Multimodality imaging in the characterization and risk-stratification of cardiac disease and CRT recipients

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General introduction and outline of the thesis

GENERAL INTRODUCTION

Cardiac resynchronization therapy (CRT), the implantation of a dedicated device to resynchronize the ventricles in heart failure, is an established treatment for patients who remain symptomatic despite optimal medical therapy. It has a multitude of potentially beneficial effects, which include: improvement of symptoms, left ventricular reverse remodeling, improvement of left ventricular ejection fraction (LVEF), reduction of functional mitral regurgitation (FMR), decrease in the risk of ventricular arrhythmias and improvement in survival (Figure 1).[1-4] The probability of these favorable outcomes occurring after CRT implantation, is dependent on the appropriate patient characterization by echocardiography.

Risk-stratification of cardiac disease entails the scientific estimation of the probability for serious, disease-related events, e.g. heart failure and sudden cardiac death (SCD), either to inform prognosis or guide management. Multimodality cardiac imaging (echocardiography, magnetic resonance and radionuclide techniques) has assumed a central role in the risk-stratification of various cardiac diseases, encompassing multiple etiologies (Figure 2).[5]

Echocardiography for the prediction of outcome after CRT

Patients with a left bundle branch block (LBBB) morphology on the surface ECG, as well as a QRS duration of ≥150 ms, appear to derive most benefit from CRT in terms of symptom improvement and survival.[6-8] It is less clear if these baseline characteristics also translate into a greater degree of left ventricular reverse remodeling and improvement in LVEF, both of which are quantified by means of echocardiography.[9] Reverse remodeling is most commonly defined as a ≥15% reduction in the left ventricular end-systolic volume (LVESV) at 6 months after CRT implantation.[10] Long-term outcome after CRT is strongly linked to reverse remodeling, but also to improvement in global longitudinal strain (GLS), which can be measured with speckle tracking strain echocardiography.[11-13] These two measures, i.e. a reduction in LVESV and an improvement in GLS, reflect different mechanisms of CRT response – resynchronization and recruitment of contractile reserve, respectively. It is unknown whether an improvement in both, an improvement in only one or no improvement in either, has different prognostic implications.

Echocardiography may be useful for predicting outcome after CRT not only when performed before implantation, but also thereafter. CRT exerts its beneficial effects by resynchronization of the left ventricle.[1,2] Left ventricular dyssynchrony can be quantified with a novel, speckle tracking strain parameter, i.e. mechanical dispersion (MD).[14,15] It is calculated as the standard deviation of the time from the onset of the QRS complex on the triggered ECG to the peak longitudinal myocardial strain in a 17-segment model.[14,15] The degree to which left ventricular synchrony has been restored by CRT, quantified with MD, appears to predict outcome, i.e. a decrease in ventricular arrhythmias.[16] What remains unknown, is if MD (as a measure of residual dyssynchrony after CRT implantation) also leads to improved survival. CRT restores mechanical efficiency to the failing left ventricle by resynchronization of contraction. The less efficiently

the left ventricle operates at baseline, the greater the potential is for recovery of efficient work after CRT. It is unknown whether a greater reserve of potentially recoverable left ventricular myocardial work efficiency before CRT occasions better outcome. Global, left ventricular work efficiency can now be quantified with a non-invasive technique, which involves speckle tracking strain echocardiography.[17,18]

FMR is common in heart failure patients, and a reduction in FMR is counted among the beneficial effects of CRT.[19-27] This is achieved by a variety of mechanisms, i.e. resynchronization of the atrioventricular, inter- and intraventricular contraction, preload reduction and an increase in mitral valve closing forces.[26,28-30] The impact of the evolution of FMR after CRT on mortality has not been adequately investigated in a large cohort. Furthermore, atrial fibrillation (AF) is a common occurrence in heart failure, and may contribute to the severity of FMR through left atrial and mitral annular dilatation.[31-33] The impact of AF on the extent of FMR improvement in CRT has never specifically been investigated.

Echocardiography therefore plays a central role in the characterization of heart failure recipients of CRT, as well as in the delineation of the factors which will determine outcome. Results of research which have been included in this thesis, focus on the intersection of echocardiography and the following determinants of outcome after CRT: reverse remodeling, resynchronization and FMR improvement.

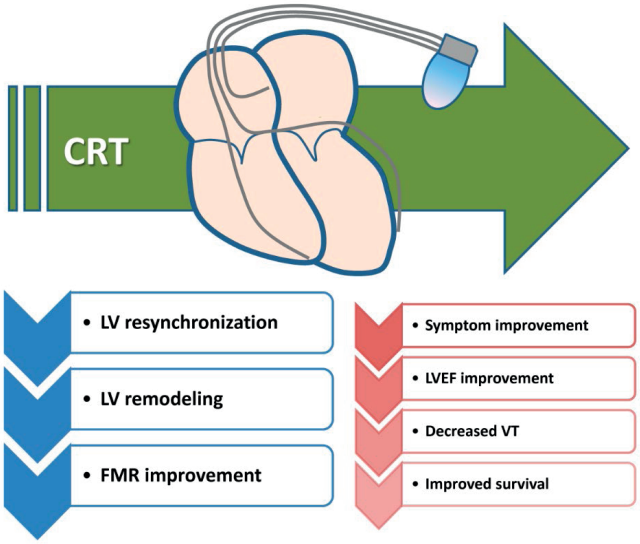

Figure 1: Summary of beneficial effects of cardiac resynchronization therapy (CRT), with highlighted (blue) determinants of outcome which are addressed in this thesis. FMR: functional mitral regurgitation, LV: left ventricular, LVEF: left ventricular ejection fraction, VT: ventricular tachycardia.

The role of multimodality imaging in the risk-stratification of cardiac disease

SCD is the cause of >4 million global deaths per year (one-fifth of all recorded deaths).[34] Since it often occurs in individuals who were not previously known with cardiac disease, its prevention remains challenging.[34] Insertion of an implantable, cardioverter-defibrillator (ICD) is the most effective approach to primary prevention (persons at high risk of SCD) and secondary prevention (patients with a previous, aborted episode of SCD).[5] Currently, ICD candidates are selected on the basis of an LVEF <35%.[34] This criterion, however, is neither sensitive, nor specific, and new approaches are required to improve upon this strategy.[5] Various cardiac imaging techniques, e.g. speckle tracking strain echocardiography, late gadolinium contrast enhanced (LGE) cardiac magnetic resonance (CMR), as well as nuclear techniques, have shown promise for more accurate SCD risk-stratification than LVEF in isolation.[5]

Genetic, dilated cardiomyopathy (DCM) is associated with more than 50 pathogenic genes (sarcomeric and lamin A/C mutations being the most common), as well as neuromuscular disorders.[35-37] Mutation carriers often remain asymptomatic until heart failure, arrhythmias or SCD supervenes.[35,38] Preventive strategies have not been adequately defined, partly because early disease is challenging to detect.[35] Advanced cardiac imaging techniques (e.g. echocardiographic tissue Doppler imaging, speckle tracking strain echocardiography, CMR and nuclear scans) can identify both structural and functional abnormalities early during the course of genetic DCM.[35] Furthermore, multimodality cardiac imaging can provide incremental benefit to LVEF for the risk-stratification of individuals with established, genetic DCM.[35]

Multimodality imaging is very promising as a risk-stratification tool for cardiac disease, and it has been reviewed, as well as further researched, in the context of genetic DCM, in this thesis.

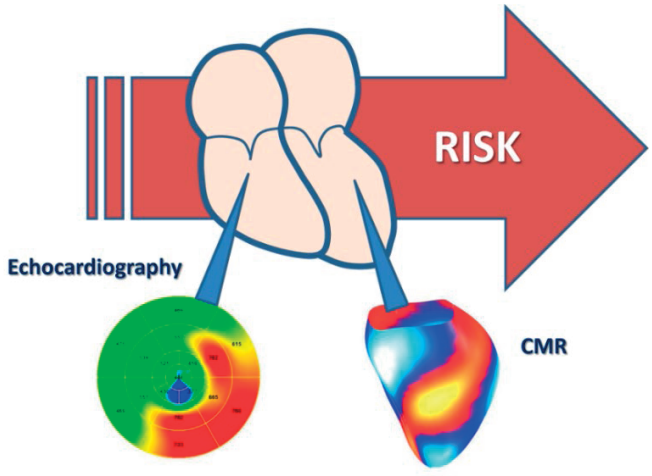

Figure 2: Examples of multimodality imaging in risk-stratification of cardiac disease. CMR: cardiac magnetic resonance.

OUTLINE OF THE THESIS

The objective of this thesis was twofold: i) to investigate the role of echocardiography in predicting outcome after CRT, and ii) to review and investigate multimodality imaging in the risk-stratification of cardiac disease.

In **Part I**, the role of echocardiography in predicting outcome after CRT is discussed. **Chapter 2** investigates the relation between baseline QRS duration and the presence of an LBBB on the one hand, and the degree of left ventricular reverse remodeling and improvement of LVEF, on the other, in CRT recipients. In **chapter 3**, results are presented on the interaction of two important determinants of outcome in CRT, i.e. left ventricular GLS and left ventricular reverse remodeling, as well as their impact on survival. The benefits of restoration of mechanical dyssynchrony (measured by MD) in CRT patients (decrease in ventricular arrhythmias, as well as survival) are discussed in **chapter 4**. A novel, non-invasive technique for assessing cardiac mechanical efficiency is applied to CRT prognostication in **chapter 5**. **Chapter 6** focuses on the prognostic influence of FMR in CRT recipients, with particular emphasis on the evolution thereof, i.e. what the impact on survival is when FMR is improved (or not improved) by CRT. In **chapter 7**, the impact of AF on the improvement in FMR in the CRT context is analyzed.

Part II provides a perspective on the use of multimodality imaging in the risk-stratification of various cardiac diseases. In **chapter 8** a brief overview of multimodality imaging in the prediction of SCD is given. **Chapter 9** reviews the role of cardiac imaging in the risk-stratification of genetic DCM, especially when associated with neuromuscular disorders. The use of speckle tracking strain echocardiography in risk-stratification of genetic DCM, is explored in **chapter 10**.

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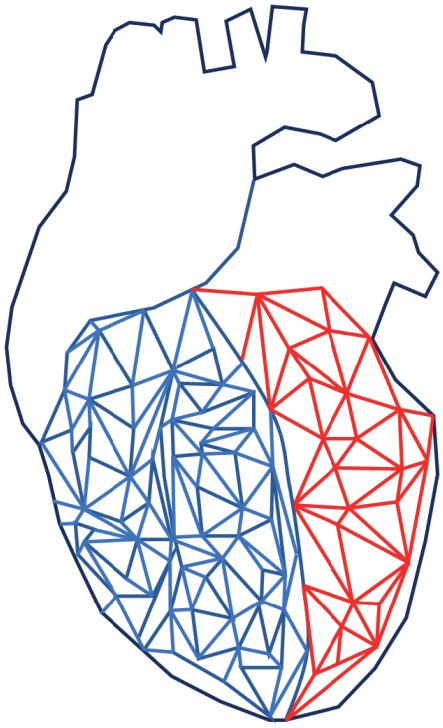
Part I:

The role of echocardiography in predicting outcome after CRT



2

Impact of QRS complex duration and morphology on left ventricular reverse remodeling and left ventricular function improvement after cardiac resynchronization therapy

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Ajmone Marsan N
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Bax JJ

Eur J Heart Fail 2017;19:1145-1151.

ABSTRACT

Background: To evaluate the impact of the interaction of QRS duration and morphology on left ventricular (LV) reverse remodeling and LV functional improvement in heart failure (HF) patients treated with cardiac resynchronization therapy (CRT).

Methods: From an ongoing registry of HF patients treated with CRT according to contemporary guidelines, demographic, clinical, electrocardiographic (ECG) and echocardiographic characteristics were analyzed. Patients were divided according to QRS duration and morphology: <150 ms vs. ≥150 ms and left bundle branch block (LBBB) vs. non-LBBB, respectively. Echocardiographic measurements were performed at baseline and at 6 months of follow-up. The effect of the interaction between QRS duration and morphology on LV reverse remodeling and LV ejection fraction (LVEF) was analyzed using linear, mixed models.

Results: Of 1 467 patients (mean age 65±10 years, 77% male), 884 (60%) had a QRS ≥150 ms and 814 (55%) showed LBBB. The group with QRS ≥150 ms demonstrated larger LV reverse remodeling (mean reduction in LV end-systolic volume 34.3 ml vs. 14.8 ml; P<0.001) and improvement in LVEF (mean increase 6.8% vs. 5.2%; P<0.001) compared with their counterparts. Similarly, patients with an LBBB evidenced greater LV reverse remodeling (mean reduction in LV end-systolic volume 30.75 ml vs. 17.4 ml; P<0.001) and improvement in LVEF (mean increase 6.9% vs. 3.7%; P<0.001) than those with non-LBBB QRS morphology.

Conclusions: LV reverse remodeling and LV functional improvement are greater among HF patients with LBBB morphology and increasing QRS duration who receive CRT.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established treatment for heart failure (HF) patients who remain symptomatic despite optimal medical therapy (New York Heart Association (NYHA) functional class II-III and ambulatory IV), with a wide QRS complex (≥120 ms) and reduced left ventricular ejection fraction (LVEF ≤35%).[1] The benefits of CRT may differ, based on QRS complex duration and morphology. Recent registries, meta-analyses and sub-studies of randomized controlled trials have shown that patients with left bundle branch block (LBBB) morphology and QRS duration ≥150 ms appear to benefit most from CRT in terms of improvement of clinical symptoms and survival,[2-4] whereas in patients with non-LBBB morphology the benefit may be less, particularly when the QRS duration is <130 ms.[5] However, little is known about the influence of QRS duration and morphology on the extent of LV reverse remodeling and improvement in LVEF. Accordingly, the present study evaluated the relation between baseline QRS duration and morphology, and LV reverse remodeling and LV systolic function improvement after CRT in a large population of HF patients (including NYHA class I-IV).

METHODS

Patient population

This retrospective, single-centre study included symptomatic HF patients who, despite receiving maximum-tolerated doses of optimal medical therapy, subsequently underwent CRT implantation according to contemporary guidelines.[1] Demographic, clinical, electrocardiographic (ECG) and echocardiographic characteristics were analyzed. QRS duration and morphology were dichotomized into groups <150 ms vs. ≥150 ms and LBBB vs. non-LBBB, respectively. Echocardiographic measurements were performed at baseline (before CRT implantation) and at 6 months' follow-up, according to current guidelines on LV chamber quantification.[6] Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and LVEF were compared at baseline and 6 months' follow-up between patients with and without LBBB, as well as between patients with QRS duration ≥150 ms and <150 ms. The Dutch Central Committee on Human-related Research (CCMO) allows the use of anonymous data without prior approval of an institutional review board provided that the data are acquired for routine patient care. All data used for this study were acquired for clinical purposes and handled anonymously.

Analysis of QRS morphology and duration

QRS duration was determined by automated, digital algorithms from a 12-lead, surface ECG. Calibration of the ECG was set at 0.1 mV/mm and the paper speed was 25 mm/s. Previously

defined criteria were employed to define an LBBB, with the intrinsic complex being evaluated in the case of pre-existing pacing.[7]

Echocardiographic data acquisition and analysis

Prior to CRT implantation and at 6 months' follow-up, transthoracic echocardiography was performed in all patients in the left lateral decubitus position using a commercially available echocardiographic system (E9 or VIVID 7, General Electric Vingmed Ultrasound, Milwaukee, USA). Images were obtained using 3.5 MHz or M5S transducers, while adjusting depth and gain settings. M-mode, 2-dimensional and Doppler data, triggered to the ECG, were acquired and digitally stored for off-line analysis (EchoPac 113, General Electric Vingmed Ultrasound, Milwaukee, USA). LVESV, LVEDV and LVEF were measured from the apical 2- and 4-chamber views, using the modified Simpson's biplane method.

Implantation of CRT

The right atrial and ventricular leads were positioned conventionally through a subclavian or cephalic vein. For implantation of the LV lead, a coronary sinus venogram was obtained using a balloon catheter and the LV pacing lead was inserted in the coronary sinus with the help of an 8 Fr guiding catheter and positioned, preferably, in a (postero-) lateral vein. All leads were connected to a dual-chamber biventricular CRT device. The majority of the patients (94%) received a CRT device with defibrillator function (ICD) and 6% received a CRT device without defibrillator capability. Evaluation of the device function was combined with the regular controls at the HF outpatient clinic. The atrioventricular and inter-ventricular delays were set empirically at 120-140 ms and 0 ms, respectively, and CRT optimization was performed at follow-up at the discretion of the treating physician.

Statistical analysis

Continuous variables are presented as mean and standard deviation when normally distributed. Dichotomous data are presented as numbers and percentages. Student t-tests were used to compare continuous variables, and χ^2 tests were used to compare dichotomous data. Changes in LVESV, LVEDV and LVEF at 6 months' follow-up were compared within and between groups using linear, mixed models corrected for gender and HF etiology. All analyses were performed with SPSS for Windows, version 23.0 (SPSS, Armonk, NY, USA). All statistical tests were two-sided. A P-value <0.05 was considered statistically significant.

