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Incremental value of advanced cardiac imaging modalities for diagnosis and patient management : focus on real-time three-dimensional echocardiography and magnetic resonance imaging

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Citation

Marsan, N. A. (2011, November 7). *Incremental value of advanced cardiac imaging modalities for diagnosis and patient management : focus on real-time three-dimensional echocardiography and magnetic resonance imaging*. Retrieved from <https://hdl.handle.net/1887/18020>

Version: Corrected Publisher's Version

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Note: To cite this publication please use the final published version (if applicable).

CHAPTER 13

Impact of left ventricular dyssynchrony early on left ventricular function after first acute myocardial infarction

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Am J Cardiol 2010;105:306-11.

ABSTRACT

Objectives: The impact of left ventricular (LV) dyssynchrony after acute myocardial infarction (AMI) on LV ejection fraction (EF) is unknown.

Methods: One hundred twenty-nine patients with a first ST-elevation AMI (58 ± 11 years, 78% men) and QRS duration < 120 ms were included. All patients underwent primary percutaneous coronary intervention. Real-time 3-dimensional echocardiography and myocardial contrast echocardiography were performed to assess LV function, LV dyssynchrony, and infarct size. LV dyssynchrony was defined as the standard deviation of the time to reach the minimum systolic volume for 16 LV segments, expressed in percent cardiac cycle (systolic dyssynchrony index [SDI]). Myocardial perfusion at myocardial contrast echocardiography was scored (1 = normal/homogenous; 2 = decreased/patchy; 3 = minimal/absent) using a 16-segment model; a myocardial perfusion index, expressing infarct size, was derived by summing segmental contrast scores and dividing by the number of segments.

Results: SDI in patients with AMI was $5.24 \pm 2.23\%$ compared to $2.02 \pm 0.70\%$ of controls ($p < 0.001$). Patients with AMI and LVEF $< 45\%$ had significantly higher SDI compared to patients with LVEF $> 45\%$ (4.29 ± 1.44 vs 6.95 ± 2.40 , $p < 0.001$). At multivariate analysis, SDI was independently related to LVEF; in addition, the impact of SDI on LV systolic function was incremental to infarct size and anterior location of AMI (F change 16.9, $p < 0.001$).

Conclusions: LV synchronicity is significantly impaired soon after AMI. LV dyssynchrony is related to LVEF and has an additional detrimental effect on LV function, beyond infarct size and the anterior location of AMI.

INTRODUCTION

Advances in echocardiographic techniques, i.e., tissue Doppler echocardiography, speckle-tracking echocardiography, and real-time 3-dimensional echocardiography (RT3DE) have recently demonstrated an impaired left ventricular (LV) synchronicity in patients with acute myocardial infarction (AMI) ¹⁻³. In the setting of chronic heart failure, LV dyssynchrony is a phenomenon extensively described and related to impaired LV systolic function and poor prognosis ⁴⁻⁸. In the setting of AMI, however, it is unclear whether LV dyssynchrony is independently associated with LV ejection fraction (EF). Moreover, the detrimental effect of LV dyssynchrony on LV systolic function in addition to other variables remains unknown. Accordingly, the aim of the present study was twofold: (1) to assess the decrease in LV synchronicity after AMI (compared to normal values) and (2) to explore the relation between this decrease in LV synchronicity and LV systolic function. In particular, the effect of LV dyssynchrony on LVEF in addition to other variables was assessed.

METHODS

The population consisted of 159 consecutive patients admitted to the coronary care unit because of a first ST-segment elevation AMI. Patients with a QRS complex duration >120 ms were excluded from the study.

The diagnosis of AMI was made on the basis of typical ECG changes and/or ischemic chest pain associated with elevation of cardiac biomarkers ⁹. All patients underwent immediate coronary angiography and primary percutaneous coronary intervention (PCI). The infarct-related artery was identified by the site of coronary occlusion during coronary angiography and ECG criteria. During PCI, the final TIMI (Thrombolysis In Myocardial Infarction) flow was assessed. In addition, the time from onset of symptoms to first balloon dilatation (symptoms-to-balloon time) was determined.

Using the ECGs acquired on admission and 1 h after PCI, the ST-segment resolution was assessed, as previously described ¹⁰. The sum of ST-segment elevation was measured 60 ms after the J point in leads I, aVL, and V1 to V6 for anterior AMI and leads II, III, aVF, V5, and V6 for non-anterior AMI. The percentage of resolution of ST-segment elevation from before to after PCI was then calculated.

