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Deformation imaging and three-dimensional echocardiography:

**Implications on clinical management of
patients with ischemic heart disease**

Georgette Elise Hoogslag

The studies described in this thesis were performed at the Department of Cardiology of the Leiden University Medical Center, Leiden, The Netherlands.

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Deformation imaging and three-dimensional echocardiography:

Implications on clinical management of patients with ischemic heart disease

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Aan mijn ouders en aan Mihály

It always seems impossible until it's done
Nelson Rolihlahla Mandela 1918-2013

TABLE OF CONTENTS

Chapter 1	General introduction and outline of the thesis	9
Part I	<i>Echocardiography in ischemic heart disease</i>	
Chapter 2	Prognostic implications of left ventricular regional function heterogeneity assessed with 2-dimensional speckle tracking in patients with ST-segment elevation myocardial infarction and depressed left ventricular ejection fraction	25
Chapter 3	Determinants of Right Ventricular Remodeling Following ST-Segment Elevation Myocardial infarction	43
Chapter 4	Time course, predictors and prognostic implications of significant mitral regurgitation after ST-segment elevation myocardial infarction	57
Chapter 5	Changes in global longitudinal peak systolic strain in diabetic patients after ST-segment elevation myocardial infarction	77
Chapter 6	Assessment of Left Ventricular Excursion using Three-Dimensional Dobutamine Stress Echocardiography to Identify Significant Coronary Artery Disease	91
Part II	<i>Echocardiography in chronic heart failure</i>	
Chapter 7	Clinical, Echocardiographic, and Neurohormonal Response to Cardiac Resynchronization Therapy: Are They Interchangeable?	107
Chapter 8	The Relationship between Time from Myocardial Infarction, Left Ventricular Dyssynchrony, and the Risk for Ventricular Arrhythmia: Speckle-Tracking Echocardiographic Analysis	127
Chapter 9	Summary, conclusions and future perspectives Samenvatting, conclusies en toekomstperspectieven List of publications Dankwoord Curriculum Vitae	143

CHAPTER 1

General introduction and outline of the thesis



GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Introduction

Cardiovascular disease remains one of the leading causes of death in the Western world.¹ It accounts for 1 of every 3 deaths in the United States of America, of which approximately 40% caused by coronary heart disease.^{1,2} According to the World Health organization, the number of deaths due to cardiovascular disease will increase to 23.3 million by 2030.¹ Moreover, from 2000 until 2010, a 28% increase was found in the number of inpatient cardiovascular operations and procedures in the United States of America.²

Acute myocardial infarction is a major cause of death. The percentages of acute coronary syndromes with ST-segment elevation myocardial infarction (STEMI) varies between 29% and 47%.^{3,4} The use of evidence-based therapy and primary percutaneous coronary intervention (PCI) has led to improvements in short-term survival and reduction in left ventricular (LV) infarct size, thereby improving LV function and preventing LV remodeling.⁵ However, these improved short-term outcomes have resulted in a growing and aging population that is at increased risk for developing heart failure and experiencing re-infarction and sudden cardiac death during long-term follow-up, resulting in a significant socioeconomic burden.^{6,7} The current guidelines regarding management of STEMI and heart failure patients therefore focus on optimization of care, secondary prevention and risk stratification of this population.⁸⁻¹⁰ Multimodality imaging, especially echocardiography, has played a fundamental role in the risk stratification of patients with ischemic heart disease, in particular after STEMI.

Echocardiography for the risk stratification of patients with ischemic heart disease

In daily clinical practice, echocardiography has been frequently applied in the management of patients with ischemic heart disease.⁸⁻¹¹ This safe, inexpensive and widely available imaging modality can be easily used at the bedside and is the imaging technique of first choice for surveillance.¹¹ Generally, echocardiography is useful to establish the diagnosis, location and extent of a myocardial infarction and to detect complications after myocardial infarction.¹¹ More importantly, the prognosis and risk stratification in the acute phase and during follow-up of ischemic heart disease patients can be assessed using echocardiography. In Table 1, an overview is provided of prognostic echocardiographic parameters in ischemic heart disease.

LV systolic function is an important prognostic determinant in ischemic heart disease and should be assessed according to current STEMI, heart failure and echocardiographic guidelines.^{8-10,12-14} Acutely after myocardial infarction, extensive myocardial damage occurs resulting in reduced contractile reserve, which could persist or even deteriorate if ongoing ischemia exists. At follow-up, LV dilatation due to infarct expansion and stretching of the myocardial scar could result in reduced LV systolic function.

Table 1. *Echocardiographic parameters associated with prognosis in ischemic heart disease*

CONVENTIONAL ECHOCARDIOGRAPHY	
• Left ventricular function	• Wall motion score index
	• Left ventricular ejection fraction
	• Left ventricular excursion
• Left ventricular volumes	
• Mitral regurgitation	
• Left atrial volume	
• Diastolic function	
• Right ventricular function	
• Right ventricular dimensions	
• Systolic pulmonary arterial pressure	
ADVANCED ECHOCARDIOGRAPHY	
• Left ventricular function	• Wall motion score index
	• Left ventricular ejection fraction
	• Longitudinal strain (global and regional)
	• Left ventricular excursion
• Left ventricular volumes	

Traditionally, LV ejection fraction (LVEF), a volume-based measure, has been used to measure LV systolic function. Management decision making in ischemic heart disease strongly relies on LVEF, in particular the usage of device therapy such as cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillators (ICDs).^{8-10,12,15,16} However, LVEF is a relatively insensitive, observer dependent measurement. Furthermore, LVEF has proven to be a relatively insensitive tool of LV performance and has limited accuracy to identify patients at risk for ventricular arrhythmias.¹⁷⁻²⁰ In the last years, several advances in echocardiography resulted in evaluation of novel indices in order to improve characterization of LV function and thereby stratification of patients with ischemic heart disease. Speckle-tracking strain echocardiography provides more insight in cardiac mechanics and LV performance.²¹⁻²⁴ A more sensitive assessment of both regional and global myocardial contraction can be performed using this technique.^{25,26} Figure 1 provides an example of this echocardiographic method. In ischemic heart disease patients, speckle-tracking strain echocardiography has been associated with the occurrence of all-cause mortality, re-infarction and ventricular arrhythmias, indicating its value in daily clinical practice.²⁷⁻³⁰

LV volumes also add significant prognostic information to the risk stratification of patients with ischemic heart disease.³¹ LV adverse remodeling post-infarction, observed in

approximately 30% of acute myocardial infarction patients, has been associated with an increased risk of mortality and development of heart failure.³²⁻³⁶

Another prognostic echocardiographic measure is the presence and severity of MR.³⁷ Acutely after myocardial infarction, ischemic MR is frequently observed.³⁸⁻⁴⁰ On the other hand, functional ischemic MR is a highly dynamic lesion that is likely to improve after coronary revascularization or to impair as a result of progressive LV adverse remodeling and tethering of the mitral leaflets.^{41,42} Furthermore, it has been associated with long-term mortality and the development of heart failure.^{38,43} Yet, data on the time course and prognostic implications of functional ischemic MR in the contemporary era of primary PCI has not been explored to date.

Last but not least, right ventricular (RV) function and dimensions are also important prognostic markers in ischemic heart disease. Especially, RV dysfunction portends a poor prognosis post-myocardial infarction.⁴⁴⁻⁴⁶ However, RV function may recover within days or weeks, particularly after successful reperfusion.^{47,48} Not surprisingly, the current guidelines recommend evaluation of RV function in ischemic heart disease.^{8-10,13,14} Notably, while LV remodeling received much attention in ischemic heart disease, less research is conducted on RV remodeling using echocardiography in the primary PCI era, underscoring the need of additional studies regarding this phenomenon.⁴⁹⁻⁵¹

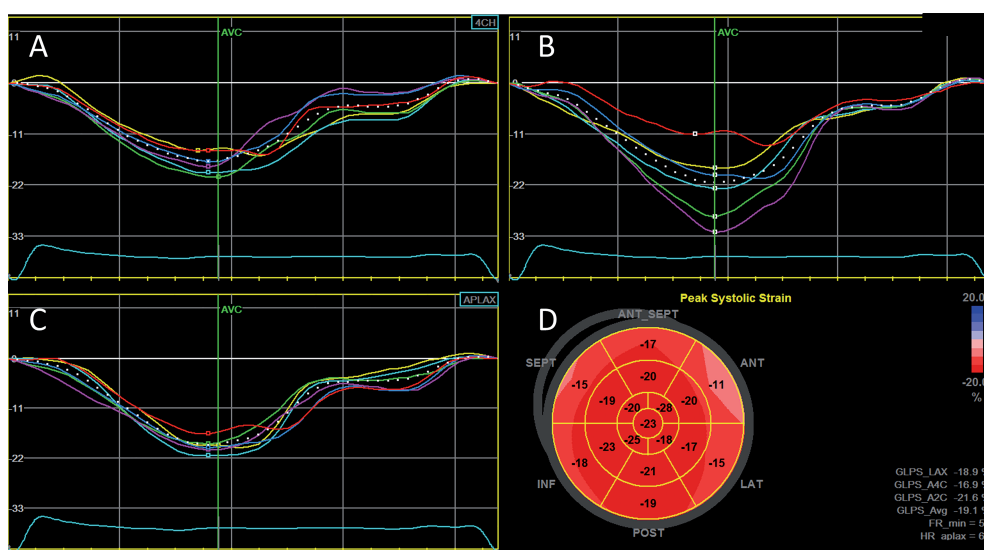


Figure 1. Example of global longitudinal peak systolic (GLPS) strain curves from the 3 apical views of the left ventricle (panel A, 4-chamber view [4CH]; panel B, 2-chamber view [2CH]; panel C, parasternal short-axis view [APLAX]) and summarizing 17-segment bull's eye plot (panel D). The software (EchoPac, GE Medical Systems, Horten, Norway) provides longitudinal peak systolic strain for every segment and for every apical view separately (GLPS_A4C, GLPS_A2C and GLPS_LAX, respectively) and calculates a global longitudinal peak systolic strain value for the entire left ventricle (GLPS_Avg). ANT = anterior wall; ANT_SEPT = antero-septal wall; AVC = aortic valve closure; HR = heart rate; INF = inferior wall; LAT = lateral wall; POST = posterior wall; SEPT = septal wall.

Stress echocardiography for detection of myocardial ischemia and viability

Following an acute myocardial infarction, the presence of residual and/or ischemia provides additional prognostic information.⁵²⁻⁵⁷ Stress echocardiography is one of the recommended tools to detect and localize (residual) ischemia post-myocardial infarction, of which dobutamine stress echocardiography (DSE) is the most widely used method.^{10,56,58,59} Conventionally, regional wall motion and thickening is visually assessed resulting in a wall motion score. However, this semi-quantitative method is challenging, since it is highly subjective and image quality dependent, even when performed by expert observers.^{60,61} Therefore, more quantitative and objective approaches, such as speckle-tracking strain echocardiography and 3-dimensional echocardiography, could overcome these practical limitations of DSE. These approaches do not depend on geometric assumptions or on experience and can be performed semi-automatically. Moreover, global and regional assessments of the myocardium are possible. Hence, these quantitative tools could be useful to accurately detect ischemia. As for speckle-tracking strain echocardiography, this method has been validated against sonomicrometry and evaluated in coronary artery disease patients.⁶²⁻⁶⁸ However, its value in STEMI patients, in whom DSE is particularly challenging due to the presence of existing wall motion abnormalities, has not been investigated to date. Three-dimensional echocardiography has the advantages of overcoming the limitations of 2-dimensional echocardiography, including no geometric assumptions, optimization of image position with no or little foreshortened views, better possibilities of endocardial boundary tracing and a good reproducibility.⁶⁹⁻⁷² An example of 3-dimensional LV volume analysis is shown in Figure 2. Three-dimensional echocardiography could be valuable in the assessment of DSE. An abnormal LV volume response during dobutamine infusion (LV dilatation) has been proposed as marker of ischemia.⁷³⁻⁷⁵ In patients with suspected coronary artery disease, this parameter was associated with more severe coronary artery disease and an increased risk of adverse events, including death and myocardial infarction.⁷³⁻⁷⁵ Another possible application of 3-dimensional echocardiography during DSE could be the assessment of LV excursion. This measure reflects the longitudinal contraction of the LV, which is initially affected in ischemia.⁷⁶⁻⁷⁹ Since previous studies demonstrated a correlation between LV excursion assessed during 2-dimensional stress echocardiography and the presence of coronary artery disease, this could be a promising tool in 3-dimensional DSE.^{76,80-82}

Treatment options in ischemic heart failure: echocardiographic evaluation

Ischemic heart failure is a complex syndrome with many treatment options aiming to improve survival and to prevent progression of symptoms. Pharmaceutical treatment and lifestyle interventions, on the one hand, are the 2 cornerstones of heart failure treatment.⁸ On the other hand, heart failure guidelines have certain recommendations regarding treatment modalities like surgical treatment (e.g. revascularization via PCI or coronary artery bypass surgery, valvular surgery, surgical ventricular restoration), device implantation (e.g.

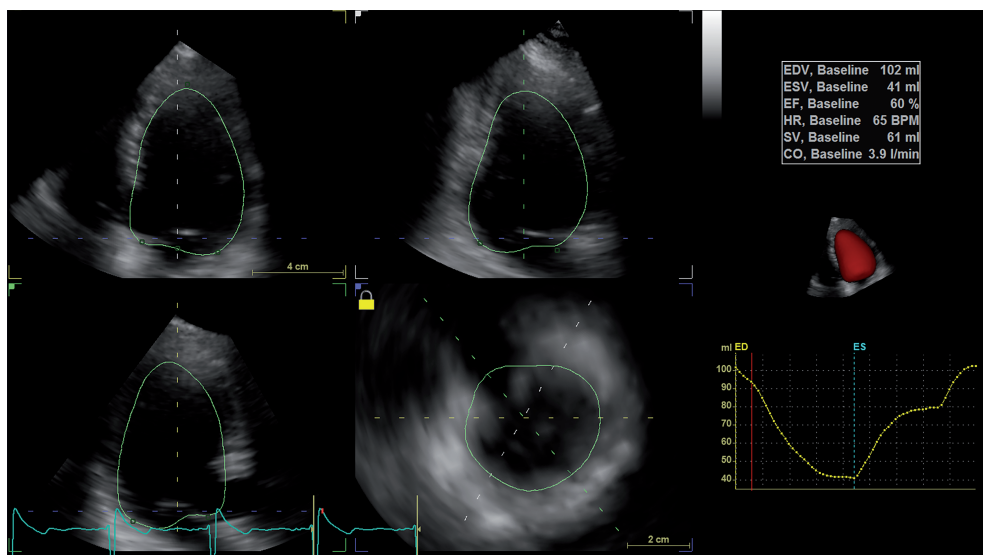


Figure 2. Example of 3-dimensional left ventricular volume analysis obtained by post-processing of a full-volume 3-dimensional dataset. In the left panel, the 3-dimensional dataset is automatically displayed (according to the software EchoPac, GE Medical Systems, Horten, Norway) to visualize the 4-chamber (top left), the 2-chamber (top right) and the parasternal short-axis views (bottom left). After manually indicating the mitral annulus by 4 points and left ventricular apex on the end-systolic and end-diastolic frames, the software automatically identifies the entire endocardial border in each frame. If required, manual adjustment of the endocardial contour is possible. From this, the 3D cast of the left ventricle is created (central right panel). Subsequently, left ventricular volumes and ejection fraction are automatically quantified (top right panel). In the lower right panel, left ventricular volume is plotted over time throughout the cardiac cycle. CO = cardiac output; ED = end-diastole; EDV = end-diastolic volume; EF = ejection fraction; ES = end-systole; ESV = end-systolic volume; HR = heart rate; SV = stroke volume.

ICD, CRT) and mechanical cardiac support (e.g. (left) ventricular assist device).^{8,12,15,16,83}

Therefore, it is of utmost importance to evaluate which treatment options are most suitable in heart failure patients. To warrant the appropriate therapy strategy, cardiac imaging, especially echocardiography, plays a key role.⁸ As recommended by the European Society of Cardiology, the echocardiographic evaluation should at least include assessment of cardiac anatomy (e.g. volumes, dimensions, mass) and function (e.g. LV function and wall motion, RV function, valvular function, pulmonary artery pressure).⁸

Patients with ischemic heart failure can present with various manifestations on echocardiography guiding treatment decision making. LV adverse remodeling, an important prognostic factor, has several treatment options. Surgical ventricular restoration, in combination with coronary artery bypass surgery, could be considered in patients with increased LV end-systolic volumes in order to exclude scar tissue from the LV wall.⁸³ Another therapeutic option could be CRT implantation, an effective therapy in selected patients, including LVEF $\leq 35\%$ and a broad QRS duration, resulting in improvements in symptoms and long-term mortality.^{16,84-86} More importantly, CRT has demonstrated to slow or even reverse LV adverse remodeling.^{85,87} However, 20% to 40% of patients do not respond to

CRT according to current definitions to CRT response.⁸⁷⁻⁹⁰ Studying the different definitions of response to CRT could enable cardiologists to select the group of patients who truly respond to CRT.

Due to LV dilatation, functional MR could be observed as a result of reduced leaflet coaptation. Depending on the symptomatology, patients' comorbidity, LV systolic function, LV dimensions (e.g. LV end-diastolic diameter) and the presence or absence of significant coronary artery disease, ischemic MR could be treated by mitral valve repair (in combination with coronary artery bypass surgery), mitral valve replacement or percutaneous edge-to-edge repair (MitraClip).⁸ However, patient selection has proved to be suboptimal: the advantageous LV reverse remodeling following surgical mitral valve repair has only been reported in 40% to 52% of heart failure patients with moderate to severe functional MR.⁹¹⁻⁹³ Consequently, research to improve identification of patients who will benefit from one of these treatment modalities is warranted.

Additionally, the risk of sudden cardiac death should be evaluated. LVEF is a major determinant of ventricular arrhythmias and an established criterion to select patients for ICD implantation.^{12,15,94} As highlighted above, LVEF has proved to have limited specificity to identify patients who will benefit from ICD.^{17,19} Therefore, more insights in the arrhythmogenic substrate of ventricular arrhythmias, including substrate characterization, could aid in implanting ICD in the appropriate patients to prevent sudden cardiac death.

Finally, if conventional treatment options are not eligible and patients are diagnosed with end-stage heart failure, advanced and experimental treatment options could be considered including heart transplantation, mechanical cardiac support (either as bridge to transplantation or as destination therapy) and cell therapy.⁸

Outline of the thesis

The objective of this thesis was to evaluate the role of echocardiography for the risk stratification and treatment guidance of patients with ischemic heart disease.

In **Part I**, the value of echocardiography was investigated in ischemic heart disease, in particular in the acute setting post-STEMI and during follow-up until 12 months after the index infarction. The time course of several parameters as well as the application of advanced echocardiography was addressed. **Chapter 2** analyses the border zone, assessed by speckle-tracking strain echocardiography, as a potential risk factor for ventricular arrhythmias. **Chapter 3** evaluates the changes in RV dimensions and function, including RV remodeling. **Chapter 4** discusses the time course of MR following STEMI in relation to adverse outcome. **Chapter 5** provides more insight in the subtle changes in LV systolic function in a cohort of STEMI patients with diabetes. **Chapter 6** describes a novel technique, LV excursion, to quantify 3-dimensional DSE in relation to the presence of coronary artery disease in patients with suspected coronary artery disease.

Part II focuses on the role of echocardiography in decision making in patients with chronic ischemic heart disease who developed heart failure, especially in CRT, cardiac surgery and ICD therapy. **Chapter 7** investigates the role of the biomarker N-terminal pro-brain natriuretic peptide as marker of CRT response. Finally, **Chapter 8** provides more insight in the temporal heterogeneity of segmental myocardial deformation in order to improve risk stratification of ventricular arrhythmias in patients with ischemic heart disease.

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PART I

Echocardiography in ischemic heart disease



CHAPTER 2

Prognostic implications of left ventricular regional function heterogeneity assessed with two-dimensional speckle tracking in patients with ST-segment elevation myocardial infarction and depressed left ventricular ejection fraction

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ABSTRACT

The aim of the current study was to evaluate the prognostic implications of myocardial tissue heterogeneity assessed with two-dimensional speckle-tracking echocardiography in patients three months after first ST-segment elevation myocardial infarction (STEMI) with left ventricular ejection fraction (LVEF) $\leq 35\%$. For this purpose, a total of 79 patients with first STEMI and LVEF $\leq 35\%$ at three months postinfarction were evaluated. Based on left ventricular (LV) speckle-tracking longitudinal strain echocardiography, the infarct core, border zone, and remote zone at baseline and three months' follow-up were defined. Patients were followed for the occurrence of the composite end point of appropriate implantable cardioverter-defibrillator (ICD) therapy and/or cardiac mortality. During a median follow-up of 46 months, 13 patients (17%) reached the composite end point. At baseline, patients with and without events showed comparable values of LV longitudinal strain at the infarct, border, and remote zones. However, at three months' follow-up, patients with events showed significantly more impaired longitudinal strain at the border zone ($-6.8 \pm 3.1\%$ vs. $-10.5 \pm 4.9\%$, $p=0.002$), whereas LVEF was comparable ($28 \pm 6\%$ vs. $31 \pm 4\%$, $p=0.09$). The median three-month LV longitudinal strain at the border zone was -9.4% . Multivariate Cox regression analysis demonstrated that three-month longitudinal strain $>-9.4\%$ at the border zone was independently associated with the composite end point (hazard ratio 3.94, 95% confidence interval 1.05–14.70, $p=0.04$). In conclusion, regional longitudinal strain at the border zone three months post-STEMI is associated with appropriate ICD therapy and cardiac mortality.

INTRODUCTION

Myocardial tissue heterogeneity has been associated with sudden cardiac death and all-cause mortality in patients with ischemic heart disease.¹⁻⁴ Among several pathophysiologic mechanisms of ventricular arrhythmias, myocardial scar has been associated with increased risk for fatal arrhythmias.⁵ Especially, the border zone between the myocardial scar tissue and preserved viable myocardial tissue is an important anatomic substrate for the occurrence of re-entrant ventricular arrhythmias.^{5,6}

An implantable cardioverter-defibrillator (ICD) for primary prevention early after myocardial infarction is a class I indication for patients who have symptoms of heart failure (New York Heart Association (NYHA) functional class II–III) and left ventricular ejection fraction (LVEF) $\leq 35\%$ at least 40 days after the index infarct.⁷ However, the results of randomized controlled trials including patients immediately after STEMI have not convincingly shown the benefit of ICD in this population.^{8,9} LVEF was an established criterion to select patients for ICD implantation in those trials and is included in current guidelines.⁷ However, LVEF has proved to have limited specificity in identifying patients who will benefit from ICD.^{10,11} Evaluation of myocardial tissue heterogeneity with novel imaging techniques has shown improved accuracy for the prediction of ventricular arrhythmias.¹²⁻¹⁴ Recently, two-dimensional (2D) speckle-tracking echocardiography has been introduced as a novel technique to assess regional myocardial function and heterogeneity in the infarct core, border zone, and remote area in patients with stable ischemic chronic heart disease.^{3,14} However, changes in tissue heterogeneity early after myocardial infarction and its impact on long-term outcome of patients have not been explored. Therefore, the objective of the current study was to evaluate the prognostic implications of myocardial tissue functional heterogeneity, assessed with 2D speckle-tracking echocardiography at three months' follow-up, after first ST-segment elevation myocardial infarction (STEMI) in patients with a LVEF $\leq 35\%$ postinfarction.

PATIENTS AND METHODS

Patient population

Patients presenting with a STEMI at the Leiden University Medical Center were included in an ongoing registry (MISSION!).¹⁵ All patients were treated with primary percutaneous coronary intervention according to the institutional MISSION! protocol, which is based on American College of Cardiology/American Heart Association and European Society of Cardiology guidelines. According to this protocol, optimal medical therapy was initiated early during hospitalization, 2D echocardiography was performed within 48 h of admission, and all patients were followed at the outpatient clinic at three, six, and 12 months. A repeat 2D echocardiography was performed at three months.

In the present evaluation, patients with a first STEMI and LVEF $\leq 35\%$ at three months' follow-up were included (Figure 1). During follow-up, patients who experienced ventricular arrhythmias (sustained monomorphic ventricular tachycardia or ventricular fibrillation) or survived an out-of-hospital cardiac arrest received an ICD device as secondary prevention (after exclusion of any completely reversible cause). Patients who developed NYHA II–III heart-failure symptoms and showed a LVEF $\leq 35\%$ or had NYHA functional class I and a LVEF $\leq 30\%$ received an ICD device as primary prevention, as recommended by current guidelines.⁷

In addition, global and regional left ventricular (LV) longitudinal strain was assessed at baseline and at three months' follow-up with 2D speckle-tracking echocardiography. The infarct core, peri-infarct or border zone, and the remote areas were identified. The association between regional LV longitudinal strain and the occurrence of the combined end point (cardiac mortality or appropriate ICD therapy) was evaluated. Patients who presented with appropriate ICD therapy before the three-month echocardiogram, who received cardiac resynchronization therapy, or who had suboptimal image quality for speckle-tracking analysis or inaccurate speckle tracking were excluded.

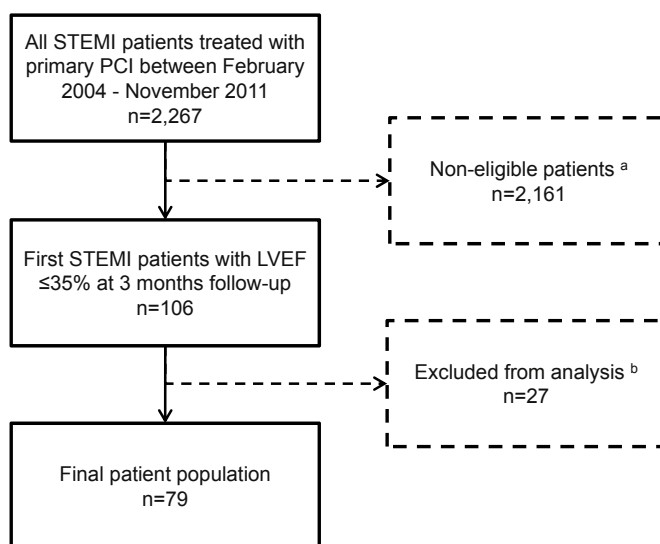


Figure 1. Flowchart of the patient population. ^a Patients were not eligible if they had a myocardial infarction prior to inclusion in the MISSION! registry, if echocardiography was not available at baseline and/or 3 months, and if left ventricular ejection fraction (LVEF) at 3 months was $>35\%$. ^b Reasons for exclusion were (1) implantation of a cardiac resynchronization therapy device with defibrillator capabilities ($n=15$), (2) speckle-tracking analysis was not feasible at baseline and/or 3 months' follow-up ($n=5$), (3) presentation of appropriate implantable cardioverter-defibrillator therapy before the 3-month echocardiogram ($n=1$), and (4) inclusion of baseline and/or 3-month echocardiograms in a previous study ($n=6$).³ PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Clinical and echocardiographic data were collected at the departmental Cardiology Information System (EPD-Vision, Leiden University Medical Center) and the echocardiography database, respectively, and retrospectively analyzed. For this retrospective analysis of clinically acquired data, the Institutional Review Board waived the need of patient written informed consent.

Echocardiography

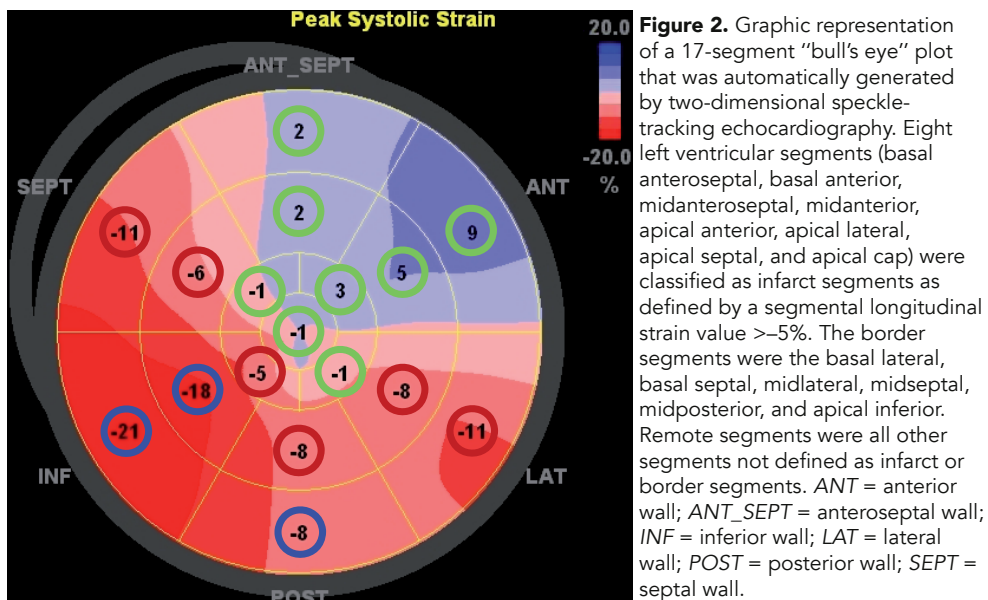
Images were obtained at rest with the patient in the left lateral decubitus position using a commercially available system (Vivid 7 and E9; General Electric-Vingmed, Horten, Norway). Data acquisition was performed with a 3.5-MHz transducer at a depth of 16 cm in the standard parasternal and apical views. During breath hold, M-mode and 2D images were obtained and saved in cine-loop format. Data analysis was performed offline (EchoPAC version 111.0.0; General Electric-Vingmed). LV volumes and function were assessed by tracing the LV end-systolic volumes and end-diastolic volumes in the apical four- and two-chamber views. Using the biplane Simpson's method, LVEF was calculated.¹⁸ Mitral regurgitation was graded as mild (vena contracta width <0.3 cm), moderate (vena contracta width 0.3–0.69 cm), or severe (vena contracta width ≥0.7 cm).¹⁹ Diastolic function was assessed by positioning the Doppler sample volume between the tips of the mitral leaflets and acquiring the pulsed-wave Doppler spectral signal of the mitral valve inflow. Peak early (E) and late (A) diastolic velocities and E-wave deceleration time were assessed. E' was measured with tissue Doppler imaging at the septal side of the mitral annulus in the apical four-chamber view and E/E' ratio was calculated.²⁰ Finally, maximal left atrial volume was measured according to the biplane Simpson's technique in the apical four- and two-chamber views and indexed to the body surface area, as recommended.¹⁸

Speckle tracking: global LV longitudinal strain and regional tissue heterogeneity

To evaluate global and regional longitudinal LV function, 2D speckle-tracking analyses were performed on standard routine gray-scale images of apical four-chamber, two-chamber, and long-axis views using Q-analysis (EchoPAC version 111.0.0; General Electric-Vingmed).²¹ For reliable analysis, images were recorded with a frame rate ≥40 frames per second. First, the LV end-systolic frame was defined by establishing the closure of the aortic valve in the apical long-axis view. Thereafter, the time between R-wave and aortic valve closure was automatically measured and used as a reference for strain analysis at the two- and four-chamber views. The LV endocardial border was automatically traced at end-systole after manual definition of the mitral annulus and LV apex with three index points in all three apical views. The width of the region of interest was manually adjusted to include the entire myocardium. The myocardium was then automatically tracked throughout the cardiac cycle by the software, allowing for manual adjustment of the region of interest to ensure proper myocardial tracking. The software indicated the segments that have poor tracking and allowed for their exclusion. The global and the regional values of peak systolic

LV longitudinal strain were provided by the software in a 17-segment “bull’s eye” plot. As described previously, an infarct segment was defined as a longitudinal strain value $>-5\%$.^{3,14} All segments immediately adjacent to an infarct segment were defined as border segments. A remote segment was defined as any segment that was not an infarct or border segment. Thereafter, the longitudinal strain values at the infarct, border, and remotes zones were manually averaged (Figure 2).³

Previous work has reported intra- and interobserver variabilities for global longitudinal strain analysis in our laboratory as mean absolute differences $\pm$ 1 standard deviation of $1.2 \pm 0.5\%$ and $0.9 \pm 1.0\%$, respectively.³ Furthermore, to define the segmental reproducibility, segmental strain measurements were repeated for 10 randomly selected patients (170 segments) at least 1 month apart by the same observer on the same echocardiographic images and by a second independent observer. For segmental strain assessment, the intra- and interobserver variability were $0.08 \pm 2.36\%$ and $-0.02 \pm 2.67\%$, respectively.