RESULTS

A total of 1 467 patients (mean age 65±10 years, 77% male) were included in the analysis (Table 1). Ischemic cardiomyopathy was diagnosed in 59% of patients. LBBB was present in

55% of patients and the mean QRS duration was 156±33 ms, with 60% of patients having a QRS duration ≥150 ms. Compared to patients with LBBB QRS morphology, patients with non-LBBB QRS morphology were more frequently male, had more frequently ischemic cardiomyopathy and atrial fibrillation and showed significantly better LVEF and smaller LV volumes. Compared to patients with QRS duration ≥150 ms, patients with QRS duration <150 ms were significantly younger, had more frequently ischemic cardiomyopathy, less frequently chronic kidney disease, showed significantly better LVEF and smaller LV volumes and were more frequently treated with beta-blockers.

Influence of QRS duration and morphology on LV reverse remodeling and LVEF improvement

The mean changes in LV volumes and LVEF, according to QRS morphology and duration, are summarized in Table 2. Patients with LBBB configuration exhibited greater LV reverse remodeling, greater decrease of LVEDV and improvement in LVEF than patients with non-LBBB QRS morphology. Similarly, patients with QRS duration ≥150 ms demonstrated greater LV reverse remodeling, greater reduction of LVEDV and improvement in LVEF compared to those with QRS duration <150 ms.

Figure 1 illustrates the influence of QRS duration on the reduction of LVEDV after CRT in patients with LBBB vs. patients with non-LBBB. Regardless of the QRS morphology, the reduction in LVEDV was more pronounced with increasing width of the QRS, particularly with QRS duration ≥150 ms (inflection point). Beyond a QRS duration >190 ms, further decrease in LVEDV was not

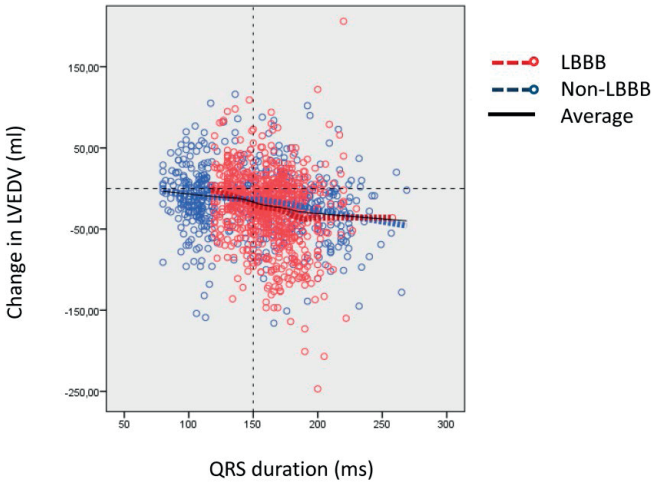

Figure 1: Influence of QRS duration as a continuous variable on left ventricular end-diastolic volume (LVEDV) reduction after CRT. Red circles represent patients with left bundle branch block (LBBB) morphology and blue circles patients with non-LBBB morphology. The dotted lines represent the interpolation curve for each group (red = LBBB and blue = non-LBBB) and the solid line the overall population (black).

observed for patients with LBBB morphology, whereas patients with a non-LBBB QRS configuration showed progressive LVEDV reduction. Figure 2 illustrates the influence of QRS duration as a continuous variable (dichotomized into patients with LBBB and non-LBBB configuration) on changes in LVESV: progressive reduction in LVESV was observed with increasing duration of the QRS, particularly ≥140 ms for both LBBB and non-LBBB patients. Figure 3 illustrates the influence of QRS duration as a continuous variable (dichotomized into patients with LBBB vs. non-LBBB) on changes in LVEF. LVEF increased particularly in patients with QRS duration ≥150 ms and LBBB morphology and appeared to reach a plateau beyond 170 ms. LVEF improvement in patients with non-LBBB morphology was similar across the various QRS durations.

Table 1: Baseline characteristics.

	LBBB (n=814)	Non-LBBB (n=653)	P-value	QRS ≥150 ms (n=884)	QRS <150 ms (n=583)	P-value
Age (years)	65.7±10.2	65.1±11.1	0.3	66.5±10.4	63.9±10.8	<0.001
Male gender, n (%)	598 (73.5)	528 (80.9)	0.001	668 (75.6)	458 (78.6)	0.206
Ischemic etiology, n (%)	439 (53.9)	427 (65.4)	<0.001	466 (52.7)	400 (68.6)	<0.001
Heart rhythm, n (%)						
- Sinus rhythm	693 (85.1)	362 (55.4)	<0.001	591 (66.9)	464 (79.6)	<0.001
- Atrial fibrillation	118 (14.5)	148 (22.7)	<0.001	158 (17.9)	108 (18.5)	0.804
- Paced	3 (<0.1)	143 (21.9)	<0.001	135 (15.3)	11 (<0.1)	<0.001
NYHA functional class, n (%)						
- I	28 (3.4)	34 (5.2)	0.114	29 (3.3)	33 (5.7)	0.033
- II	195 (24.0)	168 (25.7)	0.409	210 (23.8)	153 (26.2)	0.252
- III	519 (63.8)	379 (58.0)	0.045	557 (63.0)	341 (58.5)	0.148
- IV	57 (7.0)	52 (8.0)	0.517	70 (7.9)	39 (6.7)	0.473
6 MWT (m)	326.2±122.5	319±121.5	0.305	321.0±124.0	326.0±119.1	0.504
QoL score	32.6±19.0	33.6±19.7	0.385	33.0±18.4	33.0±20.1	0.952
Diabetes, n (%)	170 (20.9)	146 (22.4)	0.54	176 (19.9)	140 (24.0)	0.071
eGFR <60 ml/min/1.73 m^2, n (%)	326 (40.0)	262 (40.1)	0.956	381 (43.1)	207 (35.5)	0.006
LVEF (%)	25.7±7.9	28.3±8.3	<0.001	26.2±8.3	27.9±7.9	<0.001
LVEDV (ml)	219.0±80.3	192.9±71.4	<0.001	220.0±81.3	188.4±67.2	<0.001
LVESV (ml)	165.5±71.2	140.7±60.8	<0.001	165.7±72.8	137.6±55.7	<0.001
Medication, n (%)						
- Diuretic	663 (81.4)	526 (80.6)	0.71	722 (81.7)	467 (80.1)	0.494
- Digoxin	136 (16.7)	103 (15.8)	0.68	148 (16.7)	91 (15.6)	0.615
- β-blocker	606 (74.4)	462 (70.8)	0.13	621 (70.2)	447 (76.7)	0.008
- Mineralocorticoid antagonist	365 (44.8)	292 (44.7)	1.0	380 (43.0)	277 (47.5)	0.098
- ACE-inhibitor	722 (88.7)	563 (86.2)	0.18	781 (88.3)	504 (86.4)	0.318

Values are mean ± standard deviation. ACE: angiotensin-converting enzyme, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, 6 MWT: 6-minute walk test, NYHA: New York Heart Association, QoL: quality of life.

Table 2: Changes in LV volumes and ejection fraction, according to QRS morphology and duration.

	LBBB (n=814)		Non-LBBB (n=653)		P-value	QRS ≥150 ms (n=884)		QRS <150 ms (n=583)		P-value
	Mean change	95% CI	Mean change	95% CI		Mean change	95% CI	Mean change	95% CI	
LVEDV (ml)	-25.2	-28.6, -21.8	-14.5	-20.3, -8.8	0.005	-29.8	-33.5, -26.0	-8.9	-13.3, -4.6	0.003
LVESV (ml)	-30.75	-33.8, -27.7	-17.4	-22.3, -12.4	<0.001	-34.3	-37.7, -30.9	-14.8	-18,7, -11.0	<0.001
LVEF (%)	+6.9	6.3, 7.50	+3.7	2.6, 4.9	<0.001	+6.8	6.1, 7.4	+5.2	4.1, 6.1	<0.001

LBBB: left bundle branch block, CI: confidence interval, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVEF: left ventricular ejection fraction. P-values based on linear, mixed model analysis.

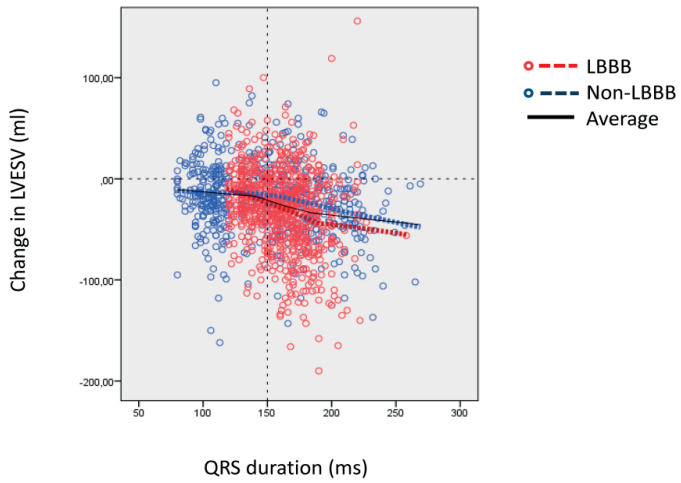

Figure 2: Influence of QRS duration as a continuous variable on left ventricular end-systolic volume (LVESV) reduction after CRT. Red circles represent patients with left bundle branch block (LBBB) morphology and blue circles patients with non-LBBB morphology. The dotted lines represent the interpolation curve for each group (red = LBBB and blue = non-LBBB) and the solid line the overall population (black).

DISCUSSION

The main findings of the present study are the greater benefit of CRT (in terms of LV reverse remodeling (defined as reduction in LVESV) and improvement in LVEF) in HF patients with LBBB and a QRS duration ≥150 ms, compared to patients with non-LBBB QRS morphology or shorter QRS duration.

Influence of QRS morphology and duration on CRT efficacy

Several studies have demonstrated the influence of QRS morphology and duration on the outcome of HF patients treated with CRT.[8-11] In a large, retrospective cohort study, including

24 169 patients treated with CRT, Peterson et al. showed that patients with LBBB morphology and a QRS duration ≥150 ms presented lower rates of all-cause mortality (20.9% at 3 years) compared to patients with LBBB and QRS <150 ms (26.5% at 3 years) or with non-LBBB morphology (30.7% for QRS ≥150 ms and 32.3% for QRS <150 ms).[4] These findings were also observed in a meta-analysis of 5 randomized trials including 5 813 CRT patients: QRS duration ≥150 ms was significantly associated with a reduction of the risk of the composite clinical endpoint (risk ratio 0.60; 95% confidence interval (CI) 0.53-0.67; P<0.001) whereas a QRS duration between 120 and 149 ms was not (risk ratio 0.95; 95% CI 0.82-1.10; P=0.49).[12]

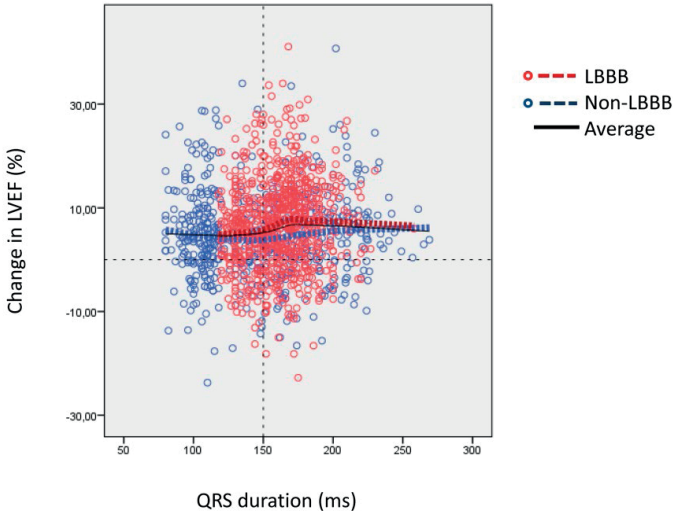

Figure 3: Influence of QRS duration as a continuous variable on left ventricular ejection fraction (LVEF) change after CRT. Red circles represent patients with left bundle branch block (LBBB) morphology and blue circles patients with non-LBBB morphology. The dotted lines represent the interpolation curve for each group (red = LBBB and blue = non-LBBB) and the solid line the overall population (black).

In the Resynchronization/defibrillation in Ambulatory Heart Failure Trial (RAFT), all-cause mortality and hospitalization for HF were reduced in patients with LBBB morphology, but not in those with non-LBBB morphology.[2] In a meta-analysis of 4 randomized controlled trials reported by Sipahi et al. (including 5 356 patients), composite clinical events (all-cause mortality and HF hospitalization) were reduced in patients with LBBB (relative risk (RR)=0.64, 95% CI 0.52-0.77, P=0.00001), but not in patients with a non-LBBB morphology (RR=0.97, 95% CI 0.82-1.15, P=0.75).[13]

Importantly, the prognosis of patients with CRT is also influenced by the response to CRT at mid-term follow-up, defined as LV reverse remodeling.[14-16] In a study including 679 patients treated with CRT, LV reverse remodeling (reduction of ≥15% in LVESV) at 6 months of follow-up was associated with better prognosis independently of improvement in clinical status.[14] How QRS duration and morphology affect the extent of LV reverse remodeling and the degree of

improvement in LV systolic function after CRT has not been extensively studied, especially in patients with more advanced stages of HF (NYHA class III and IV).

QRS morphology and duration vs. LV reverse remodeling and improvement in LVEF after CRT

The effects of CRT on LV volumes and LVEF according to the QRS duration and morphology have been studied in few randomized trials, including only patients with HF NYHA class I and II symptoms.[10,17] In the Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy (MADIT-CRT) trial, randomizing 1 820 patients (70% with LBBB morphology) with mild HF (NYHA class I and II) to CRT-D vs. ICD alone, patients with LBBB morphology had a greater decrease in LVEDV compared to those with non-LBBB (56.7±34.1 ml vs. 41.0±28.13 ml, respectively; P<0.001).[10] Patients with LBBB also experienced a greater decrease in LVESV than patients with non-LBBB (62.1±31.5 ml vs. 45.7±28.13 ml, respectively; P<0.001).[10] Lastly, LVEF improved by 11.9±5.1% in the LBBB group, vs. 8.8±4.9% in the non-LBBB group (P<0.001).[10] Similarly, in the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial, 610 patients with mild HF (NYHA class I and II; 60% with LBBB morphology) randomized to CRT-ON vs. CRT-OFF, patients with LBBB experienced a 25.3 ml/m^2 mean reduction in LVESV index (P<0.0001), whereas non-LBBB patients had smaller reductions in LVESV (6.7 ml/m^2; P=0.18).[17] Moreover, baseline QRS duration was also a strong predictor of the change in LVESV index in the REVERSE trial. When patients were divided into quartiles according to baseline QRS duration, a progressively greater decrease in LVESV index was observed at 12 months of follow-up for longer QRS durations.[17]

Our results are consistent with the MADIT-CRT and REVERSE trials,[10,17] with LBBB and increasing QRS duration (especially ≥150 ms) constituting the group of HF patients who benefit most from CRT in terms of LV reverse remodeling and LVEF improvement. In addition, similar to the REVERSE sub-study, the differences in LV reverse remodeling and improvement in LVEF remained significant after correcting for known confounders such as ischemic HF.[17] More importantly, the present study expands the results of these randomized controlled trials by including a large number of patients with severe HF (NYHA class III and IV). This is highly relevant, since the majority of patients in previous randomized controlled trials and large registries had NYHA class III HF symptoms.[4,18-20] However, the association between QRS morphology and duration and changes in LV volumes and LVEF after CRT in that group of patients has not been previously described. In addition, although the efficacy of CRT in NYHA functional class IV has been debated, our results show that this group of patients may also show significant reduction in LV volumes and improvement in LVEF, thus supporting CRT implantation in this group of patients as indicated in current guidelines.[1,21-23] Current guidelines for the diagnosis and management of HF patients recommend CRT for HF patients with LBBB morphology and QRS duration ≥150 ms (class IA) or 130-149 ms (class IB).[23] For HF patients with non-LBBB morphology the recommendation level is II (IIa for patients with QRS duration ≥150 ms and IIb for patients with QRS

duration between 130-149 ms). The present results also support these recommendations since, for the first time, they demonstrate that the greatest benefit from CRT (in terms of LV reverse remodeling and LVEF improvement) was observed in a large population of NYHA class I-IV HF patients with LBBB morphology and QRS duration ≥150 ms.

Study limitations

This study was limited by its design: a retrospective, single-centre study, but an advantage is that it reflects experience from a large, real-world, referral centre. In this population, the number of patients receiving beta-blockers was still fairly low, although it was higher compared to many landmark trials which established the utility of CRT.[18-20,24-27] This probably reflects that in daily practice, a significant percentage of severe HF patients do not tolerate beta-blockers. It is also known that other factors, such as the extent of scar tissue in the LV and the LV lead position may influence the response to CRT. These factors were not systematically available in the current population.

CONCLUSIONS

LV reverse remodeling and functional improvement are greater among HF patients with LBBB QRS morphology and increasing QRS duration (especially ≥150 ms) who received CRT. These findings are supportive of contemporary guidelines for CRT placement.

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3

Left ventricular remodeling and change in left ventricular global longitudinal strain after cardiac resynchronization therapy: prognostic implications

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) has the ability to reduce left ventricular, end-systolic volume (LVESV). A decrease of ≥15% is commonly defined as a CRT response. CRT can also improve LV global longitudinal strain (GLS). Changes in LVESV and LV GLS are individually associated with outcome post-CRT. The objective of the current study was to investigate how often improvement in both LVESV and LV GLS coincides and if this response has a different prognostic implication than an improvement in either LVESV or LV GLS alone, and when compared to no improvement in either LVESV or LV GLS.

