstrates that after a first-reperfused acute MI, an improvement in LV global performance occurs with an improvement of LV systolic function (LVEF) and of LV synchronicity. Changes in LV synchronicity at 6 months follow-up are significantly and independently related to changes in LV systolic function.

Temporal evolution of LV systolic function and LV dyssynchrony after acute myocardial infarction

In the present study, an improvement in LVEF was shown at 6 months follow-up in patients with a first acute MI successfully reperfused. Of note, LV functional recovery (expressed as positive ΔLVEF) was significantly and inversely related to peak value of troponin T (reflecting myocardial damage) and baseline LVEF. In addition, the inverse relationship between baseline LVEF and improvement in LV systolic function during follow-up is likely related to functional recovery of stunned myocardium.14–16

Furthermore, LV dyssynchrony early after acute MI has been related to LVEF and LV remodelling at follow-up.1,2 Besides infarct size as quantified with levels of Troponin or extent of wall motion abnormalities, LV dyssynchrony has shown to be an independent determinant of LV remodelling after acute MI.1 However, the relationship between changes in LV dyssynchrony and LV systolic function over time after reperfused acute MI remained unknown. The present study shows that restoration of LV synchronicity was associated with improved LV systolic function after 6 months; conversely, in the subset of patients experiencing worsening of LV dyssynchrony, a further decline in LVEF was observed. Of note, the impact of change in LV synchronicity on the change in LV systolic function was independent and incremental to other baseline variables (including baseline peak troponin T and baseline LVEF). Previous experimental and clinical reports partially explained these observations:17–20 the detrimental effects of LV dyssynchrony on LV performance may be incremental to the effects of LV structural changes. After acute MI, LV remodelling is characterized by hypertrophy and fibrosis of the non-infarcted regions and expansion and thinning of the infarct core.21 These changes determine a redistribution of myocardial fibre strain with increasing myocardial work and energy demand.17–19 The addition of LV dyssynchrony may impact negatively on myocardial fibre strain further impairing LV global performance and favouring LV remodelling.

Clinical perspective

The present study demonstrates that the impairment in LV synchronicity observed early after acute MI is not a permanent phenomenon. In the overall study population, restoration of LV synchronicity was associated with improved LVEF, and conversely, worsening of LV dyssynchrony was related to a decline in LVEF. These findings underscore the importance of assessing LV dyssynchrony in the clinical management of patients with acute MI, as it provides additional information on LV mechanical function and may guide therapeutic strategies aimed at improving LV performance.
synchronicity was observed, which was related to LV functional recovery. Conversely, progressive worsening of LV dyssynchrony during the follow-up appeared to be an ominous mechanism, which independently contributed to progression of LV dysfunction. Accordingly, beside the essential role of timely and effective revascularization of the culprit vessel, therapeutic strategies to restore a more synchronous LV contraction could potentially be useful in this group of patients.

Limitations
Some limitations should be acknowledged. First, only patients with ST-segment elevation AMI who underwent PCI were included; consequently, the results cannot be extrapolated to patients with non-ST-elevation AMI or patients who did not undergo reperfusion therapy. In addition, RT3DE image quality is highly dependent on the acoustic window; consequently, analysable 3D LV model may be technically difficult to acquire in some patients. Peak troponin T levels measured within the first 18 h of admission may not accurately reflect the infarct size. However, these peak levels are clinically relevant as they predict major cardiac events at follow-up. Finally, the present study did not focus on regional changes in LV mechanics.

Conclusion
A temporal evolution of LV synchronicity was observed after a first, mechanically reperfused, acute MI. The reduction in LV dyssynchrony independently influenced LV functional recovery in these patients.

Conflict of interest: none declared.

Funding
The department of Cardiology received research grants from Biotronik (Berlin, Germany), Lantheus Medical Imaging (North Billerica, Massachusetts), Boston Scientific (Natick, Massachusetts), Edwards Lifesciences (Irvine, California), GE Healthcare (Buckinghamshire, UK), Medtronic (Minneapolis, Minnesota), and St Jude Medical (St Paul, Minnesota).

References
A 72-year-old woman presented with severe central chest pain and a loud continuous murmur. Blood pressure was 105/70 mmHg. She had undergone elective aortic valve and root replacement 7 years previously. Her coronary angiogram was normal. Three years later, a patent ductus arteriosus (PDA) had been missed was successfully closed percutaneously using an Amplatzer duct occluder II. The main pulmonary artery was noted then to be dilated at 4.3 cm. Subsequent echocardiographic and CT scan monitoring in the outpatient clinic showed no further evidence of PDA.

Transthoracic echocardiography (Panels A and B, see Supplementary data, Video) showed dissection flaps in the dilated main pulmonary artery and the descending aorta. There was moderately severe pulmonary regurgitation and severe tricuspid regurgitation; pulmonary artery systolic pressure estimated by Doppler was 45 mmHg. Colour flow and spectral Doppler (inset in Panel B) showed continuous flow from the descending aorta into the false lumen of the main pulmonary artery characteristic of PDA. Volume-rendered CT scans with contrast enhancement (Panels C–E) showed the full extent of the dissection involving the main pulmonary artery, the PDA (green arrow), and the descending aorta. It could not be determined however whether the dissection originated from the aorta, pulmonary artery, or even the ductus arteriosus. The Amplatzer duct occluder (white arrows) remained after ST-segment elevation myocardial infarction evaluated by serial magnetic resonance imaging. Am Heart J 2007;154:929–36.


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A device-occluded ductus arteriosus rendered patent by acute dissection involving the main pulmonary artery and the descending aorta

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