RT3DE was performed 48 hours after PCI to assess global LV systolic function and LV dyssynchrony; immediately after RT3DE, myocardial contrast echocardiography was performed to assess infarct size. These echocardiographic examinations are part of the routine, comprehensive assessment of patients presenting with AMI in our clinics.

In addition, 30 subjects without evidence of structural heart disease and without known risk factors for coronary artery disease, matched for age, gender and body surface area, who

underwent RT3DE, were included as a normal control group. These individuals were derived from the echo database and were clinically referred for echocardiographic evaluation because of atypical chest pain, palpitations or syncope without murmur.

To determine the impairment of LV synchronicity after AMI, the patient data were compared with the data from the normal controls. In addition, the relation between LV systolic function and other clinical and echocardiographic variables (including LV dyssynchrony, infarct size, and infarct location) was evaluated.

Patients were imaged in 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 3D data sets were acquired in harmonic mode, integrating, during a brief breath-hold, 8 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 for the off-line analysis.

Off-line analysis was performed by an observer who had no knowledge of the patient's identity and standard 2DE and MCE results. A dedicated software (4D LV-Analysis®; TomTec, Munich, Germany) was used. The algorithm used by the software to calculate LV end-diastolic volume, LV end-systolic volume and LVEF is described in detail elsewhere ¹¹. Briefly, a semi-automated method for the detection of the apical 4-chamber view and the 60° and 120° incremental views and for the tracing of the endocardial border in the entire 3D dataset (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. In addition, the same LV model was used for the assessment of LV dyssynchrony, as previously described ¹². Briefly, the

LV model was automatically divided in 16 pyramidal subvolumes (6 basal segments, 6 mid segments, and 4 apical segments) based around a nonfixed central point. For each volumetric segment, the time–volume curve for the entire cardiac cycle was derived and the time taken to reach the minimum systolic volume was calculated. The standard deviation of the time taken to reach the minimum systolic volume expressed as percent cardiac cycle (systolic dyssynchrony index [SDI]) was then calculated as a marker of global LV dyssynchrony ¹².

Immediately after RT3DE, myocardial contrast echocardiography was performed to evaluate myocardial perfusion, to assess infarct size after AMI. The same ultrasound system equipped with a 3.5-MHz transducer was used. The 3 standard apical views were acquired using a low-power technique (mechanical index 0.10 to 0.26). Background gains were set so that minimal tissue signal was seen, and the focus was set at the level of the mitral valve. Luminity® (Bristol-Myers Squibb Pharma, Brussels, Belgium) was used as contrast agent. Each patient received an infusion of 1.3 mL of echo contrast diluted in 50 mL of 0.9% NaCl solution through a 20 gauge intravenous catheter in a proximal forearm vein. Infusion rate was initially set at 4.0 mL/min and then titrated to achieve optimal myocardial enhancement without attenuation artifacts ¹³. Machine settings were optimized to obtain the best pos-

sible myocardial opacification with minimal attenuation. At least 15 cardiac cycles after high mechanical index (1.7) microbubble destruction¹⁴ were stored in cine-loop format.

Analysis of myocardial contrast echocardiograms was performed off-line using EchoPAC version 7.0.0 (GE Healthcare, Horten, Norway). To evaluate myocardial perfusion, the LV was divided according to the same 16-segment model of the American Society of Echocardiography¹⁵. A semiquantitative scoring system was used to assess contrast intensity after microbubble destruction: 1) normal/homogenous opacification; 2) reduced/patchy opacification; 3) minimal or absent contrast opacification^{14,16}. A myocardial perfusion index, expressing infarct size, was derived by adding contrast scores of all segments and dividing by the total number of segments^{14,16}.

Continuous variables are expressed as mean±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 control subjects and AMI patients were assessed using the Student *t* test or the Mann-Whitney *U* test, if appropriate. *Chi*-square test or Fisher exact test, if appropriate, were computed to assess differences in categorical variables. Univariate and multivariate linear regression analysis were performed to evaluate the relationship between LVEF in patients with AMI and the characteristics of age, gender, coronary risk factors, infarct location, multi-vessel disease, symptoms-to-balloon time, TIMI flow grade 3 after PCI, QRS duration, ST-segment resolution, peak troponin T, LV dyssynchrony (expressed as SDI) and infarct size (expressed as myocardial perfusion index). Only variables with *p*-value <0.1 at univariate analysis were entered as covariates in the multivariate model. To determine the potential incremental value of SDI over the other variables, the *R*² of the multivariate model was compared to the *R*² of the same model without SDI. A *p*-value <0.05 was considered statistically significant. Statistical analysis was performed using the SPSS software package (SPSS 15.0, Chicago, Illinois).