Methods: Baseline and 6-month echocardiograms were analyzed from CRT recipients with heart failure. LV reverse remodeling was defined as a ≥15% reduction in LVESV at 6 months post-CRT. A ≥5% absolute improvement in LV GLS was defined as a change in LV GLS.

Results: 1 185 patients were included (mean age 65±10 years, 73% male). Patients with an improvement in LVESV and LV GLS (n=131, 11.1%) had significantly lower all-cause mortality, compared to other groups. On multivariable analysis, an improvement in both LVESV and LV GLS (hazard ratio 0.47; 95% confidence interval 0.31-0.71; P<0.001) or an improvement in either LVESV or LV GLS (hazard ratio 0.57; 95% confidence interval 0.47-0.71; P<0.001) was independently associated with a better prognosis, compared to no improvement in either LVESV or LV GLS.

Conclusions: Changes in LVESV and LV GLS reflect different mechanisms of CRT response, which may not always be present in the same patient. Both improvement in LVESV and LV GLS occurred in 11.1% of patients. Either a reduction in LVESV and/or an improvement in LV GLS at 6 months post-CRT, is independently associated with improved long-term prognosis, compared to no change in both LVESV and LV GLS. These observations support the use of LV GLS as a meaningful parameter in defining CRT response, in addition to the more commonly used definition of a change in LVESV.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is indicated for heart failure (HF) patients who remain symptomatic despite receiving adequate medical therapy (New York Heart Association (NYHA) functional class II-III and ambulatory IV), together with a wide QRS complex (≥130 ms) and a left ventricular ejection fraction (LVEF) ≤35%.[1,2] In appropriately selected candidates, CRT alleviates symptoms, induces LV reverse remodeling, improves LV function and decreases mortality.[1]

The ability of CRT to cause LV reverse remodeling, i.e. to reduce the LV end-systolic volume (LVESV), has been extensively documented.[3-6] This is usually measured at 6 months post-implant. In addition, the degree of reduction in LVESV by CRT has been linked to long-term outcome.[7] Myocardial strain imaging quantifies active myocardial deformation, and global LV function is most commonly reported as global longitudinal strain (GLS). CRT can improve LV GLS, which also translates into an improved long-term outcome.[8,9] From a prognostic perspective, it would be important to know to what extent these early changes (a reduction in LVESV and an improvement in LV GLS) are predictive of long-term survival. Accordingly, we have evaluated the outcome of CRT recipients with early (6 months post-implant) improvement in both these parameters (LVESV and LV GLS), compared to the outcome of patients without early (6 months) improvement, as well as of CRT recipients with either improvement in LVESV or improvement in LV GLS, but not in both parameters.

METHODS

Study population

Clinical and echocardiographic data of HF patients who received CRT according to prevailing guideline recommendations were included from an ongoing, single-center registry.[1,10] For this analysis, only patients who underwent transthoracic echocardiography at baseline and at 6 months follow-up after CRT implantation were evaluated. Ischemic etiology of HF was defined by the presence of significant coronary artery disease. The NYHA functional class was assessed in all patients, and a clinical response to CRT was defined as a ≥1 NYHA class improvement at 6 months after CRT. The quality of life was evaluated with the Minnesota Living with Heart Failure Questionnaire,[11] and if feasible, a 6-minute walk test was performed.[12]

Echocardiographic data acquisition

Transthoracic echocardiograms were performed on all patients in the left lateral decubitus position with a commercially available echocardiographic system (VIVID 7 or E9, General Electric Healthcare, Horten, Norway). Data were acquired with 3.5 MHz or M5S transducers – adjusting the depth and gain settings when required. ECG-triggered, M-mode, 2-dimensional and Doppler data were collected and stored in digital format for off-line analysis (EchoPac 113, General Electric Healthcare, Horten, Norway). LVESV and LV end-diastolic volume (LVEDV) were mea-

sured on 2-dimensional 2- and 4-chamber apical views following Simpson's method and LVEF was then calculated.[13] LV GLS was measured from standard apical views (long-axis, 2-chamber and 4-chamber) using speckle tracking echocardiography.[14] The inter- and intra-observer agreement for LV GLS measurement in this population have previously been described.[15] The inter- and intra-observer variability of LVESV and LV GLS measurement were assessed calculating the intra-class correlation coefficient (ICC) for both measures on 25 randomly selected patients. The ICC for inter- and intra-observer variability of LVESV were 0.91 (95% CI: 0.76-0.96, P<0.001) and 0.98 (95% CI: 0.96-0.99, P<0.001), respectively. The bias and 95% limits of agreement for inter-observer variability of LVESV were -15.2 ml and -71.5 to 41.1 ml, respectively, whereas the bias and 95% limits of agreement for intra-observer variability of LVESV were 0.8 ml and -27.7 to 29.4 ml, respectively. The ICC for inter- and intra-observer variability of LV GLS were 0.92 (95% CI: 0.84-0.97, P<0.001) and 0.97 (95% CI: 0.89-0.99, P<0.001), respectively. The bias and 95% limits of agreement for inter-observer variability of LV GLS were 0.1% and -2.7 to 2.9%, compared to the bias and 95% limits of agreement for intra-observer variability of LV GLS, which were -0.5% and -2.1 to 1.1%.

CRT implantation

Placement of the right atrial and ventricular leads was performed via a standard approach (subclavian or cephalic vein). A coronary sinus venogram was acquired prior to LV lead implantation. An 8 Fr guiding catheter was subsequently used for insertion of the LV pacing lead into the coronary sinus, and for positioning in a (preferred) posterior/posterolateral vein. A connection was established between all leads and a dual-chamber, biventricular CRT device. In most patients (94%), a CRT device with defibrillator function was implanted, while 6% received a CRT device without defibrillator functionality. Patients were followed up with regular intervals at the HF outpatient clinic, at which time device function was checked. The atrioventricular and inter-ventricular delays were empirically set at 120-140 ms and 0 ms, respectively. Optimization of CRT devices was performed during follow-up, and at the discretion of the treating physician.

Definitions of early (6 months) CRT response

The definition of an echocardiographic response to CRT was based on the occurrence of LV reverse remodeling and improvement in LV GLS at 6 months of follow-up. LV reverse remodeling was defined as a reduction of ≥15% in the LVESV.[16] The cut-off value of clinically meaningful LV GLS improvement after CRT has not been previously established. An absolute improvement of 5% in LV GLS was chosen as a threshold representing a substantial GLS response (Figure 1).

Statistical analysis

Means and standard deviations were used to present continuous data, while numbers and percentages were used to present categorical data. Continuous variables were compared with one-way analysis of variance (ANOVA), while χ^2 and Fisher's exact tests with post-hoc analysis of

subgroups were employed for comparison of categorical data (as appropriate). Survival analysis was conducted with the Kaplan-Meier method, and the effect of different variables on event-free survival was examined with a Cox proportional hazards model. In order to evaluate the incremental value of LV GLS over a reduction in LVESV for outcome, we performed likelihood ratio testing. All analyses were performed with SPSS for Windows, version 23.0 (SPSS, Armonk, NY, USA). All statistical tests were two-sided, and a P-value <0.05 was considered statistically significant.

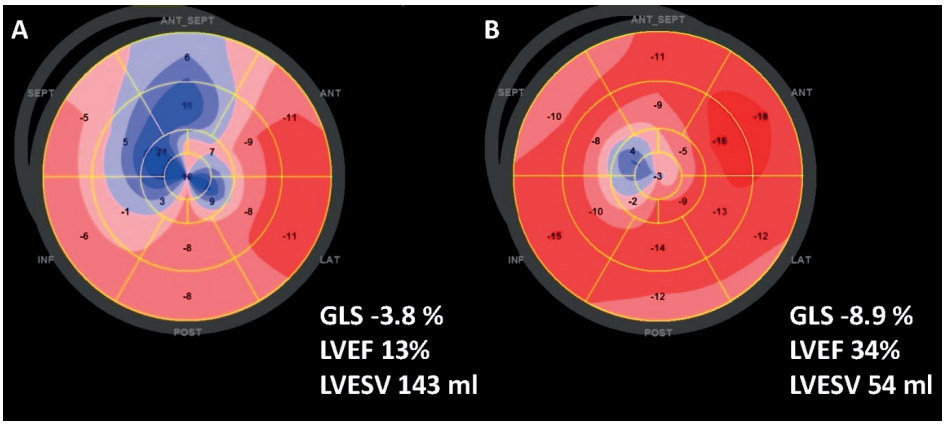


Figure 1: Parametric maps of left ventricular (LV) global longitudinal strain (GLS) for a cardiac resynchronization therapy (CRT) recipient with a substantial improvement in LV GLS. A) LV GLS parametric map before implantation of CRT, and B) the same patient after 6 months of CRT. LV segments coded in shades of blue denote elongation during systole, vs. LV segments coded in red, which indicate systolic shortening. LVEF: LV ejection fraction, LVESV: LV end-systolic volume.

RESULTS

Baseline patient characteristics

A total of 1 185 patients (mean age 65±10 years, 73% male) with available echocardiographic data at baseline and 6 months' follow-up were included (Table 1). Ischemic etiology was present in 56% of patients. The mean LVEF of the overall population was 27±8%.

Changes in LVESV and LV GLS

The mean reduction in LVESV after 6 months of CRT was 15.4±24.3 ml for the overall population (Figure 2), while LV reverse remodeling was observed in 674 patients (56.9%). The mean (absolute) change in LV GLS for the overall population after 6 months of CRT was 1.0±3.5% (Figure 2). A ≥5% absolute improvement in LV GLS was observed in 148 (12.5%) patients. Improvement in both LVESV and LV GLS was noted in 131 (11.1%) of CRT recipients, compared to 469 (39.6%) who did not improve either their LVESV or GLS. In 585 (49.4%) patients, an improvement was seen in either LVESV or GLS, but not in both.

Characteristics of patients according to CRT response pattern

Table 1 compares the baseline characteristics of patients, divided according to the CRT response pattern. Those who improved both their LVESV and LV GLS, demonstrated a longer baseline QRS duration, compared to patients who either did not improve their LVESV or LV GLS, or who showed improvement in only LVESV or LV GLS. CRT recipients with neither an improvement in LVESV nor in LV GLS, were more frequently male and more commonly had an ischemic etiology of HF. In addition, patients not manifesting a decrease in LVESV or an improvement in LV GLS, had more renal dysfunction than those with an improvement in both LVESV and LV GLS.

Table 1: Baseline characteristics.

	≥15% ↓LVESV and ≥5% ↓GLS (n=131)	≥15% ↓LVESV or ≥5% ↓GLS (n=585)	<15% ↓LVESV and <5% ↓GLS (n=469)	Overall population (n = 1 185)
Age (years)	66.6±10.2	65.7±10.2	64.2±10.5	65.2±10.3
Male gender, n (%)	79 (60.3)	419 (71.6)†	363 (77.4)*	861 (72.7)
Ischemic etiology, n (%)	50 (38.2)	317 (54.2)*	298 (63.5)*	665 (56.1)
LBBB, n (%)	58 (44.3)	284 (48.5)	225 (48.0)	567 (47.8)
QRS duration at baseline (ms)	168.4±30.6	155.8±35.5*†	149.7±33.8*	154.6±34.8
Heart rhythm, n (%)				
- Sinus rhythm	83 (63.4)	449 (76.8)*	353 (75.3)	885 (74.7)
- Paced	22 (16.8)	57 (9.7)	42 (9.0)*	121 (10.2)
- Atrial fibrillation	26 (19.8)	79 (13.5)*	74 (15.8)	179 (15.1)
NYHA class, n (%)				
- I	6 (4.6)	31 (5.3)	16 (3.4)	53 (4.5)
- II	33 (25.2)	154 (26.3)†	112 (23.9)	299 (25.2)
- III/IV	92 (70.2)	400 (68.4)	341 (72.7)	833 (70.3)
6 MWT (m)	354.7±110.6	332.8±120.2	327.5±122.1	332.8±120.2
QoL score	31.5±17.4	30.2±18.4†	34.6±20.2	32.1±19.1
Diabetes mellitus, n (%)	13 (10.0)	106 (18.1)	113 (24.1)	232 (19.6)
eGFR <60 ml/min/1.73 m^2, n (%)	33 (25.2)	225 (38.5)	184 (39.2)*	442 (37.3)
LVEF (%)	26.6±7.7	27.3±7.9	27.7±8.2	27.4±8.0
LVEDV (ml)	201.3±67.7	205.1±75.6	203.0±78.3	204.0±76.0
LVESV (ml)	149.7±58.6	151.7±65.9	149.4±67.2	150.7±65.7
LV GLS (%)	-6.0±2.9	-7.7±3.5*†	-7.2±3.3*	-7.3±3.4
Medication, n (%)				
- Diuretic	76 (58.0)	440 (75.2)	375 (80.0)*	891 (75.2)
- Digoxin	9 (6.9)	88 (15.0)*	71 (15.1)*	168 (14.2)
- β-blocker	77 (58.8)	423 (72.3)	333 (71.0)	833 (70.3)
- Mineralocorticoid antagonist	50 (38.2)	238 (40.7)	205 (43.7)	493 (41.6)
- ACE-inhibitor	94 (71.8)	500 (85.5)	400 (85.3)	994 (83.9)

Continuous variables are mean ± standard deviation. ACE: angiotensin-converting enzyme, eGFR: estimated glomerular filtration rate, GLS: global longitudinal strain, LBBB: left bundle branch block, LV: left ventricular, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, 6 MWT: 6-minute walk test, NYHA: New York Heart Association, QoL: quality of life. *P<0.05 vs. ≥15% ↓LVESV and ≥5% ↑GLS; †P<0.05 vs. <15% ↓LVESV and <5% ↑GLS.

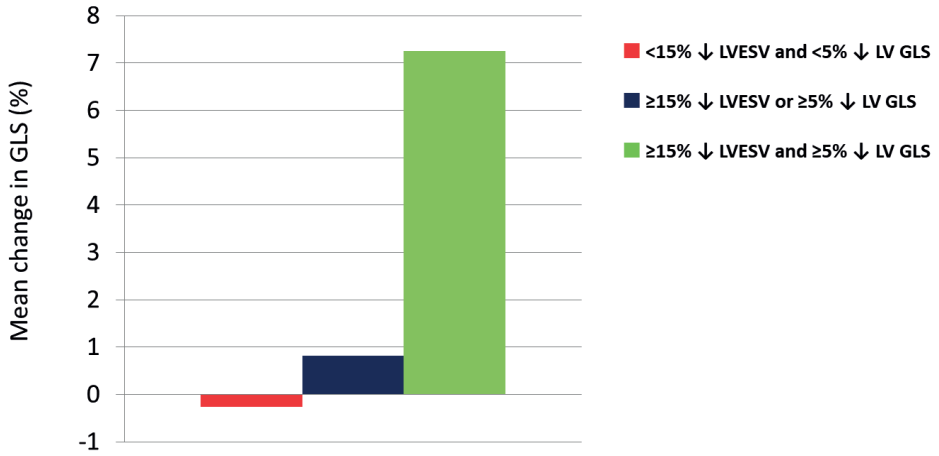


Figure 2A: Absolute changes in mean, left ventricular global longitudinal strain (GLS) from baseline to 6 months after cardiac resynchronization therapy (CRT), according to different categories of CRT response. LV: left ventricular, LVESV: left ventricular end-systolic volume.

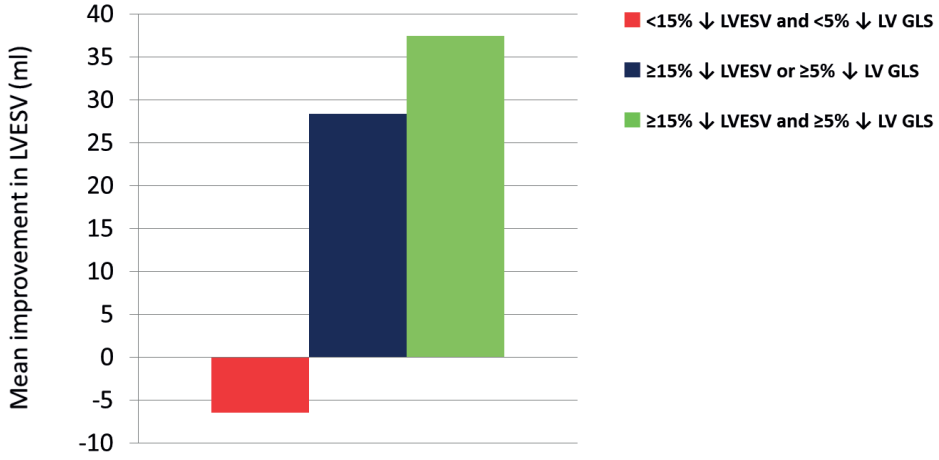
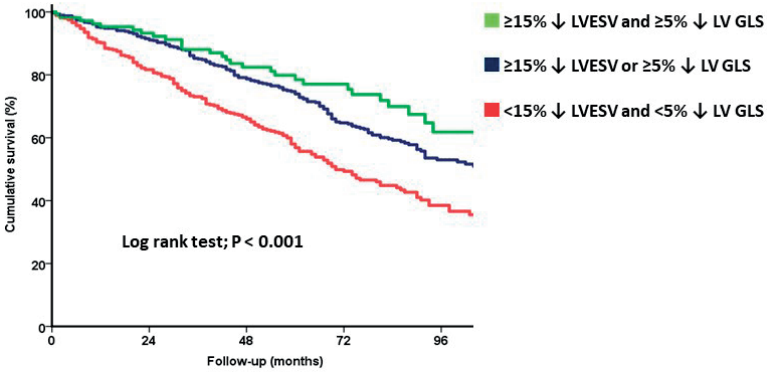


Figure 2B: Mean improvement in left ventricular end-systolic volume (LVESV) from baseline to 6 months after cardiac resynchronization therapy (CRT), according to different categories of CRT response. LV: left ventricular, GLS: global longitudinal strain.