Follow-up and end point definitions

After discharge, patients were followed according to the institutional STEMI protocol.¹⁵ By reviewing medical records, retrieval of survival status through municipal civil registries, and telephone interviews, data on the occurrence of adverse events after discharge were collected, including all-cause mortality, cardiac mortality, implantation of ICD devices, and appropriate ICD therapies, with the date of the three-month echocardiogram as the follow-up onset. Appropriate ICD therapy was defined as antitachycardia pacing or shock for ventricular tachycardia or ventricular fibrillation. This was documented from the ICD

device interrogation printouts and confirmed by independent clinical cardiologists. From the ICD device interrogation printouts, time to appropriate ICD therapy was calculated. A composite end point of cardiac mortality or appropriate ICD therapy was used. Patients without data in the last six months were considered lost to follow-up. Data of these patients were included up to the last date of follow-up.

Statistical analysis

Continuous data are expressed as mean $\pm$ standard deviation or median with 25th and 75th percentiles where appropriate. Categorical data are expressed as frequencies and percentages. To obtain a Gaussian distribution, peak troponin T and peak creatine phosphokinase (CPK) levels were log-transformed. These transformed data were used in statistical tests that required normality (or symmetry). Data were then back-transformed to the original data scales and expressed as median with interquartile ranges.

Patients were divided into two subgroups based on event status (cardiac mortality or appropriate ICD therapy, whichever came first) during long-term follow-up: patients suffering from events and patients without events. Baseline and three-month clinical and echocardiographic data were compared between these subgroups with the unpaired Student's *t* test and χ^2 test. Subsequently, baseline and three-month LV longitudinal strain measurements were compared in the two subgroups with the paired *t* test.

In addition, event rates of the composite end point were analyzed and displayed using cumulative incidence curves. Based on the median value of longitudinal strain measured at the border zone at three months' follow-up, patients were dichotomized into two groups and the groups were compared using cause-specific Cox regression modeling.

Finally, univariate and multivariate Cox proportional-hazards analyses were performed to assess the association between myocardial tissue heterogeneity assessed by 2D speckle-tracking echocardiography, global longitudinal strain, and LVEF with the composite end point. Competing risks were approached by cause-specific hazard modeling. Significant ($p < 0.05$) univariate variables were included in a multivariate Cox regression model. The number of variables included were limited to the number of events to avoid overfitting the model. To avoid multicollinearity between univariate parameters, a correlation coefficient of < 0.7 was set. Relative risks, expressed as hazard ratios (HRs) with associated 95% confidence intervals (CIs), were derived from a Cox regression model. To evaluate the relative merits of tissue heterogeneity assessed by 2D speckle-tracking echocardiography, global longitudinal strain, and LVEF to predict the occurrence of the combined end point, three-month LV longitudinal strain measurements, global longitudinal strain values, and LVEF were introduced separately to a clinical model containing age and peak CPK as univariate variables. Thereafter, the Harrell's *c* statistic for each model was calculated.

All statistical tests were two-sided and $p < 0.05$ was considered to be statistically significant. All statistical analyses were performed with SPSS software (version 17.0; SPSS, Chicago, IL, USA).

RESULTS

Baseline characteristics

A total of 106 patients presenting with a first STEMI and LVEF $\leq 35\%$ at three months' follow-up were eligible for the current study. Fifteen patients received a cardiac resynchronization therapy device with defibrillator capabilities and, accordingly, were excluded from the analysis. Furthermore, in five patients (5%), speckle-tracking analysis was not feasible at baseline and/or three months' follow-up. One patient presented with appropriate ICD therapy before the three-month echocardiogram and was also excluded. Finally, another six patients were excluded, since the echocardiograms of these patients (the baseline echocardiogram of three patients and the three-month echocardiogram of another three patients) were already included in a previous study.³ Therefore, the final patient population included 79 patients. Baseline clinical and echocardiographic characteristics of the total patient population are summarized in Table 1. Most patients were men (81%) and the mean age of the patients was 61 ± 11 years. At baseline, mean LVEF was $36 \pm 7\%$ and moderate to severe mitral regurgitation was observed in 11 patients (14%).

Follow-up

In total, 42 patients (53%) received an ICD device during follow-up after STEMI. The median duration between the date of admission for the index infarction and the date of device implantation was six months (interquartile range 3–11 months). The reason for ICD implantation was primary prevention in 93% of the recipients ($n=39$) and secondary prevention in 7% ($n=3$).

Long-term follow-up was completed in all patients and the median follow-up duration was 46 months (interquartile range 26–60 months). During follow-up, eight patients (10%) presented with appropriate ICD therapy for ventricular tachycardia/fibrillation. All-cause mortality rate in the overall population was 13% ($n=10$). Cardiac cause of death was reported in six patients while the remaining four patients died of noncardiac cause. A total of 13 patients (17%) reached the composite end point of cardiac mortality or appropriate ICD therapy.

The study population was divided into two groups: patients with events (cardiac mortality or appropriate ICD therapy) and patients without events. Baseline clinical and echocardiographic characteristics of these patients are summarized in Table 1. Patients with events had higher peak cardiac enzymes compared with patients without events (6,543 (interquartile range 4,126–9,085) vs. 3438 (interquartile range 1,997–5,392) U/L, $p=0.007$

and 14.2 (interquartile range 10.8–22.3) vs. 8.5 (interquartile range 4.5–15.1) $\mu\text{g/L}$, $p=0.04$ for peak CPK and peak cardiac troponin T levels, respectively). No significant differences were observed in LVEF between patients with and without events ($33 \pm 7\%$ vs. $36 \pm 7\%$, $p=0.16$).

Table 1. *Patients' characteristics*

	Total patient population (n=79)	Events (n=13)	No events (n=66)	p*
Clinical characteristics				
Age (years)	61 $\pm$ 11	56 $\pm$ 9	62 $\pm$ 11	0.06
Male gender	64 (81%)	12 (92%)	52 (79%)	0.26
Killip class ≥ 2	7 (9%)	3 (23%)	4 (6%)	0.05
QRS duration (ms)	103 $\pm$ 22	113 $\pm$ 25	101 $\pm$ 21	0.12
Medical history				
Current smoking	33 (42%)	9 (69%)	24 (36%)	0.03
Diabetes	16 (20%)	3 (23%)	13 (20%)	0.78
Family history of CAD	36 (46%)	6 (46%)	30 (46%)	0.96
Hypercholesterolemia	14 (18%)	4 (31%)	10 (15%)	0.19
Hypertension	33 (42%)	3 (23%)	30 (46%)	0.14
Coronary angiography				
LAD as culprit vessel	58 (73%)	12 (92%)	46 (70%)	0.09
Multivessel disease	48 (61%)	9 (69%)	39 (59%)	0.49
TIMI 2–3 flow	77 (98%)	13 (100%)	64 (97%)	0.53
Laboratory tests				
Peak CPK level (U/L)	3,962 (2,174–5,678)	6,543 (4,126–9,085)	3,438 (1,997–5,392)	0.007
Peak cTnT level ($\mu\text{g/L}$)	9.8 (4.7–15.9)	14.2 (10.8–22.3)	8.5 (4.5–15.1)	0.04
eGFR (mL/min/1.73 m^2)	96 $\pm$ 33	113 $\pm$ 38	93 $\pm$ 32	0.06

Table 1. Patients' characteristics (continued)

	Total patient population (n=79)	Events (n=13)	No events (n=66)	p*
Medication at discharge				
ACE-inhibitors/ARBs	78 (99%)	12 (92%)	66 (100%)	0.02
Antiplatelets	79 (100%)	13 (100%)	66 (100%)	1.00
β-Blockers	72 (91%)	11 (85%)	61 (92%)	0.37
Statins	78 (99%)	13 (100%)	65 (99%)	0.66
Antiarrhythmics class I	1 (1%)	0 (0%)	1 (2%)	0.66
Antiarrhythmics class II	71 (90%)	11 (85%)	60 (91%)	0.49
Antiarrhythmics class III	3 (4%)	0 (0%)	3 (5%)	0.43
Antiarrhythmics class IV	1 (1%)	0 (0%)	1 (2%)	0.66
Echocardiography				
LVESV (mL)	83 ± 34	90 ± 34	82 ± 34	0.46
LVEDV (mL)	129 ± 47	134 ± 43	128 ± 48	0.69
LVEF (%)	36 ± 7	33 ± 7	36 ± 7	0.16
Global longitudinal strain (%)	−10.8 ± 2.9	−8.9 ± 3.7	−11.1 ± −2.6	0.01
LAVI (mL/m ²)	20 ± 7	16 ± 5	21 ± 8	0.01
E/A ratio	1.00 ± 0.44	1.07 ± 0.35	0.98 ± 0.46	0.51
DT (ms)	182 ± 70	179 ± 81	183 ± 68	0.87
E/E' ratio	16 ± 9	13 ± 5	17 ± 9	0.17
Moderate to severe MR grade	11 (14%)	2 (15%)	9 (14%)	0.87
ICD recipients	42 (53%)	11 (85%)	31 (47%)	0.01

Data are presented as mean ± standard deviation, median (interquartile range), or number (percentage).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CPK = creatine phosphokinase; cTnT = cardiac troponin T; DT = deceleration time; E/A = mitral inflow peak early velocity (E)/mitral inflow peak late velocity (A); E/E' = mitral inflow peak early velocity (E)/mitral annular peak early velocity (E'); eGFR = glomerular filtration rate estimated with the Cockcroft–Gault formula; ICD = implantable cardioverter-defibrillator; LAD = left anterior descending coronary artery; LAVI = left atrial indexed volume; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; TIMI = Thrombolysis In Myocardial Infarction.

* p-values are given for the comparisons of patients with and without the composite end point (cardiac mortality or appropriate implantable cardioverter-defibrillator therapy).

Table 2. Echocardiographic characteristics at 3 months' follow-up

	Events (n=13)	No events (n=66)	p*
LVESV (mL)	143 ± 48	107 ± 32	0.001
LVEDV (mL)	198 ± 64	154 ± 44	0.003
LVEF (%)	28 ± 6	31 ± 4	0.09
Global longitudinal strain (%)	-7.4 ± 2.3	-11.6 ± 3.6	<0.001
LAVI (mL/m ²)	33 ± 10	27 ± 10	0.07
E/A ratio	2.49 ± 1.61	1.19 ± 0.78	0.02
DT (ms)	154 ± 50	210 ± 95	0.04
E/E' ratio	34 ± 22	19 ± 12	0.03
Moderate to severe MR grade	8 (62%)	27 (41%)	0.17

Data are presented as mean ± standard deviation or as number (percentage).

DT = deceleration time; E/A = mitral inflow peak early velocity (E)/mitral inflow peak late velocity (A); E/E' = mitral inflow peak early velocity (E)/mitral annular peak early velocity (E'); LAVI = left atrial indexed volume; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation.

* p-values are given for the comparisons of patients with and without the composite end point (cardiac mortality or appropriate implantable cardioverter-defibrillator therapy).

Echocardiographic characteristics at three months' follow-up for patients with and without events are illustrated in Table 2. At three months' follow-up, patients with events had larger LV volumes than patients without events, whereas LVEF was comparable in patients with and without events (LVEF 28 ± 6% vs. 31 ± 4%, p=0.09). Compared with patients without events, diastolic function was significantly more impaired in patients with events (E/A ratio 2.49 ± 1.61 vs. 1.19 ± 0.78, p=0.02; deceleration time 154 ± 50 vs. 210 ± 95 ms, p=0.04; E/E' ratio 34 ± 22 vs. 19 ± 12, p=0.03). Finally, the percentage of patients with moderate to severe mitral regurgitation was comparable in patients with and without events (62% vs. 41%, p=0.17).

Time course of tissue heterogeneity after STEMI

Longitudinal strain values at the infarct, border, and remote zones in patients with and without events are summarized in Table 3 and Figure 3. All segments were considered to have good tracking and, therefore, no segments were excluded. Although both baseline and three-month global longitudinal strain values were different between patients with and without events, no change was observed from baseline to three months' follow-up in patients without events (from -11.1 ± 2.6% to -11.6 ± 3.6%, p=0.28), whereas patients with events demonstrated a trend toward more impaired global longitudinal strain values (from -8.9 ± 3.7% to -7.4 ± 2.3%, p=0.09) (Table 3).

Table 3. The course of LV longitudinal strain values at the infarct, border, and remote zones, and global longitudinal strain in STEMI patients

LV longitudinal strain	Events (n=13)	No events (n=66)	p*
Baseline			
Infarct zone (%)	1.4 ± 1.9	0.6 ± 4.0	0.28
Border zone (%)	−9.4 ± 1.3	−10.5 ± 2.4	0.13
Remote zone (%)	−15.3 ± 2.1	−15.4 ± 3.0	0.96
Global (%)	−8.9 ± 3.7	−11.1 ± 2.6	0.01
3 months			
Infarct zone (%)	−3.6 ± 4.4 [†]	−6.3 ± 5.9 [†]	0.12
Border zone (%)	−6.8 ± 3.1 [†]	−10.5 ± 4.9	0.002
Remote zone (%)	−10.0 ± 5.0 [†]	−13.1 ± 4.9 [†]	0.06
Global (%)	−7.4 ± 2.3	−11.6 ± 3.6	<0.001

Data are presented as mean ± standard deviation.

LV = left ventricular; STEMI = ST-segment elevation myocardial infarction.

* p-values are given for the comparisons of patients with and without the composite end point (cardiac mortality or appropriate implantable cardioverter-defibrillator therapy).

[†] p<0.05 compared with baseline values.

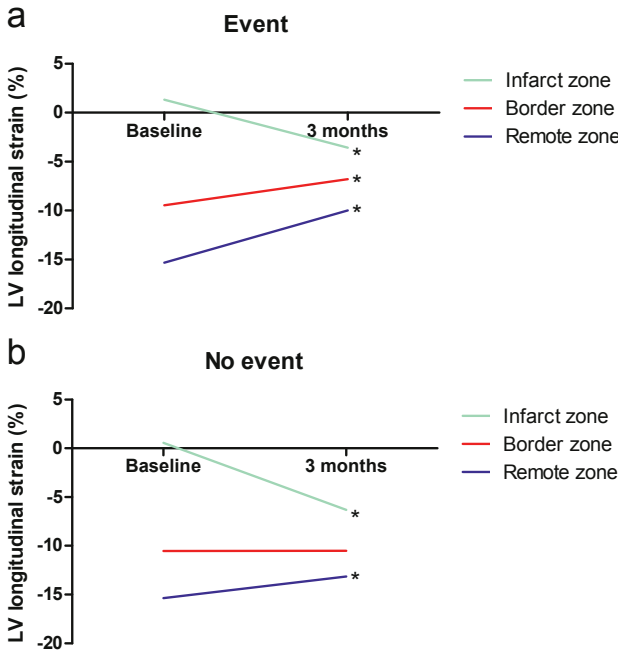


Figure 3. Time course of tissue heterogeneity in patients with events (cardiac mortality or appropriate implantable cardioverter-defibrillator therapy) (a) and patients without events (b). Asterisks denote p<0.05 compared with baseline values. LV = left ventricular.

Baseline longitudinal strain values at the infarct, border, and remote zones were comparable in patients with and without events. However, at three months' follow-up, the border zone showed significantly more impaired longitudinal strain values in patients with events than in patients without events; the infarct and remote zones in patients with events showed a trend toward a more impaired function (infarct zone $-3.6 \pm 4.4\%$ vs. $-6.3 \pm 5.9\%$, $p=0.12$; border zone $-6.8 \pm 3.1\%$ vs. $-10.5 \pm 4.9\%$, $p=0.002$; remote zone $-10.0 \pm 5.0\%$ vs. $-13.1 \pm 4.9\%$, $p=0.06$). Importantly, in patients with events, longitudinal strain values at the border zone significantly worsened from baseline to three months' follow-up. However, longitudinal strain values at the border zone in patients without events did not change during the three months of follow-up.

Tissue heterogeneity and outcome after STEMI

The cumulative incidence curves of the composite end point are shown in Figure 4, with the patient population dichotomized based on the median value of -9.4% measured at the border zone three months postinfarction. The patient population was censored when cardiac mortality or appropriate ICD therapy occurred, whichever came first. Patients with more impaired three-month LV longitudinal strain at the border zone ($>-9.4\%$) showed a significantly worse long-term outcome compared with patients with a border zone $\leq -9.4\%$ (HR 4.52, 95% CI 1.24–16.50, $p=0.02$). The 12-, 24-, and 36-month cumulative incidence rates of the composite end point for patients with more impaired three-month longitudinal strain at the border zone were 13%, 21%, and 24%, respectively; in patients with longitudinal strain at the border zone $\leq -9.4\%$, the 12-, 24-, and 36-month cumulative incidence rates of the composite end point were 2%, 5%, and 5%, respectively (Figure 4). Every 1% increase in longitudinal strain value at the border zone at three months' follow-up was associated with an increased risk of the composite end point of 16% ($p=0.01$).

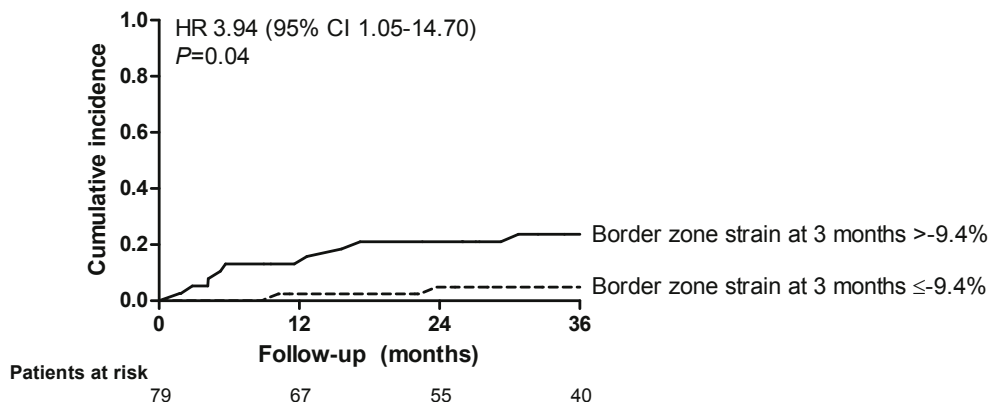


Figure 4. Cumulative incidence curves for the composite end point (cardiac mortality or appropriate implantable cardioverter-defibrillator therapy) in patients dichotomized based on the median value of the left ventricular longitudinal strain values at the border zone at 3 months' follow-up of -9.4% . CI = confidence interval; HR = hazard ratio.

Significant univariate parameters of cardiac mortality or appropriate ICD therapy were Killip class ≥ 2 , smoking, peak CPK and peak cardiac troponin T levels, estimated glomerular filtration rate, three-month LV end-systolic volume, LV end-diastolic volume, LVEF, global longitudinal strain, E/A ratio, deceleration time, and E/E' ratio and three-month longitudinal strain values at the border zone. In Table 4, three multivariate models are presented assessing the association between the composite end point and three-month LVEF or three-month global longitudinal strain or three-month longitudinal strain at the border zone, adjusted for clinical variables (age and peak CPK). While three-month LVEF was no longer independently associated with the composite end point, three-month longitudinal strain at the border zone $>-9.4\%$ was independently associated with an almost fivefold increased risk of cardiac mortality or appropriate ICD therapy after STEMI (HR 3.94, 95% CI 1.05–14.70, $p=0.04$). Moreover, three-month global longitudinal strain was independently associated with the composite end point (HR 1.49, 95% CI 1.18–1.89, $p=0.001$). The relative merits of the three models were assessed by calculating the Harrell's c statistic. The multivariate model including three-month LVEF provided a c statistic of 0.81 for the composite of cardiac mortality and appropriate ICD therapy. A c statistic of 0.90 was provided for the multivariate model including three-month global longitudinal strain. The multivariate model including three-month longitudinal strain values at the border zone provided a c statistic of 0.85 for the composite end point.

Table 4. Predictors of cardiac mortality and appropriate ICD therapy in STEMI patients

	Multivariate analyses	
	HR (95% CI)	p
Model 1		
Age (years)	0.98 (0.93–1.04)	0.47
Peak CPK level (U/L)	3.85 (1.29–11.46)	0.02
LVEF at 3 months (%)	0.94 (0.85–1.04)	0.22
Model 2		
Age (years)	0.97 (0.92–1.03)	0.33
Peak CPK level (U/L)	2.03 (0.83–4.99)	0.12
Global longitudinal strain at 3 months (%)	1.49 (1.18–1.89)	0.001
Model 3		
Age (years)	0.98 (0.93–1.03)	0.37
Peak CPK level (U/L)	3.64 (1.34–9.89)	0.01
LV strain at border zone at 3 months $>-9.4\%$	3.94 (1.05–14.70)	0.04

CI = confidence interval; CPK = creatine phosphokinase; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; STEMI = ST-segment elevation myocardial infarction.

DISCUSSION

The present study demonstrated that patients with a first STEMI who remained with a LVEF $\leq 35\%$ at three months' follow-up and showed a more impaired function of the border zone, assessed with speckle-tracking longitudinal strain, had an increased risk for ventricular arrhythmias and/or cardiac mortality.

LVEF versus speckle-tracking echocardiography for risk stratification of patients with STEMI

Current guidelines recommend ICD implantation for primary prevention in patients at least 40 days after STEMI who have symptoms of heart failure (NYHA class II–III) and LVEF $\leq 35\%$.⁷ Although LVEF is an established parameter for the selection of patients for ICD, several studies have reported its limited specificity for the identification of patients who will benefit from ICD therapy.^{10,11,22} In addition, a time-dependent benefit from ICD therapy after myocardial infarction has been described in several randomized trials only immediately after STEMI and in remote infarctions (≥ 18 months).^{23–26} On the other hand, the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) and Immediate Risk Stratification Improves Survival (IRIS) trial, in which ICD therapy was randomly assigned to patients immediately after myocardial infarction, did not show benefit from ICD implantation in this subset of patients.^{8,9} These studies suggest that the mechanisms of ventricular arrhythmias may change over time after STEMI. Further changes in the tissue characteristics of the scar and surrounding areas may alter the substrate, forming regional re-entry circuits that favour the occurrence of ventricular arrhythmias at follow-up.^{27–29} Therefore, characterization of myocardial tissue, including the infarct core, border, and remote zones, has been proposed to improve the risk stratification of patients after STEMI.

Speckle-tracking echocardiography has been introduced to evaluate more subtle changes in regional and global LV function. In the present evaluation, regional longitudinal strain assessed at three months after STEMI was an independent determinant of long-term outcome in STEMI patients with LV dysfunction, whereas LVEF was not. Specifically, longitudinal strain at the border zone three months after infarction was independently associated with appropriate ICD therapy and/or cardiac mortality. With the use of this tool the risk stratification of STEMI patients may improve, identifying the patients who may benefit from ICD implantation. Although these results are promising, the small patient population and the low number of patients reaching the end point in the present study preclude us to generalize the results.

Border zone as determinant of ventricular arrhythmias

Previous studies have demonstrated that the peri-infarct or border zone is the origin of re-entrant ventricular tachycardia following myocardial infarction.³⁰ This arrhythmogenic anatomic substrate consists of dense, fibrous scar tissue incapable of depolarization,

interspersed with bundles of surviving myocytes capable of depolarization.³⁰ Contrast-enhanced magnetic resonance imaging has shown to accurately identify the border zone in patients with ischemic heart disease, which was independently associated with arrhythmic events.^{2,6,13,31} Moreover, with the developments in echocardiographic deformation imaging techniques, similar evaluations of regional tissue function and heterogeneity, related to the presence of infarct core, border, and remote zones, can be performed.^{3,14} In 424 ICD recipients with chronic ischemic heart failure, Ng et al.³ assessed the regional myocardial function in the infarct, border, and remote zones using 2D speckle-tracking imaging. After adjustment for clinical and other echocardiographic parameters, longitudinal strain at the border zone was an independent predictor of all-cause mortality and ventricular arrhythmias during follow-up.³

However, these studies have been performed in patients with chronic heart disease and remote myocardial infarctions. The present study evaluated changes in regional function during the three months after STEMI, when myocardial scar is still developing and further changes in extracellular matrix have not yet taken place.^{28,29} Importantly, in patients who presented with appropriate ICD therapy or died of a cardiac cause during long-term follow-up, the border zone, assessed by speckle-tracking longitudinal strain, significantly impaired over time. In addition, the border zone at three months' follow-up was independently associated with adverse outcome.

Limitations

The present study has several limitations. First, the relatively small sample size and the retrospective observational single-center design of the study preclude us to generalize the results. Therefore, the present evaluation should be considered as a hypothesis-generating study, with the results to be confirmed in larger multicenter study populations with strict enrollment before this technique can be implemented in guidelines and daily clinical routine.³² Furthermore, despite the relatively low intra- and interobserver variability of global longitudinal strain,³ the relatively wide limits of agreement of segmental longitudinal strain indicate that the implementation of segmental analysis in daily clinical practice demands further improvement of the technique. Moreover, test/retest variability data were not available. Finally, definition of infarct core, infarct border zone, and remote zone by means of speckle-tracking echocardiography may be less accurate than with contrast-enhanced cardiac magnetic resonance imaging.

CONCLUSIONS

The longitudinal strain value at the border zone three months after STEMI is associated with appropriate ICD therapy or cardiac mortality and may be useful in risk-stratifying patients following STEMI.

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CHAPTER 3

Determinants of Right Ventricular Remodeling Following ST-Segment Elevation Myocardial Infarction

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ABSTRACT

Right ventricular (RV) function after ST-segment elevation myocardial infarction (STEMI) has important prognostic implications. However, the changes in RV function over time after STEMI and the incidence of RV remodeling remain unknown. The present study evaluated changes in RV dimensions and function in contemporary patients with first STEMI and assessed the independent determinants of RV dysfunction at follow-up. Patients with first STEMI ($n=940$, 60 ± 11 years, 77% men) treated with primary percutaneous coronary intervention underwent echocardiography at baseline and 6- and 12-month follow-up. The prevalence of RV dysfunction (tricuspid annular plane systolic excursion [TAPSE] ≤ 15 mm) decreased significantly at 6 months follow-up (from 15% to 8%, $p<0.001$) and the incidence of RV remodeling (increase in RV end-diastolic area [RVEDA] $\geq 20\%$) was observed in 200 patients (25%). Absolute changes in RVEDA were independently associated with absolute changes in wall motion score index and left ventricular (LV) remodeling ($p<0.001$ for both parameters), whereas absolute changes in TAPSE were independently related with absolute changes in wall motion score index and mitral regurgitation grade ($p<0.001$ for both parameters). Independent correlates of RV dysfunction at 6 months follow-up were multivessel coronary disease (odds ratio [OR] 2.13), peak cardiac troponin T (OR 1.05), angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers use (OR 0.27), baseline LV ejection fraction (OR 0.96) and baseline TAPSE (OR 0.88). In conclusion, despite the non-negligible incidence of RV remodeling in patients with first STEMI, RV function improves early after STEMI. Multivessel coronary disease, infarct size, baseline LV ejection fraction and TAPSE and the nonuse of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers are independent determinants of RV dysfunction.

INTRODUCTION

Right ventricular (RV) dysfunction portends a poor prognosis in patients after acute myocardial infarction.¹⁻⁴ However, RV function may recover within days or weeks, especially after successful reperfusion.⁵⁻⁷ Changes in RV dimensions and function after ST-segment elevation myocardial infarction (STEMI) have received less attention than the left ventricle despite the possibility of RV remodeling and dysfunction after STEMI.⁸⁻¹¹ The incidence of RV dysfunction in patients with STEMI may vary considerably depending on the imaging technique and definition used.^{6,12} Furthermore, the time course of RV remodeling and RV dysfunction development and the factors influencing these processes after STEMI remain unexplored in the era of primary percutaneous coronary intervention (PCI). Therefore, the aims of the present evaluation were to describe the changes in RV dimensions and function over time after STEMI in a contemporary cohort of patients treated with primary PCI according to current guidelines^{13,14} and to investigate the independent correlates of RV dysfunction at follow-up.

METHODS

Patients admitted with a STEMI at the Leiden University Medical Center were included in an ongoing registry (MISSION!).¹⁵ All patients were treated with primary PCI according to the institutional protocol, which is based upon the recent European Society of Cardiology and American College of Cardiology and/or American Heart Association guidelines.¹³⁻¹⁵ In brief, this protocol includes optimal medical therapy initiated early during hospitalization, 2-dimensional echocardiography performed within 48 hours of admission, and standardized outpatient clinical follow-up at 6 and 12 months. Two-dimensional echocardiography was repeated at each outpatient visit. In the present evaluation, patients with a first STEMI with available echocardiograms at baseline and 6- and 12-month follow-up were included. Patients with previous revascularization (PCI and/or coronary artery bypass grafting) were excluded. Other exclusion criteria were clinical signs of heart failure at admission (Killip class III or IV), out-of-hospital cardiac arrest, pulmonary disease, lobectomy, and congenital heart disease. Clinical and echocardiographic data were collected at the departmental Cardiology Information System (EPD-Vision, Leiden University Medical Center, Leiden, The Netherlands) and the echocardiography database, respectively, and these were retrospectively analyzed. For this retrospective analysis of clinically acquired data, the institutional review board waived the need of patient written informed consent.

Echocardiographic images were acquired with the patient at rest in the left lateral decubitus position using a commercially available system (Vivid 7 and Vivid E9, General Electric-Vingmed, Horten, Norway). Data acquisition was performed with 3.5 MHz and M5S transducers in the standard parasternal and apical views. Standard M-mode, 2-dimensional, color, pulse-wave and continuous-wave Doppler images were obtained during breath hold

and saved in cine-loop format. Data analysis was performed offline with commercially available postprocessing data software (EchoPac 112.0.1, General Electric Medical Systems, Horten, Norway).

LV function was assessed by measuring the LV end-systolic and end-diastolic volumes in the apical 4- and 2-chamber views, calculating the LV ejection fraction (LVEF) using the biplane Simpson's method.¹⁶ The wall motion score index (WMSI) was calculated as the sum of the segment scores divided by the number of segments scored.¹⁶ Severity of mitral regurgitation was semiquantitatively assessed from the jet area of color flow Doppler images and the width of the vena contracta.¹⁷ LV diastolic function was evaluated by positioning the pulse-wave Doppler sample volume between the tips of the mitral leaflets and obtaining the spectral signal of the mitral valve inflow. Peak early (E) and late (A) diastolic velocities and E-wave deceleration time were measured. E' was assessed with tissue Doppler imaging at the septal side of the mitral annulus in the apical 4-chamber view and E/E' ratio was calculated.¹⁸

RV dimensions were assessed by measuring RV end-diastolic area and end-systolic area in the apical 4-chamber view. RV remodeling was defined as an increase in RV end-diastolic area $\geq 20\%$ from baseline to 6 months follow-up. According to current recommendations, RV function was evaluated by measuring the tricuspid annular plane systolic excursion (TAPSE) in the apical 4-chamber view using M-mode.¹⁹ RV dysfunction was defined as TAPSE ≤ 15 mm.¹⁹ Right atrial area was traced in the apical 4-chamber view at the end-systole. Severity of tricuspid regurgitation was evaluated based on ratio of the regurgitant jet and right atrial area.¹⁷ Systolic pulmonary artery pressure was estimated by adding RV pressure to right atrial pressure. RV pressure was estimated by calculating the systolic pressure gradient between the RV and right atrium by the maximum velocity of the regurgitant jet using the modified Bernoulli equation.¹⁹ Right atrial pressure was estimated by measuring the diameter and the inspiratory collapse of the inferior vena cava.¹⁹

Continuous data are reported as mean $\pm$ SD or standard error and categorical data as frequencies and percentages. Absolute changes in RV dimensions and function during follow-up (from baseline to 6 and 12 months follow-up) were evaluated using linear mixed model analyses. Associations between absolute changes in RV dimensions and function and absolute changes in other echocardiographic parameters were assessed with linear mixed models, correcting for potential confounders. RV dysfunction (TAPSE ≤ 15 mm) was assessed at baseline and at 6 months follow-up. Changes in prevalence of RV dysfunction at baseline and at 6 months follow-up were analyzed with the McNemar's test. Baseline clinical and echocardiographic differences between patients with and without RV dysfunction at 6 months follow-up were analyzed using the Student *t* test and chi-squared test. Univariate and multivariate logistic regression analyses were performed to identify independent baseline clinical and echocardiographic correlates of RV dysfunction at 6 months follow-up. All clinically relevant variables were included in a multivariate logistic regression model.