RESULTS

Reliable RT3DE and myocardial contrast echocardiographic data were obtained in 129 patients; consequently, 30 patients were excluded from further analysis. All control subjects had reliable RT3DE data.

Clinical and echocardiographic characteristics of AMI patients are listed in Table 1. A total of 60 (46%) patients had an anterior AMI; obstructive multi-vessel disease (i.e. > 1 vessel with a luminal narrowing ≥70%) was present in 46 (36%) patients.

As compared to control subjects, AMI patients had significantly lower LVEF (64±6% vs. 46±9%, *p* <0.001) and significantly higher SDI (2.02±0.70% vs. 5.24±2.23%, *p* <0.001). The observed impairment of LV synchronicity in AMI patients is shown in Figure 1.

Table 1. Clinical and echocardiographic characteristics of control subjects and patients with acute myocardial infarction (AMI)

	Control subjects (n = 30)	AMI patients (n = 129)	p-value
Age (years)	57±11	58±11	0.53
Male gender	23 (77%)	100 (78%)	0.92
Body surface area (m2)	1.96±0.58	1.98±0.22	0.76
Diabetes	-	14 (11%)	-
Family history of coronary artery disease*	-	49 (38%)	-
Hypercholesterolemia†	-	19 (15%)	-
Hypertension‡	-	47 (36%)	-
Current or previous smoking	-	76 (59%)	-
Anterior myocardial infarction	-	60 (46%)	-
Infarct-related artery			
- left anterior descending coronary artery	-	60 (46%)	-
- left circumflex coronary artery	-	22 (18%)	-
- right coronary artery	-	46 (36%)	-
Multi-vessel disease	-	46 (36%)	-
TIMI flow 3	-	109 (85%)	-
Symptoms-to-balloon time (min)	-	177 (134-219)	-
QRS duration	-	96±13	-
ST-segment resolution (%)	-	62±31	-
Peak troponin T (µg/l)	-	3.10 (1.52-6.89)	-
LVEDV (ml)	90±23	110±30	0.01
LVESV (ml)	35±14	60±23	<0.001
LVEF (%)	64±6	46±9	<0.001
SDI (%)	2.02±0.70	5.24±2.23	<0.001
MPI	-	1.25 (1.09-1.50)	-

EF: ejection fraction; EDV: end-diastolic volume; ESV: end-systolic volume; LV: left ventricular; MPI: myocardial perfusion index; SDI: systolic dyssynchrony index; TIMI: Thrombolysis In Myocardial Infarction. Data are expressed as mean±SD, median (interquartile range), or number of subjects (percentage).

* Defined when close relatives had premature coronary artery disease

(men <55 years old and women <65 years old).

† Defined as total cholesterol level ≥240 mg/dl.

‡ Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg. Table 2. Clinical and echocardiographic characteristics of patients with acute myocardial infarction in relation to left ventricular systolic function.

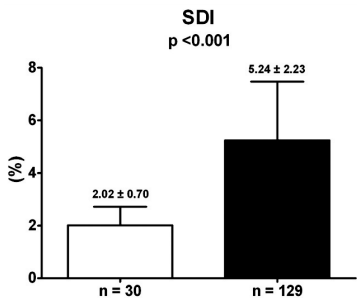


Figure 1. Systolic dyssynchrony index in control subjects (white bars) and acute myocardial infarction (AMI) patients (black bars) (p <0.001).

Table 2. Clinical and echocardiographic characteristics of patients with acute myocardial infarction in relation to left ventricular systolic function

Variable	LVEF $\geq 45\%$ (n = 83)	LVEF $< 45\%$ (n = 46)	p-value
Age (years)	57 $\pm$ 11	60 $\pm$ 11	0.090
Male gender	60 (72%)	40 (87%)	0.056
Diabetes	9 (11%)	5 (11%)	1.00
Family history of coronary artery disease	31 (37%)	18 (39%)	0.84
Hypercholesterolemia	12 (15%)	7 (15%)	0.91
Hypertension	35 (42%)	12 (26%)	0.069
Current or previous smoker	47 (57%)	29 (63%)	0.48
Anterior myocardial infarction	34 (41%)	26 (57%)	0.090
Multivessel-disease	24 (29%)	22 (48%)	0.032
TIMI flow 3	74 (89%)	35 (76%)	0.049
Symptoms-to-balloon time (min)	170 (127–215)	184 (150–231)	0.16
QRS duration (ms)	94 $\pm$ 13	99 $\pm$ 13	0.027
ST-segment resolution (%)	65 $\pm$ 31	56 $\pm$ 30	0.13
Peak troponin T (μ g/l)	2.69 (1.23–5.39)	4.82 (1.85–1.02)	0.006
LVEDV (ml)	105 $\pm$ 25	118 $\pm$ 38	0.042
LVESV (ml)	51 $\pm$ 14	75 $\pm$ 28	<0.001
LVEF (%)	51 $\pm$ 5	37 $\pm$ 6	<0.001
SDI (%)	4.29 $\pm$ 1.44	6.95 $\pm$ 2.40	<0.001
MPI	1.19 (1.00–1.38)	1.56 (1.23–1.81)	<0.001

Abbreviations as in Table 1. Data are expressed as mean $\pm$ SD, median (interquartile range), or number of subjects (percentage).