Changes in LV GLS and LVESV before and after CRT implantation, according to different groups of CRT response, are summarized in Figure 2. A greater improvement of LV GLS was observed in those patients who improved in both LVESV and LV GLS, than in patients who improved only in terms of LVESV or LV GLS, or neither (P<0.001). The LVESV decreased more significantly in CRT recipients with LVESV and LV GLS improvement than in those recipients with an improvement in only LVESV or LV GLS, while LVESV increased in recipients without an improvement in either LVESV or LV GLS (P<0.001).

CRT response pattern and survival

After a median follow-up of 53 months (interquartile range 25-80 months), 323 (27%) patients died. CRT recipients in whom a reduction in LVESV was seen together with an improvement in LV GLS, had significantly better survival compared to those who improved either in LVESV or LV GLS, or did not improve in LVESV and LV GLS (log-rank test, P<0.001; Figure 3). In patients with an improved LVESV and LV GLS, the cumulative survival rates at 24, 48, 72 and 96 months of follow-up were 92, 82, 75 and 62%, respectively. The group that demonstrated an improvement in either LVESV or LV GLS but not both, showed slightly worse cumulative survival (91, 79, 64 and 53%, at 24, 48, 72 and 96 months of follow-up, respectively). In contrast, patients without improvement in LVESV or LV GLS had lower cumulative survival rates (81, 66, 49 and 37%, at 24, 48, 72 and 96 months of follow-up, respectively).



Number of patients at risk

≥15% ↓ LVESV and ≥5% ↓ LV GLS	131	91	68	46	12
≥15% ↓ LVESV or ≥5% ↓ LV GLS	585	457	332	198	85
<15% ↓ LVESV and <5% ↓ LV GLS	469	317	210	91	42

Figure 3: Kaplan-Meier survival curves for time to cumulative survival, according to different categories of cardiac resynchronization therapy (CRT) response. LV: left ventricular, LVESV: left ventricular end-systolic volume, GLS: global, longitudinal strain.

A Cox proportional hazards model was used to investigate the association between response to CRT at 6 months' follow-up and all-cause mortality, including as covariates, factors known to impact on mortality in HF (Table 2). On multivariable analysis, both a CRT response encompassing an improvement in LVESV and LV GLS (hazard ratio 0.47; 95% confidence interval (CI) 0.31-0.71; P<0.001) and a response characterized by an improvement in either LVESV or LV GLS (hazard ratio 0.57; 95% CI 0.47-0.71; P<0.001) were independently associated with better survival compared to patients without improvement in LVESV or LV GLS.

Table 2: Predictors of all-cause mortality risk, uni- and multivariate Cox proportional hazards models.

	Univariable analysis			Multivariable analysis		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Age at implantation (years)	1.04	1.03-1.05	<0.001	1.03	1.02-1.04	<0.001
Male gender	1.48	1.16-1.89	0.001	1.39	1.07-1.82	0.015
Body mass index (kg/m^2)	0.97	0.95-0.99	0.008	0.96	0.94-0.99	0.006
Diabetes mellitus	1.65	1.33-2.05	<0.001	1.37	1.08-1.74	0.010
Ischemic etiology of heart failure	1.55	1.27-1.89	<0.001	1.29	1.03-1.63	0.029
Diuretic use	1.75	1.33-2.31	<0.001	1.38	1.02-1.86	0.037
Hemoglobin (g/dL)	0.81	0.73-0.89	<0.001	0.92	0.82-1.02	0.114
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)	2.55	2.11-3.08	<0.001	1.91	1.55-2.37	<0.001
Clinical response	0.84	0.69-1.01	0.068	0.86	0.70-1.05	0.132
QRS duration pre-implantation (ms)	1.00	1.00-1.01	0.108	1.00	1.00-1.01	0.165
Atrial fibrillation	1.75	1.38-2.22	<0.001	1.43	1.10-1.85	0.007
CRT response category						
<15% ↓LVESV and <5% ↓LV GLS	-	-	-	-	-	-
≥15% ↓LVESV or ≥5% ↓LV GLS	0.60	0.49-0.73	<0.001	0.57	0.47-0.71	<0.001
≥15% ↓LVESV and ≥5% ↓LV GLS	0.43	0.29-0.64	<0.001	0.47	0.31-0.71	<0.001

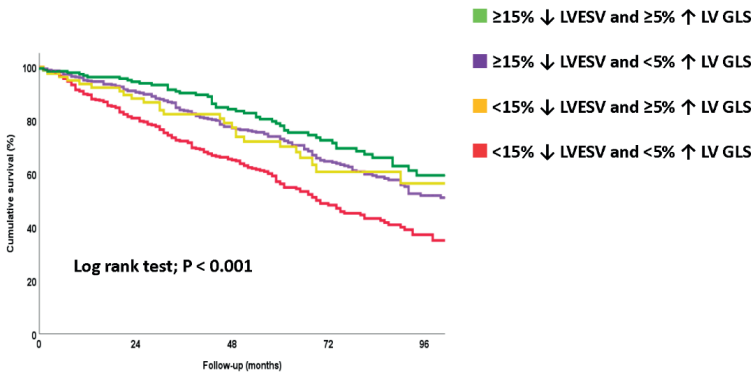
CI: confidence interval, CRT: cardiac resynchronization therapy, eGFR: estimated glomerular filtration rate, GLS: global longitudinal strain, HR: hazard ratio, LV: left ventricular, LVESV: left ventricular end-systolic volume.

In order to further stratify those responders who showed an improvement in either LVESV or LV GLS but not both, and to investigate the association with outcome, this group of patients was divided into two subcategories, i.e. those with a decrease in LVESV, and another with an improvement in LV GLS. Patients with an improved LV GLS but without a decrease in LVESV, demonstrated similar event rates to those with a reduced LVESV but no change in LV GLS (log-rank test P<0.001; Figure 4). An identical, multivariable model was constructed, and analyzed according to four patterns of CRT response, i.e. i) improvement in LVESV and LV GLS, ii) improvement in LVESV, iii) improvement in LV GLS, iv) neither improvement in LVESV nor improvement in LV GLS. The hazard ratios of patients with improved LV GLS but without a decrease in LVESV (hazard ratio 0.58; 95% CI 0.33-0.99; P=0.05) and those with a reduced LVESV but no improvement in LV GLS (hazard ratio 0.57; 95% CI 0.46-0.71; P<0.001) were similar, while the first group demonstrated a trend towards better survival, and the second group retained an independent association with outcome.

Incremental value of LV GLS

In order to evaluate the incremental value of an improvement in GLS over a reduction in LVESV for mortality, likelihood ratio testing was performed. The baseline model (model 1) comprised all risk factors which were included in the multivariable regression model, i.e.: age at implantation, male gender, body mass index, diabetes mellitus, ischemic etiology of heart failure, diuretic use, hemoglobin, renal dysfunction, clinical response, QRS duration pre-implantation and atrial fibrillation. Addition of a ≥15% decrease in LVESV to model 1, provided incremental

value (P<0.001; Figure 5). A third model, which included an improvement in GLS of ≥5%, was of further incremental value (P=0.039; Figure 5).



Number of patients at risk

≥15% ↓ LVESV and ≥5% ↑LV GLS	131	91	68	46	12
≥15% ↓ LVESV and <5% ↑LV GLS	536	425	309	188	79
<15% ↓ LVESV and ≥5% ↑LV GLS	49	32	23	10	6
<15% ↓ LVESV and <5% ↑LV GLS	469	317	210	91	42

Figure 4: Kaplan-Meier survival curves for time to cumulative survival. Survival is categorized according to four different cardiac resynchronization therapy (CRT) responses. LV: left ventricular, LVESV: left ventricular, end-systolic volume, GLS: global, longitudinal strain.

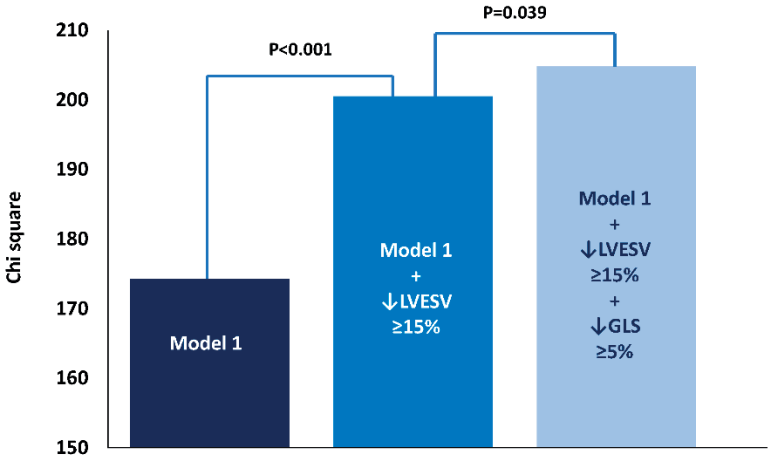


Figure 5: Likelihood ratio test. Bars represent the incremental value of a ≥15% decrease in left ventricular end-systolic volume (LVESV) and an improvement in LV global longitudinal strain (GLS) in addition to clinical risk factors (Model 1).

DISCUSSION

Improvement in both LVESV and LV GLS was noted in 11.1% of CRT recipients. Furthermore, it was demonstrated that CRT responses defined by i) improvement in both LVESV (reduction of ≥15%) and LV GLS (≥5% absolute improvement), or ii) improvement in either LVESV or LV GLS at 6 months after implantation, are independently associated with a better prognosis, compared to the absence of both an improvement in LVESV and LV GLS. Additionally, we showed that the groups of CRT recipients with either a decrease in LVESV or an increase in LV GLS, had a similar prognosis.

Decrease of LVESV after CRT

The response to CRT has been defined by a spectrum of both clinical (change in NYHA, change in 6-minute walking distance, change in quality of life (QoL) score) and echocardiographic (change in LVESV, change in LVEDV, change in LVEF and change in LV GLS) parameters.[7,8,17-19] The most frequently used definition of CRT response is a ≥15% reduction in LVESV at 6 months' follow-up, due to evidence supporting its prognostic implications.[7,17] The reduction which CRT causes in LVESV, has been documented in a number of landmark trials.[3-5] In the Multicenter InSync ICD Randomized Clinical Evaluation II (MIRACLE-ICD II) trial, the LVESV decreased by 14±57 ml in the control group, compared to 42±77 ml in the CRT group (P=0.01).[5] In the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study, indexed LVESV declined by 25.3±28.5 ml/m^2 in patients receiving CRT with a LBBB, compared to 1.7±25.8 ml/m^2 in a control group (P<0.0001).[3]

The degree of LV response at 6 months after CRT is also predictive of long-term outcome (log-rank test, P<0.001).[7] Since survival is a very robust measure of outcome, a reduction in the LVESV ≥15% has become the most accepted definition of CRT response. This definition, however, has certain limitations: change in LVESV reflects only the change in LV volume following CRT, and does not take into account whether it has improved exclusively by increasing the effective forward stroke volume. In addition, a CRT response defined only by a reduction in LVESV, does not reflect active deformation of the myocardium. Speckle tracking strain echocardiography can overcome this limitation by imaging active myocardial deformation. Global LV deformation, measured by speckle tracking strain echocardiography, is most commonly reported as LV GLS.[20]

Improvement of LV GLS after CRT

In 141 CRT recipients significant improvement in LV GLS (from -7.8±2.8% to -8.5±3.5%; P=0.01) was noted in responders (defined as a ≥15% reduction in LVESV) but not in non-responders.[9] Pouleur et al.[8] reported an improvement in LV GLS after CRT, which was associated with an improved outcome (24% reduction in death or HF for every 1% recovery in LV GLS) over the first 12 months of CRT. The mean change in LV GLS was 1.4±3.1% in this population.[8]

CRT response: LVESV and LV GLS

Inherent to the fact that a response to CRT is defined by means of different parameters, they may not all improve in the same patient, i.e. they may be discordant. Such discordant clinical and LV volumetric responses were witnessed in 440 CRT recipients.[21] The combined clinical endpoint of ≥1 point improvement in NYHA class and/or ≥15% improvement in the 6-minute walking test distance was compared to an echocardiographic, volumetric response defined as ≥15% reduction in the LVESV.[21] While a clinical response was recorded in 84% of patients, an echocardiographic response was seen in only 63%.[21] Discordance of CRT response parameters can be best investigated by the two measures which have been firmly linked to outcome after CRT, i.e. LVESV and LV GLS.

A discordant CRT response, defined as an improvement in LVESV or LV GLS, but not both, reflects different underlying mechanisms of CRT response. A reduction in LVESV without an improvement in LV GLS likely results from effective resynchronization of the LV by CRT, but without recruitment of contractile reserve. Contractile reserve describes the potential of poorly contractile, though viable, areas of myocardium, to improve their systolic function in response to CRT. The presence of contractile reserve in CRT candidates has been demonstrated with dobutamine stress-echocardiography, and it is associated with better event-free survival.[22-25] On the other hand, an improved LV GLS without a substantial change in LVESV can be attributed to the recruitment of contractile reserve. These two echocardiographic parameters (LVESV and LV GLS) therefore represent two different mechanisms of the LV response to CRT, and they do not always occur in the same patient concurrently.

The results of the present study indicate that no improvement in either LVESV or LV GLS, is significantly associated with a worse outcome, while improvement in both of these parameters or either one of them is associated with a survival benefit. Even though an improvement in LV GLS has previously been linked to an improved outcome, ≥15% reduction in the LVESV is a more commonly used definition of CRT response. Our results therefore support the use of an improvement in LV GLS as a useful parameter for the evaluation of a CRT response. Furthermore, the fact that CRT recipients with either a reduction in LVESV or an improvement in LV GLS had similar associations with outcome, provides insight into the different mechanisms of CRT response. Patients with an improvement in LV GLS but without a reduction in LVESV would have been classified as non-responders by the conventional definition of a CRT response, i.e. ≥15% reduction in LVESV, although they experience similar survival rates at 6 months as compared with patients with reduction in LVESV ≥15%. This observation further strengthens the importance of a change in LV GLS in defining CRT response. Furthermore, the incremental value of an improvement in LV GLS over a reduction of LVESV (in addition to clinical risk factors) for survival, lends additional support to the independent contribution of LV GLS in CRT response.

Study limitations

This was a retrospective, single-center study, which included patients who completed 6 months of follow-up. Patients who died during the first 6 months after CRT implantation could not be included, and could therefore have caused a selection bias. The measurement of LV GLS is not vendor-independent, and the threshold of LV GLS employed to define a response in the present study may not be generalizable to other patients in whom LV GLS was measured on a different vendor platform.[14]

CONCLUSIONS

Various clinical and echocardiographic parameters have been used to define a response to CRT, and due to different underlying mechanisms, they may not always be in agreement in the same patient. By observing the LV response to CRT in terms of two measures which have previously been associated with outcome, i.e. LVESV and LV GLS, we have demonstrated three different patterns of response, i.e. i) an improvement in both LVESV and LV GLS, ii) an improvement in either LVESV or LV GLS, but not both, iii) no improvement in either LVESV or LV GLS. An improvement in both LVESV and LV GLS, or an improvement in either LVESV or LV GLS, at 6 months after CRT, are associated with better long-term outcome, compared to no improvement in LVESV or LV GLS. These findings support the use of LV GLS as a meaningful parameter in defining CRT response, since it reflects a different aspect of LV response to CRT than a change in LVESV, and clearly impacts on long-term prognosis.

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4

Reduced left ventricular mechanical dyssynchrony at 6 months after cardiac resynchronization therapy is associated with superior long-term outcome

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ABSTRACT

Background: In heart failure (HF) patients, left ventricular mechanical dispersion (LVMD) reflects heterogeneous mechanical activation of the left ventricle. In these patients, LVMD can be reduced after CRT. Whether lesser LVMD is associated with improved outcome is unknown. The purpose of the current study was to relate LVMD to long-term prognosis in a large cohort of HF patients after 6 months of cardiac resynchronization therapy (CRT).

Methods: Clinical, echocardiographic and ventricular arrhythmia (VA) data were analyzed from an ongoing registry of HF recipients of CRT. Baseline (prior to CRT) and 6-month echocardiograms were evaluated. LVMD was calculated as the standard deviation of the time from onset of the QRS complex to the peak longitudinal strain in a 17-segment model. Patients were divided into two groups, according to the median LVMD (84 ms) at 6 months post-CRT.

Results: Of 1 185 patients (mean age 65±10 years, 76% male), 343 (29%) died during a mean follow-up of 55±36 months. Baseline LVMD was not associated with all-cause mortality and VA at follow-up. In contrast, patients with less LVMD (≤84 ms) at 6 months post-CRT had lower event rates (VA and mortality) compared to those with LVMD >84 ms. On multivariable analysis, greater LVMD at 6 months after CRT was independently associated with an increased risk of mortality (hazard ratio 1.002; P=0.037) and VA (hazard ratio 1.003; P=0.026).