LV end-diastolic volume, LV end-systolic volume, and LVEF were not included in the same model to avoid collinearity.

A 2-sided p-value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS software (version 20.0, SPSS Inc., Chicago, Illinois).

RESULTS

A total of 940 patients (mean age 60 ± 11 years, 77% men) with a first STEMI treated with primary PCI and with complete echocardiographic data at baseline and 6- and 12-month follow-up were eligible for the present study (Figure 1). The culprit vessel was the left anterior descending coronary artery in 47% of the patients, the right coronary artery in 38%, and the circumflex artery in 15%. Mean peak cardiac enzymes were $2,158 \pm 3,029$ U/L for creatine phosphokinase and 5.5 ± 5.4 mg/L for cardiac troponin T, respectively. At baseline, mean LV end-systolic and end-diastolic volumes, and LVEF were 56 ± 20 mL, 105 ± 32 mL, and $47 \pm 8\%$, respectively. Mean WMSI was 1.45 ± 0.28 and moderate to severe mitral regurgitation was observed in 55 patients (6%). Mean RV end-diastolic and end-systolic areas were 18.3 ± 4.4 cm² and 10.5 ± 3.0 cm², respectively. Baseline TAPSE was 19 ± 3.3 mm and moderate to severe tricuspid regurgitation was observed in 46 patients (5%).

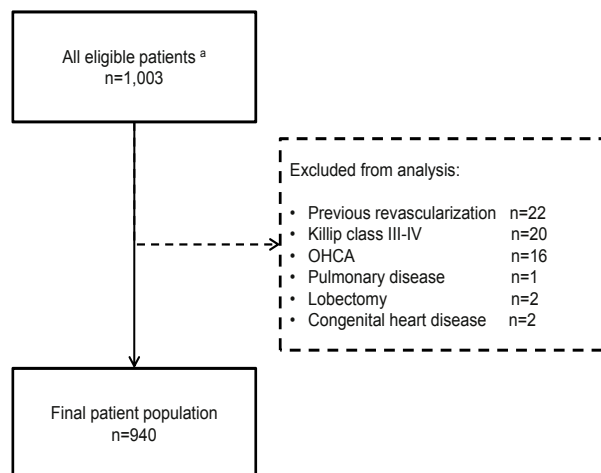


Figure 1. Flowchart of the patient population. ^a Patients were eligible if they were admitted with a first STEMI treated with primary PCI and if echocardiograms were available at baseline and 6- and 12-month follow-up. OHCA = out-of-hospital cardiac arrest.

Table 1 lists the absolute changes in RV dimensions and function over time, from baseline to 6 and 12 months follow-up after STEMI. During the 12 months of follow-up, RV end-diastolic area increased modestly but significantly (Figure 2). Based on the upper limit of normality of RV end-diastolic area ($<19.0 \text{ cm}^2$),¹⁹ patients demonstrated on average dilated RVs at 6 and 12 months follow-up. In contrast, RV end-systolic area did not change over time ($p=0.07$). RV remodeling (increase in RV end-diastolic area $\geq 20\%$) at 6 months follow-up was observed in 200 patients (25%).

Table 1. Time course of right ventricular dimensions and function after ST-segment elevation myocardial infarction

	Baseline	6 months	12 months	p*
Right ventricular end-diastolic area (cm^2)	18.4 ± 0.2	$19.2 \pm 0.2^\dagger$	$19.0 \pm 0.1^\dagger$	<0.001
Right ventricular end-systolic area (cm^2)	10.5 ± 0.1	10.6 ± 0.1	10.5 ± 0.1	0.07
Tricuspid annular plane systolic excursion (mm)	19 ± 0.1	$20 \pm 0.1^\dagger$	$20 \pm 0.1^\dagger$	<0.001
Right atrial area (cm^2)	12.9 ± 0.1	$14.1 \pm 0.1^\dagger$	$13.8 \pm 0.1^\dagger$	<0.001
Tricuspid regurgitation grade	0.52 ± 0.02	$0.58 \pm 0.02^\dagger$	$0.58 \pm 0.02^\dagger$	0.005
Estimated systolic pulmonary arterial pressure (mm Hg)	24.6 ± 0.3	23.9 ± 0.3	24.2 ± 0.3	0.09

Data are presented as mean value $\pm$ standard error.
 * p-values are given for the overall change over time.
[†] $p<0.05$ compared with baseline (adjusted for multiple comparisons).

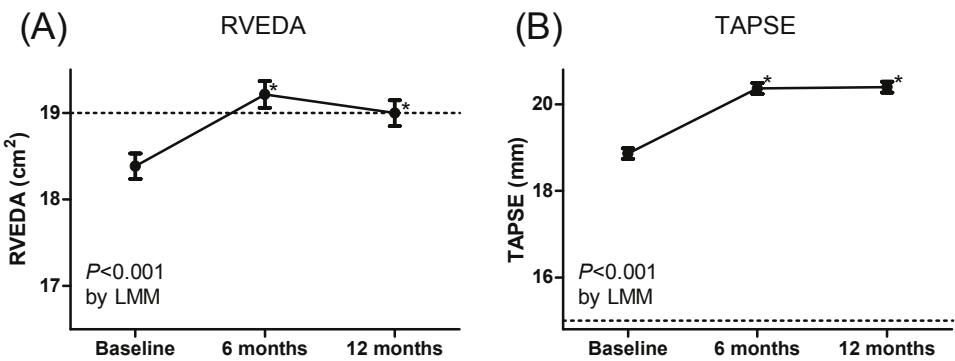


Figure 2. Time course of RV end-diastolic area (RVEDA) (A) and TAPSE (B) after STEMI. In (A), the upper limit of normality of RVEDA, indicated by the echocardiographic guidelines, is shown by the dotted line (at a value of 19.0 cm^2).¹⁹ In (B), the dotted line indicates the prespecified definition of RV dysfunction (TAPSE $\leq 15 \text{ mm}$).¹⁹ Data are presented as mean $\pm$ standard error. LMM = linear mixed model.
 * $p<0.05$ compared with baseline.

Significant univariate correlates of absolute change in RV end-diastolic area are listed in Table 2. On multivariate analysis, absolute changes in LV end-diastolic volume and WMSI were independent correlates of absolute change in RV end-diastolic area. Of note, right coronary artery as culprit vessel was not significantly associated with absolute change in RV end-diastolic volume in the univariate analysis ($p=0.21$).

Table 2. *Correlates of absolute change in right ventricular end-diastolic area and change in tricuspid annular plane systolic excursion*

	Univariate analysis			Multivariate analysis*		
	B	95% confidence interval	p	B	95% confidence interval	p
<i>Right ventricular end-diastolic area</i>						
Change in LVESV (mL)	0.030	0.023 to 0.037	<0.001			
Change in LVEDV (mL)	0.026	0.021 to 0.030	<0.001	0.028	0.023 to 0.032	<0.001
Change in LVEF (%)	0.0037	-0.014 to 0.022	0.68			
Change in WMSI	-1.09	-0.53 to -1.66	<0.001	-1.51	-0.95 to -2.06	<0.001
Change in E/E' ratio	-0.0018	-0.026 to 0.022	0.88			
Change in MR grade	0.15	-0.10 to 0.39	0.25			
<i>Tricuspid annular plane systolic excursion</i>						
Change in LVESV (mL)	-0.0076	-0.0014 to -0.014	0.016			
Change in LVEDV (mL)	0.0034	-0.00062 to 0.0075	0.097			
Change in LVEF (%)	0.061	0.046 to 0.077	<0.001			
Change in WMSI	-2.01	-1.53 to -2.49	<0.001	-1.89	-1.42 to -2.37	<0.001
Change in E/E' ratio	-0.029	-0.0081 to -0.050	0.007			
Change in MR grade	-0.54	-0.32 to -0.75	<0.001	-0.43	-0.22 to -0.65	<0.001

E/E' = mitral inflow peak early velocity (E)/mitral annular peak early velocity (E'); LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; WMSI = wall motion score index.

* In the 2 multivariate analyses, only changes in LVEDV and WMSI for change in RVEDA and only changes in WMSI and MR grade for change in TAPSE were included, respectively, as indicated by the bold text.

At 6 months follow-up, TAPSE measurement was feasible in 95% of patients. RV dysfunction at baseline (TAPSE ≤ 15 mm) was observed in 133 patients (15%) and 73 patients (8%) remained with RV dysfunction at 6 months follow-up ($p<0.001$ compared with baseline; Figure 2).¹⁹ Table 2 provides the significant univariate correlates of absolute change in RV function, measured by TAPSE. On multivariate analysis, absolute change in TAPSE was independently associated with absolute changes in WMSI and mitral regurgitation grade

(Table 2). No significant correlation was found between right coronary artery as culprit vessel and absolute change in TAPSE (univariate $p=0.94$).

Baseline characteristics of patients with and without RV dysfunction at 6 months follow-up are listed in Table 3. Patients with RV dysfunction at 6 months follow-up had a lesser prevalence of smoking and a greater prevalence of multivessel coronary disease compared with patients without RV dysfunction. Peak cardiac troponin T levels were higher in patients with RV dysfunction. At discharge, the use of angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs) was lesser in patients with RV dysfunction at 6 months follow-up. Patients with RV dysfunction showed larger LV end-systolic volumes and poorer LV functions at baseline compared with their counterparts. In patients with RV dysfunction, E/E' ratio was higher and TAPSE was lower compared with patients without RV dysfunction at 6 months follow-up.

Table 3. *Patients with right ventricular dysfunction versus patients with preserved right ventricular function at follow-up*

	Right ventricular dysfunction		p*
	Yes (n=73)	No (n=824)	
Age (years)	61 ± 12	59 ± 11	0.18
Men	57 (78%)	636 (77%)	0.86
Current smoker	25 (34%)	426 (52%)	0.004
Diabetes mellitus	7 (10%)	66 (8%)	0.64
Family history of coronary artery disease	27 (38%)	377 (46%)	0.16
Hypercholesterolemia	13 (18%)	150 (18%)	0.92
Hypertension	28 (38%)	258 (31%)	0.22
Left anterior descending artery as culprit coronary artery	38 (52%)	377 (46%)	0.30
Right coronary artery as culprit coronary artery	26 (36%)	323 (39%)	0.55
Left circumflex as culprit coronary artery	9 (12%)	124 (15%)	0.53
Multivessel coronary disease	47 (64%)	387 (47%)	0.004
Thrombolysis In Myocardial Infarction 2–3 flow	72 (99%)	812 (99%)	0.98
Peak creatine phosphokinase level (U/L)	2,439 ± 1,965	2,142 ± 3,165	0.43
Peak cardiac troponin T level (µg/L)	7.6 ± 6.3	5.3 ± 5.3	0.003

Table 3. Patients with right ventricular dysfunction versus patients with preserved right ventricular function at follow-up (continued)

	Right ventricular dysfunction		p*
	Yes	No	
	(n=73)	(n=824)	
Echocardiography			
Left ventricular end-systolic volume (mL)	64 ± 28	56 ± 19	0.01
Left ventricular end-diastolic volume (mL)	113 ± 44	105 ± 31	0.15
Left ventricular ejection fraction (%)	43 ± 8	47 ± 8	<0.001
Wall motion score index	1.55 ± 0.29	1.44 ± 0.28	0.001
E/A ratio	1.01 ± 0.52	0.97 ± 0.34	0.50
Deceleration time (ms)	199 ± 72	209 ± 69	0.27
E/E' ratio	14 ± 6	13 ± 6	0.02
Moderate to severe mitral regurgitation grade	8 (11%)	45 (6%)	0.06
Right ventricular end-diastolic area (cm²)	17.9 ± 5.5	18.3 ± 4.3	0.42
Right ventricular end-systolic area (cm²)	10.4 ± 3.5	10.5 ± 2.9	0.93
Tricuspid annular plane systolic excursion (mm)	17 ± 3.3	19 ± 3.2	<0.001
Right atrial area (cm²)	12.7 ± 4.1	12.9 ± 3.8	0.58
Moderate to severe tricuspid regurgitation grade	3 (4%)	39 (5%)	0.80
Estimated systolic pulmonary arterial pressure (mm Hg)	24.6 ± 9.8	24.7 ± 8.9	0.88
Medication at discharge			
Angiotensin-converting enzyme-inhibitors and/or angiotensin receptor blockers	69 (95%)	810 (98%)	0.03
Antiplatelets	73 (100%)	824 (100%)	1.00
β-Blockers	69 (95%)	777 (94%)	0.94
Statins	72 (99%)	821 (100%)	0.22

Data are presented as mean value ± SD and as frequencies and percentages.

* p-values are provided for the comparisons of patients with and without RV dysfunction (defined as TAPSE ≤15 mm) at 6 months follow-up.

Univariate and multivariate logistic regression analyses were performed to identify determinants of RV dysfunction at 6 months follow-up (Table 4). Significant univariate correlates of RV dysfunction were multivessel coronary disease, peak cardiac troponin T level, use of ACEIs and/or ARBs at discharge, baseline LV end-systolic volume, LVEF, WMSI, E/E' ratio, and TAPSE. In the multivariate model, multivessel coronary disease, peak cardiac troponin T level, use of ACEIs and/or ARBs at discharge, baseline LVEF, and baseline TAPSE were independently associated with RV dysfunction at 6 months follow-up (Table 4).

Table 4. *Correlates of right ventricular dysfunction at follow-up after ST-segment elevation myocardial infarction*

	Odds ratio	Multivariate analysis	
		95% confidence interval	p
Multivessel coronary disease	2.13	1.22–3.72	0.008
Peak cardiac troponin T level (µg/L)	1.05	1.01–1.09	0.022
Angiotensin-converting enzyme-inhibitors and/or angiotensin receptor blockers	0.27	0.08–0.94	0.040
Baseline left ventricular ejection fraction (%)	0.96	0.93–0.99	0.014
Baseline E/E' ratio	1.02	0.98–1.05	0.36
Baseline tricuspid annular plane systolic excursion (mm)	0.88	0.81–0.96	0.006

RV dysfunction was defined as TAPSE ≤ 15 mm at 6-month follow-up.

DISCUSSION

The current evaluation demonstrated that in a contemporary population of patients with STEMI treated with primary PCI, the incidence of RV remodeling was approximately 25%. Absolute changes in RV dimensions were correlated with changes in LV volumes and function. Furthermore, at 6 months follow-up, RV dysfunction was observed in 8% of the patients. Multivessel coronary disease, high peak troponin T, hospital discharge without ACEIs or ARBs, and diminished baseline LV and RV functions were independent determinants of RV dysfunction during follow-up.

Cardiac remodeling occurs at early stages of myocardial infarction as a consequence of scar formation, infarct expansion, and increase in filling pressures. At follow-up, ventricular dilatation may result from further remodeling of residual viable myocardium to maintain stroke volume.^{20,21} Although LV remodeling has been well described, changes in RV dimensions after STEMI remain less elucidated, especially in the era of primary PCI. In a serial cine-computed tomography study, Hirose et al assessed RV remodeling in 27 patients with myocardial infarction treated with percutaneous transluminal coronary angioplasty, thrombolytic therapy or without reperfusion.¹⁰ During 1 year follow-up, an increase in RV volumes was demonstrated in both anterior and inferior myocardial infarctions reaching a plateau phase at 6 months postinfarction.¹⁰ In the present evaluation, RV remodeling was observed in 25% of our modern era population with STEMI. Additionally, changes in LV volumes and function were associated with RV dilatation, highlighting the interventricular dependence^{22,23} and, thereby, the importance of assessing both LV and RV after STEMI.

Despite the observed RV remodeling, RV function remained preserved up to 12 months of follow-up in most of the patients of the present population. Previous studies

described a baseline prevalence of RV dysfunction varying from 15% to 54%, depending on the imaging technique and definition used.^{3,4,6} In the present study, RV dysfunction (defined as TAPSE ≤ 15 mm measured on echocardiography) was observed early after STEMI in 15% of patients. The time course of RV function improvement after myocardial infarction has been documented in previous studies, usually occurring within days or weeks, especially when rapid reperfusion of the culprit vessel was achieved.^{5-7,24} In the GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)-3 echocardiographic substudy, including 71% of patients treated with thrombolysis, RV function measured by TAPSE improved over time and was correlated with LV function.⁵ However, RV dysfunction may persist or develop after myocardial infarction.^{2,25} Larose et al evaluated RV function in 147 patients with previous myocardial infarction (mean age of infarction was 6.7 years) using cardiac magnetic resonance imaging.² RV dysfunction (defined as RV ejection fraction $< 40\%$) was observed in 25 patients (17%).² Furthermore, in 143 patients with acute RV myocardial infarction who underwent RV function assessment with radionuclide angiocardiographic scanning, the prevalence of persistent RV dysfunction at 3 months postinfarction was 38%.²⁵

So far, the underlying mechanism of RV dysfunction after myocardial infarction has been poorly understood. Previous studies demonstrated a modest association between LV and RV functions following infarction.^{2,4,5,22} Other proposed mechanisms are abnormalities in LV diastolic function and mitral regurgitation. Likewise, the current evaluation demonstrated that absolute changes in RV function postinfarction over time were associated with changes in LV function and in mitral regurgitation grade. The present cohort of patients was treated according to current guidelines^{13,14} including high percentage of ACEIs and/or ARBs at follow-up, which may explain also the low prevalence of RV dysfunction at baseline and follow-up.

Several limitations should be acknowledged. First, right precordial leads were not used during electrocardiography to identify RV myocardial infarction and thus the influence of RV infarction on RV remodeling and RV dysfunction cannot be determined. Second, the present evaluation is a single-center retrospective study. However, a large cohort of contemporary patients with STEMI treated according to current guidelines was evaluated.^{13,14} Furthermore, strict inclusion and exclusion criteria were applied resulting in a low-risk patient population, whereby possible selection bias could be induced. However, with the improved outcomes of patients with STEMI due to therapeutic advances, knowledge on the time course of ventricular dimensions and function in this low-risk patient population is of clinical importance. Also, RV function was based on TAPSE which is angle- and load-dependent and a single-segment analysis of a complex 3-dimensional structure.¹⁹ Nevertheless, it has been extensively studied, showing good reproducibility independent of image quality and a strong correlation with radionuclide angiography.¹⁹ Finally, no data were available on the presence or absence of pulmonary hypertension before STEMI.

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CHAPTER 4

Time course, predictors and prognostic implications
of significant mitral regurgitation after ST-segment
elevation myocardial infarction

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Submitted



ABSTRACT

Background: Ischemic mitral regurgitation (MR) is a known complication of ST-segment elevation myocardial infarction (STEMI). We evaluated changes in ischemic MR after STEMI, the incidence and predictors of significant (grade ≥ 2) MR at 12 months and the prognostic implications of significant MR at follow-up.

Methods: STEMI patients ($n=1,599$; 77% male; 60 ± 12 years) treated with primary percutaneous coronary intervention underwent echocardiography <48 h of admission and at 12 months. MR was graded on a 3-point scale. Mortality data were collected during long-term follow-up.

Results: At baseline, significant MR was present in 103 (6%) patients. After 12 months, MR worsened ≥ 1 grade in 321 (20%) patients, remained stable in 963 (60%) and improved ≥ 1 grade in 315 (20%). Significant MR was present in 135 patients at 12 months (8%, $p=0.01$ vs. baseline). Age, left ventricular end-systolic volume (LVESV) and significant MR at baseline were independently associated with significant MR at follow-up, after correcting for other clinical and echocardiographic parameters. During follow-up (median 50 months), 121 (8%) patients died (48 [40%] of cardiovascular cause). Significant MR at follow-up was independently associated with all-cause (hazard ratio [HR] 1.65, 95% confidence interval [CI] 1.02–2.99) and cardiovascular mortality (HR 2.47, 95% CI 1.24–4.92).

Conclusions: The incidence of significant MR after STEMI increases over time. Age, baseline LVESV and baseline significant MR are independently associated with significant MR at follow-up. Significant MR at 12 months was associated with all-cause and cardiovascular mortality.

INTRODUCTION

In the acute phase of ST-segment elevation myocardial infarction (STEMI), ischemic mitral regurgitation (MR) may be observed in 8% to 64% of patients.¹⁻³ However, functional ischemic MR is a highly dynamic lesion that may improve after coronary revascularization or impair due to progressive adverse left ventricular (LV) remodelling and tethering of the mitral leaflets.⁴⁻⁶ The prognostic implications associated with ischemic MR underscore the need of accurate identification and treatment of patients with STEMI that may develop MR after STEMI.^{1,7} The time course of ischemic MR in the contemporary era of primary percutaneous coronary intervention (PCI) has not been explored. In addition, identification of baseline characteristics independently associated with the development of ischemic MR at follow-up is important. Therefore, the aim of the present evaluation was 3-fold: (1) to evaluate changes of MR grade during 12 months follow-up in a contemporary cohort of STEMI patients treated with primary PCI; (2) to assess the incidence and the early predictors of significant MR (moderate and severe) at 12 months follow-up; and (3) to determine the long-term prognostic implications of significant MR at 12 months follow-up.

METHODS

Study population and data collection

Patients admitted with STEMI at the Leiden University Medical Center were included in an ongoing registry (MISSION!).⁸ According to the institutional MISSION! protocol, which is based upon the most recent American College of Cardiology/American Heart Association and European Society of Cardiology guidelines, all STEMI patients were treated with primary PCI.⁸⁻¹⁰ Optimal medical therapy was initiated promptly during hospitalization and 2-dimensional echocardiography was performed within 48 hours of admission. All patients were followed at the outpatient clinic at 3, 6 and 12 months and echocardiography was repeated at each visit. Clinical and echocardiographic data were collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, The Netherlands) and in the echocardiography database, respectively, and all data were retrospectively analyzed. For this retrospective analysis of clinically acquired data, the Institutional Review Board waived the need of patient written informed consent.

In the present evaluation, consecutive STEMI patients treated with primary PCI, in whom echocardiography was available at baseline and at 12 months follow-up, were included. The infarct-related artery was identified by electrocardiographic criteria and confirmed by coronary angiography. Final Thrombolysis In Myocardial Infarction flow was assessed during PCI. The changes over time in MR grade were assessed from baseline to 12 months follow-up.

Echocardiography

Patients were examined at rest in the left lateral decubitus position using a commercially available ultrasound system (Vivid 7 and E9, General Electric-Vingmed, Horten, Norway). Data acquisition was performed with a 3.5-MHz transducer in the standard transthoracic echocardiographic views. Standard 2-dimensional, color, pulsed wave and continuous wave Doppler images were obtained and saved in cine-loop format. Data analysis was performed offline (EchoPAC 112.0.1; GE Medical Systems, Horten, Norway).

LV end-systolic volume (LVESV) and end-diastolic volumes were measured in the apical 4- and 2-chamber view and indexed to body surface area. Using the biplane Simpson's method, LV ejection fraction was subsequently calculated and expressed as a percentage.¹¹ Adverse LV remodelling was defined as an increase in LVESV $\geq 15\%$ at 12 months follow-up.¹²⁻¹⁵

LV diastolic function was assessed by positioning the Doppler sample volume between the tips of the mitral leaflets and acquiring the pulsed wave Doppler spectral signal of the mitral valve inflow. Peak early (E) and late (A) diastolic velocities and E-wave deceleration time were assessed. E' was measured with tissue Doppler imaging at the septal side of the mitral annulus in the apical 4-chamber view and E/E' ratio was calculated.¹⁶

Severity of MR was evaluated using a multi-parametric integrative approach including qualitative and quantitative (vena contracta width in all patients and proximal isovelocity surface area method when feasible) assessments as currently recommended.^{7,17-19} Specifically, severity of MR was graded on a 3-point scale: mild=1, moderate=2 and severe=3. Significant MR was defined as a MR grade ≥ 2 .²⁰

Follow-up and endpoint definitions

After discharge, patients were followed according to the institutional MISSION! protocol.⁸ By reviewing medical records, the occurrence of adverse events between baseline and follow-up echocardiogram were collected, including coronary revascularization and myocardial re-infarction. By retrieval of survival status through municipal civil registries in December 2012, data on the occurrence of death were collected. Cause of death was obtained from medical records, data from the municipal civil registries and patients' general practitioners. The primary endpoint was all-cause mortality. The secondary endpoint was cardiovascular mortality.

Statistical analysis

Continuous data are expressed as mean $\pm$ standard deviation or median with interquartile range, where appropriate. Categorical data are expressed as frequencies and percentages. Changes in MR grade from baseline to 12 months follow-up were assessed with the McNemar's test.

Patients were divided into 2 subgroups based on the presence or absence of significant MR at 12 months follow-up. Baseline clinical and echocardiographic data were compared between subgroups with the unpaired Student's *t*-test and χ^2 test.

In addition, univariate and multivariate binary logistic regression analyses were performed to identify potential baseline predictors of significant MR at 12 months follow-up. All variables with a *p*-value <0.10 in univariate analyses were entered in the multivariate model. To avoid multicollinearity between univariate parameters, LVESV was chosen among other variables (peak creatine phosphokinase level, peak cardiac troponin T level, LV end-diastolic volume, LV ejection fraction) as the parameter reflecting infarct size.

To assess the association between the presence of significant MR and adverse LV remodelling at 12 months follow-up, we evaluated the phi-coefficient value and odds ratio with associated 95% confidence interval.

Finally, survival analysis was performed with the date of the follow-up echocardiogram set as follow-up onset. Event rates of the primary and secondary endpoint were analyzed and displayed using Kaplan-Meier curves. The groups were compared using Cox regression modelling for all-cause and cardiovascular mortality. Relative risks, expressed as hazard ratios with associated 95% confidence intervals, were derived from Cox regression models. To evaluate the independent association between significant MR at 12 months follow-up and the primary and secondary endpoints, multivariate Cox proportional-hazards analyses were performed. Only clinical and 12-month echocardiographic parameters were considered as potential confounders. To avoid multicollinearity, adverse LV remodelling was chosen as the parameter reflecting infarct size. All variables with a *p*-value <0.10 in the univariate analyses were entered in the multivariate model. In order not to overfit the model, the number of variables included in the multivariate model was limited to the number of events. Survival analyses were also performed in the group of excluded patients evaluating the independent association between significant MR at baseline and the primary endpoint (Supplemental material). The date of the index infarction was set as follow-up onset. LV end-diastolic volume was chosen as parameter reflecting infarct size.

All statistical tests were 2-sided, a *p*-value <0.05 was considered statistically significant. All statistical analyses were performed with SPSS software (IBM SPSS Statistics for Windows. Armonk, NY: IBM Corp.).

RESULTS

A total of 1,935 patients were included in the current evaluation. In 332 patients (17%), 12-month follow-up echocardiographic examination was not available (in 93 patients because of death before the 12-month visit) and in 4 (0.2%), MR quantification by echocardiography was not feasible. Comparison of baseline characteristics between patients with and without echocardiographic follow-up is included in the Supplemental material and revealed a higher cardiovascular risk profile, a larger myocardial infarction

and a suboptimal medical therapy in the patients without follow-up echocardiography, explained by the inclusion of patients who died within 12 month after STEMI. The final population consisted of 1,599 patients.

Baseline characteristics

Clinical and echocardiographic characteristics of the patient population are listed in Table 1. Multivessel disease (defined as the presence >1 vessel with luminal narrowing $\geq 50\%$) was present in 54% of patients. According to our institutional protocol,⁸ all patients were optimally treated with antiplatelets, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and statins. Regarding the baseline echocardiographic characteristics, LV systolic function was mildly reduced and LV volumes were within the normal range.

Table 1. Baseline characteristics

	Total patient population (n=1,599)	Significant MR at 12 months follow-up (n=135)	No significant MR at 12 months follow-up (n=1,464)	p*
Clinical characteristics				
Age (years)	60 $\pm$ 12	67 $\pm$ 12	60 $\pm$ 11	<0.001
Male gender	1,229 (77%)	92 (68%)	1,137 (78%)	0.01
Killip class ≥ 2	64 (4%)	9 (7%)	55 (4%)	0.10
Medical history				
Current smoking	765 (48%)	44 (33%)	721 (49%)	<0.001
Diabetes	170 (11%)	16 (12%)	154 (11%)	0.63
Family history of CAD	685 (43%)	46 (34%)	639 (44%)	0.03
Hypercholesterolemia	334 (21%)	28 (21%)	306 (21%)	0.95
Hypertension	563 (35%)	55 (41%)	508 (35%)	0.17
Previous MI	137 (9%)	15 (11%)	122 (8%)	0.27
Coronary angiography				
LAD as culprit vessel	690 (43%)	64 (47%)	626 (43%)	0.30
RCA as culprit vessel	627 (39%)	44 (33%)	583 (40%)	0.10
Multivessel disease	868 (54%)	83 (62%)	785 (54%)	0.08
TIMI 2–3 flow	1,575 (99%)	132 (98%)	1,443 (99%)	0.38

Table 1. Baseline characteristics (continued)

	Total patient population (n=1,599)	Significant MR at 12 months follow-up (n=135)	No significant MR at 12 months follow-up (n=1,464)	p*
Laboratory tests				
Peak CPK level (U/L)	2,136 ± 2,760	3,082 ± 2,576	2,049 ± 2,761	<0.001
Peak cTnT level (µg/L)	5.4 ± 5.4	8.1 ± 6.6	5.1 ± 5.3	<0.001
Medication at discharge				
ACE-inhibitors/ARBs	1,560 (98%)	129 (96%)	1,431 (98%)	0.18
Antiplatelets	1,594 (100%)	134 (100%)	1,460 (100%)	0.99
β-Blockers	1,514 (95%)	125 (93%)	1,389 (95%)	0.35
Statins	1,586 (100%)	132 (99%)	1,454 (100%)	0.09
Echocardiography				
LVESV (mL/m ²)	28.5 ± 10.9	32.9 ± 14.6	28.1 ± 10.4	<0.001
LVEDV (mL/m ²)	53.3 ± 15.5	57.1 ± 18.4	53.0 ± 15.2	0.003
LVEF (%)	47 ± 9	43 ± 10	47 ± 9	<0.001
MR grade				<0.001
MR grade 0	961 (60%)	39 (29%)	922 (63%)	
MR grade 1	535 (34%)	56 (42%)	479 (33%)	
MR grade 2	69 (4%)	26 (19%)	43 (3%)	
MR grade 3	34 (2%)	14 (10%)	20 (1%)	
E/A ratio	0.99 ± 0.39	1.12 ± 0.60	0.97 ± 0.36	0.009
DT (ms)	212 ± 74	211 ± 89	212 ± 73	0.84
E/E' ratio	12.8 ± 4.5	14.9 ± 5.6	12.6 ± 4.3	<0.001

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CPK = creatine phosphokinase; cTnT = cardiac troponin T; DT = deceleration time; E/A = mitral inflow peak early velocity (E)/mitral inflow peak late velocity (A); E/E' = mitral inflow peak early velocity (E)/mitral annular peak early velocity (E'); MI = myocardial infarction; LAD = left anterior descending coronary artery; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

Data are presented as mean ± standard deviation or as number (percentage).

* p-values are given for the comparisons of patients with and without significant mitral regurgitation (MR) at 12 months follow-up (defined as grade ≥2).

Time course of mitral regurgitation after acute myocardial infarction

At baseline, 961 (60%) patients showed no MR, 535 (34%) patients had MR grade 1, and significant MR (grade ≥ 2) was present in 103 (6%) patients. Figure 1 shows the evolution of MR grade from baseline to 12 months follow-up. At 12 months follow-up, MR improved ≥ 1 grade in 315 (20%) patients. On the other hand, MR grade remained stable over time in 963 (60%) patients. Moreover, MR worsened ≥ 1 grade in 321 (20%) patients; of note, 39 (4%) patients with no MR at baseline and 56 (10%) patients with MR grade 1 at baseline developed MR grade ≥ 2 at 12 months. Eventually, significant MR was present in 135 patients at 12 months follow-up (8%, $p=0.01$ compared to baseline).