Patients with AMI were subdivided into 2 groups according to LV systolic function (LVEF $\geq 45\%$, n = 83; LVEF $< 45\%$, n = 46). Clinical and echocardiographic characteristics of these 2 groups are presented in Table 2. Patients with LVEF $< 45\%$ had more frequently multivessel disease (p = 0.032), less frequently TIMI flow grade 3 after primary PCI (p = 0.049) and higher peak troponin T (p = 0.006) compared to patients with LVEF $\geq 45\%$ (Table 2).

Regarding LV synchronicity, patients with LVEF $< 45\%$ had significantly higher SDI (p < 0.001) compared to patients with LVEF $\geq 45\%$ (Table 2). Figure 2 shows the impairment of

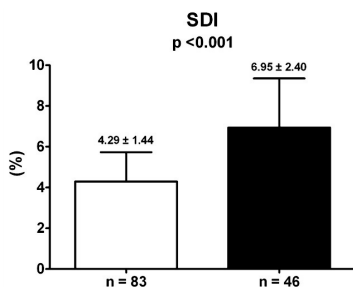


Figure 2. Systolic dyssynchrony index in patients with AMI in relation to LV systolic function, namely LVEF $\geq 45\%$ (white bars) and LVEF $< 45\%$ (black bars) (p < 0.001).

LV synchronicity in patients with AMI and LVEF <45% compared to those with LVEF $\geq$ 45%. Indeed, a significant relation ($r = 0.69$, $p < 0.001$) was noted between LVEF and SDI.

Table 3 shows the results of the univariate and multivariate linear regression analysis performed to determine the factors related to LV systolic function. At univariate analysis, several variables were significantly related to LVEF. However, at multivariate analysis, only anterior location of AMI (beta -0.16, $p = 0.037$), SDI (beta -0.52, $p < 0.001$), and myocardial perfusion index (beta -0.28, $p = 0.034$) were independent factors associated with LVEF. Adding SDI to the multivariate model significantly increased R^2 from 0.45 to 0.52 (F change 16.9, $p < 0.001$).

Figure 3 shows an example of a patient with severe impairment of LV systolic function and synchronicity after AMI.

Table 3. Univariate and multivariate linear regression analyses to determine the independent correlates of left ventricular systolic function in patients with acute myocardial infarction.

	Univariate		Multivariate	
	β	p-value	β	p-value
Age	-0.17	0.058	0.025	0.72
Male gender	-0.14	0.10	-	-
Diabetes	0.017	0.85	-	-
Family history of coronary artery disease	0.092	0.30	-	-
Hypercholesterolemia	-0.031	0.73	-	-
Hypertension	0.051	0.57	-	-
Current or previous smoker	-0.005	0.96	-	-
Anterior myocardial infarction	-0.19	0.036	-0.16	0.037
Multi-vessel disease	-0.19	0.032	-0.94	0.35
TIMI flow	0.15	0.092	0.001	0.99
Symptoms-to-balloon time	-0.077	0.38	-	-
QRS duration	-0.17	0.061	-0.0079	0.24
ST-segment resolution	0.21	0.015	0.028	0.69
Peak troponin T	-0.28	0.001	0.037	0.62
SDI	-0.69	<0.001	-0.52	<0.001
MPI	-0.65	<0.001	-0.28	0.034

The R^2 of the model selected at multivariate analysis was 0.52.

Abbreviations as in Table 1.

DISCUSSION

The results of the present study show that LV synchronicity (assessed by RT3DE) is significantly impaired soon after AMI. The severity of this impairment is related to LV systolic function. In addition, the impact of SDI on LV systolic function was incremental to infarct size and anterior location of AMI.