Conclusions: Larger LVMD at 6 months after CRT is independently associated with all-cause mortality and VA. LVMD may be valuable in identifying patients who remain at high mortality risk after CRT implantation.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is indicated in heart failure (HF) patients who remain symptomatic despite optimal medical therapy (New York Heart Association (NYHA) functional class II-III and ambulatory IV), with a wide QRS complex (≥120 ms) and a reduced left ventricular ejection fraction (LVEF ≤35%).[1] CRT has been shown to improve symptoms, induce LV reverse remodeling, improve LVEF and reduce mitral regurgitation by resynchronizing the LV.[1,2] These favorable effects have been associated with a decreased risk of ventricular arrhythmias and reduced mortality.[3,4]

LV mechanical dispersion (LVMD) is a novel, echocardiographic parameter based on speckle tracking echocardiography that measures the time dispersion to reach the peak systolic deformation in the different LV segments.[5,6] LVMD reflects mechanical heterogeneity, which has been related to ventricular arrhythmias in a number of cardiac diseases.[5,7-11] A reduction in LVMD after CRT is related to a decrease in ventricular arrhythmias.[9] Whether reduced LVMD after CRT translates into superior outcome is unclear. Accordingly, the present study evaluated the relation between LVMD at 6 months after CRT implantation, and the prognosis of HF patients.

METHODS

Patient population and data collection

HF patients who received CRT according to current guidelines and who completed clinical and echocardiographic follow-up at 6 months after CRT implantation were retrospectively evaluated.[1] Various clinical, laboratory and imaging data were collected at baseline and 6 months' follow-up. Ischemic HF was defined by the presence of coronary artery disease, i.e. evidence in previous medical records or from non-invasive or invasive investigations. The Dutch Central Committee on Human-related Research (CCMO) allows the use of anonymous data without prior approval of an institutional review board, provided that the data are acquired for routine patient care. All data used for the present study were acquired for clinical purposes and handled anonymously.

Among the clinical variables, the quality of life, according to the Minnesota Living with Heart Failure Questionnaire, the 6-minute walking distance and the NYHA functional class were considered to define the severity of HF.[12,13] Renal function was defined by the estimated glomerular filtration rate (eGFR), calculated according to the Modification of Diet in Renal Disease Study (MDRD) equation.[14] The efficacy of CRT was analyzed as the percentage of patients receiving <98% and <90% of biventricular pacing, respectively.[15] A significant burden of premature, ventricular contractions (PVCs) was defined as >10 000 per 24 hours.[16,17]

Transthoracic echocardiography was performed in the left lateral decubitus position prior to and at 6 months after CRT implantation in all patients, utilizing a commercially available

echocardiographic system (E9 or VIVID 7, General Electric Vingmed Ultrasound, Milwaukee, USA) equipped with 3.5 MHz or M5S transducers. As previously described,[18] M-mode, 2-dimensional and Doppler data were acquired and digitally stored for off-line analysis (EchoPac 113, General Electric Vingmed Ultrasound, Milwaukee, USA).

Speckle tracking echocardiography was used to measure LVMD at baseline and at 6 months after CRT implantation. LVMD was calculated as the standard deviation of the time from the onset of the QRS complex on the triggered ECG, to the peak longitudinal myocardial strain in a 17-segment LV model (Figure 1). The inter-observer and intra-observer variability of LVMD measurement were assessed by calculating the intra-class correlation coefficient (ICC) for both measures on 25 randomly selected patients. The ICC for inter-observer and intra-observer variability of LVMD were 0.84 (95% confidence interval (CI) 0.64-0.93; P<0.001) and 0.93 (95% CI 0.85-0.97; P<0.001), respectively.

Implantation of CRT

The subclavian or cephalic veins were utilized to place the right atrial and ventricular leads in a standard fashion. Coronary sinus venography was performed (with a balloon catheter) to guide LV lead implantation. The LV pacing lead was introduced into the coronary sinus through an 8 Fr guiding catheter, and preferably positioned in a (postero-) lateral vein. Thereafter all the leads were connected to a dual-chamber, biventricular CRT device. A CRT device with defibrillator function was implanted in most of the recipients. Patients were scheduled for regular follow-up at the HF outpatient clinic and to evaluate device function. The atrioventricular and interventricular delays were empirically set at 120-140 ms and 0 ms respectively, while optimization of the CRT device was left to the discretion of the treating physician.

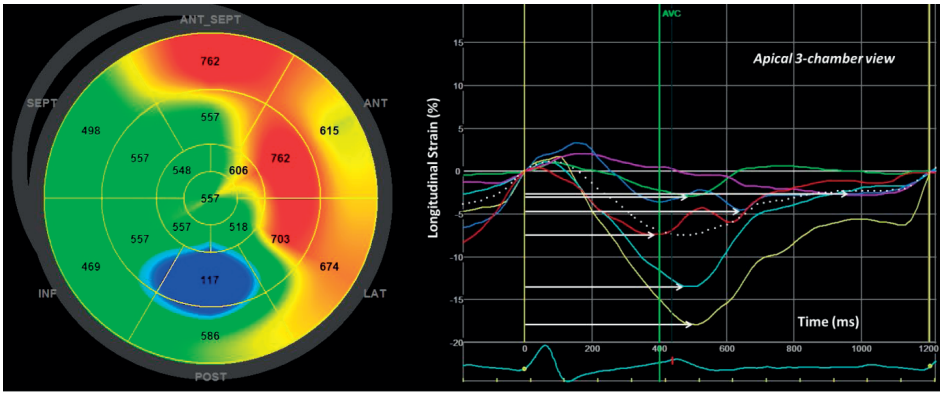


Figure 1: Assessment of left ventricular mechanical dispersion with 2-dimensional speckle tracking echocardiography. Left ventricular mechanical dispersion was calculated as the standard deviation of the time from the onset of the QRS complex on the ECG, to the peak longitudinal strain in 17 segments of the left ventricle. The segmental time to peak longitudinal strain data are presented in a color-coded, bull's eye plot with the earliest segments presented in green and the most delayed segments in red. LVMD: left ventricular mechanical dispersion.

Follow-up

The clinical response to CRT was defined as improvement ≥1 NYHA functional class at 6 months of follow-up.[19] LV reverse remodeling was defined as ≥15% reduction in the LV end-systolic volume (LVESV) at 6 months of follow-up. Patients were followed up for the occurrence of all-cause mortality, as well as the occurrence of ventricular arrhythmias (appropriate antitachycardia pacing and/or appropriate defibrillation by a CRT defibrillator). The follow-up started at 6 months when the clinical, electrocardiographic and echocardiographic responses were assessed.

Statistical analysis

Continuous variables are expressed as means and standard deviations, and categorical data as numbers and percentages. Survival analysis was performed according to the Kaplan-Meier method for all-cause mortality as well as ventricular arrhythmias. Comparisons between groups were performed according to the log-rank test. A Cox proportional hazards model was used to investigate the association between LVMD at 6 months' follow-up and all-cause mortality, as well as ventricular arrhythmias. To show hazard change across the range of LVMD, as a continuous variable, a spline curve was fit for LVMD vs. mortality as well as vs. ventricular arrhythmias, with overlaid confidence intervals (CI). Subsequently, multivariate spline models were constructed, after adjusting for the following covariates: gender, body mass index, diabetes mellitus, etiology of HF, diuretics, hemoglobin, renal dysfunction, left ventricular reverse remodeling and clinical CRT response. All analyses were performed with SPSS for Windows, version 23.0 (SPSS, Armonk, NY, USA) and R, version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-sided. A P-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

A total of 1 185 patients (mean age 65±10 years, 76% male) with analysable echocardiographic data to calculate LVMD at baseline and 6 months after CRT were included. Strain analysis was not feasible in 90 (8%) patients. Baseline characteristics of the patient population are presented in Table 1. The etiology of HF was ischemic in 60% of patients and the mean LVEF at 6 months after CRT was 33.4±9.8%. The median baseline LVMD was 96.3 ms (interquartile range (IQR) 74.5-126.4 ms), which decreased to 84.1 ms (IQR 65.4-112.4 ms) after 6 months of CRT. The percentage of patients with biventricular pacing <98% was 37%, and the percentage of patients with biventricular pacing <90% was 9%. The percentage of patients in our cohort with >10 000 premature ventricular complexes per 24 hours, was 2.2%.

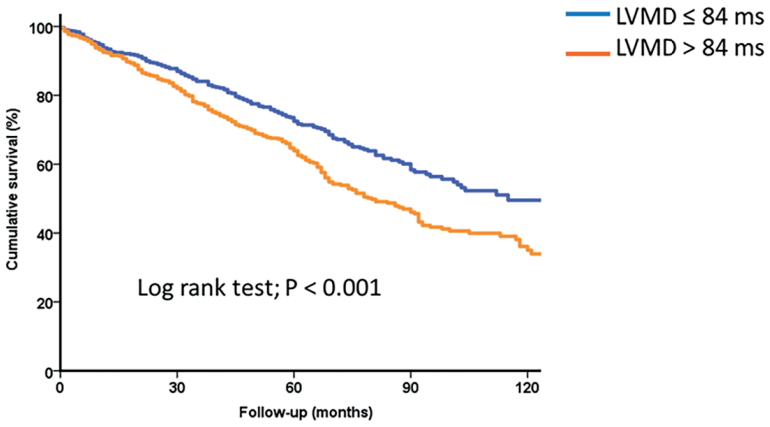
Association between LVMD at baseline and 6 months of follow-up and survival

In total, 343 (29%) patients died during a mean follow-up of 55±36 months after the 6-month echocardiography. The patient population was dichotomized according to the median value of LVMD at baseline (96 ms). There were no differences in all-cause mortality rates between those patients with a greater (>96 ms) and a lesser (≤96 ms) LVMD at baseline (log-rank test, P=0.253). The patient population was subsequently dichotomized according to the median value of LVMD at 6 months (84 ms). Patients with lesser LVMD at 6 months (≤84 ms) had significantly lower all-cause mortality compared with patients with more LVMD (>84 ms) (log-rank test, P<0.001; Figure 2). In patients with LVMD ≤84 ms at 6 months, the cumulative all-cause mortality rates were 13, 42 and 55% at 30, 90 and 120 months' follow-up, respectively. In contrast, in the group of patients with LVMD >84 ms, the cumulative event rates were 18, 54 and 65% for the same follow-up time points.

Table 1: Patient characteristics at baseline.

	N=1185
Age (years)	65±10
Male gender, n (%)	904 (76)
Ischemic etiology, n (%)	712 (60)
Heart rhythm at baseline, n (%)	
- Sinus rhythm	867 (73)
- Paced rhythm	192 (16)
- Atrial fibrillation	126 (11)
NYHA functional class, n (%)	
- I	57 (5)
- II	318 (27)
- III	733 (62)
- IV	77 (6)
6 MWT (m)	331±121
QoL score	32±19
Diabetes n (%)	253 (21)
eGFR <60 ml/min/1.73 m^2, n (%)	466 (39)
LVEF (%)	27±8
LVEDV (ml)	203±76
LVESV (ml)	150±65
LVMD (ms)	96.3 (74.5-126.4)

Values are mean ± standard deviation. eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVMD: left ventricular mechanical dispersion, 6 MWT: 6-minute walk test, NYHA: New York Heart Association; QoL: quality of life.



Number of patients at risk					
LVMD ≤ 84 ms	592	427	269	100	19
LVMD > 84 ms	593	413	242	100	32

Figure 2: Kaplan-Meier curves for all-cause mortality. Time to all-cause mortality in patients with left ventricular mechanical dispersion ≤84 ms and >84 ms after 6 months of cardiac resynchronization therapy. LVMD: left ventricular mechanical dispersion.

To investigate the association between LVMD at 6 months and all-cause mortality, a Cox proportional hazards model was constructed with variables known to influence mortality of HF patients (Table 2). On multivariable analysis, LVMD at 6 months was independently associated with increased mortality (hazard ratio 1.002; 95% CI 1.000-1.005; P=0.037). To show hazard

Table 2: Uni- and multivariate Cox proportional hazards models for all-cause mortality.

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
LVMD at 6 months (ms)	1.004	1.002-1.006	<0.001	1.002	1.000-1.005	0.037
Age at implant (years)	1.040	1.029-1.050	<0.001	1.030	1.019-1.041	<0.001
Male gender	1.482	1.164-1.887	0.001	1.495	1.157-1.933	0.002
Body mass index (kg/m^2)	0.969	0.947-0.992	0.008	0.960	0.936-0.985	0.002
Diabetes mellitus	1.649	1.329-2.046	<0.001	1.470	1.165-1.854	0.001
Ischemic etiology of heart failure	1.547	1.265-1.893	<0.001	1.184	0.950-1.475	0.133
Diuretics	1.751	1.325-2.313	<0.001	1.445	1.080-1.933	0.013
Hemoglobin (g/dl)	0.806	0.731-0.890	<0.001	0.935	0.842-1.039	0.212
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)	2.546	2.105-3.080	<0.001	1.983	1.612-2.439	<0.001
LV reverse remodeling	0.537	0.380-0.759	<0.001	0.628	0.514-0.767	<0.001
Clinical response	0.839	0.694-1.013	0.068	0.921	0.756-1.121	0.412

CI: confidence interval, eGFR: estimated glomerular filtration rate, HR: hazard ratio, LVMD: left ventricular mechanical dispersion.

change across the range of LVMD, as a continuous variable, a spline curve was fit for LVMD vs. mortality. For all-cause mortality, predicted from the 6-month LVMD, the assumption of linearity was not violated (χ^2 4.4; P=0.12). There was an increase of hazards for LVMD between 50 ms and 130 ms, after which a plateau appeared. At higher 6-month LVMD values, there is a decrease of the hazards, although there are too few observations in this range to support a meaningful, clinical interpretation (also reflected in the wider CIs at higher LVMD) (Figure 3A). When adjusted for multiple covariates, the assumption of linearity was also not violated (χ^2 3.0; P=0.23), and the curve demonstrated a similar shape to the unadjusted model, with hazards increasing for LVMD between 50 and 130 ms, whereafter a plateau was noted (Figure 3B).

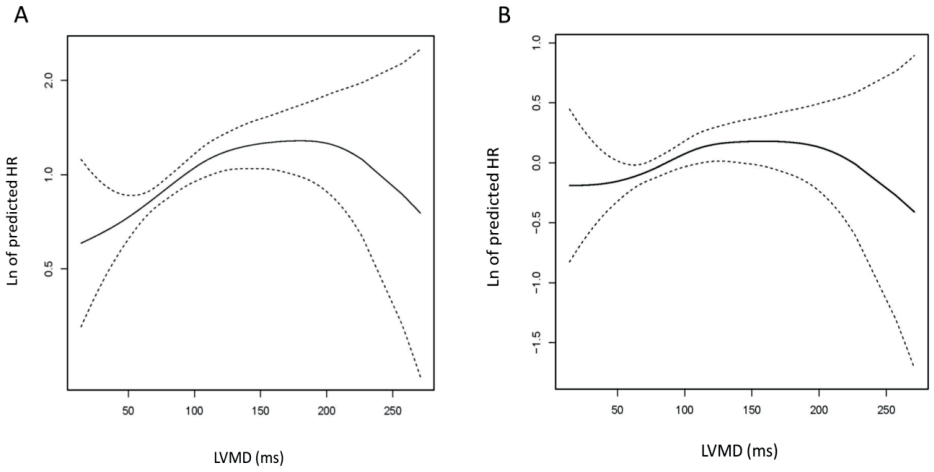
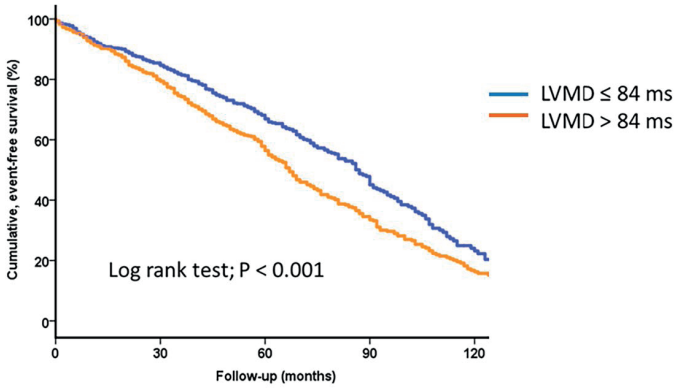


Figure 3: Spline curves for left ventricular mechanical dispersion (LVMD) vs. all-cause mortality. Predicted mortality across a range of LVMD, plotted as a fitted spline model on a log-hazard scale, with overlaid confidence intervals. The unadjusted model is shown in panel A, and the adjusted model in panel B. Ln: logarithm, HR: hazard ratio.

Association between LVMD at baseline and 6 months of follow-up and ventricular arrhythmias

After a mean follow-up of 55±36 months, 403 (34%) of patients experienced a ventricular arrhythmia for which appropriate device therapy was delivered. No difference in freedom from ventricular arrhythmias was seen between those patients with a greater (>96 ms) and a lesser (≤96 ms) LVMD at baseline (log-rank test, P=0.781). Patients with lesser LVMD at 6 months (≤84 ms) experienced greater freedom from ventricular arrhythmias, compared to those with more LVMD (>84 ms) (log-rank test, P<0.001; Figure 4). In patients with LVMD ≤84 ms at 6 months, the cumulative rates for ventricular arrhythmia were 15, 55 and 77% at 30, 90 and 120 months' follow-up, respectively. In contrast, in those individuals with LVMD >84 ms, the cumulative event rates were 21, 66 and 84% for the identical time points.



Number of patients at risk					
LVMD ≤ 84 ms	592	411	258	93	25
LVMD > 84 ms	593	394	232	94	31

Figure 4: Kaplan-Meier curves for freedom from ventricular arrhythmias. Ventricular arrhythmia-free survival in patients with left ventricular mechanical dispersion ≤84 ms and >84 ms after 6 months of cardiac resynchronization therapy. LVMD: left ventricular mechanical dispersion.