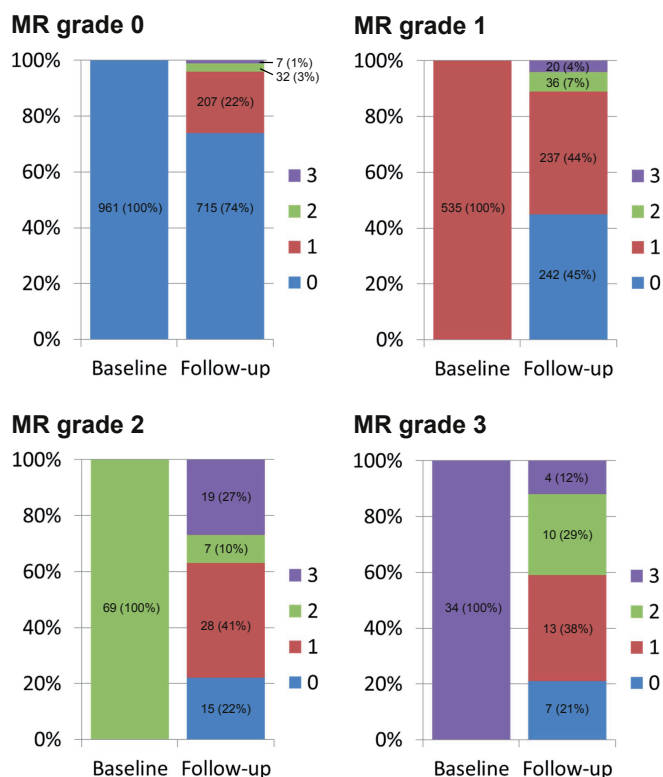


Figure 1. Time course of MR grade after STEMI from baseline to 12 months follow-up. The patient population was divided according to MR grade at baseline (upper left panel, MR grade 0 $n=961$ [60% of the total population]; upper right panel, MR grade 1 $n=535$ [34%]; lower left panel, MR grade 2 $n=69$ [4%]; lower right panel, MR grade 3 $n=34$ [2%]). MR = mitral regurgitation; STEMI = ST-segment elevation myocardial infarction.

Significant mitral regurgitation at follow-up

The clinical and echocardiographic characteristics of patients with and without significant MR at 12 months follow-up are presented in Table 1. Patients with MR grade ≥ 2 were older ($p<0.001$) and more likely to be women ($p=0.01$) compared to those with MR grade <2 at

12 months. This group of patients also included less current smokers ($p<0.001$) and a lower prevalence of family history for coronary artery disease ($p=0.03$). Furthermore, patients with MR grade ≥ 2 showed significantly higher peak cardiac enzymes ($p<0.001$ for both peak creatine phosphokinase and peak cardiac troponin T levels).

Regarding baseline echocardiographic data, as compared to patients without significant MR, those with MR grade ≥ 2 had significantly larger LV volumes and lower LV ejection fraction ($p<0.05$ for all parameters). Furthermore, they demonstrated a higher grade of diastolic dysfunction measured by E/A ratio ($p=0.009$) and E/E' ratio ($p<0.001$).

At 12 months follow-up, in the group of patients that showed MR grade ≥ 2 , 56 (42%) also demonstrated adverse LV remodelling. Conversely, among patients with MR grade <2 at 12 months, 343 (24%) showed adverse LV remodelling. The association between the presence of significant MR and adverse LV remodelling at follow-up was moderate but significant (odds ratio 2.37 [95% confidence interval 1.64–3.41]; phi-coefficient 0.12; $p<0.001$).

Associates of significant mitral regurgitation at follow-up

Significant baseline univariate associates of MR grade ≥ 2 at 12 months follow-up after STEMI were age, gender, multivessel disease, peak creatine phosphokinase level, peak cardiac troponin T level and baseline LVESV, LV end-diastolic volume, LV ejection fraction, significant MR, E/A ratio and E/E' ratio. Of note, between the baseline and follow-up echocardiogram, 180 (11%) patients were revascularized and 43 (3%) patients had a re-

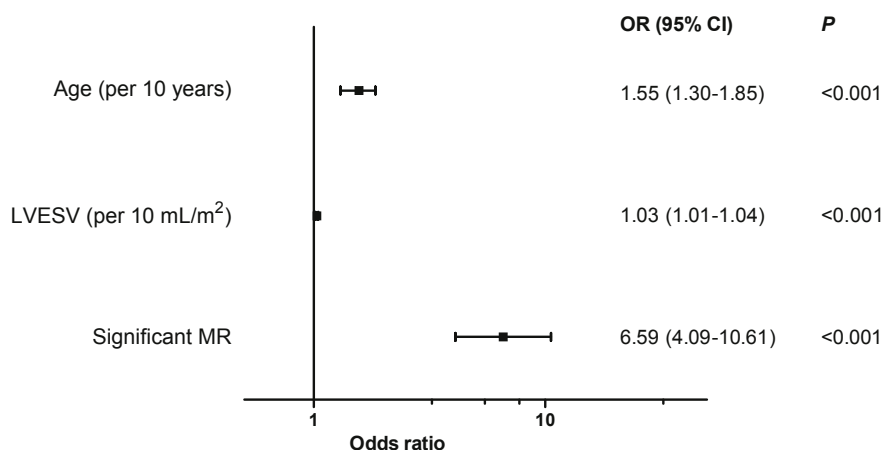


Figure 2. Prediction of significant MR.

Multivariate logistic regression analysis for the prediction of significant MR at 12 months follow-up following ST-segment elevation myocardial infarction. Significant MR was defined as grade ≥ 2 . CI = confidence interval; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; OR = odds ratio.

infarction. Both events were not significantly associated with MR grade ≥ 2 at follow-up ($p=0.43$ for revascularization and $p=0.84$ for re-infarction). At multivariate analysis, age, LVESV and MR grade ≥ 2 remained independent baseline predictors of MR grade ≥ 2 at 12 months while male gender and multivessel disease were not (Figure 2).

Significant mitral regurgitation and long-term outcome

During a median follow-up of 50 months, 121 (8%) patients died. The cause of death was cardiovascular in 48 (40%) patients. Non-cardiovascular deaths were mostly due to malignancy.

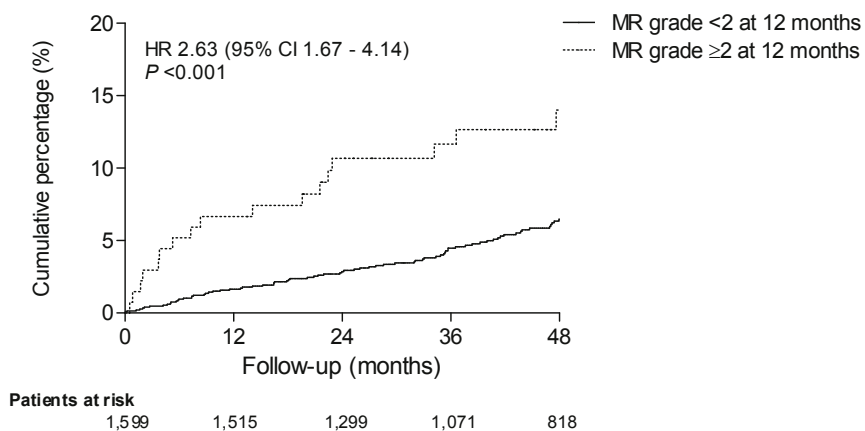


Figure 3. Kaplan-Meier curves for all-cause mortality. Patients were divided according to the presence or absence of significant MR at 12 months follow-up (defined as grade ≥ 2) following ST-segment elevation myocardial infarction. CI = confidence interval; HR = hazard ratio; MR = mitral regurgitation.

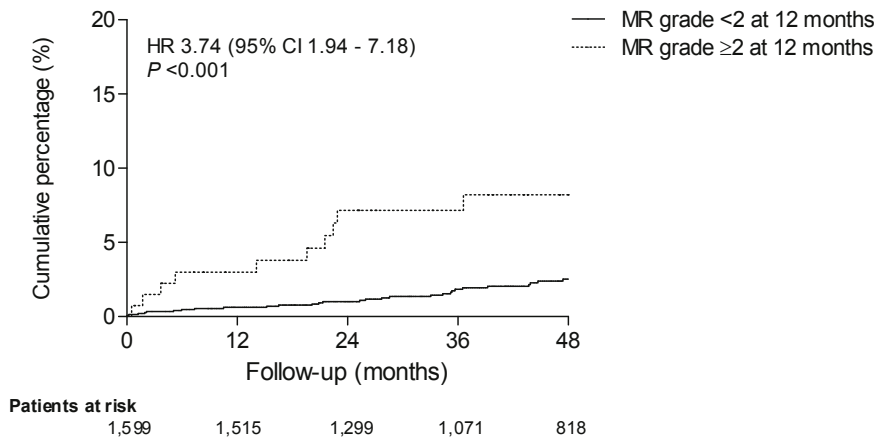


Figure 4. Kaplan-Meier curves for cardiovascular mortality. Patients were divided according to the presence or absence of significant MR at 12 months follow-up (defined as grade ≥ 2) following ST-segment elevation myocardial infarction. CI = confidence interval; HR = hazard ratio; MR = mitral regurgitation.

Kaplan-Meier curves for all-cause and cardiovascular mortality with patients divided according to the presence or absence of significant MR at 12 months follow-up are shown in Figure 3 and 4, respectively. Event rates of all-cause mortality at 12, 24, 36 and 48 months were 6.7%, 10.7%, 11.7% and 14.0%, respectively, for patients with significant MR and 1.6%, 2.9%, 4.5% and 6.5%, respectively, for patients without significant MR ($p<0.001$). Event rates of cardiovascular mortality at 12, 24, 36 and 48 months were 3.0%, 7.2%, 7.2% and 8.2%, respectively, for patients with significant MR and 0.6%, 1.0%, 1.8% and 2.5%, respectively, for patients without significant MR ($p<0.001$). Univariate analysis showed that significant MR at 12 months follow-up was associated with a significant increased risk of all-cause mortality (hazard ratio 2.63, 95% confidence interval 1.67–4.14, $p<0.001$; Figure 3) and cardiovascular mortality (hazard ratio 3.74, 95% confidence interval 1.94–7.18, $p<0.001$; Figure 4).

At multivariate level, significant MR at 12 months was independently associated with all-cause mortality (hazard ratio 1.65, 95% confidence interval 1.02–2.66) together with age, multivessel disease and diabetes (Table 2). Finally, significant MR at 12 months was also independently associated with cardiovascular mortality together with age, multivessel disease, diabetes, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers treatment and adverse LV remodelling (Table 2). Revascularization and re-infarction between the baseline and follow-up echocardiogram were not significantly associated with the primary or secondary endpoint ($p=0.16$ and $p=0.20$ for revascularization and $p=0.27$ and $p=0.05$ for re-infarction, respectively).

DISCUSSION

The main findings of the current evaluation can be summarized as follows. First, the incidence of significant MR after STEMI increases over time and significant MR was observed in 8% of STEMI patients at 12 months follow-up. Secondly, age, baseline systolic LV volume and significant MR were independent correlates of significant MR at follow-up. Lastly, significant MR at 12 months was associated with all-cause and cardiovascular mortality.

Time course of mitral regurgitation after acute myocardial infarction

The reported incidence of significant MR after STEMI is variable depending on the methodology of MR assessment (angiography versus qualitative/quantitative echocardiographic measurements) and the timing of MR evaluation (acutely before hospital discharge or during follow-up).²¹ Furthermore, data on the course of ischemic MR over time after acute myocardial infarction treated with PCI are scant.^{22,23} It is well known that the degree of ischemic MR can change over time, either improving due to successful revascularization (in the acute phase) or worsening due to adverse LV remodelling (in the chronic phase).^{5-7,24} Neskovic et al reported a 38% incidence of MR at 1 year after acute

Table 2. Determinants of all-cause and cardiovascular mortality following STEMI

	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
<i>All-cause mortality</i>				
Age (years)	1.08 (1.06–1.10)	<0.001	1.06 (1.04–1.08)	<0.001
Diabetes	2.07 (1.31–3.26)	0.002	1.88 (1.18–2.99)	0.008
Family history of CAD	0.58 (0.39–0.86)	0.006	0.85 (0.56–1.28)	0.43
Multivessel disease	2.23 (1.51–3.28)	<0.001	1.73 (1.16–2.58)	0.007
ACE-inhibitors/ARBs	0.34 (0.16–0.72)	0.005	0.57 (0.25–1.29)	0.18
β-Blockers	0.45 (0.25–0.80)	0.007	0.72 (0.37–1.37)	0.32
MR grade ≥2	2.63 (1.67–4.14)	<0.001	1.65 (1.02–2.66)	0.04
Adverse LV remodelling*	1.59 (1.09–2.33)	0.02	1.47 (0.99–2.17)	0.06
<i>Cardiovascular mortality</i>				
Age (years)	1.08 (1.05–1.11)	<0.001	1.06 (1.03–1.09)	<0.001
Diabetes	2.61 (1.33–5.11)	0.005	2.31 (1.17–4.57)	0.02
Multivessel disease	2.61 (1.38–4.94)	0.003	2.00 (1.04–3.85)	0.04
ACE-inhibitors/ARBs	0.23 (0.08–0.63)	0.004	0.30 (0.11–0.86)	0.03
MR grade ≥2	3.74 (1.94–7.18)	<0.001	2.47 (1.24–4.92)	0.01
Adverse LV remodelling*	2.34 (1.31–4.18)	0.004	2.12 (1.17–3.84)	0.01

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; LV = left ventricular; MR = mitral regurgitation; STEMI = ST-segment elevation myocardial infarction.

* Adverse left ventricular remodelling was defined as an increase in left ventricular end-systolic volume ≥15% at 12 months follow-up.

myocardial infarction, with 40% of patients having moderate MR and 6% severe MR.²² However, the population was mostly treated with thrombolysis. Another study by Meris et al evaluated the degree of MR until 20 months after myocardial infarction in 610 high-risk patients with LV dysfunction, heart failure or both.²³ At 20 months follow-up, 150 (44%) patients had no detectable MR, 139 (41%) patients had mild MR and 52 (15%) patients had moderate to severe MR.²³ In the present study, although 60% of patients had no MR at baseline and MR grade remained stable in the vast majority of patients, there was also a large group of patients (20%) in whom MR worsened ≥1 grade and 4% of patients progressed from no MR to significant MR at 12 months; consequently, we noted an increase in the incidence of significant MR over time (8%, $p=0.01$ compared to baseline). Therefore, the present study supports the need for further surveillance of MR after STEMI since the prognostic consequences of significant MR at follow-up are not benign.

Associates of significant mitral regurgitation at follow-up

It is known that ischemic MR can be considered as a ventricular, rather than valvular, disorder.²¹ In fact, local and global adverse LV remodelling are key determinants of ischemic MR progression, leading to mitral annular dilatation and papillary muscle displacement with malcoaptation of the mitral valve leaflets. In addition, the reduced LV contractility that can result after a myocardial infarction, further impairs the mitral valve closing forces and increases the grade of MR.²¹ Supported by these pathophysiological mechanisms, we found significant association between the presence of significant MR and adverse LV remodelling. Furthermore, in the present study, baseline LVESV (a marker for infarct size) was a significant correlate of MR grade ≥ 2 at follow-up; this finding emphasizes that the LV enlargement already present in the acute phase after a myocardial infarction has a negative influence on MR progression. Moreover, the current study underscored the importance of baseline MR as correlate of MR progression: presence of MR immediately after infarction not only has per se an important prognostic value, as previously demonstrated,^{1,7} but also contributes to volume overload and further LV enlargement over time, which further impairs mitral leaflet coaptation, increasing the grade of MR during follow-up.²³ Data from the Valsartan in Acute Myocardial Infarction Echo substudy showed that baseline tenting area (as a measure of leaflet tethering) and worsening by ≥ 1 grade in MR at 1-month follow-up were independently associated with MR progression ($p=0.018$ and $p<0.001$, respectively).²³

Significant mitral regurgitation and outcome

Ischemic MR has shown to be an independent predictor of mortality and cardiovascular morbidity.^{1,25} In the Survival And Ventricular Enlargement (SAVE) study, even mild MR predicted cardiovascular mortality during 3.5 years follow-up.²⁵ In another study including 711 patients with acute coronary syndrome undergoing PCI, only 58% of patients with moderate to severe MR were alive at 5 years in contrast to 97% of those without MR.²⁶

However, the majority of existing data on ischemic MR and outcome did not include STEMI patients treated with primary PCI.^{25,26} More recent data on STEMI patients¹⁹ confirmed the negative prognostic role of moderate to severe MR assessed in the early postinfarction period. Furthermore, Uddin et al⁷ demonstrated that MR detected within 72 hours after PCI for STEMI stratified mortality risk, although it was not an independent predictor of mortality when accounting for age.

Importantly, in the previous reports MR was assessed only in the acute phase.^{7,19} Therefore, the prognostic role of significant MR detected at follow-up was not well elucidated. One of the few studies evaluating the relationship between MR at follow-up and prognosis involved 496 high-risk myocardial infarction patients, including 66% with Q-wave myocardial infarction, 39% treated with thrombolytic therapy and 19% treated with primary PCI.²⁴ Progression of MR from baseline to 1 month was associated with a significantly increased risk of death or heart failure hospitalization; furthermore, progression of MR over 20 months follow-up was related to increased likelihood of hospitalizations

for heart failure.²⁴ The current study provides new data in the setting of contemporary STEMI patients treated with primary PCI, confirming that significant MR at 12 months is independently associated with all-cause mortality and cardiovascular mortality. It might therefore represent a further therapeutic target including heart failure medications, device implantation and surgical treatment.

Study limitations

The present study was retrospective and included patients from a single center. Therefore, the results of the present evaluation should be confirmed by prospective studies. Furthermore, the present study was limited by survivor bias, since patients who died before the 12 months echocardiographic assessment were excluded. Similarly, absence of echocardiographic follow-up in excluded surviving patients may also introduce a bias. However, analysis in the excluded patients is provided in the Supplemental material. Finally, patients with clearly organic MR due to flail or Barlow disease were excluded. However, there may be cases with mild forms of organic MR that cannot be differentiated from ischemic MR from transthoracic echocardiography.

CONCLUSIONS

Ischemic MR is a frequent complication after STEMI and has a dynamic nature. Age, baseline systolic LV volume and baseline significant MR are independent correlates of significant MR at 12 months follow-up. Finally, significant MR at 12 months is independently associated with all-cause and cardiovascular mortality.

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SUPPLEMENTAL MATERIAL

Differences in baseline characteristics between patients who completed echocardiographic follow-up (n=1,599) and patients who did not (n=332) are outlined in the Supplementary Table 1.

Supplementary Table 1. *Baseline characteristics of patients with and without echocardiographic follow-up*

	Echocardiographic follow-up		p*
	Yes	No	
	(n=1,599)	(n=332)	
Clinical characteristics			
Age (years)	60 ± 12	66 ± 13	<0.001
Male gender	1,229 (77%)	235 (71%)	0.02
Killip class ≥2	64 (4%)	41 (12%)	<0.001
Medical history			
Current smoking	765 (48%)	134 (42%)	0.04
Diabetes	170 (11%)	54 (16%)	0.003
Family history of CAD	685 (43%)	116 (37%)	0.03
Hypercholesterolemia	334 (21%)	65 (20%)	0.73
Hypertension	563 (35%)	140 (43%)	0.01
Previous MI	137 (9%)	35 (11%)	0.24
Coronary angiography			
LAD as culprit vessel	690 (43%)	148 (45%)	0.52
RCA as culprit vessel	627 (39%)	118 (36%)	0.27
Multivessel disease	868 (54%)	202 (61%)	0.03
TIMI 2–3 flow	1,575 (99%)	314 (95%)	<0.001
Laboratory tests			
Peak CPK level (U/L)	2,136 ± 2,760	2,368 ± 2,378	0.16
Peak cTnT level (µg/L)	5.4 ± 5.4	8.4 ± 18.9	0.004
Medication at discharge			
ACE-inhibitors/ARBs	1,560 (98%)	269 (95%)	0.002
Antiplatelets	1,594 (100%)	282 (100%)	0.99
β-Blockers	1,514 (95%)	254 (89%)	<0.001
Statins	1,586 (100%)	274 (96%)	<0.001

Supplementary Table 1. Baseline characteristics of patients with and without echocardiographic follow-up (continued)

	Echocardiographic follow-up		p*
	Yes (n=1,599)	No (n=332)	
Echocardiography			
LVESV (mL/m ²)	28.5 ± 10.9	29.2 ± 11.0	0.35
LVEDV (mL/m ²)	53.3 ± 15.5	53.1 ± 15.6	0.84
LVEF (%)	47 ± 9	45 ± 10	0.003
MR grade			<0.001
MR grade 0	961 (60%)	177 (55%)	
MR grade 1	535 (34%)	109 (34%)	
MR grade 2	69 (4%)	32 (10%)	
MR grade 3	34 (2%)	3 (1%)	
Significant MR (grade ≥2)	103 (6%)	35 (11%)	0.005
E/A ratio	0.99 ± 0.39	1.07 ± 0.59	0.02
DT (ms)	212 ± 74	200 ± 79	0.01
E/E' ratio	12.8 ± 4.5	15.3 ± 9.2	<0.001

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CPK = creatine phosphokinase; cTnT = cardiac troponin T; DT = deceleration time; E/A = mitral inflow peak early velocity (E)/mitral inflow peak late velocity (A); E/E' = mitral inflow peak early velocity (E)/mitral annular peak early velocity (E'); MI = myocardial infarction; LAD = left anterior descending coronary artery; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

Data are presented as mean ± standard deviation or as number (percentage).

* p-values are given for the comparisons of patients with echocardiographic follow-up in whom MR quantification by echocardiography was feasible and patients without echocardiographic follow-up.

In the 332 excluded patients, we performed survival analyses with all-cause mortality as endpoint and date of index infarction as follow-up onset and analyzed the impact of baseline MR on survival. At baseline 177 (55%) patients showed no MR, 109 (34%) patients had MR grade 1 and 35 (11%) patients had MR grade ≥2. In 11 patients, MR quantification was not feasible at baseline. During a median follow-up of 62 months (interquartile range 51–81 months), 135 (41%) patients died. Event rates at 12, 24, 36, 48 and 60 months were 55.8%, 58.7%, 58.7%, 61.7% and 61.7%, respectively, for patients with significant MR and 23.4%, 26.4%, 28.6%, 30.1% and 34.2%, respectively, for patients without significant MR (log-rank $p < 0.001$). Univariate Cox regression analysis showed that significant MR at baseline was associated with a significant increased risk of all-cause mortality (hazard ratio 2.35, 95% confidence interval 1.46–3.78, $p < 0.001$). At multivariate level, significant MR

at baseline was independently associated with all-cause mortality (hazard ratio 2.78, 95% confidence interval 1.39–5.54, $p=0.004$) together with age, diabetes and baseline LV end-diastolic volume (Supplementary Table 2).

Supplementary Table 2. *Determinants of all-cause mortality following STEMI in the 332 excluded patients*

	Univariate		Multivariate	
	HR (95% CI)	p	HR (95% CI)	p
<i>All-cause mortality</i>				
Age (years)	1.06 (1.04–1.07)	<0.001	1.03 (1.01–1.06)	0.01
Killip class ≥ 2	4.14 (2.74–6.26)	<0.001	1.55 (0.59–4.03)	0.37
Diabetes	2.75 (1.90–3.98)	<0.001	2.72 (1.54–4.79)	0.001
Family history of CAD	0.40 (0.26–0.61)	<0.001	0.84 (0.46–1.53)	0.56
Previous MI	1.62 (1.01–2.61)	0.05	1.43 (0.63–3.28)	0.40
Multivessel disease	1.81 (1.25–2.62)	0.002	1.23 (0.72–2.12)	0.45
TIMI 2–3 flow	0.18 (0.10–0.32)	<0.001	0.30 (0.07–1.30)	0.11
ACE-inhibitors/ARBs	0.36 (0.19–0.69)	0.002	0.97 (0.38–2.51)	0.95
β -Blockers	0.27 (0.17–0.44)	<0.001	0.50 (0.24–1.03)	0.06
Statins	0.38 (0.17–0.88)	0.02	0.75 (0.23–2.44)	0.63
MR grade ≥ 2	2.35 (1.46–3.78)	<0.001	2.78 (1.39–5.54)	0.004
LVEDV (mL/m ²)	0.98 (0.96–0.99)	0.001	0.98 (0.96–1.00)	0.04
E/E' ratio	1.05 (1.03–1.06)	<0.001	1.00 (0.98–1.03)	0.80

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CI = confidence interval; E/E' = mitral inflow peak early velocity (E)/mitral annular peak early velocity (E'); HR = hazard ratio; LVEDV = left ventricular end-diastolic volume; MI = myocardial infarction; MR = mitral regurgitation; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

CHAPTER 5

Comparison of Changes in Global Longitudinal Peak Systolic Strain After ST-Segment Elevation Myocardial Infarction in Patients With Versus Without Diabetes Mellitus

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ABSTRACT

Global longitudinal strain (GLS) measured by 2-dimensional longitudinal speckle-tracking echocardiography may be a more sensitive measure of left ventricular (LV) mechanics than conventional LV ejection fraction (EF) to characterize adverse post-ST-segment elevation myocardial infarction (STEMI) remodeling. The aim of the present evaluation was to compare changes in LV GLS in patients with versus without diabetes after the first STEMI. Patients with first STEMI and diabetes ($n=143$; age 64 ± 12 years; 68% men; 50% left anterior descending artery as culprit vessel) and 290 patients with first STEMI and without diabetes matched on age, gender, and infarct location were included. LV volumes and function and 2-dimensional LV GLS were measured after primary percutaneous coronary intervention (baseline) and at 6-month follow-up. At baseline, patients with and without diabetes had similar LVEF ($46.8 \pm 0.7\%$ vs. $48.0 \pm 0.5\%$, $p=0.19$) and infarct size (peak cardiac troponin T: $3.1 [1.2 \text{ to } 6.5]$ vs. $3.7 [1.3 \text{ to } 7.3]$ $\mu\text{g/l}$, $p=0.10$; peak creatine phosphokinase: $1,120 [537 \text{ to } 2,371]$ vs. $1,291 [586 \text{ to } 2,613]$ U/l, $p=0.17$), whereas LV GLS was significantly more impaired in diabetic patients ($-13.7 \pm 0.3\%$ vs. $-15.3 \pm 0.2\%$, $p<0.001$). Although diabetic patients showed an improvement in LVEF over time similar to nondiabetic patients ($52.0 \pm 0.8\%$ vs. $53.1 \pm 0.6\%$, $p=0.25$), GLS remained more impaired at 6-month follow-up compared with nondiabetic patients ($-15.8 \pm 0.3\%$ vs. $-17.3 \pm 0.2\%$, $p<0.001$). After adjusting for clinical and echocardiographic characteristics, diabetes was independently associated with changes in GLS from baseline to 6-month follow-up (β 1.41, 95% confidence interval 0.85 to 1.96, $p<0.001$). In conclusion, after STEMI, diabetic patients show more impaired LV GLS at both baseline and follow-up compared with a matched group of patients without diabetes, despite having similar infarct size and LVEF at baseline and follow-up.

INTRODUCTION

After ST-segment elevation myocardial infarction (STEMI), patients with diabetes mellitus have shown similar changes in left ventricular (LV) volumes and ejection fraction (EF) compared with patients without diabetes.¹⁻⁷ However, the long-term prognosis of diabetics remains poor with an increased rate of heart failure and all-cause mortality.^{1,2,7-9} Despite showing a similar degree of LV remodeling after STEMI, one of the mechanisms that may explain why diabetic patients have a worse outcome compared with nondiabetic subjects may be related to the presence of more impaired LV mechanics, which are associated with an increased risk of heart failure. Previous studies in diabetic patients with normal LVEF have demonstrated the presence of subclinical LV dysfunction as assessed with 2-dimensional (2D) global longitudinal strain (GLS) speckle-tracking echocardiography.¹⁰⁻¹⁶ On the basis of these findings, it was hypothesized that LV GLS in diabetic patients after STEMI remains more impaired than in patients without diabetes, possibly explaining the increased risk for adverse events. The present evaluation aimed at (1) evaluating changes in LV GLS in a contemporary cohort of patients with STEMI with and without diabetes and (2) determining if diabetes alongside other relevant postinfarction parameters is independently associated with changes in GLS at 6-month follow-up.

METHODS

Patients admitted with STEMI treated with primary percutaneous coronary intervention (PCI) at the Leiden University Medical Center were included in an ongoing registry (MISSION!).¹⁷ All patients were treated according to contemporary American College of Cardiology/American Heart Association and European Society of Cardiology guidelines.¹⁷⁻¹⁹ This included prompt initiation of optimal medical therapy and acquisition of 2D echocardiography within 48 hours of admission. Repeated clinical and echocardiographic evaluations are periodically performed during the first year after STEMI. Clinical and echocardiographic data are collected in the departmental Cardiology Information System (EPD-Vision; Leiden University Medical Center, Leiden, The Netherlands) and in the echocardiography database, respectively, and all data were retrospectively analyzed. For this retrospective analysis of clinically acquired data, the institutional review board waived the need of patient written informed consent.

Diabetes status was assessed during the presentation of index infarction by the treating physician and defined as known history of diabetes treated with diet or insulin and/or oral glucose-lowering agents.^{4,20} Patients with new-onset diabetes diagnosed at the index admission were not included. Furthermore, only patients in whom echocardiography was available at baseline and 6-month follow-up were included. Subsequently, a control group including patients without diabetes was selected from the MISSION! registry. Patients were eligible as controls if they were admitted with a first STEMI treated with primary PCI

and if echocardiography was available at baseline and 6-month follow-up. Nondiabetic patients were matched to the diabetic group according to age, gender, and left anterior descending coronary artery as culprit vessel in a 2:1 ratio.

Images were obtained with patients at rest in the left lateral decubitus position using a commercially available ultrasound system (Vivid 7 and E9; General Electric-Vingmed, Horten, Norway). Data acquisition was performed with a 3.5-MHz or M5S transducer in the parasternal and apical views. Standard M-mode and 2D, color, pulsed wave and continuous wave Doppler images were acquired and saved in cine loop format. Echocardiographic data analysis was performed offline (EchoPac 112.0.1; GE Medical Systems, Horten, Norway).