The presence and clinical relevance of LV dyssynchrony in the setting of chronic heart failure has been extensively investigated in the previous decade; in this group of patients, loss of LV

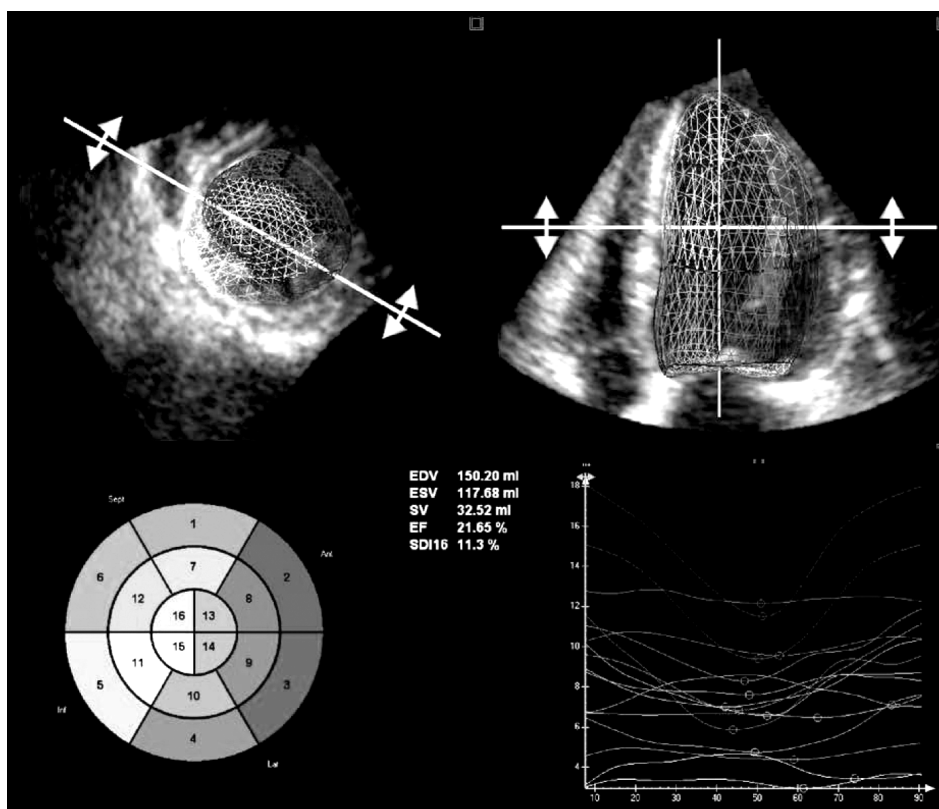


Figure 3. Example of a patient showing severe impairment of LV systolic function (LVEF 22%) and synchronicity (SDI 11.3%) after AMI.

synchronous contraction is related to impaired LV systolic function and poor hemodynamic status and is a predictor of worse outcome^{4–8}. In addition, restoration of LV synchronicity, by cardiac resynchronization therapy, has been shown to reverse LV remodeling and to improve LV function and prognosis^{17–19}.

More recently, LV dyssynchrony has been described to occur also in patients with AMI^{1–3,20}. However, the clinical meaning of this phenomenon has not been yet fully elucidated. In particular, it is unclear whether the presence of LV dyssynchrony after AMI independently influences LV function in these patients. Moreover, the detrimental effect of LV dyssynchrony in addition to other variables (e.g., infarct size and anterior location of AMI) on LV systolic function remains unknown.

In the present study, RT3DE was used to assess LV systolic function and LV synchronicity after AMI. This approach has been documented to provide highly accurate measurements of LVEF²¹; in addition, it is more robust than tissue Doppler echocardiography for the evaluation of LV dyssynchrony, being more reproducible and more consistent in differentiating healthy subjects from those affected by LV dyssynchrony²². Moreover, myocardial contrast

echocardiography was used to obtain information about myocardial perfusion abnormalities after AMI and, hence, infarct size ²³.

In line with previous observations ¹, impairment of LV synchronicity (expressed as SDI) was observed in patients with AMI compared to control subjects. In addition, LV dyssynchrony was significantly associated to LV systolic function. Importantly, this relation remained after adjustment for infarct size and anterior location of AMI, being incremental over these variables in determining LVEF. LV dyssynchrony results in a non-homogenous distribution of myocardial load and deformation and thus increases myocardial energy demand ²⁴; this may negatively influence the contractility of residual viable myocardium, thus further impairing LV function. The results of the present study suggest that LV dyssynchrony soon after AMI has an additional detrimental impact on LV performance, beyond the infarct size itself; moreover, it may potentially contribute to the vicious circle of progression of LV dysfunction ². In this perspective, therapeutic approaches aiming to recover a more synchronous LV contraction (e.g., with cardiac resynchronization therapy) may be beneficial and improve LV systolic function, thus preventing LV remodeling. However, further studies are needed to support this hypothesis.

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