To investigate the association between LVMD at 6 months and all-cause mortality, a Cox proportional hazards model was constructed with variables known to influence the mortality of HF patients (Table 3). On multivariable analysis, LVMD at 6 months was independently associated with ventricular arrhythmias (hazard ratio 1.003; 95% CI 1.000-1.005; P=0.026). To show hazard change for ventricular arrhythmias across the range of LVMD as a continuous variable, a spline curve was fit for LVMD vs. ventricular arrhythmias. For ventricular arrhythmias, predicted from the 6-month LVMD, the assumption of linearity was not violated (χ^2 6.0; P=0.06). There was an increase of hazards for LVMD between 50 ms and 130 ms, after which a plateau appeared. At higher 6-month LVMD values, there was a decrease of the hazards, although there were too few observations in this range to support a meaningful, clinical interpretation (also reflected in the wider CIs at higher LVMD) (Figure 5A). When adjusted for multiple covariates, the assumption of linearity was also not violated (χ^2 1.2; P=0.55), and the curve demonstrated a similar shape to the unadjusted model, with hazards increasing for LVMD between 50 and 130 ms, whereafter a plateau was noted (Figure 5B).

Table 3: Uni- and multivariate Cox proportional hazards models for ventricular arrhythmias.

	Univariate analysis			Multivariate analysis		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
LVMD at 6 months (ms)	1.003	1.001-1.006	0.006	1.003	1.000-1.005	0.026
Age at implant (years)	1.020	1.009-1.030	<0.001	1.018	1.008-1.030	0.001
Male gender	1.704	1.305-2.225	0.001	1.723	1.306-2.273	<0.001
Body mass index (kg/m^2)	0.999	0.976-1.023	0.957	-	-	-
Diabetes mellitus	1.243	0.967-1.596	0.089	1.176	0.910-1.520	0.216
Ischemic etiology of heart failure	1.339	1.089-1.648	0.006	1.046	0.839-1.305	0.688
Diuretics	1.126	0.873-1.451	0.361	-	-	-
Hemoglobin (g/dl)	0.975	0.874-1.087	0.646	-	-	-
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)	1.334	1.086-1.639	0.006	1.259	1.011-1.567	0.040
LV reverse remodeling	0.672	0.551-0.821	<0.001	0.704	0.569-0.872	0.001
Clinical response	0.759	0.621-0.928	0.007	0.832	0.675-1.026	0.086

CI: confidence interval, eGFR: estimated glomerular filtration rate, HR: hazard ratio, LVMD: left ventricular mechanical dispersion.

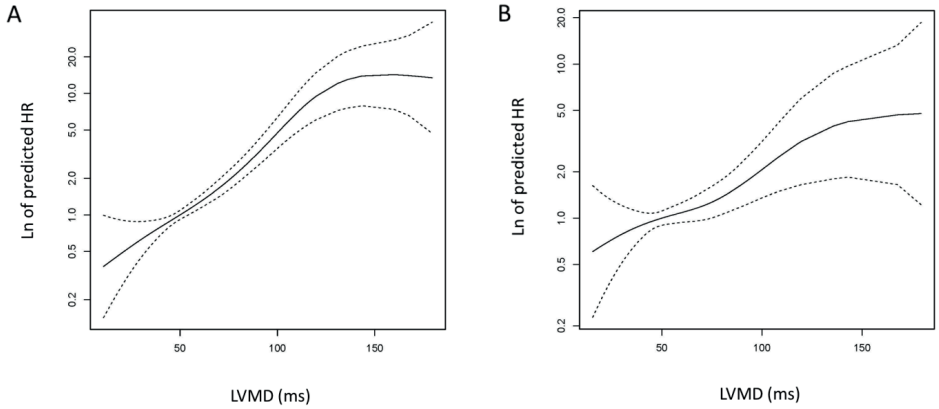


Figure 5: Spline curves for LVMD vs. ventricular arrhythmias. Predicted occurrence of ventricular arrhythmias across a range of left ventricular mechanical dispersion (LVMD), plotted as a fitted spline model on a log-hazard scale with overlaid confidence intervals. The unadjusted model is shown in panel A, and the adjusted model in panel B. Ln: logarithm, HR: hazard ratio.

DISCUSSION

Patients with HF with greater LVMD at 6 months after receiving a CRT device, experienced a worse long-term outcome and more frequent ventricular arrhythmias, compared to patients with lesser LVMD. Additionally, the association between LVMD and mortality, as well as ventricular arrhythmias was independent of the occurrence of LV reverse remodeling at 6 months.

Role of LVMD in diagnosis and risk-stratification

LVMD has been proposed as a marker of electromechanical heterogeneity of the left ventricle and is calculated as the standard deviation of the time from the onset of the QRS complex to the peak longitudinal myocardial strain (obtained with 2-dimensional speckle tracking echocardiography) in a 16- or17-segment LV model.[5,6] LVMD has been utilized in the diagnosis and risk-stratification of various cardiac disorders.[5,6,8-11,20-22] In post-infarct patients, LVMD has shown incremental value over LVEF to predict ventricular arrhythmias.[22]

Similarly, LVMD discriminated between post-infarct patients with and without ventricular arrhythmias in a prospective study.[5] In addition, LVMD has been associated with ventricular arrhythmias in HF patients with ischemic and non-ischemic etiologies.[8] A greater LVMD, 6 months after CRT, has been demonstrated in recipients with ventricular arrhythmias at follow-up, compared to those without arrhythmias.[9] Our data support this observation, with more frequent ventricular arrhythmias documented in individuals with greater LVMD after CRT. However, the association between residual LVMD after CRT and all-cause mortality has not been evaluated.

LVMD and outcome after CRT

The main finding of this study is that LVMD after 6 months of CRT is independently associated with long-term outcome. Long-term outcome after CRT is influenced by a number of baseline characteristics, i.e. male gender, body mass index, diabetes mellitus, hemoglobin and impaired renal function.[23-26] It is also well-established that LV reverse remodeling, as well as the extent thereof, impacts on long-term prognosis.[27,28] In the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial, a ≥15% decrease in the indexed LVESV was an independent predictor of outcome.[29] In contrast, although the clinical response to CRT was associated with better outcome, it was not independently associated with all-cause mortality in a study of 679 patients.[30]

LVMD and LV reverse remodeling after CRT are therefore more firmly linked to improved survival than a clinical response. A lesser LVMD likely reflects restoration of a more homogenous pattern of LV electromechanical activation by CRT, which accompanies LV reverse remodeling. Apical rocking, another surrogate of heterogenous LV activation, has demonstrated incremental value over LV reverse remodeling to predict mortality after CRT (hazard ratio 0.405; 95% CI 0.283-0.579; P<0.0001).[31] In addition, correction of apical rocking by CRT translated into lower all-cause mortality. Our results provide further support to the association of reestablishment of a more coordinated pattern of LV contraction and improved outcome after CRT.

In a recent meta-analysis, including 3 667 patients, the risk of ventricular arrhythmias was found to be significantly lower in CRT responders (i.e. in whom LV remodeling has taken place) than in non-responders (odds ratio 0.436; 95% CI 0.323-0.589; P<0.05).[32] LV remodeling is therefore strongly related to both the risk of ventricular arrhythmias and outcome after CRT. In light of the connection between restoration of coordinated LV contraction (reflected by LVMD) and LV remodeling, the presence of more frequent ventricular arrhythmias in patients with a

greater LVMD after 6 months of CRT, is consistent with ventricular arrhythmia burden as the cause of increased mortality in this group.

The present study shows that LVMD after 6 months of CRT was significantly associated with long-term outcome independently of clinical response and LV reverse remodeling. Greater LVMD may thus identify a subgroup of patients who remain at high risk of mortality despite CRT. Such patients are candidates for close follow-up, as well as interventions which may modify their outcome, e.g. optimization of device programming, adjustment of pharmacotherapy and eventually mechanical LV support or cardiac transplantation.

Study limitations

This was a retrospective, single-center study and included patients who completed the 6 months of follow-up echocardiographic evaluation. Therefore, there may be a selection bias, since LVMD could not be measured in patients who deceased during the first 6 months after CRT implantation. The mode of death was not systematically available. The measurements of LVMD are not vendor independent and the cut-off value of LVMD provided in this study may not be generalizable to other patients in whom LVMD was measured with different software.

CONCLUSIONS

LVMD after 6 months of CRT is independently associated with all-cause mortality and ventricular arrhythmias, and may therefore be valuable in identifying patients who remain at high risk after CRT implantation.

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5

Prognostic implications of global, left ventricular myocardial work efficiency before cardiac resynchronization therapy

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) restores mechanical efficiency to the failing left ventricle (LV) by resynchronization of contraction. Global, LV myocardial work efficiency can be quantified non-invasively with echocardiography, although the prognostic implication of this parameter remains unexplored. The objective was to relate global, LV myocardial work efficiency before CRT to long-term prognosis.

Methods: Data were analyzed from an ongoing registry of heart failure patients with class I indications for CRT according to contemporary guidelines. Global, LV myocardial work efficiency was defined as the ratio of the constructive work in all LV segments, divided by the sum of constructive and wasted work in all LV segments, as a percentage ((constructive work/(constructive work + wasted work)) x 100%). It was derived from speckle tracking strain echocardiography and non-invasive blood pressure measurements, taken before CRT implantation. Patients were dichotomized according to the baseline, median global, LV myocardial work efficiency (75%; interquartile range 66-81%).

Results: A total of 153 patients (mean age 66±10 years, 72% male, 48% ischemic heart disease) were analyzed. After a median follow-up of 57 months (interquartile range 28-76 months), 31% of patients died. CRT recipients with less efficient energetics at baseline (global, LV myocardial work efficiency <75%) demonstrated lower event rates than patients with more efficient baseline energetics (global, LV myocardial work efficiency ≥75%) (log-rank test, P=0.029). On multivariable analysis, global LV myocardial work efficiency <75% pre-CRT was independently associated with a decreased risk of all-cause mortality (hazard ratio 0.48, 95% confidence interval 0.25-0.92; P=0.027), suggesting that the potential for improvement in LV efficiency is an important mechanism in CRT benefit.

Conclusions: Global, LV myocardial work efficiency can be derived non-invasively from speckle tracking strain echocardiography data and non-invasive blood pressure recordings. A lower global, LV myocardial work efficiency before CRT, is independently associated with improved long-term outcome.

INTRODUCTION

Cardiac work refers to the amount of mechanical energy which is expended in the process of left ventricular (LV) contraction and relaxation.[1] Electrical conduction disturbances strongly influence LV work. In the presence of a left bundle branch block (LBBB), the interventricular septum is activated early and contracts before aortic valve opening. The early contraction of the septum thereby stretches the LV lateral wall before it has contracted, and when the lateral wall is activated late, the interventricular septum is stretched, leading to inefficient cardiac work (without LV ejection of blood or stroke volume).[2] Cardiac resynchronization therapy (CRT), an effective therapy in selected heart failure patients,[3] restores mechanical efficiency to the failing LV by resynchronization of contraction. The less efficiently the LV operates at baseline, the greater the potential for recovery of efficient LV work with CRT. Whether a greater reserve of potentially recoverable global, LV myocardial work efficiency before CRT translates into improved outcome, is unknown. Global, LV myocardial work efficiency can be quantified non-invasively with a novel, echocardiography-based technique.[4] Speckle tracking strain echocardiography data are combined with non-invasive blood pressure recordings to calculate segmental cardiac work and subsequently, the global, LV myocardial work efficiency.[2] Both preclinical and clinical studies have shown the validity of using this technique to quantify global, LV myocardial work efficiency non-invasively, including in a LBBB context.[2,4,5] However, the prognostic implications of global, LV myocardial work efficiency in heart failure patients undergoing CRT have not been explored. We investigated the prognostic implication of the global, LV myocardial work efficiency measured before CRT implantation.

METHODS

Study population and definition of clinical measures

From an ongoing registry of heart failure patients treated with CRT,[6] those with class I recommendations for CRT (sinus rhythm and QRS duration ≥130 ms with LBBB morphology, LV ejection fraction (EF) ≤35% and New York Heart Association (NYHA) class II, III and ambulatory IV symptoms, despite adequate medical treatment),[3] and simultaneous, non-invasive measurement of blood pressure with brachial artery sphygmomanometry during echocardiography were selected. The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent.

Ischemic heart failure etiology was defined as the presence of significant coronary artery disease. The NYHA functional class was assessed in all patients, and a clinical response to CRT was subsequently defined as an improvement of ≥1 NYHA class at 6-month follow-up.[7] Quality of life was evaluated with the Minnesota Living with Heart Failure Questionnaire, and if the patient's condition allowed, a 6-minute walk test was also conducted.[8,9] Renal function was

characterized by the estimated glomerular filtration rate (eGFR), according to the Modification of Diet in Renal Disease (MDRD) study equation.[10]

Conventional analysis of echocardiographic data

All patients underwent transthoracic echocardiography in the left lateral decubitus position with a commercially available echocardiography system (VIVID 7 or E9, General Electric Vingmed Ultrasound, Milwaukee, USA). Echocardiographic data were acquired with either 3.5 MHz or M5S transducers, while adjusting depth and gain settings as necessary. ECG-triggered, M-mode, 2-dimensional and Doppler data were digitally archived for off-line analysis (EchoPac 202, General Electric Vingmed Ultrasound, Milwaukee, USA). The LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV) and the LVEF were calculated with the Simpson's method from 2-dimensional, apical, 2- and 4-chamber views.[11]

Calculation and definition of global, LV myocardial work efficiency

The global, LV myocardial work efficiency was calculated by proprietary software (EchoPac 202, General Electric Vingmed Ultrasound, Milwaukee, USA) from speckle tracking echocardiographic strain data, as well as non-invasive blood pressure recordings. Speckle tracking analysis was used to measure longitudinal LV strain from standard apical views (long-axis, 2-chamber and 4-chamber).[12] The opening and closing time points of the aortic and mitral valves were identified from the parasternal, 2-dimensional images of the LV. Non-invasive blood pressure values were recorded with brachial artery sphygmomanometry at the time of transthoracic echocardiography. An LV pressure-strain curve was then constructed from the LV longitudinal strain data of the entire cardiac cycle, the mitral and aortic valve opening and closing times as well as non-invasive blood pressure values. Cardiac work was calculated automatically per myocardial segment by the abovementioned software by differentiation of the strain values over time to yield the segmental shortening rate, which was then multiplied by the LV instantaneous pressure. The resultant, i.e. instantaneous power, was subsequently integrated over time, providing values for LV segmental and total LV work as a time function.[2] Constructive work was defined as cardiac work performed during shortening of a myocardial segment in systole or during lengthening in isovolumic relaxation, whereas wasted work was defined as work performed by a segment during lengthening in systole, or during shortening against a closed aortic valve in isovolumic relaxation. The global, LV myocardial work efficiency was defined as the ratio of the constructive work in all LV segments, divided by the sum of constructive and wasted work in all LV segments, as a percentage ((constructive work/(constructive work + wasted work)) x 100%) (Figure 1).

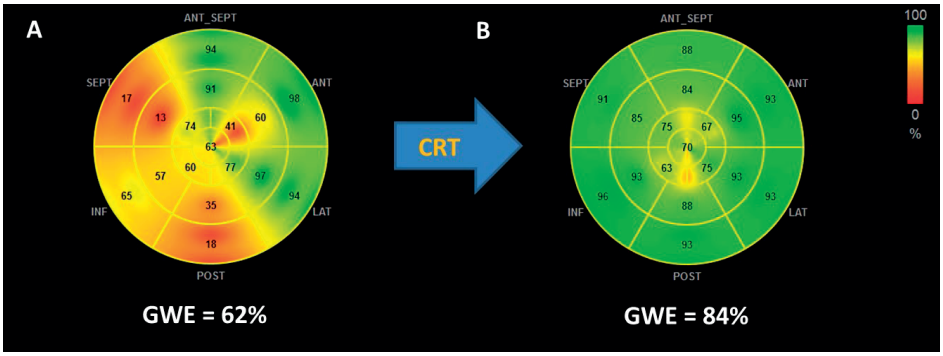

Figure 1: Change in global, left ventricular (LV) myocardial work efficiency due to effective cardiac resynchronization therapy (CRT). Parametric maps of global LV myocardial work efficiency in a patient A) before CRT and B) after 6 months of CRT. The global LV work efficiency increased from 62% to 84% after 6 months of CRT. Segmental values of LV work efficiency are expressed as percentages. CRT: cardiac resynchronization therapy, GWE: global, LV work efficiency.

CRT implantation and follow-up

Implantation of CRT was performed according to a standard approach, i.e. insertion of the right atrial and right ventricular leads via the subclavian or cephalic veins. Before insertion of the LV lead, coronary sinus venography was performed. The LV pacing lead was then introduced into the coronary sinus through an 8 Fr guiding catheter, and positioned in a posterior or posterolateral vein, if possible. All leads were connected to a dual-chamber, biventricular CRT device. Defibrillator functionality was included in most (99%) of the implanted devices. CRT recipients were followed up at regular intervals at the heart failure outpatient clinic, and the device was interrogated. Atrioventricular and interventricular delays were empirically set at 120-140 ms and 0 ms, respectively. CRT optimization was performed during follow-up visits at the discretion of the treating physician. A CRT response was defined by a ≥15% reduction in the LVESV after 6 months of CRT.[7] The national death registry and case records were reviewed for the occurrence of all-cause mortality during follow-up. Patients were followed up for the occurrence of the primary outcome, i.e. all-cause mortality.