From the parasternal long-axis view, LV dimensions were measured, and LV mass was calculated and indexed to body surface area.²¹ Using the biplane Simpson method, LV end-diastolic and end-systolic volumes and LVEF were measured in the apical 4- and 2-chamber views.²¹ To calculate wall motion score index (WMSI), the LV was divided into 16 segments, as previously described.^{21,22} Mitral regurgitation severity was graded according to present guidelines.²³ LV diastolic parameters included peak early (E) and late (A) diastolic velocities and E-wave deceleration time measured on pulsed wave Doppler recordings of the transmitral flow. E' was measured with tissue Doppler imaging at the septal and lateral side of the mitral annulus in the apical 4-chamber view, and E/septal E' ratio and E/lateral E' ratio, respectively, were calculated.²⁴ Finally, according to the biplane Simpson technique, maximal left atrial volume was measured in the apical 4- and 2-chamber views and indexed to the body surface area.²¹

To quantify LV GLS, 2D speckle-tracking analyses were performed offline on standard routine grayscale images of apical 4-, 2-chamber, and long-axis views as previously described.²⁵ Images were acquired with a frame rate ≥ 40 frames/sec for a reliable analysis. LV GLS was provided by the software as the average of the peak systolic longitudinal strain of the 3 apical views, displayed in a 17-segment "bull's eye" plot. GLS measurement was feasible at baseline and 6-month follow-up in 98% of patients. Intraobserver and interobserver variabilities for LV GLS analysis in our laboratory have been reported ($-0.09 \pm 2.2\%$ and $-0.20 \pm 1.1\%$, respectively).²⁶ For LV circumferential strain, 2D speckle-tracking analyses were performed on the LV short-axis midventricular view at the papillary muscle level, as previously described.¹³ LV circumferential strain was calculated as the average of the peak systolic circumferential strain of the short-axis midventricular view. At baseline and 6-month follow-up, LV circumferential strain measurement was feasible in 84% and 89% of patients, respectively. Intraobserver and interobserver variabilities for LV circumferential strain analysis in our laboratory have been reported in previous studies ($1.2 \pm 1.0\%$ and $2.3 \pm 2.4\%$, respectively).¹³

Continuous data are reported as mean $\pm$ SD or SE and median with interquartile range, as appropriate, and categorical data as frequencies and percentages. To obtain a Gaussian distribution, peak troponin T, peak creatine phosphokinase, and estimated

glomerular filtration rate levels were log transformed. In statistical tests that required normality (or symmetry), these transformed data were used. Thereafter, data were back-transformed to the original data scales and expressed as median with interquartile range. Differences in baseline clinical parameters between patients with and without diabetes were analyzed using the Student *t* test and chi-square test. Using linear mixed model analyses, differences in echocardiographic variables were assessed between patients with and without diabetes from baseline to 6-month follow-up, including changes from baseline to 6-month follow-up within each group and differences between groups at each time point. Finally, unadjusted and adjusted linear mixed modeling was used to test the association between diabetes and changes in GLS. Covariates (baseline clinical characteristics and changes in echocardiographic parameters) with a *p*-value <0.10 at the univariate level were included in a linear mixed regression model including diabetes and changes in GLS. Peak creatine phosphokinase and peak cardiac troponin levels were not included in the same model to avoid multicollinearity. Likewise, changes in LV end-diastolic volume, LV end-systolic volume, LVEF, WMSI, and circumferential strain and changes in diastolic function parameters (E/A ratio, deceleration time, E/septal E' ratio, and E/lateral E' ratio) were not included in the same model. Moreover, age, gender, and left anterior descending coronary artery as culprit vessel were not included in the multivariate model because patients were matched for these variables. All statistical tests were 2 sided, and a *p*-value <0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS software version 20.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Of 2,443 patients with first STEMI treated with primary PCI, 263 (11%) were diabetic and 2,180 (89%) were nondiabetic. In diabetics, echocardiography was available at baseline and 6-month follow-up for 154 patients (59%). Of the nondiabetic patients, 1,569 patients (72%) were eligible as the potential control group. On the basis of age, gender, and left anterior descending coronary artery as culprit vessel, the 154 patients with diabetes were matched in a 1:2 ratio with 308 patients without diabetes. A further 11 diabetic and 18 nondiabetic patients were excluded owing to the presence of a pacing device at the baseline and/or 6-month echocardiogram. Therefore, the final patient population comprised 143 diabetic and 290 nondiabetic patients.

Most diabetic patients had type 2 diabetes (77%). Antidiabetic treatment at admission consisted of diet only (13%), oral glucose-lowering agents (75%; including metformin, sulfonylureas, glitazones, and dipeptidyl peptidase-4 inhibitors), and insulin (27%). At admission, the mean hemoglobin A_{1c} level was 58 ± 9 mmol/mol (or $7.4 \pm 1.8\%$), and the mean nonfasting glucose level was 11.6 ± 4.3 mmol/L. Table 1 summarizes the baseline characteristics of patients with and without diabetes. Patients with diabetes presented more often with cardiovascular risk factors compared with nondiabetic patients,

Table 1. Baseline characteristics

Variable	Diabetes Mellitus		p*
	Yes (n=143)	No (n=290)	
Clinical characteristics			
Age (years)	64 ± 12	63 ± 12	0.55
Men	97 (68%)	201 (69%)	0.76
Killip class ≥2	8 (6%)	11 (4%)	0.39
Current smoker	38 (27%)	130 (45%)	<0.001
Family history of CAD	65 (46%)	132 (46%)	0.99
Hypercholesterolemia [†]	58 (41%)	46 (16%)	<0.001
Hypertension [‡]	77 (54%)	105 (36%)	<0.001
Coronary angiography			
LAD as culprit vessel	72 (50%)	150 (52%)	0.79
Multivessel coronary disease	81 (57%)	153 (53%)	0.45
TIMI 2–3 flow	143 (100%)	286 (99%)	0.16
Laboratory tests			
Peak CPK level (U/L)	1,120 (537–2,371)	1,291 (586–2,613)	0.17
Peak cTnT level (µg/L)	3.1 (1.2–6.5)	3.7 (1.3–7.3)	0.10
eGFR level (mL/min/1.73 m²)	97 (71–125)	91 (70–112)	0.26
Medication at discharge			
ACE-inhibitors/ARBs	139 (97%)	286 (99%)	0.30
Antiplatelets	143 (100%)	290 (100%)	1.00
β-Blockers	139 (97%)	274 (95%)	0.21
Statins	143 (100%)	286 (99%)	0.16

Data are presented as mean ± standard deviation, median (interquartile range) or as number (percentage).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CPK = creatine phosphokinase; cTnT = cardiac troponin T; eGFR = glomerular filtration rate estimated with the Cockcroft-Gault formula; LAD = left anterior descending coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

* p-values are provided for the comparisons between patients with and without diabetes.

[†] Total cholesterol ≥190 mg/dL or previous pharmacological treatment.

[‡] Blood pressure ≥140/90 mmHg or previous pharmacological treatment.

including hypercholesterolemia and hypertension. The groups were comparable for other variables.

Median time between PCI and baseline echocardiography was 24 (interquartile range 17 to 41) hours. Table 2 illustrates the echocardiographic parameters at baseline and 6-month follow-up in patients with and without diabetes. LV volumes were similar in patients with and without diabetes at baseline and 6-month follow-up. Although both baseline LVEF and WMSI were comparable between patient groups, LV GLS at baseline was more impaired in diabetic patients than in those without diabetes (Figure 1). Over time, both groups demonstrated an improvement in LV function from baseline to 6-month follow-up. Despite similar LVEF in patients with and without diabetes at 6-month follow-up, 6-month GLS values remained more impaired in diabetic patients compared with those without diabetes (Figure 1).

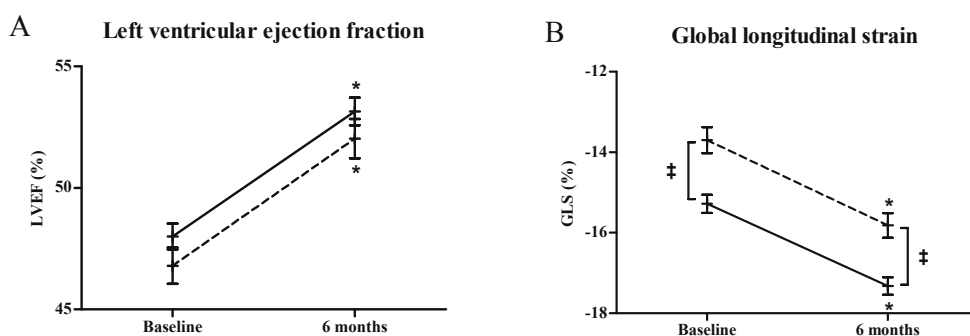


Figure 1. Changes from baseline to 6-month follow-up in LVEF (panel A) and LV GLS (panel B) in patients with diabetes (dashed line) and without diabetes (solid black line). * $p < 0.05$ compared with baseline. # $p < 0.05$ between patients with or without diabetes at this time point. Data are presented as mean $\pm$ SE.

Unadjusted models showed that diabetes was significantly associated with changes in LV GLS (β 1.54, 95% confidence interval 0.87 to 2.20, $p < 0.001$). Other significant unadjusted correlates of changes in GLS are reported in Table 3. The final adjusted model included diabetes, Killip class ≥ 2 , hypertension, peak cardiac troponin level, statin usage at discharge, changes in LV end-diastolic volume, E/septal E' ratio, mitral regurgitation grade, and LV mass. In this model, diabetes emerged as an independent determinant of changes in LV GLS (β 1.41, 95% confidence interval 0.85 to 1.96, $p < 0.001$; Table 3).

DISCUSSION

Compared with matched patients with first STEMI without diabetes, diabetic patients had worse LV GLS values directly after STEMI which persisted at 6-month follow-up despite comparable LVEF at baseline and 6-month follow-up and enzymatic infarct size. Importantly,

Table 2. Echocardiographic variables at baseline and 6 months follow-up in first ST-segment elevation myocardial infarction patients with and without diabetes

Variable	Diabetes Mellitus (n=143)			No Diabetes Mellitus (n=290)		
	Baseline	6 months	p within group*	Baseline	6 months	p within group*
Left ventricular end-systolic volume (mL)	53.8 ± 1.7	55.0 ± 2.1	0.50	52.3 ± 1.2	51.2 ± 1.5	0.33
Left ventricular end-diastolic volume (mL)	100.4 ± 2.6	110.6 ± 3.1	<0.001	100.0 ± 1.8	106.7 ± 2.1	<0.001
Left ventricular ejection fraction (%)	46.8 ± 0.7	52.0 ± 0.8	<0.001	48.0 ± 0.5	53.1 ± 0.6	<0.001
Wall motion score index	1.46 ± 0.03	1.35 ± 0.03†	<0.001	1.42 ± 0.02	1.28 ± 0.02†	<0.001
Global longitudinal strain (%)	-13.7 ± 0.3†	-15.8 ± 0.3†	<0.001	-15.3 ± 0.2†	-17.3 ± 0.2†	<0.001
Circumferential strain (%)	-10.3 ± 0.4†	-12.1 ± 0.4	<0.001	-11.5 ± 0.3†	-12.6 ± -0.3	0.001
Left atrial indexed volume (mL/m ²)	19.5 ± 0.7	22.1 ± 0.7	<0.001	19.8 ± 0.5	21.4 ± 0.5	0.001
E/A ratio	0.94 ± 0.04	0.97 ± 0.03	0.41	0.95 ± 0.03	0.92 ± 0.02	0.15
Deceleration time (ms)	207.5 ± 6.2	229.4 ± 6.4	0.008	212.8 ± 4.4	243.5 ± 4.5	<0.001
E/septal E' ratio	14.3 ± 0.4†	15.1 ± 0.8†	0.27	13.0 ± 0.3†	13.0 ± 0.5†	1.00
E/lateral E' ratio	13.3 ± 0.9	11.7 ± 0.5†	0.01	12.6 ± 0.6	10.4 ± 0.3†	0.001
Mitral regurgitation grade	0.52 ± 0.06	0.57 ± 0.06	0.43	0.47 ± 0.04	0.50 ± 0.04	0.47
Left ventricular mass (g/m ²)	110.9 ± 2.6†	105.5 ± 2.4	0.04	103.5 ± 1.8†	102.1 ± 1.7	0.34

Data are presented as mean ± standard error.

* p-values within groups are provided for the differences from baseline to 6 months follow-up within each group.

† p<0.05 for the comparison between patients with and without diabetes at that particular time point.

Table 3. Correlates of changes in left ventricular global longitudinal strain

Variable	Univariate analysis			Multivariate analysis*		
	B	95% CI	p	B	95% CI	p
Age	0.04	0.01 to 0.07	0.004			
Killip class ≥ 2	2.39	0.84 to 3.94	0.003	1.44	0.18 to 2.70	0.03
Diabetes	1.54	0.87 to 2.20	<0.001	1.41	0.85 to 1.96	<0.001
Hypertension	0.70	0.05 to 1.35	0.03	0.10	-0.44 to 0.63	0.72
LAD as culprit vessel	2.64	2.04 to 3.23	<0.001			
Peak CPK level (U/L)	0.0008	0.0006 to 0.0009	<0.001			
Peak cTnT level ($\mu\text{g/L}$)	0.28	0.23 to 0.34	<0.001	0.24	0.19 to 0.29	<0.001
Statin usage at discharge	-4.17	-0.78 to -7.56	0.02	-1.24	-3.99 to 1.51	0.38
Changes in LVESV (mL)	0.06	0.05 to 0.07	<0.001			
Changes in LVEDV (mL)	0.02	0.01 to 0.03	<0.001	0.01	0.01 to 0.02	<0.001
Changes in LVEF (%)	-0.16	-0.19 to -0.14	<0.001			
Changes in WMSI	4.95	4.21 to 5.68	<0.001			
Changes in circumferential strain (%)	0.23	0.17 to 0.29	<0.001			
Changes in LAVI (mL/m^2)	0.03	0.003 to 0.07	0.03			
Changes in DT (ms)	-0.004	-0.0009 to -0.007	0.01			
Changes in E/septal E' ratio	0.12	0.09 to 0.16	<0.001	0.10	0.07 to 0.13	<0.001
Changes in E/lateral E' ratio	0.10	0.07 to 0.13	<0.001			
Changes in MR grade	0.78	0.43 to 1.12	<0.001	0.38	0.04 to 0.71	0.03
Changes in LV mass (g/m^2)	0.02	0.02 to 0.03	<0.001	0.01	0.004 to 0.02	0.002

CPK = creatine phosphokinase; cTnT = cardiac troponin T; DT = deceleration time; LAD = left anterior descending coronary artery; LAVI = left atrial indexed volume; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; WMSI = wall motion score index.

* In the multivariate analysis, only diabetes, Killip class ≥ 2 , hypertension, peak cardiac troponin level, statin usage at discharge, and changes in LV end-diastolic volume, E/septal E' ratio, mitral regurgitation grade, and LV mass were included.

after adjusting for clinical and echocardiographic parameters, the presence of pre-existing diabetes was independently associated with changes in GLS after STEMI.

After STEMI, patients with diabetes have an increased risk of heart failure and all-cause mortality.^{1,2,7-9} LV remodeling has been described as one of the most important processes leading to adverse outcome after STEMI. Nevertheless, differences in outcome between patients with and without diabetes may not be explained by this mechanism only.¹⁻⁷ In a study by Lamblin et al investigating 512 patients with first acute anterior STEMI treated with primary PCI, diabetes was neither associated with LV volumes and LVEF at

baseline nor 3-month nor 1-year follow-up.³ In addition, the VALIANT Echo study, including 594 patients with acute myocardial infarction complicated with heart failure and/or LV systolic dysfunction, demonstrated no difference in changes in LV volumes and LVEF from baseline to 1-month and from 1-month to 20-month follow-up between patients with and without diabetes.⁴ Likewise, the present analysis showed similar LV volumes and LVEF at baseline and 6-month follow-up in diabetic and nondiabetic patients.

Furthermore, experimental and clinical studies suggest that the diabetic heart is more susceptible to injury. The pathophysiologic processes in diabetes, including metabolic disturbances, structural changes, microvascular perfusion abnormalities, and cardiac autonomic neuropathy, are proposed to reduce the compensatory capacity of the heart leading to diabetic cardiomyopathy and impaired LV mechanics.²⁷⁻³⁰ Previous studies evaluating diabetic patients without overt heart disease demonstrated the presence of subclinical LV systolic dysfunction, measured by deformation imaging.¹⁰⁻¹⁶ Using tissue Doppler imaging, Andersen et al showed decreased longitudinal peak systolic strain and strain rate values in 32 patients with type 2 diabetes having normal LVEF compared with 32 normal subjects.¹⁰ In addition, in a study by Ng et al, 47 asymptomatic patients with type 2 diabetes demonstrated reduced LV systolic function measured by speckle-tracking echocardiography compared with 53 matched healthy controls although LVEF was not different.¹³

So far, LV GLS had not been systematically evaluated in patients with STEMI with diabetes. In the present study, diabetic patients with first STEMI demonstrated a reduced baseline LV systolic function, measured with speckle-tracking strain, compared with nondiabetic patients, whereas LVEF was similar in both patient groups. Because peak cardiac enzyme levels were comparable between groups, infarct size would not be the only pathophysiologic explanation for these findings. Moreover, although in diabetic patients, LV function improved from baseline to 6-month follow-up, GLS remained more impaired compared with nondiabetic subjects, despite similar 6-month LVEF. Notably, after adjusting for relevant postinfarction parameters, diabetes was independently associated with changes in GLS from baseline to 6-month follow-up after STEMI. Consequently, these results confirm the presence of impaired LV mechanics and reduced cardiac compensatory capacity after STEMI in diabetic patients, highlighting the importance of increased surveillance of this high-risk patient group.

Present guidelines recommend evaluation of LV systolic function at discharge after STEMI and during follow-up using LVEF.^{18,19} However, 2D longitudinal speckle-tracking strain has shown to be more sensitive than conventional echocardiographic measurements of LV function to detect subtle LV dysfunction in diabetics.^{12-14,16} On the basis of the findings of the present evaluation, LV GLS may be more appropriate for the assessment of LV systolic function in patients with STEMI with diabetes than LVEF. LV GLS could also be a useful tool to early identify patients with diabetes who may benefit from therapeutic strategies to prevent heart failure progression and to improve prognosis.

Several limitations should be acknowledged. First, this was a single-center, retrospective, observational evaluation. In addition, patients who had died before completing their 6-month echocardiogram were excluded, introducing a potential selection bias. However, in patients with and without diabetes, similar incidences were noted for those events. Furthermore, after adjusting for revascularization, re-myocardial infarction, and hospitalization for heart failure, diabetes was still independently associated with changes in GLS.

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CHAPTER 6

Assessment of Left Ventricular Excursion using
Three Dimensional Dobutamine Stress
Echocardiography to Identify Significant Coronary
Artery Disease

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Submitted



ABSTRACT

Aims: Quantitative three-dimensional (3D) dobutamine stress echocardiography (DSE) for myocardial ischemia detection may be an adjuvant to left ventricular (LV) wall motion analysis. The aim of the current study was to assess the association between 3D LV excursion at global level during DSE and presence of significant coronary artery disease (CAD) on coronary angiography.

Methods and results: 3D DSE was performed in 40 patients (67 ± 12 years, 68% male) who underwent subsequent coronary angiography (median 1.6 months later). Using 3D echocardiography, global LV excursion was measured (in a total of 680 segments) at rest and peak dose and change between stages was calculated (peak-rest = Δ global LV excursion). Significant CAD was defined as $>70\%$ stenosis on coronary angiography. In total, 25 patients (63%) demonstrated significant CAD on coronary angiography. At rest, global LV excursion was similar in patients with and without significant CAD (5.1 ± 0.2 vs. 5.0 ± 0.2 mm, $p=0.74$). However, patients with significant CAD demonstrated a worsening in global LV excursion from rest to peak stress (from 5.1 ± 0.2 to 4.1 ± 0.2 mm, $p<0.001$) while global LV excursion in patients without significant CAD remained unchanged (from 5.0 ± 0.2 to 5.5 ± 0.2 mm, $p=0.10$). After adjusting for clinically relevant characteristics, Δ global LV excursion was independently associated with significant CAD (odds ratio 0.29, 95% confidence interval 0.12–0.72, $p=0.008$).

Conclusion: Analysis of 3D echocardiographic LV excursion at global level on full protocol DSE may be a helpful tool to detect CAD on coronary angiography.

INTRODUCTION

Dobutamine stress echocardiography (DSE) has been widely used to detect and localize myocardial ischemia in patients with suspected coronary artery disease (CAD).¹⁻³ Detection of hemodynamically significant CAD relies on the assessment of changes in left ventricular (LV) wall motion and thickening between rest and at peak dose of dobutamine. However, this assessment is challenging, often highly subjective, requires training and is dependent on observer and image quality.^{4,5} Quantitative approaches using three-dimensional (3D) echocardiography may overcome these limitations. Three-dimensional echocardiography permits the acquisition of the LV full volume enabling comparison the same LV walls (or segments) on a tomographic approach between rest and peak dose of dobutamine and avoiding misalignments and foreshortening. In addition, in the last years, advances in semi-automated software to post-process the data have reduced observer dependence and novel quantitative parameters of LV mechanics (excursion and deformation) may permit objective detection of myocardial ischemia.⁶⁻⁸

Left ventricular (LV) excursion (or left atrioventricular plane displacement) is a surrogate of the LV longitudinal contraction that can be reduced during myocardial ischemia.⁹ Previous studies have shown the association between changes in LV excursion assessed during 2-dimensional DSE with the presence of significant CAD.¹⁰⁻¹³ However, the role of 3D LV excursion at global level in DSE for the detection of myocardial ischemia remains unexplored to date. Therefore, the aim of the current study was to evaluate the association between changes in LV excursion, assessed at global level, during full protocol 3D DSE and presence of significant CAD on coronary angiography in patients with suspected CAD.

METHODS

Patient population

Patients with suspected CAD who were referred for DSE and subsequently underwent invasive coronary angiography or multi-detector row computed tomography coronary angiography within 6 months after the DSE were included in the present evaluation. Patients with a recent acute coronary syndrome or recent revascularization, severe valvular disease or prosthetic valves, congenital heart disease, previous coronary artery bypass grafting and left bundle branch block or pacemaker rhythm were excluded. Clinical and echocardiographic data were collected at the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, The Netherlands) and the echocardiography database, respectively, and were retrospectively analyzed. Patients provided consent for the procedure.

Dobutamine stress protocol and image acquisition

Dobutamine stress echocardiography was performed according to current recommendations.^{2,14} Dobutamine was infused through a peripheral intravenous line with a starting dose of 5 or 10 µg/kg/min, after which the dose increased every 5 minutes up to 40 µg/kg/min. Blood pressure and 12-lead electrocardiogram were monitored at every stage of DSE. Three-dimensional echocardiographic data were acquired at baseline, low and peak dose dobutamine and at recovery. If necessary, intravenous atropine (up to 1 mg) was administered during the last stage of the DSE to achieve the target heart rate (defined as 85% of age-predicted maximal heart rate). Standard endpoints for DSE included target heart rate, extensive new wall motion abnormalities, ischemic ECG changes (>2mV ST-segment shift), severe angina, systolic blood pressure fall or rise and significant (supra-) ventricular arrhythmias.^{2,3} In patients with regional wall motion abnormalities at rest, a new or worsening wall motion abnormality (biphasic response) defined a positive test.

Three-dimensional images were obtained with the patient in the left lateral decubitus position using a commercially available system (iE33, Philips Medical Systems, Bothell, Washington, USA) equipped with an X5-1 fully sampled matrix array transducer. At rest, low dose and peak dose, apical 3D LV full-volume data sets were obtained during breath hold and were digitally stored. Four small real-time sub-volumes were acquired from alternate cardiac cycles and combined to provide a larger pyramidal volume (up to 103x103 degrees) and to ensure a complete capture of the LV. For the assessment of LV volumes and ejection fraction (LVEF), the lowest scan line density was used and gain and compression were adjusted to obtain a good image quality and a clearly defined endocardial border. Subsequently, 3D data analysis was performed offline using Q-Lab Version 9.0 (Philips Medical Systems).

Three-dimensional echocardiographic analysis

The apical 4- and 2-chamber views and the parasternal short-axis view were automatically displayed by the software. After manually indicating the mitral annulus by 4 points and the LV apex on both end-systolic and end-diastolic frames, the software automatically identified the entire endocardial border in each frame. If required, manual adjustment of the endocardial contour was possible. Subsequently, a 3D model was generated from which LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV) and LVEF were automatically quantified. The papillary muscles were considered part of the LV cavity. For the calculation of global LV excursion at rest and peak stress, the results of the volume tracking analysis were exported in an Excel spreadsheet file. Subsequently, global LV excursion was noted for each segment and global LV excursion was calculated by averaging original segmental data (Figure 1). In addition, the change in global LV excursion between stages (peak-rest) was calculated (Δ global LV excursion).

Coronary angiography

Invasive coronary angiography was performed in 36 patients and the presence and the degree of CAD was assessed by computer-assisted quantitative coronary angiography using multiple planes. Multi-detector computed tomography coronary angiography was performed in 4 patients using a 320-row scanner (Acquilion ONE, Toshiba Medical Systems, Otaware, Japan). Significant CAD was defined as $>70\%$ luminal diameter stenosis in ≥ 1 of the 3 major epicardial vessels or associated large side branches.

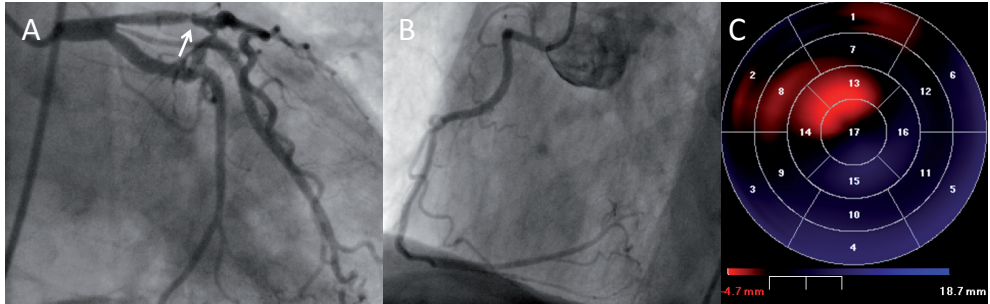


Figure 1. Example of a patient with a significant stenosis on coronary angiography of the left anterior descending artery. Panel A shows the angiography of the left coronary system with a significant proximal stenosis of the left anterior descending coronary artery. Panel B shows a right coronary artery without significant lesions. At peak stress dobutamine stress echocardiography, the polar map obtained from 3-dimensional LV full volume data shows reduced excursion of the LV segments supplied by the left anterior descending coronary artery (Panel C). The LV excursion is color-coded from red to blue indicating in red the segments with no excursion or lengthening and in blue the segments with preserved or enhanced excursion. In this example, the segments that present reduced excursion or lengthening at peak stress are the apical anteroseptal and anterior and the mid septal and anteroseptal.

Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation, mean $\pm$ standard error or as median and interquartile range, where appropriate. Categorical data are presented as absolute numbers and percentages. The Student's paired *t*-test was used to assess differences between stages for individual DSE parameters in the total patient population. Differences in DSE parameters between patients with and without significant CAD on coronary angiography across both stages (group stage interaction) were evaluated using linear mixed models. Moreover, differences within groups and differences between groups at each stage were evaluated. Logistic regression analysis was used to assess the relationship between significant CAD on coronary angiography and 3D LV excursion at global level. Variables with a *p*-value <0.10 in univariate analyses were entered in a multivariate model. In order to avoid overfitting the model the number of variables included were limited due to the number of patients with significant CAD. To avoid multicollinearity, a correlation coefficient of <0.7 was set.

All statistical tests were 2-sided and a p-value of <0.05 was considered statistically significant. All statistical analyses were performed with SPSS software (version 20.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

A total of 40 patients with analyzable 3D DSE data were included. Patients with atrial fibrillation during the DSE ($n=2$) and patients with poor image quality ($n=4$) were excluded. The clinical characteristics of the patients are summarized in Table 1. Mean age of the patient population was 67 ± 12 years and most patients were male (68%). Median time from DSE to coronary angiography was 1.6 (interquartile range 0.9–3.0) months. A total of 25 patients (63%) demonstrated significant CAD $>70\%$ in ≥ 1 epicardial vessel or associated large side branch (left anterior descending artery 50%; left circumflex artery 35%; right coronary artery 25%). Of the patients with significant CAD on coronary angiography, 11 (44%) had single-vessel disease, 9 (36%) had 2-vessel disease and 5 (20%) had 3-vessel disease.

DSE and 3D echocardiography

For the entire patient population, mean heart rates were 67 ± 10 and 128 ± 12 beats/minute at rest and peak stress, respectively. A total of 26 (65%) patients had a positive DSE based on wall motion analysis. A total of 656 segments (96%) and 661 segments (97%) were available at rest and peak stress, respectively, for the calculations of rest, peak and Δ global LV excursion. Mean frame rate at rest and peak stress were 24 ± 2 and 25 ± 3 frames/second, respectively. In the total population, from rest to peak dose significant decreases in LVEDV (from 94.2 ± 26.8 to 87.6 ± 24.9 mL, $p=0.002$), LVEF (from 54.3 ± 5.6 to $51.5 \pm 9.1\%$, $p=0.04$) and in global LV excursion (from 5.0 ± 0.9 to 4.6 ± 1.1 mm, $p=0.03$) were observed. However, LVESV did not change (from 43.3 ± 14.5 to 43.1 ± 17.9 mL, $p=0.88$).

Differences in 3D DSE parameters between patients with and without significant CAD on coronary angiography across stages are illustrated in Figure 2. At rest, patients with and without significant CAD showed comparable LV volumes (LVESV: 44.3 ± 2.9 vs. 41.7 ± 3.8 mL, $p=0.59$; LVEDV: 95.8 ± 5.4 vs. 91.6 ± 7.0 mL, $p=0.64$) and LV function (LVEF: 54.1 ± 1.1 vs. $54.6 \pm 1.5\%$, $p=0.81$; global LV excursion: 5.1 ± 0.2 vs. 5.0 ± 0.2 mm, $p=0.74$). In patients with significant CAD, LVESV increased from rest to peak stress (from 44.3 ± 2.9 to 48.1 ± 3.4 mL, $p=0.02$) while patients without significant CAD demonstrated a decrease in LVESV (from 41.7 ± 3.8 to 34.7 ± 4.4 mL, $p=0.005$). A significant difference was observed in changes in LVESV from rest to peak stress in patients with and without significant CAD (group stage interaction $p<0.001$). Also, LVEDV decreased in patients without significant CAD (from 91.6 ± 7.0 to 80.5 ± 6.4 mL, $p=0.02$). Patients with significant CAD demonstrated a trend towards a decrease in LVEDV (from 95.8 ± 5.4 to 91.8 ± 4.9 mL,

Table 1. Patient characteristics

	Total patient population (n=40)
Clinical characteristics	
Age (years)	67±12
Male gender, n (%)	27 (68%)
Medical history, n (%)	
Previous PTCA	10 (25%)
Previous myocardial infarction	6 (15%)
Current or previous smoking	21 (57%)
Diabetes	6 (15%)
Family history of CAD	17 (45%)
Hyperlipidemia	18 (45%)
Hypertension	23 (58%)
Medical therapy, n (%)	
ACE inhibitors/ARBs	25 (63%)
β-Blockers	26 (65%)
Statins	27 (68%)
Calcium antagonists	10 (25%)

Data are presented as mean ± standard deviation or as number (percentage).

ACE-inhibitor = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAD = coronary artery disease; PTCA = percutaneous transluminal coronary angioplasty.

$p=0.06$). In line, only a trend was observed in the difference in LVEDV changes between patients with and without significant CAD (group stage interaction $p=0.09$). Furthermore, patients with significant CAD showed a decrease in LV systolic function (LVEF: from 54.1 ± 1.1 to $47.9 \pm 1.6\%$, $p<0.001$) while in patients without significant CAD, LVEF demonstrated a trend towards improvement from rest to peak stress (from 54.6 ± 1.5 to $57.6 \pm 2.0\%$, $p=0.12$). Changes in LVEF from rest to peak dose across patient groups were different (group stage interaction $p<0.001$). Global LV excursion demonstrated the same pattern as LVEF: in patients with significant CAD, global LV excursion worsened (from 5.1 ± 0.2 to 4.1 ± 0.2 mm, $p<0.001$) while global LV excursion in patients without significant CAD showed a trend towards improvement (from 5.0 ± 0.2 to 5.5 ± 0.2 mm, $p=0.10$). A significant difference in changes in global LV excursion between patients with and without significant CAD was also observed (group stage interaction $p<0.001$).

Univariate and multivariate logistic regression analyses were performed to assess the association between the presence of significant CAD on coronary angiography and Δ global LV excursion. At univariate level, Δ global LV excursion was associated with

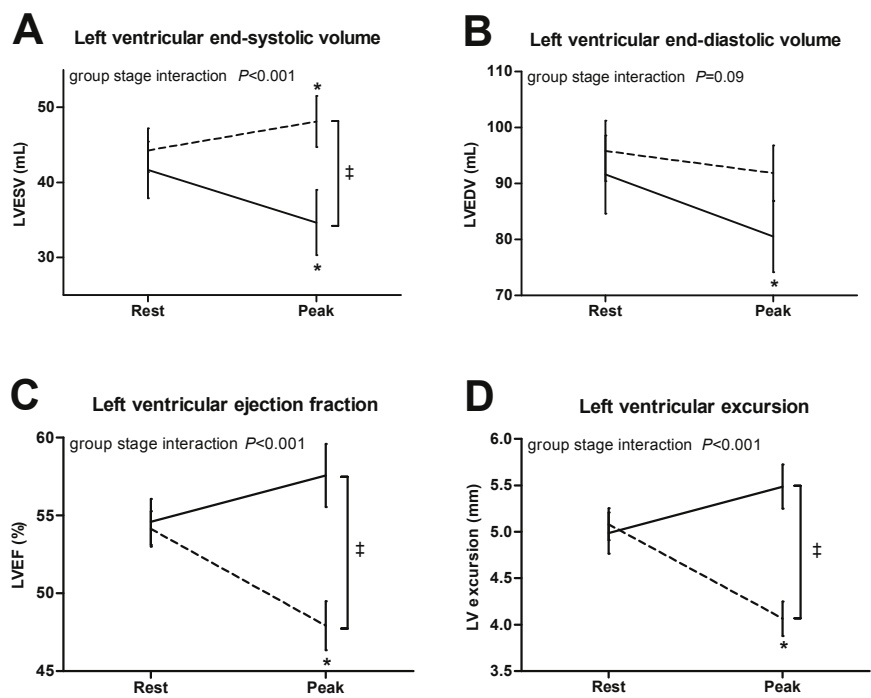


Figure 2. Three-dimensional dobutamine stress echocardiography analysis (LVESV, LVEDV, LVEF and global LV excursion) compared across patients with (dashed line) and without (solid black line) significant coronary artery disease on coronary angiography (defined as >70% stenosis). Group stage interaction p-values (differences in parameters between groups across both stages) are shown. * $p < 0.05$ compared to rest stage. # $p < 0.05$ between patients with and without significant coronary artery disease at that particular stage. LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume.

