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Chapter 13

Temporal Evolution of Left Ventricular Dyssynchrony After Myocardial Infarction: Relation With Changes in Left Ventricular Systolic Function

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ABSTRACT

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 ($\beta = -0.63$; $p < 0.001$). 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.

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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.[5] 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.[6,7] 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.[8] In addition, the same LV model was used for the assessment of LV dyssynchrony, as previously described.[9] 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 (Tmsv) is calculated. The standard deviation (SD) of the 16 segments Tmsv expressed in percentage of cardiac cycle (the systolic dyssynchrony index, SDI) was then calculated as a marker of global LV dyssynchrony.[9]

As previously reported,[2] a normal control group value of SDI was $2.02 \pm 0.70\%$; 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.[10] As previously described,[11] transmitral 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 singed 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 R^2 of the multivariate model was compared with the R^2 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 5.01±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 ≥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.

Table 1. Baseline characteristics of acute MI patients

Variable	n = 147
Age (years)	58±11
Male gender	116 (79%)
Diabetes	15 (10%)
Family history of CAD	59 (40%)
Hypercholesterolemia	23 (16%)
Hypertension	50 (34%)
Current or previous smoking	87 (59%)
Anterior myocardial infarction	59 (40%)
Infarct-related artery	
- left anterior descending coronary artery	59 (40%)
- left circumflex coronary artery	25 (17%)
- right coronary artery	63 (43%)
Multi-vessel disease	52 (35%)
Peak troponin T (μg/l)	2.97 (1.41-6.06)
Symptom onset to balloon time (minutes)	192±100
Medical therapy at discharge	
- Antiplatelets	147 (100%)
- ACE inhibitors and/or ARBs	147 (100%)
- Beta-blockers	143 (97%)
- Statins	146 (99%)
LVEDV (ml)	105±27
LVESV (ml)	56±18
LVEF (%)	47±8
WMSI	1.65±0.34
Mitral Regurgitation	
- absent/mild/moderate/severe	100 (68%)/43 (29%)/3 (2%)/1 (1%)
Diastolic dysfunction	
- absent/grade 1/grade 2/grade 3	59 (40%)/79 (54%)/7 (5%)/2 (1%)
SDI (%)	5.01±2.10

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.
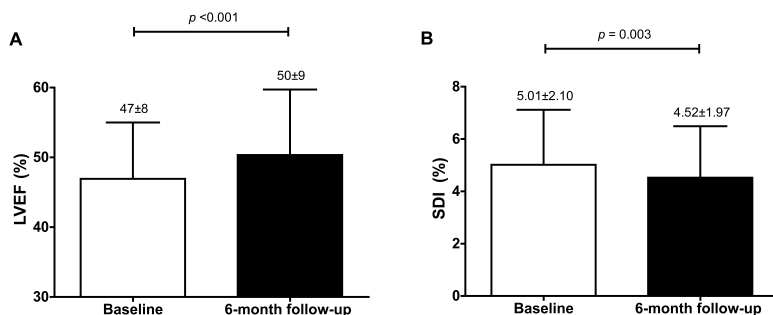
Figure 1. Changes in left ventricular ejection fraction (LVEF) and systolic dyssynchrony index (SDI) at 6-month follow-up. (**Panel A**) A significant increase in LVEF at 6 months follow-up. (**Panel B**) A significant decrease in SDI at 6 months follow-up.
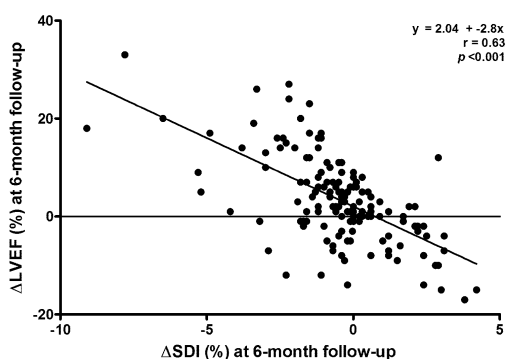
Figure 2. Relation between the change in left ventricular ejection fraction (ΔLVEF) and the change in systolic dyssynchrony index (ΔSDI) after 6 months follow-up in the study population. In patients with a decrease in SDI (restoration of LV synchronicity), LVEF improved. In contrast, in patients with an increase in SDI (impairment in LV dyssynchrony), LVEF decreased.

Of note, patients with anterior AMI improved in SDI to a larger extent when compared with non-anterior AMI patients (ΔSDI: -1.30 ± 2.32 vs. $0.53\pm1.55\%$; p <0.001). Conversely, no difference in ΔSDI was observed between patients with single-vessel and multi-vessel disease (-0.55 ± 1.85 vs. $-0.39\pm2.27\%$; p = 0.66).

A strong correlation was found between ΔLVEF and ΔSDI ($\beta = -0.63$; 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 ΔLVESV and ΔSDI ($\beta = 0.33$; p <0.001).

Table 2. Univariate and multivariate regression analyses to determine the independent correlates of change in LVEF at 6 months follow-up

	Univariate		Multivariate	
	β	p value	β	p value
Age	0.070	0.40	-	-
Female gender	0.081	0.33	-	-
Diabetes	-0.053	0.52	-	-
Family history of CAD	0.059	0.48	-	-
Hypercholesterolemia	-0.26	0.002	-0.12	0.038
Hypertension	-0.24	0.003	-0.11	0.057
Current or previous smoker	0.14	0.089	-	-
Anterior acute MI	0.16	0.047	0.017	0.78
Multi-vessel coronary disease	-0.048	0.56	-	-
Peak troponin T	-0.29	0.001	-0.35	<0.001
Symptom onset to balloon time	-0.017	0.84	-	-
Baseline LVESV	-0.031	0.71	-	-
Baseline LVEF	-0.39	<0.001	-0.30	<0.001
Baseline WMSI	-0.039	0.64	-	-
Presence of mitral regurgitation at baseline	-0.16	0.062	-	-
Presence of diastolic dysfunction at baseline	0.088	0.29	-	-
Baseline SDI	0.11	0.18	-	-
ΔSDI	-0.63	<0.001	-0.46	<0.001

The R^2 of the model selected at multivariate analysis was 0.57. Abbreviations as in Table 1.

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 R2 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 synchronicty. 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 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.[7] Peak troponin T levels measured within the first 18 h of admission may not accurately reflect the infarct size.[22] 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.

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