Statistical analysis

Means and standard deviations were used for presenting continuous data; numbers and percentages for categorical data. Continuous variables were compared by means of Student t-tests, while χ^2 and Fisher's exact tests (as appropriate) were used for the comparison of categorical data. Values of the baseline, global, LV myocardial work efficiency were compared with a log-rank test. A Cox proportional hazards model was used to investigate the independent association between baseline, global, LV myocardial work efficiency and all-cause mortality. To show hazard change across the range of baseline global, LV myocardial work efficiency, as a continuous variable, a spline curve was fit for global, LV myocardial work efficiency vs. mortality,

with overlaid confidence intervals. Subsequently, a multivariate spline model was constructed, after adjusting for the following covariates: age at implantation, gender, body mass index, ischemic etiology of heart failure, beta-blockers, diuretics, hemoglobin, renal dysfunction, LVEDV at baseline, LVEF at baseline and CRT response. In order to evaluate the incremental value of baseline, global LV myocardial work efficiency over global longitudinal strain for outcome, we performed likelihood ratio testing. SPSS for Windows, version 23.0 (SPSS, Armonk, NY, USA) and R, version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) were used for performing all the analyses. All statistical tests were two-sided, and a P-value of <0.05 was considered significant.

RESULTS

Baseline patient characteristics

In total, 153 heart failure patients treated with CRT (class I recommendation) and with echocardiographic and blood pressure data were included for analysis (mean age 66±10 years, 72% male, 48% ischemic heart disease). Strain analysis and calculation of global, LV myocardial work efficiency were feasible in all 153 (100%) patients. Baseline characteristics for the overall population are presented in Table 1. The median baseline, global, LV myocardial work efficiency was 75% (interquartile range (IQR) 66-81%). Patients were subsequently dichotomized according to the median value of baseline, global, LV myocardial work efficiency, i.e. <75% and ≥75%. CRT recipients with baseline, global, LV myocardial work efficiency <75% were more frequently female, and had larger chamber dimensions (LVEDV, LVESV) and worse systolic function (LVEF) than those with baseline, global, LV myocardial work efficiency ≥75% (Table 1).

Baseline, global, LV myocardial work efficiency and survival

In total, 47 (31%) patients died during a median follow-up of 57 months (IQR 28-76 months). Patients with less efficient mechanics at baseline (global, LV myocardial work efficiency <75%), demonstrated lower event rates than those with more efficient baseline mechanics (global, LV myocardial work efficiency ≥75%) (log-rank test, P=0.029; Figure 2). In patients with baseline, global, LV myocardial work efficiency <75%, the cumulative, all-cause mortality rates were 5, 21 and 30% at 25, 50 and 75 months follow-up, respectively. In contrast, in the group of patients with baseline, global, LV myocardial work efficiency ≥75%, the cumulative event rates were 19, 37 and 49% at the same follow-up time points.

To investigate the association between baseline, global, LV myocardial work efficiency and all-cause mortality, a Cox proportional hazards model was constructed with variables known to influence mortality of heart failure patients (Table 2). On multivariable analysis, global, LV myocardial work efficiency <75% at baseline was independently associated with better survival (hazard ratio 0.48; 95% confidence interval 0.25-0.92; P=0.027). To show hazard change across

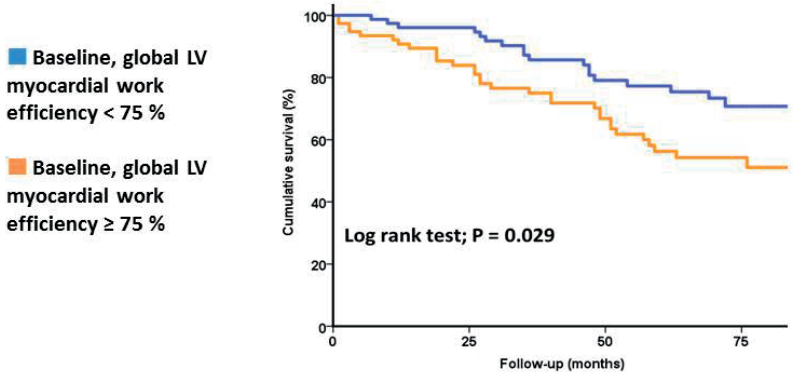

Figure 2: Kaplan-Meier curves depicting time to cumulative survival in cardiac resynchronization (CRT) recipients. Data are shown according to those with baseline, global, left ventricular (LV) myocardial work efficiency <75% and ≥75%. LV: left ventricular.

Table 1: Baseline patient characteristics.

	Overall population (n=153)	Global, LV myocardial work efficiency <75% (n=77)	Global, LV myocardial work efficiency ≥75% (n=76)	P-value
Age (years)	65.5±10.2	64.0±9.9	66.9±10.3	0.081
Male gender, n (%)	110 (71.9)	48 (62.3)	62 (81.6)	0.008
Ischemic etiology, n (%)	74 (48.4)	33 (42.9)	41 (53.9)	0.170
Heart rhythm at baseline, n (%)				
- Sinus rhythm	139 (90.8)	72 (93.5)	67 (88.2)	0.400
- Paced rhythm	14 (9.2)	5 (6.5)	9 (11.8)	0.251
NYHA class, n (%)				
- I	0 (0.0)	0 (0.0)	0 (0.0)	-
- II	48 (31.4)	22 (26.8)	26 (34.2)	0.489
- III	90 (58.8)	47 (61.0)	43 (56.6)	0.575
- IV	15 (9.8)	8 (10.4)	7 (9.2)	0.806
6 MWT (m)	344.7±114.7	371.3±111.3	316.7±112.4	0.011
QoL score	30.2±19.4	27.8±17.8	33.0±20.9	0.135
Diabetes, n (%)	24 (15.7)	8 (10.4)	16 (21.1)	0.070
eGFR <60 ml/min/1.73 m^2, n (%)	55 (35.9)	27 (38.0)	28 (40.0)	0.810
LVEF (%)	24.9±6.9	22.4±6.9	27.5±5.8	<0.001
LVEDV (ml)	216.1±78.5	232.3±81.8	199.8±71.8	0.010
LVESV (ml)	164.2±67.2	182.2±71.8	146.0±57.1	<0.001
Global, LV myocardial work efficiency (%)	74.6 (IQR 66.2-81.4)	66.3 (IQR 61.1-70.6)	81.4 (IQR 77.5-85.3)	<0.001*

Values are mean ± standard deviation, unless otherwise specified. eGFR: estimated glomerular filtration rate, IQR: interquartile range, LV: left ventricular, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, 6 MWT: 6-minute walk test, NYHA: New York Heart Association, QoL: quality of life, *per definition.

Table 2: Uni- and multivariable Cox proportional hazards models for all-cause mortality.

	Univariable analysis			Multivariable analysis		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Baseline, global, LV myocardial work efficiency <75%	0.535	0.302-0.948	0.032	0.484	0.254-0.922	0.027
Age at implant (years)	1.040	1.006-1.075	0.019	1.009	0.974-1.045	0.620
Male gender	1.074	0.578-1.996	0.822	-	-	-
Body mass index (kg/m^2)	0.996	0.933-1.063	0.901	-	-	-
Ischemic etiology	1.816	1.031-3.201	0.039	1.229	0.646-2.341	0.530
Beta-blockers	0.740	0.403-1.359	0.332	-	-	-
Diuretics	1.894	0.807-4.445	0.142	-	-	-
Hemoglobin (g/dl)	0.967	0.728-1.283	0.814	-	-	-
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)	3.471	1.901-6.339	<0.001	3.463	1.761-6.809	<0.001
LVEDV at baseline	0.999	0.995-1.003	0.581	-	-	-
LVEF at baseline	0.995	0.955-1.036	0.804	-	-	-
Responder (≥15% reduction LVESV after 6 months)	0.534	0.294-0.969	0.039	0.575	0.302-1.095	0.092

CI: confidence interval, eGFR: estimated glomerular filtration rate, HR: hazard ratio, LV: left ventricular, LVEDV: left ventricular, end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV: left ventricular, end-systolic volume.

the range of baseline, global, LV myocardial work efficiency, as a continuous variable, a spline curve was fit for baseline, global, LV myocardial work efficiency vs. mortality. For all-cause mortality, predicted from the baseline, global, LV myocardial work efficiency, the assumption of linearity was violated (χ^2, 7.8; P=0.02). There was an increase of hazards for baseline, global, LV myocardial work efficiency between 70% and 85%. At very low, global, LV myocardial work efficiency values (<65%), there was also an increase of the hazards, giving a parabolic shape to the curve, although a lower frequency of observations in this range makes a meaningful, clinical interpretation less robust (also reflected in the wider confidence intervals at low baseline, global, LV myocardial work efficiency) (Figure 3A). When adjusted for multiple covariates, the assumption of linearity was not violated (χ^2, 3.7; P=0.16), and the curve demonstrated a similar shape to the unadjusted model for higher values, with hazards increasing for baseline, global, LV myocardial work efficiency between 70% and 85% (Figure 3B). At lower values (<65%) however, a plateau developed, although a low number of observations and wide confidence intervals again made clinical interpretation more challenging.

Incremental value of global, LV myocardial work efficiency

In order to evaluate the incremental value of global, LV myocardial work efficiency over global longitudinal strain for mortality, likelihood ratio testing was performed. The baseline model (model 1) comprised all risk factors which were included in the multivariable regression model, i.e.: age at implantation, ischemic etiology of heart failure, renal dysfunction and a response to cardiac resynchronization therapy (≥15% decrease in LV, end-systolic volume). Addition of

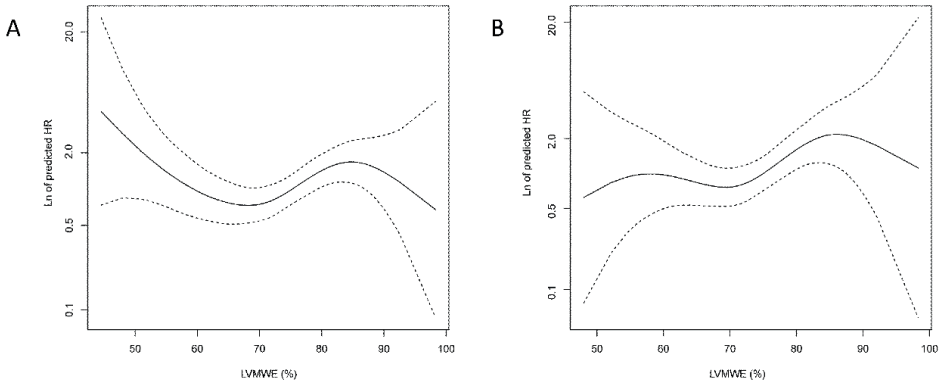

Figure 3: Spline curves for baseline, global, LV myocardial work efficiency vs. all-cause mortality. Predicted mortality across a range of baseline, global, LV myocardial work efficiency, plotted as a fitted spline model on a log-hazard scale, with overlaid confidence intervals. The unadjusted model is shown in panel A, and the adjusted model in panel B. HR: hazard ratio, Ln: logarithm, LVMWE: left ventricular, myocardial work efficiency.

baseline, global longitudinal strain to model 1, provided incremental value (P=0.029; Figure 4). A third model, which included baseline global, myocardial work efficiency, proved to be of further incremental value (P=0.002; Figure 4).

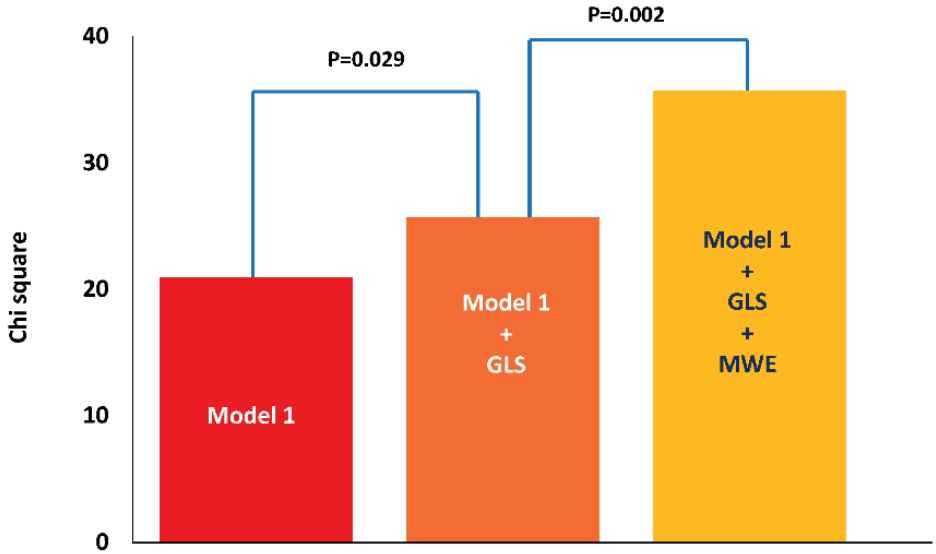

Figure 4: Likelihood ratio test. Bars represent the incremental value of global longitudinal strain and global, left ventricular myocardial work efficiency in addition to clinical risk factors (Model 1). GLS: global longitudinal strain, MWE: myocardial work efficiency.

DISCUSSION

The primary finding of the present study, is that a lower global, LV myocardial work efficiency before institution of CRT is independently associated with better long-term outcome in patients with a class I indication for CRT, according to current guidelines.

Non-invasive estimation of global, LV myocardial work efficiency

Cardiac work which is performed by an early-activated LV segment on an opposing, late-activated LV segment (elongating the late-activated segment during contraction of the early-activated segment), does not contribute to the LV stroke volume, and leads to inefficient LV function.[2] This can be quantified by the global, LV myocardial work efficiency, i.e. the ratio of the constructive work in all LV segments, divided by the sum of constructive and wasted work in all LV segments, as a percentage ((constructive work/(constructive work + wasted work)) x 100%). In order to estimate the global, LV myocardial work efficiency non-invasively, wasted LV work and constructive LV work have to be measured. Since the principles of non-invasive determination apply equally well to wasted and constructive LV work (the former representing work performed by a segment during lengthening in systole, or during shortening against a closed aortic valve in isovolumic relaxation, and the latter work performed during shortening of a myocardial segment in systole or during lengthening in isovolumic relaxation), experimental studies have focused on the validity of the non-invasive estimation of cardiac work.

Echocardiography-based, non-invasive estimation of cardiac work is a novel technique, with the objective to quantify the energy efficiency of the LV.[4] In a canine validation study, a good correlation was demonstrated between invasive and non-invasive LV pressure-strain loops (r=0.96).[4] In the same study, LV work was then calculated non-invasively in humans, and compared to regional, myocardial glucose metabolism (visualized with positron emission tomography (PET)).[4] A very robust correlation was found between the non-invasive LV work and the regional, myocardial glucose metabolism (r=0.81).[4] Further evidence for the validity of the non-invasive estimation of LV work has been provided in a murine model, which indicated a strong correlation between myocardial work (non-invasively estimated with magnetic resonance imaging) and the influx rate constant of 18-fluoro-deoxyglucose (as a marker of the rate of myocardial glucose metabolism) on PET (r=0.75).[5] Since LV work can be reliably estimated non-invasively, the global, LV myocardial work efficiency can be calculated from wasted and constructive LV work. This is achieved using echocardiography and sphygmomanometric blood pressure recordings. Since electrical conduction disturbances – specifically LV dyssynchrony – influence the global, LV myocardial work efficiency, this technique can be applied to investigate the effects of CRT on myocardial energetics.

Global, LV myocardial work efficiency before CRT: implications for outcome

A lesser global, LV myocardial work efficiency before CRT was independently associated with better long-term outcome in our study. Abnormal LV activation due to a LBBB leads to dyssynchronous LV contraction, which causes an early-activated LV segment to stretch an opposing late-activated segment and vice versa, but does not contribute to stroke volume and therefore leads to inefficient LV mechanics.[2] Both the presence of an LBBB and other baseline LV dyssynchrony measures are associated with long-term outcome in CRT.[3,13-16]

Inclusion criteria for our study comprised class I indications for CRT according to contemporary guidelines, i.e. including the presence of an LBBB.[3] Despite selection of CRT recipients on the basis of a pre-existing LBBB and QRS ≥130 ms, the degree of baseline, global, LV myocardial work efficiency was independently associated with long-term survival. This difference in outcome between CRT recipients with a greater or lesser baseline, global, LV myocardial work efficiency can therefore not be attributed to the presence of LBBB-induced dyssynchrony alone. Improvement of function in areas of poorly contractile but viable myocardium by CRT, will increase the amount of constructive work performed by the LV. This so-called recruitment of contractile reserve in CRT candidates has been demonstrated with dobutamine stress-echocardiography, and it is associated with both the acute and long-term remodeling response to CRT, as well as better event-free survival.[17-21] Since global, LV constructive work correlates with myocardial metabolic activity on PET, it can be considered an indication of contractile reserve in CRT recipients.[4,20] Since the global, LV myocardial work efficiency is calculated from wasted and constructive LV work, it will improve with recruitment of contractile reserve. It therefore seems likely that, in our study patients, a difference in the contractile reserve is reflected in the baseline global, LV myocardial work efficiency, which is subsequently recruited, thereby increasing the global, LV myocardial work efficiency. Since the activation of contractile reserve in LV segments after CRT is associated with a better outcome, it is not surprising that the baseline, global, LV myocardial work efficiency is also associated with outcome. The trend towards a higher risk at very low values of global, LV myocardial work efficiency seen on both the unadjusted and adjusted spline curves (Figure 3), suggests that there may be a lower limit of contractile reserve, below which the myocardial contractile reserve is exhausted.