Table 2. Determinants of significant coronary artery disease on coronary angiography

	Multivariate analysis	
	OR (95% CI)	p
Age (years)	1.12 (1.01–1.24)	0.04
Systolic blood pressure at rest (mmHg)	1.03 (0.97–1.09)	0.30
Δglobal LV excursion (mm)	0.29 (0.12–0.72)	0.008

Significant CAD was defined on coronary angiography as >70% luminal diameter stenosis in ≥ 1 of the 3 major epicardial vessels or associated large side branches.
Δ = delta (peak-rest); CI = confidence interval; LV = left ventricular; OR = odds ratio.

significant CAD (odds ratio 0.28, 95% confidence interval 0.13–0.61, $p=0.001$). Other significant univariate parameters for the prediction of significant CAD were age, systolic blood pressure at rest, Δ systolic blood pressure, LVESV at peak, Δ LVESV, LVEF at peak, Δ LVEF and global LV excursion at peak. The final multivariate model included Δ global LV excursion, age and systolic blood pressure at rest (Table 2). In this model, Δ global LV excursion remained an independent determinant of significant CAD (odds ratio 0.29, 95% confidence interval 0.12–0.72, $p=0.008$; Table 2).

DISCUSSION

The present study evaluated the quantitative measure LV excursion at global level on 3D DSE in 40 patients with suspected CAD undergoing coronary angiography. At rest, global LV excursion was similar in patients with and without significant CAD. From rest to peak stress, however, patients with significant CAD demonstrated a decrease in global LV excursion while patients without significant CAD showed an improvement. Furthermore, after adjusting for clinically relevant parameters, change in global LV excursion from rest to peak stress was independently associated with the presence of significant CAD on coronary angiography. Therefore, 3D LV excursion at global level may be helpful in detecting the presence of significant CAD during full protocol DSE.

Quantitative analysis of DSE: 3D LV excursion

Detection of myocardial ischemia with conventional 2-dimensional DSE using visual detection of myocardial thickening and motion remains challenging and highly dependent on observer experience and image quality.^{4,5} Quantitative techniques based 3D echocardiography may overcome these limitations. Three-dimensional echocardiography minimizes the risk of foreshortened image acquisition improving the accuracy of this technique to detect ischemia in apical segments compared with 2-dimensional echocardiography.^{6–8} In addition, advances in post-processing softwares that provide quantitative parameters of LV mechanics permit objective detection of myocardial ischemia.

The longitudinal myocardial fibers, which are located in the subendocardium, are highly susceptible to ischemia and are therefore the first to be affected when hemodynamically significant coronary lesions exist. Consequently, quantifying longitudinal fiber function using LV excursion may be a helpful objective measure to detect myocardial ischemia in patients with suspected CAD. Previous studies used M-mode echocardiography to analyze the mitral plane displacement during systole toward the apex (left atrioventricular plane displacement).^{9,15–17} In a study by Rydberg et al evaluating 333 patients with stable CAD and abnormal coronary angiogram, LV excursion was associated with poor outcome in patients with significant CAD.¹⁸ In addition, LV excursion demonstrated a good correlation with global LV function measured by LVEF^{19,20} and with the degree and extent of CAD.²¹ Importantly, almost all patients with abnormal LV excursion but normal regional wall motion,

had some form of structural heart disease, including myocardial infarction, angina pectoris, hypertension and abnormal angiograms, suggesting at least a complementary role of LV excursion to visual wall motion assessment.²²

Prior studies applying LV excursion during exercise or DSE demonstrated a good correlation with the presence of CAD.^{10,12,13} In a study by Alam et al, 48 patients with stable angina without prior myocardial infarction and 20 age-matched healthy controls underwent 2-dimensional exercise echocardiography and coronary angiography.¹⁰ LV excursion was measured at the septal, anterior, lateral and posterior LV walls using M-mode from the 2- and 4-chamber views.¹⁰ At rest, LV excursion was comparable between groups while immediately post-exercise healthy subjects demonstrated an increase in LV excursion and patients with CAD showed a decrease.¹⁰ Cain et al calculated LV excursion for all individual LV segments using color tissue Doppler imaging on 2-dimensional echocardiography in 70 patients undergoing DSE and coronary angiography.¹¹ At rest, LV excursion was comparable between normal, ischemic, viable and scar segments.¹¹ Although all differently diagnosed segments increased in displacement from rest to peak stress, ischemic, viable and scar segments demonstrated at peak stress a significantly lower LV excursion compared to normal segments.¹¹

The current study evaluated LV excursion at global level based 3D volume tracking analysis. The feasibility of semi-automated quantitative volumetric analysis of 3D echocardiography was demonstrated by Corsi et al in rest images²³ and by Walimbe et al during stress echocardiography.²⁴ In line with those studies, the present evaluation demonstrated that global LV excursion at rest was not able to discriminate between patients with and without significant CAD confirmed on coronary angiography. Nevertheless, global LV excursion from rest to peak stress decreased in patients with significant CAD while in patients without significant CAD, global LV excursion improved. Importantly, change in global LV excursion from rest to peak stress was independently correlated with the presence of significant CAD. These results suggest that 3D LV excursion at global level could identify patients with significant CAD during full protocol DSE and may therefore be a useful quantitative tool in detecting CAD.

Limitations

The current study has several limitations. Firstly, because observational data were collected from one center, this study should be considered as hypothesis-generating and confirmation of the results in future studies is warranted, including larger patient populations from multiple centers and inclusion of patients with irregular heart rhythm and poor image quality. Furthermore, the small patient cohort precluded us from performing receiver operating characteristic curve analyses and analyzing data of 3D LV excursion per coronary territory.

CONCLUSIONS

Analysis of 3D echocardiographic LV excursion at global level on full protocol DSE may be a helpful tool to detect significant CAD on coronary angiography.

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PART II

Echocardiography in chronic heart failure



CHAPTER 7

Clinical, Echocardiographic, and Neurohormonal Response to Cardiac Resynchronization Therapy: Are They Interchangeable?

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ABSTRACT

Background: The relationship between changes in N-terminal pro-brain natriuretic peptide (NT-proBNP) and echocardiographic or clinical definitions of response to cardiac resynchronization therapy (CRT) has not been evaluated. The aims of the present evaluation were to assess: (1) the relationship between changes in NT-proBNP after 6 months of CRT and clinical and echocardiographic responses; (2) the association between NT-proBNP changes and long-term outcome.

Methods: In 170 patients treated with CRT (age 61 ± 11 years, 75% male), clinical and echocardiographic parameters and circulating NT-proBNP levels were assessed at baseline and 6 months after CRT. At 6 months follow-up, improvement in New York Heart Association class ≥ 1 point, decrease in left ventricular end-systolic volume $\geq 15\%$, and decrease in NT-proBNP $\geq 15\%$ defined clinical, echocardiographic, and neurohormonal CRT response, respectively. All-cause mortality data were collected and related to neurohormonal response.

Results: Neurohormonal, echocardiographic, and clinical response rates were 54%, 58%, and 66%, respectively. The majority of patients (71%) showing echocardiographic response had NT-proBNP reduction $\geq 15\%$. In contrast, only 58% of patients who showed clinical response also had NT-proBNP reduction $\geq 15\%$. During a median follow-up of 32 months, 40 patients died. Patients with neurohormonal response demonstrated a superior long-term outcome compared to patients without neurohormonal response (log-rank $p=0.02$).

Conclusions: NT-proBNP reduction $\geq 15\%$ showed better agreement with echocardiographic response compared to clinical response. Neurohormonal response was associated with superior long-term outcome compared to insufficient reduction in NT-proBNP levels.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an effective therapy in selected patients with heart failure inducing significant improvements in clinical symptoms, long-term morbidity, and mortality.¹⁻³ More importantly, CRT has shown to prevent progression of heart failure by slowing or reversing the left ventricular (LV) remodeling process.^{2,4} Neurohormonal activation influences this remodeling process.⁵ In recent years, brain natriuretic peptide (BNP) and its amino-terminal portion (NT-proBNP) have emerged as diagnostic and prognostic surrogates in heart failure patients.⁶⁻⁸ BNP is secreted by the cardiac myocytes in response to pressure or volume overload and counterbalances the vasoconstriction, sodium retention, and antidiuretic effects of the activated renin-angiotensin-aldosterone system and the increased sympathetic autonomic tone.⁷ BNP and NT-proBNP circulating levels increase along with progression of heart failure and, therefore, may be considered as biomarkers of LV remodeling. In addition, several heart failure therapies such as CRT may induce significant reductions in NT-proBNP levels which have been associated with long-term prognosis.⁹

So far, response to CRT has been defined by clinical or echocardiographic endpoints such as improvement in New York Heart Association (NYHA) functional class, 6-minute walked distance, or LV reverse remodeling.¹⁰ However, changes in clinical symptoms have repeatedly shown to be a suboptimal surrogate of CRT effects.¹¹ In addition, several studies have shown significant decreases in NT-proBNP levels after CRT, suggesting that CRT targets the underlying mechanisms of LV remodeling and heart failure.^{9,12} So far, the correlation between echocardiographic response to CRT and changes in neurohormonal status has not been studied extensively. Characterization of the relationship between clinical, echocardiographic, and neurohormonal parameters may provide important prognostic information on the effects of CRT in heart failure. Therefore, the objective of the current evaluation was twofold: (1) to assess the relationship between changes in NT-proBNP and clinical and echocardiographic response to CRT in heart failure patients; and (2) to evaluate the long-term outcome in patients with and without neurohormonal response to CRT.

METHODS

Patient Population and Data Collection

Between September 2005 and February 2011, a total of 835 patients received a CRT. From this cohort, moderate and severe chronic heart failure patients who had measurements of NT-proBNP circulating levels at baseline and 6 months follow-up were included in the present evaluation.¹³ According to the institutional protocol, prior to CRT implantation, all patients underwent extensive clinical and echocardiographic evaluation.¹⁴ Medical therapy was optimized in all patients, following current guidelines.¹³ At 6 months follow-up, clinical

and echocardiographic evaluations were repeated. All clinical and echocardiographic data were entered into the departmental cardiology information system (EPD-Vision®, Leiden University Medical Center, Leiden, The Netherlands) and analyzed retrospectively. The Institutional Review Board of the Leiden University Medical Center approved this retrospective evaluation of clinically collected data and waived the need for written informed consent.

The agreement between clinical, echocardiographic, and neurohormonal response to CRT was evaluated. Furthermore, the differences in long-term mortality and hospitalization for heart failure were evaluated in patients with and without neurohormonal response to CRT.

Clinical Data

Heart failure patients were evaluated and treated according to the MISSION! Heart failure protocol, an outpatient and inpatient clinical framework that follows the most recent American College of Cardiology/American Heart Association and European Society of Cardiology guidelines for heart failure.¹³⁻¹⁵ Clinical variables, NYHA functional class, quality of life score (according to the Minnesota Living with Heart Failure questionnaire), and 6-minute walked distance were collected at baseline and at 6 months follow-up. Patients were classified as clinical responders to CRT based on improvement in NYHA functional class by ≥ 1 point at 6 months follow-up.¹⁶

Echocardiography

Two-dimensional echocardiographic data were acquired at rest with the patient in left lateral decubitus position using a commercially available system (Vivid 7 and E9, General Electric-Vingmed, Horten, Norway). M-mode, two-dimensional and color, continuous, and pulsed-wave Doppler data were obtained from the parasternal and apical views with a 3.5-MHz transducer and stored in cine-loop format for subsequent analysis with dedicated software (EchoPAC version 111.0.0, General Electric-Vingmed, Horten, Norway).

LV end-systolic and LV end-diastolic volumes were quantified in the apical 2- and 4-chamber views using the biplane Simpson's technique and LV ejection fraction was calculated.¹⁷ Moreover, the severity of mitral regurgitation was assessed with color and continuous wave Doppler echocardiography and scored according to current recommendations of the American Society of Echocardiography.¹⁸ Echocardiographic response to CRT was defined by a reduction of $\geq 15\%$ in LV end-systolic volume at 6 months follow-up.¹⁹

NT-proBNP Levels

Blood samples were acquired from peripheral venous blood with the patient at rest. The samples were stored at -80°C . Serum concentrations of NT-proBNP were determined by using proBNP and proBNP II kits from Roche Diagnostics on a Modular Analytics E170

analyzer (Roche Diagnostics, Mannheim, Germany). A “sandwich”-type quantitative immunoassay was performed using antibodies against epitopes in the amino-terminal part of pro-BNP. The lower detection limit was 5 pg/mL. Total coefficients of variance at low concentrations (77 pg/mL) and high concentrations (2,170 pg/mL) were both 2.7%. NT-proBNP levels <125 pg/mL exclude cardiac dysfunction with a high level of certainty in patients with symptoms suggestive of heart failure or dyspnea.²⁰ In the present evaluation, only patients with available levels of NT-proBNP were included. A decrease in NT-proBNP levels of $\geq 15\%$ at 6 months of follow-up defined the neurohormonal response to CRT.²¹

CRT Implantation

Implantation of the CRT device was performed through transvenous approach. The right atrial and right ventricular leads were positioned in the atrial appendage and ventricular apex, respectively. A balloon catheter was used to obtain a coronary sinus venogram to identify the most appropriate vein to insert the LV pacing lead (preferably posterolateral vein) (Easytrak, Guidant Corp., St. Paul, MN, USA; Attain, Medtronic Inc., Minneapolis, MN, USA; or Corox, Biotronik GmbH, Berlin, Germany). Finally, the leads were connected to a dedicated CRT device (Contak Renewal, Guidant Corp.; Insync III or Insync Sentrym Medtronic Inc.; or Lumax, Biotronik).

Follow-Up

According to the institutional protocol, all patients were scheduled for 6-month and annual visits at the outpatient clinic. Events after CRT implantation, including all-cause mortality and hospitalization for heart failure, were recorded in the departmental cardiology information system (EPD-Vision®). The primary endpoint was all-cause mortality during long-term follow-up (until October 2011) with the initial time set at 6 months after device implantation. By reviewing medical records the cause of death was collected. The secondary endpoint was defined by a composite endpoint of all-cause mortality or hospitalization for heart failure during follow-up (until October 2011) with the initial time set at 6 months after the device implantation. Lost to follow-up was considered in patients without data on the last 6 months. Data of these patients were included up to the last date of follow-up.

Statistical Analysis

Continuous data are expressed as mean $\pm$ standard deviation or median with 25th and 75th percentiles where appropriate and were compared with the Student's *t*-test. Categorical data are expressed as frequencies and percentages and were compared with the χ^2 test. Comparisons between baseline and follow-up were performed with the two-sided Student's *t*-test for paired data. To obtain a Gaussian distribution, NT-proBNP and creatinine values were 10-log-transformed to perform comparisons between patients with and without neurohormonal response to CRT. In addition, 10-log-transformed NT-proBNP values

were used for the comparison between baseline and 6 months follow-up. To assess the agreement between the different definitions of response, the odds ratio and ψ -coefficient were used. Using the method of Kaplan-Meier, event rates of the primary and secondary endpoints were analysed with the initial time set at 6 months after the device implantation in patients with and without neurohormonal response to CRT, in patients with and without echocardiographic response to CRT and in patients with and without clinical response to CRT. The groups were compared using the log-rank test. Relative risks, expressed as hazard ratios (HRs) with associated 95% confidence intervals (CIs), were derived from Cox regression models. Multivariate Cox proportional-hazards analyses were performed to evaluate the independent association between neurohormonal, echocardiographic, and clinical response to CRT and the primary and secondary endpoints adjusted for predetermined variables (age, etiology of heart failure, QRS duration, and severity of mitral regurgitation at baseline). To evaluate the relative merits of neurohormonal and echocardiographic response to CRT, the Harrell's c-statistic for each model was calculated.

All statistical tests were two-sided and a p-value <0.05 was considered to be statistically significant. All statistical analyses were performed with SPSS software (version 17.0, IBM Corp., Armonk, NY, USA).

RESULTS

Baseline Characteristics

A total of 170 heart failure patients (61 ± 11 years, 75% men) with available NT-proBNP circulating levels at baseline and 6 months follow-up were evaluated. Baseline characteristics of the study cohort and patients without NT-proBNP data are further detailed in Table S1. Patients in the study cohort were younger and demonstrated higher quality of life scores and 6-minute walked distances compared to patients without measurement of NT-proBNP levels. Furthermore, hyperlipidemia was less frequently noted and diabetes was more frequently noted in the study cohort. No differences were observed in gender, NYHA functional class, etiology of heart failure, medical treatment, and echocardiographic parameters. Table 1 summarizes the baseline characteristics of the patient population. In total, 74% of the patients were in NYHA functional class III or IV. Mean LV ejection fraction was $27 \pm 7\%$ and the mean QRS duration was 154 ± 30 ms. The etiology of heart failure was ischemic in 110 patients (65%). Medical treatment included diuretics (83%), β -blockers (76%), angiotensin converter-enzyme inhibitors or angiotensin II receptor blockers (93%), and spironolactone (49%). Moderate or severe mitral regurgitation was observed in 33 patients (19%). Laboratory tests showed a mean creatinine of 114 ± 48 $\mu\text{mol/L}$, mean hemoglobin of 8.6 ± 1.1 mmol/L, and mean NT-proBNP of $2,862 \pm 7,090$ pg/mL.

Clinical, Echocardiographic, and Neurohormonal Response to CRT

At 6 months follow-up, significant improvements in NYHA functional class (from 2.76 ± 0.56 to 2.16 ± 0.75 , $p < 0.001$), quality of life score (from 34 ± 19 to 27 ± 20 , $p < 0.001$), and 6-minute walked distance (from 351 ± 136 m to 372 ± 130 m, $p = 0.01$) were demonstrated in the overall population. On the basis of the prespecified definition of clinical CRT response, the percentage of responders was 66% ($n = 113$).

The repeat echocardiogram at 6 months follow-up showed a significant reduction in LV volumes (LV end-systolic volume: from 145 ± 59 mL to 122 ± 54 mL, $p < 0.001$; LV end-diastolic volume: from 197 ± 69 mL to 178 ± 64 mL, $p < 0.001$) and a significant improvement in LV ejection fraction (from $27 \pm 7\%$ to $33 \pm 9\%$, $p < 0.001$). A total of 98 patients (58%) showed $\geq 15\%$ LV end-systolic volume reduction and were considered echocardiographic responders.

Finally, a significant reduction in NT-proBNP levels was observed (log-transformed values: from 3.19 ± 0.44 to 3.04 ± 0.54 , $p < 0.001$; nonlog-transformed values: from $2,862 \pm 7,090$ pg/mL to $2,134 \pm 2,783$ pg/mL). When a definition of CRT response of $\geq 15\%$ reduction in NT-proBNP levels was applied, 92 patients (54%) were classified as responder.

Table 1. Baseline characteristics

	All patients (n=170)	NT-proBNP reduction (n=92)	No NT-proBNP reduction (n=78)	p*
Clinical characteristics				
Age (years)	61 ± 11	61 ± 12	62 ± 10	0.63
Men, n (%)	128 (75%)	72 (78%)	56 (72%)	0.33
QRS duration (ms)	154 ± 30	160 ± 33	147 ± 24	0.004
QRS morphology, n (%)				0.08
LBBB	111 (65%)	57 (62%)	54 (69%)	
RBBB	8 (5%)	3 (3%)	5 (6%)	
IVCD	21 (12%)	9 (10%)	12 (15%)	
Narrow	8 (5%)	6 (7%)	2 (3%)	
VP	22 (13%)	17 (19%)	5 (6%)	
NYHA class III/IV, n (%)	117 (69%)/8 (5%)	59 (64%)/4 (4%)	58 (74%)/4 (5%)	0.11
QoL score	34 ± 19	31 ± 19	37 ± 18	0.05
6MWT (m)	353 ± 132	366 ± 135	339 ± 128	0.19

Table 1. Baseline characteristics (continued)

	All patients (n=170)	NT-proBNP reduction (n=92)	No NT-proBNP reduction (n=78)	p*
Heart failure etiology, n (%)				0.62
Ischemic	110 (65%)	58 (63%)	52 (67%)	
Nonischemic	60 (35%)	34 (37%)	26 (33%)	
Medical history, n (%)				
Hypertension	75 (44%)	40 (44%)	35 (45%)	0.91
Hyperlipidemia	65 (39%)	36 (40%)	29 (37%)	0.75
Diabetes	48 (28%)	26 (28%)	22 (28%)	0.99
Family history for CAD	79 (47%)	37 (41%)	42 (55%)	0.08
Previous myocardial infarction	86 (51%)	46 (50%)	40 (51%)	0.87
Medication, n (%)				
ACE-inhibitors/ARBs	158 (93%)	84 (91%)	74 (95%)	0.37
β -Blockers	129 (76%)	70 (76%)	59 (76%)	0.95
Aldosterone antagonists	84 (49%)	44 (48%)	40 (51%)	0.65
Statins	121 (71%)	64 (70%)	57 (73%)	0.61
Diuretics	141 (83%)	81 (88%)	60 (77%)	0.06
Echocardiography				
LVESV (mL)	145 $\pm$ 58	148 $\pm$ 59	142 $\pm$ 58	0.52
LVEDV (mL)	197 $\pm$ 69	200 $\pm$ 69	194 $\pm$ 68	0.55
LVEF (%)	27 $\pm$ 7	27 $\pm$ 7	28 $\pm$ 7	0.42
MR grade III/IV, n (%)	29 (17%)/4 (2%)	17 (19%)/2 (2%)	12 (15%)/2 (3%)	0.66
Laboratory tests				
Creatinine (μ mol/L)	114 $\pm$ 48	114 $\pm$ 54	114 $\pm$ 39	–
Log creatinine	2.03 $\pm$ 0.15	2.02 $\pm$ 0.16	2.03 $\pm$ 0.14	0.69
Hb (mmol/L)	8.6 $\pm$ 1.1	8.5 $\pm$ 1.0	8.7 $\pm$ 1.1	0.27
NT-proBNP (pg/mL)	2,862 $\pm$ 7,090	3,739 $\pm$ 9,442	1,828 $\pm$ 1,728	–
Log NT-proBNP	3.19 $\pm$ 0.44	3.26 $\pm$ 0.47	3.10 $\pm$ 0.38	0.02

* p-values are given for the comparisons of patients with and without neurohormonal response (NT-proBNP reduction $\geq 15\%$ at 6 months of follow-up).

δ MWT = 6-minute walked test; ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; CAD = coronary artery disease; Hb = hemoglobin; IVCD = interventricular conduction delay; LBBB = left bundle branch block; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; NT-proBNP = amino-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; QoL = quality of life; RBBB = right bundle branch block; VP = ventricular paced.

In Table 1, baseline characteristics of patients with and without neurohormonal response to CRT (a reduction in NT-proBNP $\geq 15\%$ at 6 months follow-up) are summarized. At baseline, patients showing neurohormonal CRT response had significantly longer QRS durations (160 ± 33 ms vs 147 ± 24 ms, $p=0.004$) compared to patients without neurohormonal response. In addition, baseline NT-proBNP circulating levels were significantly higher in patients with neurohormonal response (log-transformed values: 3.26 ± 0.47 vs 3.10 ± 0.38 , $p=0.02$; nonlog-transformed values: $3,739 \pm 9,442$ pg/mL vs $1,828 \pm 1,728$ pg/mL).

Neurohormonal Response versus Clinical Response to CRT

In order to evaluate whether the changes in neurohormonal status after CRT implantation reflect the clinical response to CRT, the concordance between clinical and NT-proBNP definitions of response to CRT was assessed (Figure 1). At 6 months follow-up, 58% of patients ($n=65$ of 113) showing clinical response also showed NT-proBNP response. In contrast, 47% of patients ($n=27$ of 57) without a clinical improvement did show a reduction in circulating levels of NT-proBNP. A poor association between neurohormonal response and clinical response to CRT was demonstrated; odds ratio is 1.51 (95% CI 0.79–2.85) (ψ -coefficient = 0.10, $p=0.21$).

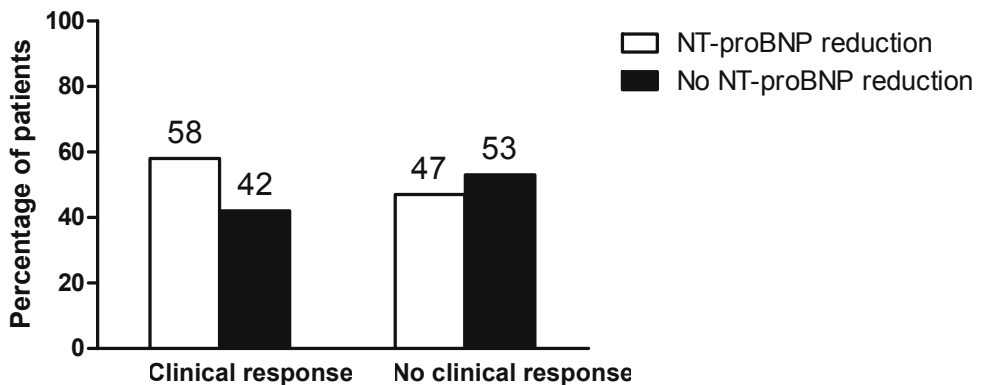


Figure 1. Agreement between two different definitions of response to CRT. The bars show the percentages of patients with concordant or discrepant clinical response, as defined by an improvement of NYHA functional class of ≥ 1 point, with NT-proBNP response defined as a $\geq 15\%$ reduction at 6 months of follow-up. CRT = cardiac resynchronization therapy; NYHA = New York Heart Association; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Neurohormonal Response versus Echocardiographic Response to CRT

Figure 2 shows the concordance between echocardiographic and NT-proBNP definitions of CRT response. Seventy-one percent of patients (n=70 of 98) showing significant LV reverse remodeling also demonstrated a reduction in NT-proBNP $\geq 15\%$ at 6 months follow-up. In addition, most of the patients who did not show LV reverse remodeling did not exhibit a reduction of $\geq 15\%$ in NT-proBNP (70%, n=50 of 71). In contrast to the discordance between clinical and neurohormonal definitions of response, only 21 patients who showed significant reduction in NT-proBNP levels did not demonstrate significant LV reverse remodeling, resulting in a disagreement rate of 23%. The association between neurohormonal response and echocardiographic response to CRT was clinically relevant; odds ratio is 5.95 (95% CI 3.04–11.66) (ψ -coefficient = 0.41, $p < 0.001$).

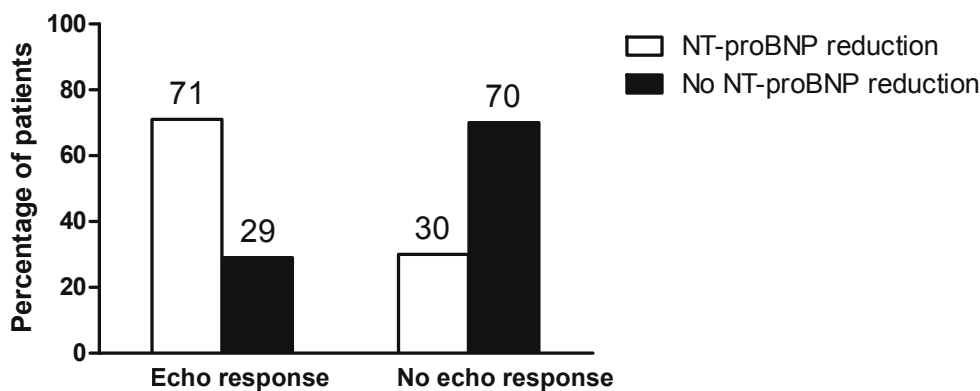


Figure 2. Agreement between two different definitions of response to CRT. The bars show the percentage of patients with concordant or discrepant echocardiographic response, as defined by a decrease of LV end-systolic volume of $\geq 15\%$, with NT-proBNP response, defined as a $\geq 15\%$ reduction at 6 months of follow-up. CRT = cardiac resynchronization therapy; Echo = echocardiographic; LV = left ventricular; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Long-Term Follow-Up

Survival analysis was performed with the initial time set at 6 months after the CRT device implantation. Long-term follow-up was completed in 163 patients (96%) with a median follow-up duration of 32 months (interquartile range 17–44 months). Forty patients (24%) died of all-cause mortality and 19% of the patients (n=33) were hospitalized for heart failure during follow-up. The secondary endpoint, a composite of all-cause mortality or hospitalization of heart failure, was reached by 52 patients (31%). Cardiovascular mortality was recorded in 18% of the patients (n=31).

The mortality rates for patients with and without neurohormonal response to CRT are shown in Figure 3A. Patients with neurohormonal response to CRT had a significantly better long-term survival compared to patients without neurohormonal response (log-rank $p=0.02$). The 12-, 24-, and 36-month survival rates for patients with neurohormonal response were 94%, 89%, and 82%, respectively; in patients without neurohormonal response, the 12-, 24-, and 36-month survival rates were 83%, 75%, and 67%, respectively (Figure 3A). Cumulative event rates for the composite endpoint of all-cause mortality or hospitalization for heart failure in both groups are shown in Figure 3B. The event-free survival rates showed a significantly better long-term outcome in patients with neurohormonal response; 12-, 24-, and 36-month event-free survival were 90%, 84%, and 79% in the responder group versus 75%, 63%, and 58% in the nonresponder group, respectively (Figure 3B, log-rank $p=0.003$).

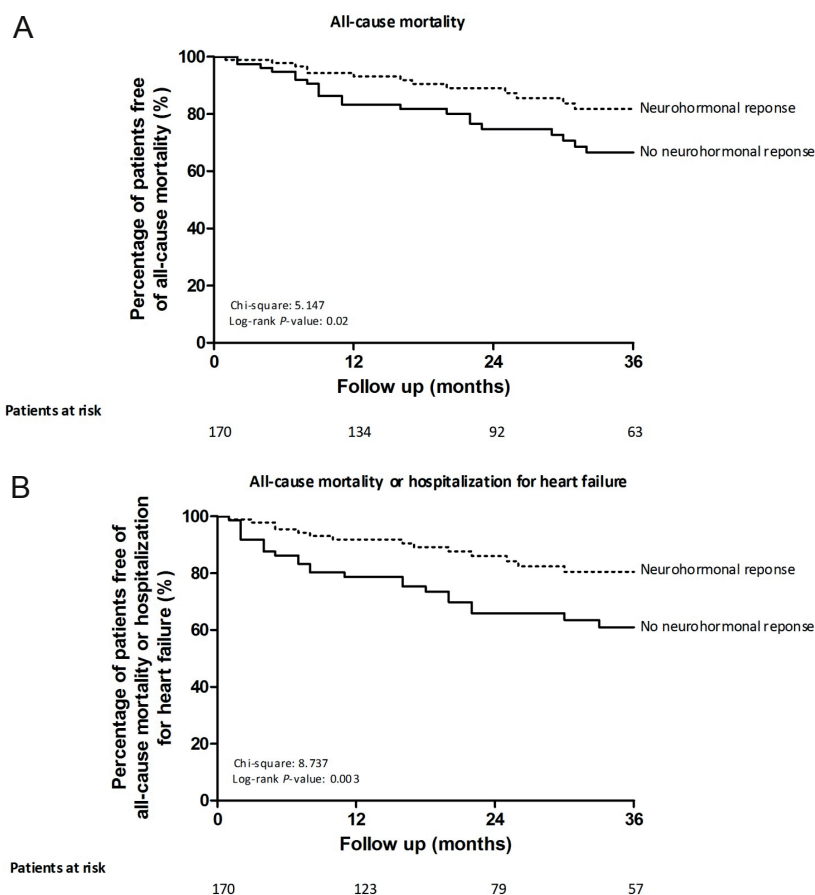


Figure 3. Kaplan-Meier curves estimates of the primary endpoint (all-cause mortality) (A) and secondary endpoint (all-cause mortality or hospitalization for heart failure) (B) in patients with and without neurohormonal response to CRT at 6 months follow-up (defined as: NT-proBNP reduction $\geq 15\%$). CRT = cardiac resynchronization therapy; NT-proBNP = N-terminal pro-brain natriuretic peptide.

Univariate analysis showed that neurohormonal response to CRT was associated with a significant reduced risk of all-cause mortality (HR 0.48, 95% CI 0.26–0.92, $p=0.03$) and the composite endpoint of all-cause mortality or hospitalization for heart failure (HR 0.44, 95% CI 0.25–0.77, $p=0.004$). After adjusting for clinical and echocardiographic parameters, neurohormonal response to CRT remained independently associated with all-cause mortality (HR 0.39, 95% CI 0.20–0.77, $p=0.007$) and the composite endpoint of all-cause mortality or hospitalization for heart failure (HR 0.36, 95% CI 0.20–0.67, $p=0.001$). The same results were observed after also adjusting for baseline NT-proBNP levels (all-cause mortality: HR 0.30, 95% CI 0.15–0.61, $p=0.001$; composite endpoint: HR 0.23, 95% CI 0.12–0.44, $p<0.001$).

Figure 4 illustrates the cumulative event rates for the primary and secondary endpoints for patients with and without echocardiographic response to CRT. The event-free survival rates showed a significantly better long-term outcome in patients with echocardiographic response (log-rank $p=0.001$ and $p<0.001$ for the primary and secondary endpoint, respectively). Univariate analysis demonstrated that echocardiographic response to CRT was associated with a significant reduced risk of all-cause mortality (HR 0.33, 95% CI 0.17–0.64, $p=0.001$) and the composite endpoint of all-cause mortality or hospitalization for heart failure (HR 0.33, 95% CI 0.19–0.58, $p<0.001$). At multivariate analysis, after adjusting for clinical and echocardiographic parameters, echocardiographic response to CRT remained independently associated with all-cause mortality (HR 0.25, 95% CI 0.12–0.50, $p<0.001$) and the composite endpoint of all-cause mortality or hospitalization for heart failure (HR 0.26, 95% CI 0.15–0.48, $p<0.001$).

The survival and the event-free survival rates for patients with clinical response to CRT were significantly better compared to patients without clinical response (log-rank $p<0.001$ and $p=0.001$ for the primary and secondary endpoint, respectively). At multivariate analysis, after adjusting for clinical and echocardiographic parameters, clinical response to CRT was a strong predictor of long-term outcome, both regarding all-cause mortality (HR 0.29, 95% CI 0.15–0.57, $p<0.001$) and the composite endpoint of all-cause mortality or hospitalization for heart failure (HR 0.40, 95% CI 0.23–0.72, $p=0.002$). Furthermore, in patients showing clinical response ($n=113$), the prognostic value of echocardiographic and/or neurohormonal response was evaluated. Clinical responders without echocardiographic or neurohormonal response ($n=29$) demonstrated a worse long-term outcome compared to clinical responders with echocardiographic and/or neurohormonal response ($n=83$), both regarding all-cause mortality (log-rank $p=0.04$) and the composite endpoint (log-rank $p=0.002$). Also, after correcting for clinical and echocardiographic parameters, clinical response without echocardiographic or neurohormonal response remained independently associated with all-cause mortality (HR 2.82, 95% CI 1.03–7.69, $p=0.04$) and the composite endpoint (HR 3.38, 95% CI 1.55–7.37, $p=0.002$).

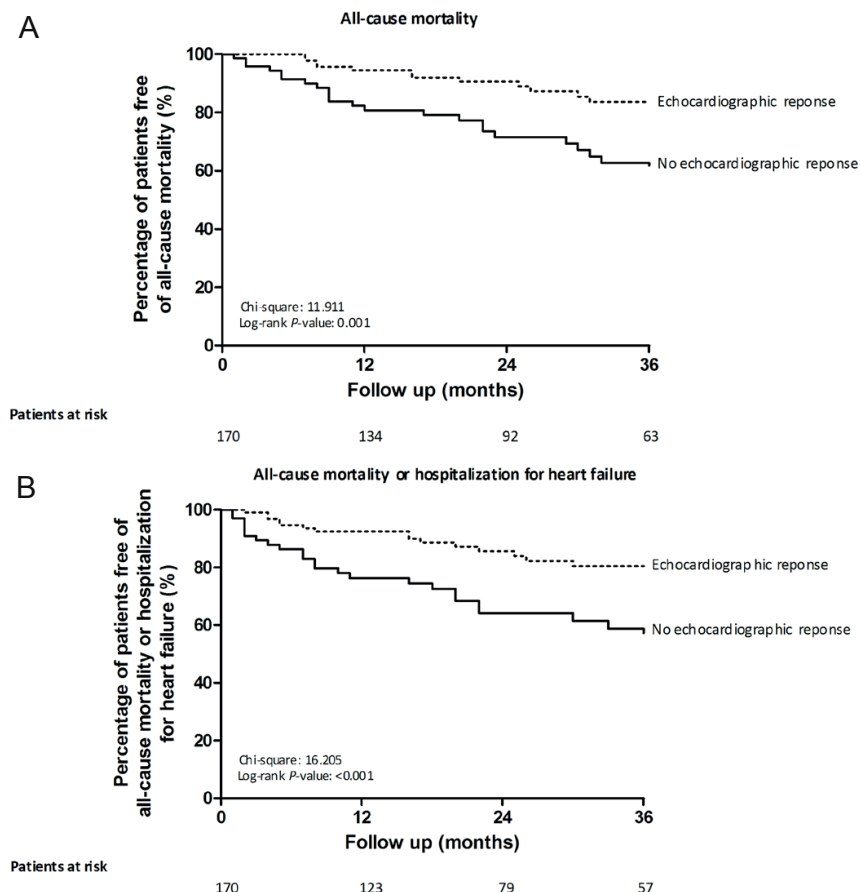


Figure 4. Kaplan-Meier curves estimates of the primary endpoint (all-cause mortality) (A) and secondary endpoint (all-cause mortality or hospitalization for heart failure) (B) in patients with and without echocardiographic response to CRT at 6 months follow-up (defined as: LV end-systolic volume reduction $\geq 15\%$). CRT = cardiac resynchronization therapy; LV = left ventricular.

The relative merits of neurohormonal and echocardiographic responses were assessed calculating the Harrell's c-statistic. For the neurohormonal response the Harrell's c-statistics of the models were 0.66 and 0.66 for the primary and the secondary endpoint, respectively. For the echocardiographic response the respective Harrell's c-statistics for the primary and the secondary endpoint were 0.69 and 0.68.

DISCUSSION

This study demonstrated an agreement of 58% between clinical and neurohormonal response to CRT. In contrast, the agreement between reduction of NT-proBNP and echocardiographic definition of CRT response was 70%, suggesting that an objective evaluation of CRT response may be more accurate than an assessment including clinical

surrogates. In addition, patients with neurohormonal response to CRT at 6 months follow-up showed a better long-term outcome regarding both survival and hospitalization for heart failure.

Defining CRT Response: Subjective Clinical versus Objective Changes in LV Remodeling and Neurohormonal Status

There is no established definition of response to CRT yet. The efficacy of heart failure therapies has been evaluated with improvements in clinical symptoms, LV function, or decrease in NT-proBNP.²² Ultimately, these improvements should determine a superior long-term outcome. In this regard, several studies have shown that the prognostic implications of therapeutic efficacy based on clinical symptoms are controversial.¹¹ Ingle et al demonstrated in 1,592 patients with heart failure that the prognostic value of patient-perceived physical symptoms is little in contrast with more objective measures, for example, 6-minute walked distance and NT-proBNP.¹¹ Although the patient perspective is an important parameter of therapeutic efficacy, objective measures such as LV reverse remodeling may be more accurate.²³ Indeed, definition of the efficacy of heart failure therapies based on LV reverse remodeling and improvement in LV ejection fraction is associated with superior long-term outcome.²² The RESynchronization reVERses Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial, for example, including patients with mildly symptomatic heart failure, demonstrated that CRT prevented progression of heart failure and was associated with superior prognosis.^{24,25}

In terms of heart failure biomarkers, NT-proBNP circulating levels at baseline have shown to be a powerful prognostic marker in patients with heart failure.⁶⁻⁸ More importantly, significant decreases in NT-proBNP levels have shown an incremental prognostic value over the baseline levels.⁹ In 813 patients undergoing CRT implantation, the Cardiac Resynchronization in Heart Failure (CARE-HF) trial showed that serial assessment of NT-proBNP at baseline and 3 months follow-up was a stronger predictor of all-cause mortality than baseline NT-proBNP.⁹ As demonstrated by two other reports of the CARE-HF trial, CRT decreases the circulating levels of NT-proBNP, indicating the value of changes in levels of this biomarker as a measure of efficacy of CRT.^{26,27}

However, it remains controversial whether improvements in clinical, echocardiographic, and neurohormonal parameters after CRT implantation may always coincide. This study provides further insights into this issue. A reasonable agreement between neurohormonal changes and echocardiographic response to CRT was observed. In contrast, the agreement between reduction of NT-proBNP and clinical response was poor. These results suggest that clinical, echocardiographic, and neurohormonal parameters of CRT response may reflect different aspects of chronic heart failure. For example, Tarquini et al demonstrated in 47 heart failure patients undergoing CRT implantation that a decrease in activation of renin–angiotensin–aldosterone system was accompanied by LV reverse remodeling at 12 months follow-up.²⁸ In contrast, patients without LV reverse

remodeling experienced no change in activation of renin-angiotensin-aldosterone system.²⁸ Moreover, clinical improvement was observed in both echocardiographic responders and nonresponders, implying that assessment of clinical response to CRT may have less value.²⁸ This was also demonstrated by other studies reporting that CRT reduces NT-proBNP levels in patients with reduction in LV end-systolic volume during 3–6 months follow-up.^{21,29}

Neurohormonal Response to CRT and Prognosis

Previous studies already pointed out the use of NT-proBNP levels as marker of response to CRT, especially changes in NT-proBNP levels from baseline.^{9,22,26,27} In addition, Magne et al provided a cutoff value for percentage change in NT-proBNP level ($\geq 15\%$ reduction) which could accurately predict LV reverse remodeling after CRT implantation.²¹ In this study, patients without sufficient reduction in NT-proBNP levels using this cutoff value of 15% had a worse long-term outcome compared to patients with $\geq 15\%$ reduction in NT-proBNP levels. Therefore, the use of change in NT-proBNP levels may contribute to the evaluation of the effects of CRT.

Definition of CRT Response: Future Directions

Despite the well-known efficacy of CRT, standardized definitions of response to CRT and their prognostic implications have not been established. In this study, echocardiographic and neurohormonal definitions of CRT response showed better agreement than reduction in NT-proBNP and clinical response. The presence of two objective methods to assess CRT efficacy and the agreement between them may select the group of patients who truly respond to CRT. Among patients with discrepant objective responses, further adjustments of medical therapy and CRT device settings may be needed. In this regard, large randomized studies evaluating the effect of CRT settings optimization on LV reverse remodeling and neurohormonal status in patients who do not show benefit from CRT are warranted.

Study Limitations

The present evaluation has some limitations. First, this is a single-center study with a retrospective design. However, all patients were treated and followed according to the most recent heart failure guidelines of American College of Cardiology/American Heart Association and European Society of Cardiology.^{13,15} Therefore, this study is representative of current standard clinical practice. Another important limitation of this study is the relatively small sample size that may have precluded us to perform a receiver operating characteristic curve analysis to define the cutoff value of NT-proBNP change to predict response to CRT. In addition, the small sample population may have reduced the accuracy of the model to predict long-term outcome, as reflected by modest Harrell's c-statistics. Furthermore, due to the relatively low number of patients, the results of the present evaluation need to be confirmed in larger populations.

CONCLUSION

Clinical, echocardiographic, and neurohormonal markers of CRT response may reflect different aspects of chronic heart failure. NT-proBNP reduction and LV reverse remodeling after CRT show a better agreement compared to NT-proBNP reduction and clinical response. Furthermore, patients with neurohormonal response show a better long-term outcome compared to patients without neurohormonal response. Our results, therefore, suggest that NT-proBNP in combination with LV reverse remodeling may be more useful to evaluate the effects of CRT in heart failure patients.

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Table S1. Baseline characteristics of patients included and patients not included in the present evaluation

	Study cohort (n=170)	No NT-proBNP data (n=665)	p*
Clinical characteristics			
Age (years)	61 ± 11	66 ± 11	<0.001
Men, n (%)	128 (75%)	504 (76%)	0.89
QRS duration (ms)	154 ± 30	152 ± 33	0.45
NYHA class III/IV, n (%)	117 (69%)/8 (5%)	402 (63%)/39 (6%)	0.22
QoL score	34 ± 19	24 ± 21	<0.001
6MWT (m)	353 ± 132	316 ± 114	0.002
Heart failure etiology, n (%)			
Ischemic/nonischemic	110 (65%)/60 (35%)	408 (61%)/257 (39%)	0.42
Medical history, n (%)			
Hypertension	75 (44%)	249 (41%)	0.38
Hyperlipidemia	65 (39%)	228 (49%)	0.02
Diabetes	48 (28%)	136 (21%)	0.03
Medication, n (%)			
ACE-inhibitors/ARBs	158 (93%)	585 (88%)	0.07
β-Blockers	129 (76%)	493 (74%)	0.64
Aldosterone antagonists	84 (49%)	292 (44%)	0.20
Statins	121 (71%)	420 (63%)	0.05
Diuretics	141 (83%)	528 (79%)	0.30
Echocardiography			
LVESV (mL)	145 ± 58	150 ± 62	0.35
LVEDV (mL)	197 ± 69	203 ± 72	0.34
LVEF (%)	27 ± 7	27 ± 8	0.76
Laboratory tests			
Creatinine (μmol/L)	114 ± 48	108 ± 59	–
Log creatinine	2.03 ± 0.15	2.00 ± 0.15	0.05

* p-values are provided for the comparisons of patients with and without measurement of amino-terminal pro-brain natriuretic peptide (NT-proBNP) levels.

6MWT = 6-minute walked test; ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NT-proBNP = amino-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; QoL = quality of life.

CHAPTER 8

The Relationship between Time from Myocardial Infarction, Left Ventricular Dyssynchrony, and the Risk for Ventricular Arrhythmia: Speckle-Tracking Echocardiographic Analysis

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ABSTRACT

Background: Differences in arrhythmogenic substrate may explain the variable efficacy of implantable cardioverter-defibrillators (ICDs) in primary sudden cardiac death prevention over time after myocardial infarction (MI). Speckle-tracking echocardiography allows the assessment left ventricular (LV) dyssynchrony, which may reflect the electromechanical heterogeneity of myocardial tissue. The aim of the present study was to evaluate the relationship among LV dyssynchrony, age of MI, and their association with the risk for ventricular tachycardia (VT) after MI.

Methods: A total of 206 patients (median age 67 years; 87% men) with prior MIs (median MI age 6.2 years; interquartile range 0.66–15 years) who underwent programmed electrical stimulation, speckle-tracking echocardiography, and ICD implantation were retrospectively evaluated. LV dyssynchrony was defined as the standard deviation of time to peak longitudinal systolic strain values using speckle-tracking strain echocardiography. LV scar burden was evaluated by the percentage of segments exhibiting scar (defined as an absolute longitudinal strain of magnitude $<4.5\%$). Patients were followed up for the occurrence of first monomorphic VT requiring ICD therapy (antitachycardia pacing or shock) for a median of 24 months.

Results: In total, 75 individuals experienced the primary end point of monomorphic VT. LV dyssynchrony was independently associated with the occurrence of VT at follow-up (hazard ratio per 10-msec increase 1.12, 95% confidence interval 1.07–1.18, $p<0.001$), together with nonrevascularization of the infarct-related artery and VT inducibility. Patients with older (>180 months) MIs had a higher likelihood of VT inducibility (88% vs 63%, $p=0.003$) and greater scar burden ($14.7 \pm 15.8\%$ vs. $10.7 \pm 11.4\%$, $p=0.03$) compared with patients with recent (<8 months) MIs.

Conclusions: LV dyssynchrony is independently associated with the occurrence of VT after MI.

INTRODUCTION

Sudden cardiac death (SCD), which is attributed mostly to ventricular tachycardia (VT), accounts for approximately 50% of all deaths in patients with coronary heart disease.¹ The interaction between the arrhythmogenic substrate and several factors that influence electrical stability (e.g., autonomic tone, myocardial ischemia) is crucial in the genesis of VT. The use of an implantable cardioverter-defibrillator (ICD) in patients with left ventricular (LV) ejection fractions (LVEFs) $\leq 35\%$ within 40 days after myocardial infarction (MI) has not demonstrated a survival advantage,² despite the known survival benefit of ICD use in other patients with LVEFs $\leq 35\%$.³ Moreover, a progressive increase in mortality risk late after MI has been described among ICD recipients.⁴ Differences in arrhythmogenic substrate early and late after MI may explain those findings and underscore the importance of substrate characterization to determine the mechanisms of SCD. A key feature of the myocardial substrate after MI is slow conduction through inhomogeneous scar tissue.^{5,6} Collagen deposition in particular within the infarct border zone may occur over years after the index MI, resulting in progressive separation of viable myocardial fibers and thus more dispersed electrical impulse propagation through the left ventricle.⁷

The emergence of speckle-tracking echocardiography has permitted more refined evaluation of LV myocardial function and tissue characteristics after MI.⁸ This technique allows the assessment of the temporal heterogeneity of segmental myocardial deformation, which may reflect the electromechanical heterogeneity of myocardial tissue.⁹ With the use of speckle-tracking echocardiography, in the present evaluation we investigated (1) the relationship between MI age and LV mechanical and electrophysiologic characteristics and (2) the association between LV dyssynchrony and risk for VT in ICD recipients after MI.

METHODS

Patient Population

The population comprised patients with prior MIs who underwent programmed electrical stimulation (PES) followed by ICD implantation at the Leiden University Medical Center. All patients underwent transthoracic echocardiography before or < 6 months after ICD implantation. For patients undergoing biventricular ICD (CRT-D) implantation, echocardiography was performed after CRT-D placement, with the pacemaker on to ensure representation of current physiology. Exclusion criteria were an uncertain date of MI, the presence of reversible ischemia, pacemaker dependence before ICD implantation, and the occurrence of VT between ICD insertion and echocardiography.

All clinical, electrophysiologic, and echocardiographic data were collected in the departmental cardiology information system (EPD-Vision; Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analyzed.

Echocardiography

Patients were imaged in the left lateral decubitus position using a commercially available system equipped with 3.5-MHz and 5S transducers (Vivid 7 and E9; GE Vingmed Ultrasound AS, Horten, Norway). Two-dimensional grayscale, color, pulsed-wave, and continuous-wave Doppler data were acquired in the parasternal and apical views. Images were recorded digitally in cine-loop format and analyzed offline with EchoPAC version 11.0.0 (GE Vingmed Ultrasound AS). Left atrial volume and LV end-systolic and end-diastolic volumes were measured from the apical two- and four-chamber views and indexed to body surface area. LVEF was calculated using the biplane Simpson's technique.⁹ Mitral regurgitation severity was graded as none/mild or moderate/severe by incorporating a number of echocardiographic indicators, including regurgitant jet vena contracta width, proximal flow convergence, effective regurgitant orifice area measured with the proximal isovelocity surface area method, color jet area, continuous-wave Doppler spectral profile intensity, E-wave velocity, and pulmonary venous flow reversal.¹⁰

Strain Analysis

Evaluation of LV myocardial deformation was performed with speckle-tracking echocardiography.¹¹ These measurements were performed by two investigators blinded to patient outcomes using the Q-analysis application on an EchoPAC version 11.0.0 workstation. In each of the three apical views, the LV myocardium was manually contoured, and the contours were adjusted to achieve optimal tracking of all myocardial segments over the cardiac cycle. The software automatically generated curves of strain as a function of time (Figure 1). Using an 18-segment model derived from the three apical views, segmental peak systolic longitudinal myocardial strain and time to peak longitudinal strain were recorded. Longitudinal strain in normally contracting myocardium is by convention negative, but for simplicity, we report absolute strain values, denoted as *lstrainl*. Thus, poorer myocardial contraction is reflected by a lower *lstrainl* value. Myocardial segments were classified as having transmural scar if the longitudinal *lstrainl* value was <4.5%. This threshold has been previously validated against late gadolinium enhancement cardiac magnetic resonance imaging.¹²

LV scar burden was evaluated by the percentage of LV segments exhibiting transmural scar. LV dyssynchrony was defined as the standard deviation of values of time to peak longitudinal systolic strain in this 18-segment model (Figure 1).¹¹ Global longitudinal strain (GLS) was measured as the mean of peak *lstrainl* values from each myocardial segment.¹¹

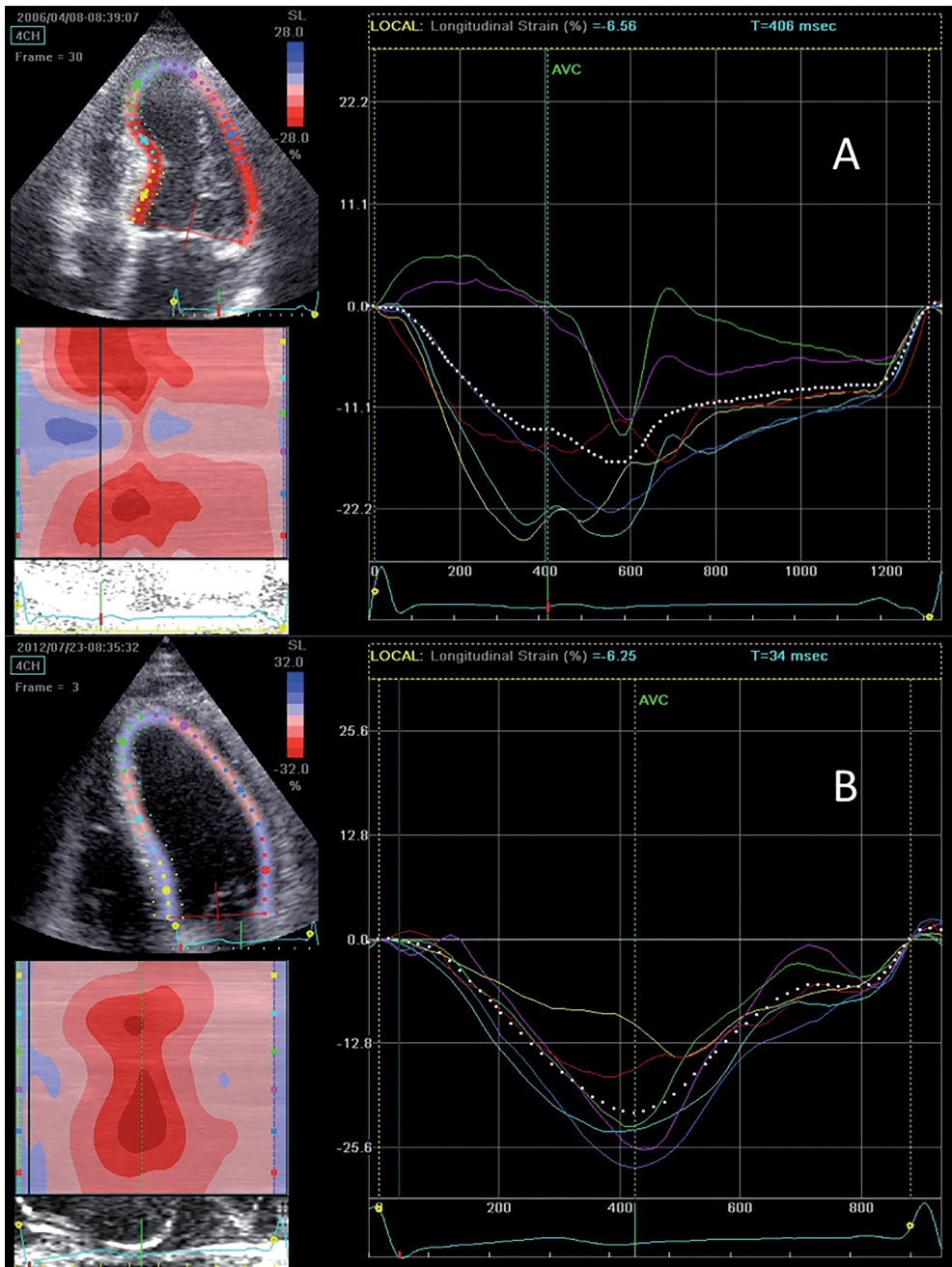


Figure 1. Speckle-tracking echocardiographic strain. Representative examples of speckle-tracking strain curves from two patients with LVEFs of 55%. Patient A demonstrated greater heterogeneity in time to peak segmental strain compared with patient B. LVEF = left ventricular ejection fraction.

PES

PES was performed according to current guidelines.¹³ In brief, patients were studied in a fasting, nonsedated state and after the discontinuation of antiarrhythmic medications (except for amiodarone) for five half-lives.¹⁴ PES included up to three drive-cycle lengths (600, 500, and 400 msec) with up to three ventricular extrastimuli and burst pacing from the right ventricular apex and right ventricular outflow tract. Positive response to PES was defined as the reproducible induction of sustained monomorphic VT lasting >30 sec or requiring termination because of hemodynamic compromise.

Outcomes

VT was identified from examination of ICD electrograms stored after device therapy administration. The appropriateness of this therapy and the nature of the ventricular arrhythmia (to distinguish monomorphic VT from polymorphic VT or ventricular fibrillation) were adjudicated by an electrophysiologist who was blinded to patients' clinical characteristics. The primary end point was the occurrence of first monomorphic VT requiring device therapy (antitachycardia pacing or shock) after ICD implantation. Patients were censored at the date of most recent outpatient appointment unless the primary end point occurred earlier. In addition, the occurrence and date of occurrence of the following significant competing risks were recorded if they took place after ICD implantation and before VT occurrence: polymorphic VT, ventricular fibrillation, upgrade to CRT-D, VT ablation, revascularization for acute coronary syndrome, or LV reconstructive surgery.

Statistical Analysis

Patients were divided into quartiles according to age of MI (i.e., time from index MI to ICD insertion). Nominally, these groups were described as very old for the quartile with the oldest MI age and recent for the quartile with the youngest MI age. Categorical data are summarized as frequencies and percentages and were compared using χ^2 or Fisher exact tests as appropriate. Continuous variables are presented as mean $\pm$ SD or median (interquartile range [IQR]) and were compared between groups using analysis of variance or Kruskal-Wallis tests for normally and non-normally distributed data, respectively. Post hoc testing for pairwise comparisons was performed with Bonferroni adjustment. The relationship between scar percentage and MI age was evaluated by generalized linear modeling. Because of the highly skewed distribution and wide variance relative to the mean of scar percentage, a negative binomial probability distribution was assumed.

For time-to-event (monomorphic VT) analysis, a competing-risks strategy was adopted. A competing risk is an event whose occurrence alters or precludes the occurrence of an event of interest (monomorphic VT). When competing risks are present, competing-risks regression is regarded as an appropriate approach to time-to-event analysis.^{15,16} In the present analysis, the following events occurring before the occurrence of the primary end point of monomorphic VT were treated as competing risks: ventricular fibrillation,

polymorphic VT, ICD upgrade, coronary revascularization, and LV reconstructive surgery.¹⁷⁻¹⁹ The covariates that were examined as potential predictors of monomorphic VT were chosen on the basis of clinical relevance or demonstrated prognostic value after MI. These covariates included.

- Clinical factors (age, gender, hypertension, diabetes mellitus, infarct territory, New York Heart Association functional class III or IV, creatinine clearance, ICD indication [secondary vs primary], revascularization of the infarct-related artery, and age of MI),
- QRS duration on electrocardiography,
- Conventional echocardiographic parameters (LV end-systolic volume index, left atrial volume index, and LVEF),
- Speckle-tracking echocardiographic parameters that formed the focus of the present study (GLS, LV scar burden, and LV dyssynchrony), and
- VT inducibility on PES.

Those covariates achieving p-values <0.20 at the univariate level were evaluated in a multivariate competing-risks analysis that was performed with backward elimination. Differences in the cumulative incidence of monomorphic VT between groups were assessed.²⁰

The incremental benefit of novel predictors of monomorphic VT was evaluated first by the Wald test comparing the model with the novel predictor and the model without the novel predictor. Second, the incremental value of novel risk predictors was evaluated using the integrated discrimination improvement index; a value significantly greater than zero is indicative of additive discriminatory value of the new risk predictor of interest.²¹

In 10 randomly selected individuals, echocardiographic strain measurements were repeated by a second investigator to determine interobserver variability. The interrater agreement for classification of scar was evaluated by the κ statistic and the interobserver variability for LV dyssynchrony and GLS by the intraclass correlation coefficient for a two-way random-effects model for consistency of agreement and by the absolute difference between observers divided by the mean of the repeated observations expressed as a percentage.

For all tests, a two-sided α value of 0.05 was adopted to determine statistical significance. Analysis was performed using Stata version 13.1 (StataCorp LP, College Station, TX).

RESULTS

Patient Characteristics

A total of 206 patients (median age 67 years; IQR 57–73 years; 180 [87%] men) meeting the inclusion criteria were studied. These comprised 171 ICD recipients (83%) and 35 CRT-D recipients (17%). The median MI age was 6.2 years (IQR 0.66–15 years). Patient characteristics are displayed as a function of age of MI in Table 1. Individuals with very old MIs (MI age in the highest quartile, >180 months prior) were of more advanced age ($p<0.001$), had worse renal function ($p=0.007$), and had longer QRS durations ($p<0.001$). They also had less frequent revascularization of the infarct-related artery ($p<0.001$), and the infarct-related artery more often subtended the inferoposterior LV segments ($p=0.03$) compared with those with more recent MIs. These patients more often received ICDs as secondary prevention ($p=0.002$).

Echocardiographic and Electrophysiologic Characteristics

Table 2 summarizes the echocardiographic and electrophysiologic characteristics of the patient population. Patients with very old MIs exhibited greater scar burden ($14.7 \pm 15.8\%$ vs. $10.7 \pm 11.4\%$, $p=0.03$) and more left atrial dilatation (36 mL/m^2 [IQR 27–50 mL/m^2] vs. 28 mL/m^2 [IQR 23–35 mL/m^2], $p=0.005$) compared with patients with recent MIs (MI age in the lowest quartile, <8 months). Patients with very old MIs showed a higher likelihood of VT inducibility compared with those with recent MIs (88% vs. 63%, $p=0.003$). To examine the possibility that the increase in scar burden with infarct age was related to the confounding effects of changing practice over time with regard to revascularization of the culprit artery, we also adjusted for revascularization status in the generalized linear model of infarct age. This adjusted analysis did not significantly affect the positive relationship between scar burden and infarct age (coefficient 0.15, 95% confidence interval [CI] 0.013–0.28, $p=0.03$). We undertook two post hoc sensitivity analyses in which a scarred segment was defined as one with $|\text{strain}| <4\%$ and $<5\%$, respectively. The adjusted coefficients for the relationship between scar burden and infarct age were 0.18 (95% CI 0.043 to 0.32, $p=0.01$) and 0.11 (95% CI –0.022 to 0.25, $p=0.10$), respectively.

Outcomes

The median follow-up time after ICD implantation was 24 months (IQR 7.8–47 months). In total, 75 individuals experienced the primary end point of monomorphic VT, and 18 patients had competing events. VT ablation was performed in six patients (3%) after ICD implantation: in four individuals, this occurred after a primary end point event, whereas in the remaining two, the date of ablation was treated as the study exit date. In a further eight patients, subsequent ICD upgrade to CRT-D resulted in study exit at the time of the upgrade. LV reconstructive surgery was performed in four individuals (2%) after ICD

Table 1. Patient characteristics

	Quartile 1 (<8 mo) (n=52)	Quartile 2 (8–75 mo) (n=52)	Quartile 3 (75–180 mo) (n=51)	Quartile 4 (>180 mo) (n=51)	p
Age (y)	63 (51–71)	62 (53–67)	68 (58–73)	74 (67–76)*,†,‡	<0.001
Men	47 (90%)	42 (81%)	43 (84%)	48 (94%)	0.20
Hypertension	25 (48%)	16 (31%)	17 (33%)	19 (37%)	0.30
Diabetes mellitus	13 (25%)	6 (12%)	8 (16%)	8 (16%)	0.30
Smoking					0.20
Never	20 (38%)	24 (46%)	19 (37%)	27 (53%)	
Previous	11 (21%)	18 (35%)	20 (39%)	15 (29%)	
Current	21 (41%)	10 (19%)	12 (24%)	9 (18%)	
Infarct territory					0.03
Inferior/posterior	17 (33%)	15 (29%)	16 (31%)	28 (55%)	
Anterior	35 (67%)	37 (71%)	35 (69%)	23 (45%)	
NYHA class					0.04
I or II	48 (92%)	37 (71%)	38 (75%)	40 (78%)	
III or IV	4 (8%)	15 (29%)	13 (25%)	11 (22%)	
Secondary prevention ICD	34 (65%)	21 (40%)	29 (57%)	39 (76%)	0.002
Revascularized infarct-related artery	21 (40%)	24 (46%)	14 (27%)	1 (2%)	<0.001
AF/atrial flutter	5 (10%)	13 (25%)	13 (25%)	11 (22%)	0.10
Creatinine clearance (mL/min)	78 (56–103)	74 (58–98)	75 (59–94)	62 (48–77)*,†,‡	0.007
QRS duration (msec)	107 ± 26	109 ± 23	130 ± 26	138 ± 35*,†	<0.001

AF = atrial fibrillation; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association.

Data are expressed as median (IQR), number (percentage), or mean ± SD. The threshold p-value for pairwise comparisons between groups was $p < 0.004$, by Bonferroni adjustment.

* $p < 0.004$ compared with quartile 1.

† $p < 0.004$ compared with quartile 2.

‡ $p < 0.004$ compared with quartile 3.

Table 2. Echocardiographic and electrophysiologic characteristics

	Quartile 1 (<8 mo) (n=52)	Quartile 2 (8–75 mo) (n=52)	Quartile 3 (75–180 mo) (n=51)	Quartile 4 (>180 mo) (n=51)	p
LVESVI (mL/m ²)	41 (33 to 52)	49 (34 to 66)	49 (33 to 64)	47 (35 to 65)	0.20
LVEDVI (mL/m ²)	69 (57 to 85)	80 (65 to 97)	79 (59 to 100)	77 (56 to 97)	0.30
LAVI (mL/m ²)	28 (23 to 35)	27 (21 to 37)	32 (22 to 40)	36 (27 to 50)*, †	0.005
Moderate/severe MR	1 (2%)	5 (10%)	4 (9%)	6 (12%)	0.20
LVEF (%)	41 ± 9.9	40 ± 13	38 ± 11	36 ± 8.2	0.10
GLS (%)	10.9 (9.81 to 14.3)	12.8 (10.4 to 14.9)	–10.1 (8.25 to 13.6)	–11.7 (8.58 to 13.4)	0.10
LV percentage scar (%)	10.7 ± 11.4	12.1 ± 15.1	13.1 ± 12.9	14.7 ± 15.8*	0.03
Patients with ≥1 dyskinetic myocardial segment	7 (13%)	12 (23%)	11 (25%)	10 (20%)	0.60
LV dyssynchrony (msec)	82 ± 29	81 ± 34	97 ± 40	91 ± 43	0.09
VT inducible	33 (63%)	30 (58%)	36 (71%)	45 (88%)	0.003
VF/PVT inducible	8 (15%)	18 (35%)	8 (16%)	4 (8%)	0.006

GLS = global longitudinal strain; LAVI = left atrial volume index; LV = left ventricular; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; MR = mitral regurgitation; PVT = polymorphic ventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia.

Data are expressed as median (IQR), number (percentage), or mean ± SD.

* p<0.004 compared with quartile 1.

† p<0.004 compared with quartile 2.

implantation: in two cases, this occurred after a primary end point event, whereas in the other two, the date of surgery was used as the study exit date.

Time-to-Monomorphic VT Analysis

Table 3 contains the competing-risks regression for predictors of time to monomorphic VT. Those factors achieving univariate p-values <0.20 included age, creatinine clearance, QRS duration, revascularization of the infarct-related artery, age of MI, LV end-systolic volume index, LVEF, GLS, LV scar burden, LV dyssynchrony, and VT inducibility on PES. On multivariate analysis, nonrevascularization of the infarct-related artery (p=0.02), longer QRS duration (p=0.001), greater LV dyssynchrony (p<0.001), and lower GLS (p=0.02) were independently associated with later development of VT. Each 10-msec increment in LV dyssynchrony was associated with a 12% increase in the risk for monomorphic VT. In addition, the evaluation of LV dyssynchrony conferred incremental predictive value to an infarct-related artery nonrevascularization, QRS duration, and GLS, as demonstrated by the Wald test ($\chi^2 = 17$, p=0.001) and an integrated discrimination improvement index of 0.027

($p=0.001$). These indicate that the measurement of LV dyssynchrony in addition to PES provided superior prediction of subsequent VT.

The cohort was dichotomized on the basis of the median value of LV dyssynchrony into those exhibiting LV dyssynchrony ≤ 90 and >90 msec. Those with LV dyssynchrony >90 msec had a significantly greater incidence of monomorphic VT compared with those with less LV dyssynchrony ($p<0.001$) (Figure 2).

Table 3. Multiple competing-risks regression for the occurrence of VT

	Univariate		Multivariate	
	SHR (95% CI)	p	SHR (95% CI)	p
Age	1.02 (1.00–1.05)	0.03	0.995 (0.963–1.03)	0.90
Female gender	0.83 (0.43–1.6)	0.60		
Hypertension	0.81 (0.50–1.3)	0.40		
Diabetes mellitus	1.0 (0.58–1.9)	0.90		
NYHA class III or IV	1.1 (0.63–1.9)	0.70		
Creatinine clearance	0.988 (0.981–0.996)	0.002	0.998 (0.989–1.00)	0.70
QRS duration	1.012 (1.006–1.019)	<0.001	1.011 (1.004–1.019)	0.001
Anterior infarct-related territory	0.94 (0.59–1.5)	0.80		
Secondary prevention ICD	1.4 (0.86–2.4)	0.20		
Revascularized infarct-related artery	0.42 (0.23–0.79)	0.007	0.49 (0.26–0.91)	0.02
Time from index MI	1.002 (1.001–1.004)	0.005	0.9999 (0.9971–1.003)	1.00
LVESVI	1.007 (1.000–1.013)	0.05	0.9920 (0.9843–0.9998)	0.05
LAVI	1.00 (0.989–1.02)	0.70		
LVEF	0.97 (0.95–0.99)	0.008	0.99 (0.96–1.0)	0.60
GLS, % reduction in magnitude	1.08 (1.02–1.15)	0.01	1.08 (1.02–1.16)	0.02
LV percentage scar	1.03 (1.01–1.04)	0.001	0.997 (0.969–1.03)	0.80
LV dyssynchrony, 10-msec increase	1.14 (1.09–1.19)	<0.001	1.12 (1.06–1.18)	<0.001
VT inducible	2.9 (1.6–5.5)	0.001	1.8 (0.90–3.5)	0.10

GLS = global longitudinal strain; ICD = implantable cardioverter-defibrillator; LAVI = left atrial volume index; LV = left ventricular; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; MI = myocardial infarction; NYHA = New York Heart Association; SHR = subdistribution hazard ratio; VT = ventricular tachycardia.

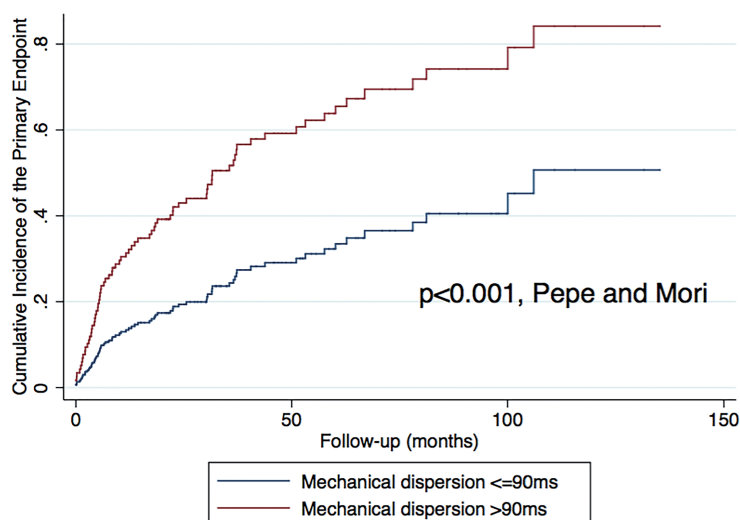


Figure 2. LV dyssynchrony and VT risk. Cumulative incidence of the primary end point of monomorphic VT that required ICD therapy, as a function of LV dyssynchrony. The p-value was obtained by the approach of Pepe and Mori.²⁰ ICD = implantable cardioverter-defibrillator; LV = left ventricular; VT = ventricular tachycardia.

Interobserver Variability

For segmental scar classification, the κ statistic for interrater agreement was 0.72, indicating substantial concordance between observers. For GLS measurement, the average intraclass correlation coefficient was 0.94 (95% CI 0.74–0.98), while for LV dyssynchrony, it was 0.96 (95% CI 0.84–0.99). The difference between observers expressed as a percentage of the mean of their measurements was 0.022% for GLS and 4.5% for LV dyssynchrony.

DISCUSSION

The main findings of this study are that (1) greater LV dyssynchrony is associated with an increased risk for monomorphic VT, independent of MI age and revascularization of the infarct-related vessel, and (2) older MI is associated with greater LV scar burden than more recent infarction, independent of whether the culprit artery was revascularized.

Myocardial Infarction Age, Myocardial Scar, and VT

LV remodeling after MI is a complex time-related process involving ultrastructural and histologic myocardial changes that may be reflected in macroscopic alterations in LV geometry and function.^{22–24} Specifically, edema and inflammation early after MI are superseded by collagen deposition and myocardial scar formation late after MI.²³ This process of scar formation in the infarct zone, as well as myocardial collagen deposition in remote areas, continues months to years after the index MI.²³ This evolution is manifest by LV dilatation and dysfunction.^{25–27} However, there is scant evidence on very late scar

progression after MI. In the present study, a trend toward worse LV systolic function was indeed observed in advancing quartiles of MI age. In fact, a more marked and significant increase in LV scar burden was demonstrated in advancing quartiles of MI age. This was accompanied by increasing left atrial volume with increasing MI age, a finding that provides some face validity to our observation of increasing LV scar with MI age. These findings add to the existing research by characterization of myocardial substrate very late after MI.

VT, an important cause of SCD after MI, has been associated with an increased scar burden on electroanatomic mapping⁶ and using late gadolinium enhanced cardiac magnetic resonance imaging.²⁸ Data from the Multicenter Automatic Defibrillator Implantation Trial II study showed a direct association between mortality risk and increasing time from MI; the presence of extensive scar after MI (as reflected by an LVEF $\leq 30\%$) was an independent determinant of lethal ventricular arrhythmias.⁴ The present study has delivered consistent findings by demonstrating that at the univariate level, scar burden by speckle-tracking echocardiography is associated with the risk for monomorphic VT. However, myocardial scar burden is only one of the characteristics of the arrhythmogenic substrate. Other factors, such as how scar influences electrical impulse propagation and electromechanical coupling, may be important in the development of reentrant VT.

LV Dyssynchrony and VT

Collagen deposition and remodeling occur after MI principally in the infarcted zone but also in the peri-infarct and remote regions. The slowed and heterogeneous electrical impulse propagation associated with scar tissue favors the development of clinical VT by permitting reentry. In the present evaluation, we hypothesized that the mechanical consequences of MI might be related to the subsequent risk for VT. LV dyssynchrony was measured using speckle-tracking strain echocardiography as an index of the heterogeneity of timing of segmental myocardial contraction. The potential slowing of global LV electromechanical coupling, which could result from both scar in the infarct zone and collagen deposition in the peri-infarct and remote zones, would result in less coordinated LV contraction and a higher LV dyssynchrony index. We found that greater LV dyssynchrony was associated with an elevated risk for subsequent VT. There are several possible explanations for this finding. First, LV dyssynchrony may promote ongoing ventricular remodeling, particularly in the infarct or peri-infarct zones that form the LV substrate for VT. Second, LV dyssynchrony may also be an indicator of scar and the functional consequences of scar that promote VT.

There is growing recognition of the importance of myocardial substrate characteristics in the pathogenesis of VT after MI.²⁹ This may be particularly true for monomorphic VT, which, in contrast to polymorphic VT and ventricular fibrillation, is mediated by fixed scar and heterogeneous scar conduction.⁶ In the present study, although LV scar burden was associated with the occurrence of VT during follow-up, LV dyssynchrony was independently associated with VT. Thus, LV dyssynchrony as a marker of

the heterogeneity of LV activation seems able to characterize the substrate that predisposes to VT.

The results of the present evaluation are consistent with those of a previous study showing that LV dyssynchrony was greater in post-MI patients with recurrent VT.⁹ The present study also demonstrates that LV dyssynchrony provides complementary information to QRS duration in the identification of patients who will experience recurrent VT. Both QRS duration and wider LV dyssynchrony, in addition to nonrevascularization of the infarct-related artery and GLS, were shown in the present study to be independently associated with the risk for subsequent VT.

Limitations

Echocardiography was performed at a single time point, so the temporal evolution of LV remodeling is inferred rather than proved by serial measurements in each individual. This research was undertaken at a tertiary center among patients referred for electrophysiologic assessment and consideration for ICD placement. Referral bias is therefore likely, which may have implications for the generalizability of the study findings. Our findings must be externally validated to confirm their clinical importance.

CONCLUSIONS

LV dyssynchrony, which results from myocardial scar tissue interspersed with viable myocytes, is independently associated with the subsequent occurrence of VT. Older MI exhibits greater scar burden, and more LV dyssynchrony independently of whether the culprit artery was revascularized or not. These observations may help understanding of the survival benefit seen with ICD implantation later after MI, compared with earlier.

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CHAPTER 9

Summary, conclusions and future perspectives

Samenvatting, conclusies en toekomstperspectieven

List of publications

Dankwoord

Curriculum Vitae



SUMMARY, CONCLUSIONS AND FUTURE PERSPECTIVES

Summary

The general introduction (**Chapter 1**) of this thesis provides an overview of current epidemiology of coronary artery disease with special focus on ST-segment elevation acute myocardial infarction (STEMI). Improvements in treatment of STEMI, including wide use of evidence-based therapy and primary percutaneous coronary intervention, resulting in an improved short-term survival, have led to a growing number of patients with left ventricular (LV) dysfunction and remodeling during follow-up. Consequently, this population has an increased risk of heart failure, re-infarction and (sudden cardiac) death. Conventional 2-dimensional echocardiography is the imaging technique of first choice to evaluate these patients, including the assessment of LV volumes and ejection fraction, diastolic function, functional mitral regurgitation (MR) and right ventricular (RV) dimensions and function. In addition, the role of advanced echocardiographic imaging techniques is introduced, including 2-dimensional speckle-tracking imaging and 3-dimensional echocardiography. The current thesis aims at investigating the role of conventional and advanced echocardiography in the risk stratification of patients with ischemic heart disease, directly after STEMI and in the chronic phase, when heart failure may have developed.

Part I: Echocardiography in ischemic heart disease

In the first part, conventional and advanced echocardiographic techniques are used to address risk stratification of patients with ischemic heart disease, in particular STEMI patients, from the acute phase to 12 months post-myocardial infarction.

Following STEMI, patients with reduced LV function are at risk of ventricular arrhythmias, especially early post-myocardial infarction and in remote myocardial infarction. However, the results of randomized controlled trials including patients immediately after STEMI did not show the benefit of implantable cardioverter defibrillators (ICDs) in this population. LV ejection fraction was an established criterion to select patients for ICD implantation in those trials and is included in current guidelines. However, LV ejection fraction has limited accuracy to identify patients who will benefit from ICD. Evaluation of functional myocardial tissue heterogeneity with novel imaging techniques, including speckle-tracking echocardiography, at the border zone 3 months post-STEMI has been associated with cardiac death and appropriate ICD therapy and, therefore, could identify STEMI patients at risk of ventricular arrhythmias (**Chapter 2**).

Another adverse evolution after STEMI is cardiac remodeling in both the LV and RV. Cardiac remodeling occurs at early stages of myocardial infarction as a consequence of scar formation, infarct expansion and increase in filling pressure. At follow-up, ventricular dilatation may result from further remodeling of residual viable myocardium to maintain stroke volume. RV dilatation occurs particularly in the first 6 months after STEMI. Additionally, changes in LV volumes and function are associated with RV dilatation,

highlighting the interventricular dependence and thereby the importance of assessing both the LV and RV following STEMI. Despite RV remodeling, RV function remains preserved up to 12 months follow-up in the vast majority of patients. The presence of multivessel disease, higher peak cardiac troponin T levels, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers use at discharge and lower baseline LV and RV function may identify 6-month RV dysfunction (**Chapter 3**) which is by itself associated with poor long-term outcome.

Moreover, routine assessment of MR severity following STEMI may also strengthen risk stratification of ischemic heart disease and may support the selection of patients who might be targeted for strict medical therapy or undergo other treatment options, such as cardiac resynchronization therapy (CRT), percutaneous or surgical approaches of functional MR. Although MR grade changes over time following STEMI, baseline significant MR is still associated with the presence of 12-month significant MR. Importantly, significant MR at follow-up portends a poor prognosis, with higher risk of all-cause and cardiac mortality (**Chapter 4**).

The LV remodeling process after STEMI may differ across several subpopulations. Post-STEMI, patients with diabetes have a poor long-term prognosis compared to non-diabetic patients, despite similar changes in LV volumes and ejection fraction. Speckle-tracking echocardiography is a more sensitive tool to evaluate subtle differences in LV systolic function and shows more impaired LV strain values in diabetic patients post-STEMI compared to non-diabetics (**Chapter 5**). Consequently, echocardiographic assessment of LV global longitudinal strain may be of more clinical value in post-STEMI diabetics than LV ejection fraction.

Quantitative 3-dimensional echocardiographic measurements during dobutamine stress echocardiography could be of help in the identification of coronary artery disease. A suitable measure could be LV excursion, since it reflects is the longitudinal contraction of the LV, which is initially affected during ischemia. Importantly, patients with significant coronary artery disease on angiography demonstrate a worsening in LV excursion from rest to peak stress, while LV excursion remains similar in patients without significant coronary artery disease (**Chapter 6**).

Part II: Echocardiography in chronic heart failure

The second part describes the role of conventional and advanced echocardiography in clinical decision making in patients with ischemic heart disease that developed chronic heart failure.

The golden standard treatment for heart failure is heart transplantation after failure of medical therapy, surgery and/or CRT. CRT has demonstrated to be an effective treatment option in selected heart failure patients by slowing or reversing the LV remodeling process, as well as improving clinical symptoms and long-term outcome. Nevertheless, according to current definitions of CRT response using clinical or echocardiographic endpoints, 20%

to 40% of patients do not respond to CRT. Adding reduction in levels of the biomarker N-terminal pro-brain natriuretic peptide to echocardiographically assessed LV reverse remodeling, creating a new definition of CRT response, may more accurately select the group of patients who truly respond to CRT (**Chapter 7**).

Finally, patients with ischemic heart disease are at increased risk of ventricular arrhythmias. Differences in arrhythmogenic substrate may explain the variable efficacy of ICDs to prevent sudden cardiac death over time. Speckle-tracking echocardiography could be useful in this regard, since it allows assessment of the temporal heterogeneity of segmental myocardial deformation, which may reflect electromechanical heterogeneity of myocardial tissue. This so called mechanical dispersion is associated with the occurrence of ventricular tachycardia in post-STEMI patients (**Chapter 8**). Consequently, fine-tuning of echocardiographic characteristics of patients with ischemic heart disease using LV mechanical dispersion may contribute to the risk stratification of ventricular arrhythmias.

Conclusions and future perspectives

Evaluation of patients with ischemic heart disease using echocardiography is indispensable. Both in the acute setting of STEMI, at follow-up and in the chronic phase during the possible development of heart failure, routine echocardiographic assessment is an essential part of daily clinical practice.

Directly following STEMI, the risk of possible future adverse outcome, such as cardiac remodeling, LV and RV dysfunction, ventricular arrhythmias and all-cause and cardiac mortality, has to be estimated using a combination of clinical and echocardiographic characteristics. Furthermore, during follow-up, assessment of the same echocardiographic measures may provide even better prognostic information. Using this strategy, patients could early be identified in whom strict medical therapy should be targeted and early additional treatment options could be considered. In patients with chronic heart failure, echocardiography may be an additional tool to identify patients who will benefit from one of the several heart failure treatment modalities. Also, therapeutic effect of these modalities should be evaluated using echocardiography.

SAMENVATTING, CONCLUSIES EN TOEKOMSTPERSPECTIEVEN

Samenvatting

De algemene introductie (**Hoofdstuk 1**) van dit proefschrift geeft een overzicht van de huidige epidemiologie van coronairlijden met speciale aandacht voor ST-segment elevatie acuut myocardinfarct (STEMI). Verbeteringen in de behandeling van STEMI, inclusief het uitgebreide gebruik van evidence-based therapie en primaire percutane coronaire interventie, resulterende in een verbeterde kortetermijnoverleving, heeft geleid tot een groeiend aantal patiënten met linker ventrikel (LV) disfunctie en remodeling gedurende follow-up. Als een gevolg heeft deze populatie een verhoogd risico op hartfalen, re-infarct en (plotse hart-) dood. Conventionele 2-dimensionele echocardiografie is de beeldvormingstechniek van eerste keus om deze patiënten te evalueren, inclusief de beoordeling van LV volumes en ejectiefractie, diastolische functie, functionele mitralisklepinsufficiëntie (mitralisklepregurgitatie, MR) en rechter ventrikel (RV) dimensies en functie. Bovendien is de rol van geavanceerde echocardiografische beeldvormingstechnieken geïntroduceerd, waaronder 2-dimensionele speckle-tracking beeldvorming en 3-dimensionele echocardiografie. Het huidige proefschrift heeft als doel de rol van conventionele en geavanceerde echocardiografie te onderzoeken in de risicostratificatie van patiënten met ischemisch hartlijden, direct na STEMI en in de chronische fase, wanneer hartfalen zich mogelijk heeft ontwikkeld.

Deel I: Echocardiografie in ischemisch hartlijden

In het eerste deel worden conventionele en geavanceerde echocardiografische technieken gebruikt gericht op de risicostratificatie van patiënten met ischemisch hartlijden, voornamelijk in STEMI-patiënten, vanaf de acute fase tot 12 maanden na het myocardinfarct.

Na een STEMI lopen patiënten met een verminderde LV functie het risico op ventriculaire aritmieën, vooral vroeg na een myocardinfarct en lang na een myocardinfarct. Desalniettemin lieten de resultaten van gerandomiseerde trials die patiënten direct na een STEMI includeerden, geen voordeel zien van een implanteerbare cardioverter defibrillator (ICD) in deze populatie. LV ejectiefractie was een gestaafd criterium om patiënten te selecteren voor ICD-implantatie in die trials en is geïnccludeerd in huidige richtlijnen. Echter, LV ejectiefractie heeft een beperkte nauwkeurigheid om patiënten te identificeren die baat zullen hebben van een ICD. Evaluatie van functionele myocardweefselheterogeniteit met nieuwe beeldvormingstechnieken, zoals speckle-tracking echocardiografie, van de peri-infarctzone 3 maanden na STEMI is geassocieerd met cardiale dood en terechte ICD-therapie en zou daarom STEMI-patiënten kunnen identificeren die risico lopen op ventriculaire arritmieën (**Hoofdstuk 2**).

Een andere ongunstige ontwikkeling na STEMI is cardiale remodeling in zowel de LV

als RV. Cardiale remodeling doet zich voor in de vroege fases van een myocardinfarct als gevolg van littekenformatie, infarctexpansie en verhoging van vullingsdrukken. Gedurende follow-up kan ventriculaire dilatatie ontstaan door verdere remodeling van residueel levend myocard om zo het stroke volume te handhaven. RV dilatatie ontstaat vooral in de eerste maanden na STEMI. Bovendien zijn veranderingen in LV volumes en functie geassocieerd met RV dilatatie. Deze gegevens ondersteunen de interventriculaire afhankelijkheid en daarmee het belang van de beoordeling van zowel de LV als RV na STEMI. Ondanks RV remodeling blijft de RV functie behouden tot 12 maanden follow-up in de overgrote meerderheid van de patiënten. De aanwezigheid van meervatslijden, hogere peak troponine T-waarden, het gebruik van angiotensine-converterend-enzymremmers/ angiotensine-receptorblokkers bij ontslag en lagere baseline LV en RV functie kunnen RV disfunctie na 6 maanden identificeren (**Hoofdstuk 3**) welke zelf geassocieerd is met slechte langetermijntkomsten.

Verder kan de routinematige beoordeling van de ernst van MR na STEMI ook de risicostratificatie van ischemisch hartlijden versterken en de selectie van patiënten ondersteunen die mogelijk een doelwit kunnen zijn voor strikte medische therapie of die eventueel andere behandelingsmogelijkheden kunnen ondergaan, zoals cardiale resynchronisatietherapie (CRT), percutane of chirurgische benaderingen van functionele MR. Hoewel de graad van MR verandert over tijd na STEMI is baseline significante MR alsnog geassocieerd met de aanwezigheid van significante MR na 12 maanden. Belangrijker, significante MR gedurende follow-up voorspelt een slechte prognose met hogere risico's op totale en cardiale mortaliteit (**Hoofdstuk 4**).

Het LV remodelingsproces na een STEMI kan verschillen tussen diverse subpopulaties. Na een STEMI hebben patiënten met diabetes een slechtere langetermijnprognose vergeleken met patiënten zonder diabetes ondanks overeenkomstige veranderingen in LV volumes en ejectiefractie. Speckle-tracking echocardiografie is een sensitiever hulpmiddel om subtiele verschillen in LV systolische functie te evalueren en laat meer gestoorde LV strainwaarden zien in diabetespatiënten na STEMI in vergelijking met niet-diabeten (**Hoofdstuk 5**). Daarom kan de echocardiografische beoordeling van LV globale longitudinale strain meer klinische waarde hebben bij diabeten na STEMI dan die van LV ejectiefractie.

Kwantitatieve 3-dimensionele echocardiografische metingen gedurende dobutamine stress echocardiografie zou behulpzaam kunnen zijn in de identificatie van coronairlijden. Een geschikte meting zou LV excursie kunnen zijn, gezien deze de longitudinale contractie van de LV reflecteert welke initieel aangedaan is gedurende ischemie. Gewichtiger, patiënten met belangrijk coronairlijden op angiografie tonen een verslechtering in LV excursie van rust tot piekstress, terwijl de LV excursie gelijk blijft in patiënten zonder belangrijk coronairlijden (**Hoofdstuk 6**).

Deel II: Echocardiografie in chronisch hartfalen

Het tweede deel beschrijft de rol van conventionele en geavanceerde echocardiografie in de klinische besluitvorming bij patiënten met ischemisch hartlijden die chronisch hartfalen hebben ontwikkeld.

De gouden standaard voor de behandeling van hartfalen is harttransplantatie na het falen van medische therapie, chirurgie en/of CRT. CRT heeft aangetoond een effectieve behandelingsoptie te zijn in geselecteerde hartfalenpatiënten door het vertragen of omkeren van het LV remodelingsproces evenals door het verbeteren van de klinische symptomen en langetermijntoekomst. Desalniettemin reageert 20% tot 40% van de patiënten niet op CRT volgens de huidige definities van CRT-respons gebaseerd op klinische of echocardiografische eindpunten. Door verlaging in de waarden van de biomarker N-terminal pro-brain natriuretisch peptide toe te voegen aan de echocardiografisch gemeten omgekeerde LV remodeling, daarmee een nieuwe definitie van CRT-respons creërend, kan meer accuraat de groep van patiënten geselecteerd worden die werkelijk reageert op CRT (**Hoofdstuk 7**).

Tot slot hebben patiënten met ischemisch hartlijden een verhoogd risico op ventriculaire aritmieën. Verschillen in het aritmogene substraat kunnen de wisselende werkzaamheid van ICDs over de tijd om plotse hartdood te voorkomen, verklaren. Speckle-tracking echocardiografie zou nuttig kunnen zijn in dit verband, aangezien deze de temporele heterogeniteit van segmentele myocarddeformatie toelaat te beoordelen, welke de elektromechanische heterogeniteit van myocardweefsel kan reflecteren. Deze zogenaamde mechanische dispersie is geassocieerd met het optreden van ventriculaire tachycardie in patiënten na STEMI (**Hoofdstuk 8**). Daarom kan het in details meten van echocardiografische karakteristieken van patiënten met ischemisch hartlijden met behulp van LV mechanische dispersie bijdragen aan de risicostratificatie van ventriculaire aritmieën.

Conclusies en toekomstperspectieven

Evaluatie van patiënten met ischemisch hartlijden middels echocardiografie is onontbeerlijk. Zowel in de acute fase van een STEMI, gedurende follow-up en in de chronische fase wanneer mogelijk hartfalen heeft ontwikkeld, is de echocardiografische beoordeling een essentieel onderdeel van de dagelijkse klinische praktijk.

Direct na STEMI moet het risico op een mogelijke toekomstige nadelige uitkomst, zoals cardiale remodeling, LV en RV disfunctie, ventriculaire aritmieën en totale en cardiale mortaliteit, geschat worden met behulp van een combinatie van klinische en echocardiografische karakteristieken. Verder kan gedurende de follow-up de beoordeling van dezelfde echocardiografische parameters nog betere prognostische informatie verschaffen. Met deze strategie kunnen patiënten mogelijk eerder geïdentificeerd worden bij wie strikte medische therapie tot doel gesteld moet worden en aanvullende behandelingsopties kunnen worden overwogen. Bij patiënten met chronisch hartfalen

kan echocardiografie een additionele waarde hebben om patiënten te identificeren die baat zullen hebben van een van de vele hartfalenbehandelingsmodaliteiten. Tevens zou het therapeutische effect van deze modaliteiten moeten worden geëvalueerd met echocardiografie.

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CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 29 januari 1988 in Voorburg. In 2006 behaalde zij cum laude het gymnasiumdiploma aan de Regionale Scholen Gemeenschap Stad en Esch te Meppel. Van 2006 tot en met 2010 studeerde zij geneeskunde aan de Universiteit Leiden. Tijdens haar doctoraal fase was zij in het kader van het Excellente studententraject betrokken bij wetenschappelijk onderzoek naar behandeling van hartfalenpatiënten onder leiding van dr. H.F. Verwey en prof. dr. E.E. van der Wall. Na het cum laude behalen van haar doctoraal examen in 2010 startte haar promotieonderzoek op de afdeling cardiologie in het Leids Universitair Medisch Centrum onder leiding van prof. dr. J.J. Bax, prof. dr. M.J. Schalij en dr. V. Delgado. Haar onderzoek richt zich voornamelijk op de risicostratificatie van patiënten met ischemisch hartlijden middels conventionele en geavanceerde echocardiografie. Een selectie van de onderzoeksresultaten staan beschreven in dit proefschrift. Voor dit onderzoek ontving zij een persoonlijke beurs van het Leids Universitair Medisch Centrum (MD/PhD-beurs). In 2014 hervatte zij de studie geneeskunde aan de Universiteit Leiden met de co-assistentenschappen. Cum laude behaalde zij haar artsexamen in november 2015. Momenteel is zij als arts-assistent aan het werk op de afdeling cardiologie van het Medisch Spectrum Twente in Enschede onder begeleiding van dr. P.M.J. Verhorst.