Furthermore, the incremental value of global, LV myocardial work efficiency over global longitudinal strain (in addition to clinical risk factors) for survival, lends additional support to the role of global, LV myocardial work efficiency as a useful imaging parameter in CRT.

Further studies, in larger populations, will be required to determine the value of measuring global, LV myocardial work efficiency before the implantation of CRT, especially with regard to selection of CRT candidates and in predicting long-term outcome. Global, LV myocardial work efficiency will be included as a parameter in the EuroCRT study, which is designed to prospectively evaluate multimodality imaging in the evaluation of various long-term outcome parameters of heart failure patients treated with CRT.[22]

Study limitations

This study is subject to the limitations of a retrospective, single-center study. Since the calculation of global, LV myocardial work efficiency is dependent on speckle tracking strain echocardiography, the results are not vendor-independent.

CONCLUSIONS

Global, LV myocardial work efficiency can be derived non-invasively from speckle tracking strain echocardiography data and sphygmomanometric blood pressure recordings. A lower global, LV myocardial work efficiency before CRT, is independently associated with better long-term outcome in heart failure patients with a class I indication for CRT, according to current guidelines. Larger studies are required to confirm the usefulness of non-invasive measurement of global, LV myocardial work efficiency in predicting CRT response, as well as in the prediction of long-term outcome after CRT.

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6

Effect of functional mitral regurgitation on outcome in patients receiving cardiac resynchronization therapy for heart failure

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ABSTRACT

Background: Functional mitral regurgitation (FMR) is common in heart failure (HF), and negatively impacts prognosis. Cardiac resynchronization therapy (CRT) can improve FMR, but the long-term changes in and impact of FMR after CRT are still unclear. The present study investigated the prevalence, evolution and impact on mortality of FMR before and after CRT in patients with HF.

Methods: A total of 1 313 patients (66±11 years, 77% male, 59% ischemic heart disease) treated with CRT were evaluated. Patients were divided into 4 groups of FMR according to the evolution at 6 months after CRT: no or mild FMR at baseline which remained unchanged at 6 months (grade 0-1 FMR unchanged, n=609 (51%)), no or mild FMR which worsened to moderate to severe (grade 0-1 FMR worsened, n=66 (6%)), moderate to severe FMR which improved to no or mild (grade 2-4 improved, n=209 (18%)), and moderate to severe FMR which remained unchanged (grade 2-4 unchanged, n=309 (26%)).

Results: Over a mean follow-up of 51±38 months, 297 (25%) patients died. Those with baseline FMR grade 0-1 which remained unchanged at 6-month follow-up, as well as baseline FMR grade 2-4 which improved, had lower mortality rates than patients with 6-month FMR grade 2-4 regardless of baseline FMR grade (P<0.001). Baseline FMR grade 2-4 that remained unchanged at 6-month follow-up was associated with increased mortality, independent of the clinical and left ventricular volumetric responses to CRT (hazard ratio 1.77; 95% confidence interval 1.41-2.22; P<0.001).

Conclusions: Moderate to severe FMR at baseline which remains unchanged at 6 months after CRT implantation is strongly associated with long-term mortality in patients with HF.

INTRODUCTION

Functional mitral regurgitation (FMR) is common in heart failure (HF), with a prevalence of approximately 50% in ischemic cardiomyopathy and 56-65% in non-ischemic cardiomyopathy.[1-3] Moderate to severe FMR portends a poor prognosis, increasing HF hospitalizations and death.[2,4] Cardiac resynchronization therapy (CRT) is a well-established HF therapy.[5] The prevalence of FMR after CRT treatment varies among studies.[6-8] FMR may diminish, remain stable or worsen after CRT, which may impact prognosis after CRT. No randomized study has investigated the prevalence, evolution and impact on mortality of FMR before and after CRT in patients with HF. We analyzed the prevalence of FMR in a large cohort of HF patients undergoing CRT. Moreover, the relation between the change in FMR after 6 months of CRT, and the clinical and echocardiographic response to CRT was evaluated. Finally, the changes in FMR after CRT were related to long-term outcome during extended follow-up.

METHODS

Patient population and data collection

HF patients who underwent quantitative assessment of MR severity at the echocardiographic core laboratory of Leiden University Medical Center and subsequent CRT implantation according to contemporary guidelines were included in this retrospective evaluation.[5] Patients who underwent mitral valve surgery (replacement or repair) prior to or after CRT implantation (n=110) and those with primary MR were excluded. Demographic, clinical, laboratory, electrocardiographic (ECG) and echocardiographic parameters were analyzed. Patients with previous infarction or revascularization, as well as significant coronary artery disease on invasive angiography, were considered to have ischemic cardiomyopathy, whereas the remainder were considered non-ischemic.

Clinical evaluation included assessment of New York Heart Association (NYHA) class, quality of life (QoL, using the Minnesota Living with Heart Failure Questionnaire)[9] and a 6-minute walk test (6 MWT) if able.[10] Clinical and echocardiographic assessments were routinely repeated at 6 months after CRT implantation. Thereafter, patients were scheduled for regular outpatient visits.

Echocardiographic data acquisition and analysis

Two-dimensional transthoracic echocardiography was performed in all patients using a commercially available echocardiographic system (VIVID 7 or E9, General Electric Vingmed Ultrasound, Milwaukee, USA) prior to CRT implantation and after 6 months. Images were acquired with 3.5 MHz or M5S transducers, adjusting depth and gain settings as appropriate. M-mode, 2-dimensional and Doppler data, triggered to the ECG, were obtained and stored digitally for

off-line analysis (EchoPac 113, General Electric Vingmed Ultrasound, Milwaukee, USA). Left ventricular end-systolic volume (LVESV), LV end-diastolic volume (LVEDV) and LV ejection fraction (LVEF) were measured from the apical 2- and 4-chamber views, using the modified Simpson's biplane method.[11] The severity of FMR was evaluated according to current recommendations, using a multiparametric approach, including qualitative and semi-quantitative indices, and was graded on a 4-point scale: no or mild=1, moderate=2, moderate to severe=3, and severe=4.[12]

Implantation of CRT

Right atrial and ventricular leads were positioned in a conventional manner, as previously described, and CRT optimization was performed during follow-up at the discretion of the treating physician.[13]

Changes in FMR grade after CRT and definitions of response to CRT

Changes in FMR were evaluated at 6-month follow-up. Patients were divided in 4 groups: patients with no or mild FMR (grade 0-1) at baseline which remained unchanged at 6 months; patients with no or mild FMR (grade 0-1) at baseline which worsened to moderate to severe MR at 6 months (grade 2-4); patients with moderate to severe FMR (grade 2-4) at baseline which improved to no or mild (grade 0-1) at 6 months; and patients with moderate to severe FMR (grade 2-4) at baseline which remained unchanged at 6 months.

These FMR changes were related to 6-month response to CRT. A positive clinical response to CRT was defined as ≥1 class improvement in NYHA class at 6-month follow-up, whereas a positive echocardiographic response was defined as ≥15% reduction in LVESV at 6-month follow-up.[13]

Long-term outcome

Patient data were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, The Netherlands) and subsequently analyzed. The institutional review board approved the research and waived the need for written patient informed consent provided that the data were acquired for routine patient care. In the present evaluation, all data were acquired for clinical purposes and handled anonymously. Data on survival were retrieved from medical records and the municipal civil registries.

Statistical analysis

Continuous variables are presented as means and standard deviations, and categorical data as numbers and percentages. Continuous variables were compared with one-way, between-group analysis of variance (ANOVA), using Bonferroni correction for multiple comparisons, and general linear mixed models. Categorical data were compared with the χ^2 and Fisher's exact tests, as appropriate. The event-free survival rates for each FMR group were evaluated with the Kaplan-Meier method and compared with the log-rank test. The follow-up period started at 6

months after CRT implantation, when change in FMR grade was assessed and FMR groups were defined. Independent associates of all-cause mortality were evaluated with the Cox proportional hazards model, with the following variables entered into the model: baseline grade 0-1 FMR unchanged, baseline grade 2-4 FMR improved, baseline grade 0-1 FMR worsened, baseline grade 2-4 FMR unchanged, age, male sex, body mass index, diabetes mellitus, ischemic etiology of HF, diuretic use, hemoglobin, renal dysfunction, LVEF at 6 months, positive echo response, positive clinical response and atrial fibrillation. All analyses were performed with SPSS for Windows, version 23.0 (SPSS, Armonk, NY, USA). All statistical tests were two-sided and a P-value <0.05 was considered statistically significant.

RESULTS

Evolution of FMR after 6 months of CRT

A total of 1 313 patients (mean age 66±11 years, 77% male) with HF and baseline echocardiography who were treated with CRT were included in the analysis. The etiology of HF was ischemic in 59% of patients, the mean LVEF was 27±8% and the mean QRS duration 156±33 ms. No or mild FMR was noted in 735 (56%) patients, whereas 578 (44%) had moderate to severe MR. During 6-month follow-up 120 patients did not return for echocardiography. Thus, the study population consisted of 1 193 patients.

The severity of FMR before and after CRT implantation is displayed in Figure 1. Overall, 675 (57%) patients had no or mild FMR at baseline, while 518 (43%) patients had moderate to severe FMR. Of the 675 patients with grade 0-1 FMR at baseline, the MR grade remained

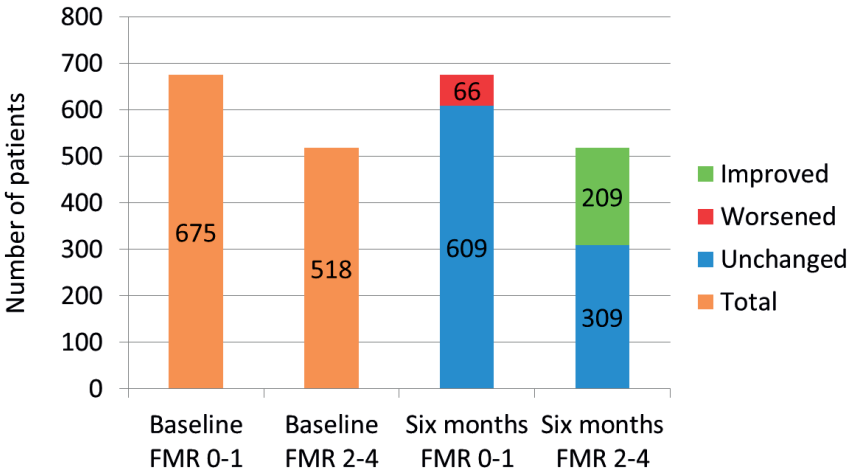


Figure 1: Distribution of no or mild functional mitral regurgitation (FMR), as well as moderate to severe FMR. Data are shown at baseline (before cardiac resynchronization therapy (CRT)) and after 6 months of CRT.

unchanged at 6-month follow-up in 609 (90%), whereas the MR grade progressed to grade 2-4 FMR in 66 (10%). Of the 518 patients with grade 2-4 FMR at baseline, the MR grade improved to grade 0-1 in 209 (40%) and remained unchanged in 309 (60%) at 6-month follow-up.

Baseline characteristics of the 1 193 patients according to the change in FMR are summarized in Table 1, while changes in clinical and echocardiographic parameters are shown in Table 2. Patients with grade 2-4 FMR at baseline which improved or remained unchanged at 6 months after CRT, had larger LV volumes and lower LVEF at baseline. Patients with grade 2-4 FMR at baseline which remained unchanged had more severe symptoms and more frequently had renal failure at baseline.

Table 1: Baseline characteristics according to FMR changes from baseline to 6 months after CRT.

	Baseline grade 0-1 FMR unchanged (n=609)	Baseline grade 0-1 FMR worsened (n=66)	Baseline grade 2-4 FMR improved (n=209)	Baseline grade 2-4 FMR unchanged (n=309)
Age (years)	64.4±10.5	65.7±9.7	67.1±9.0*	66.5±10.8*
Male gender, n (%)	494 (81.1)	56 (84.8)	150 (71.8)	225 (72.8)
Ischemic etiology, n (%)	371 (60.9)	36 (54.5)	113 (54.1)	174 (56.3)
Heart rhythm, n (%)				
- Sinus rhythm	472 (77.5)	50 (75.8)	156 (74.6)	200 (64.7)
- Paced	59 (9.7)	6 (9.1)	19 (9.1)	33 (10.7)
- Atrial fibrillation	78 (12.8)	10 (15.2)	34 (16.3)	76 (24.6)
NYHA class, n (%)				
- I	36 (5.9)	8 (12.1)	6 (2.9)	3 (1.0)
- II	178 (29.2)	16 (24.2)	66 (31.6)	57 (18.4)
- III	359 (58.9)	37 (56.1)	120 (57.4)	219 (70.9)
- IV	28 (4.6)	2 (3.0)	15 (7.2)	27 (8.7)
6 MWT (m)	346.5±1 17.0	336.35±159.1	337.8±105.5	295.1±115.4*‡
QoL score	30.8±19.1	31.8±20.3	28.9±17.7	37.2±19.0*‡
Diabetes mellitus, n (%)	142 (23.3)	15 (22.7)	36 (17.2)	57 (18.4)
eGFR <60 ml/min/1.73 m^2, n (%)	209 (34.3)	21 (31.8)	71 (34.0)	173 (56.0)
LVEF (%)	28.2±7.8	28.5±7.5	25.4±7.6*†	25.3±8.3*†
LVEDV (ml)	194.6±70.9	203.3±87.5	217.4±75.7*	231.8±86.0*†
LVESV (ml)	142.0±60.7	148.±72.4	164.5±67.0*	176.2±76.6*†
Medication, n (%)				
- Diuretic	466 (76.5)	47 (71.2)	172 (82.3)	267 (86.4)
- Digoxin	74 (12.2)	6 (9.1)	35 (16.7)	61 (19.7)
- β-blocker	472 (77.5)	50 (75.8)	159 (76.1)	203 (65.7)
- Mineralocorticoid antagonist	253 (41.5)	24 (36.4)	88 (42.1)	159 (51.5)
- ACE-inhibitor	553 (90.8)	51 (77.3)	190 (90.9)	262 (84.8)

Continuous variables are mean ± standard deviation. ACE: angiotensin-converting enzyme, eGFR: estimated glomerular filtration rate, FMR: functional mitral regurgitation, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, 6 MWT: 6-minute walk test, NYHA: New York Heart Association, QoL: quality of life. *P<0.05 vs. baseline no or mild FMR unchanged at 6 months; †P<0.05 vs. baseline no or mild FMR worsened at 6 months; ‡P<0.05 vs. baseline moderate to severe FMR improved at 6 months.

Clinical and echocardiographic responses to CRT

Changes in NYHA functional class HF symptoms at 6-month follow-up for each FMR group are presented in Figure 2. Overall there was an improvement in NYHA functional class HF symptoms across all the FMR groups. However, the clinical response rate (≥1 class improvement in NYHA class from baseline to 6 months) was significantly lower among patients with grade 0-1 FMR at baseline which worsened at follow-up (45%) compared to the other groups (63% for those with grade 0-1 FMR at baseline which remained unchanged, 70% in patients with grade 2-4 FMR which improved and 66% in patients with grade 2-4 FMR which remained unchanged (P=0.013)). Changes in LVESV at 6-month follow-up for each FMR group are presented in Figure 3. LVESV decrease was significantly greater in patients with grade 2-4 FMR at baseline which improved and in those with grade 0-1 FMR at baseline which remained unchanged at 6-month follow-up compared to patients with grade 2-4 FMR at baseline which remained unchanged and patients with grade 0-1 FMR at baseline which worsened (P<0.001). LV reverse remodeling was significantly more frequent among patients with grade 0-1 FMR at baseline which remained unchanged and grade 2-4 FMR at baseline which improved at 6-month follow-up (62% and 77%, respectively) compared to those with grade 0-1 FMR at baseline which worsened and grade 2-4 FMR at baseline which remained unchanged (29% and 58%, respectively; P<0.001).

Evolution of FMR vs. long-term outcome

During a mean follow-up of 51±38 months, 297 (25%) patients died. When stratified according to FMR responses over 6 months, a cumulative 44 (7%), 109 (18%), 162 (27%) and 187 (31%) of the 609 patients with grade 0-1 FMR at baseline which remained unchanged at 6 months after CRT, died at 24, 48, 72 and 96 months of follow-up, respectively. Similar survival rates were observed in the group of 209 patients with grade 2-4 FMR which improved at 6 months of follow-up. In contrast, the group of 66 patients with grade 0-1 FMR at baseline which worsened showed significantly higher cumulative all-cause mortality events. Finally, the group of 309 patients with baseline grade 2-4 FMR which did not improve after CRT showed the highest mortality rates (log-rank test, P<0.001; Figure 4). By multivariable analysis (Table 2), baseline grade 2-4 FMR which remained unchanged at 6 months after CRT was independently associated with increased risk of mortality (hazard ratio (HR) 1.77; 95% confidence interval (CI) 1.41-2.22, P<0.001) whereas the other groups were not associated.

DISCUSSION

In this study, a fairly high prevalence of moderate to severe FMR (43%) was present at baseline among HF recipients of CRT. The FMR grade improved to no or mild FMR after 6 months of CRT in a substantial proportion (40%) of patients. In addition, among those with no or mild FMR at baseline, a minority (10%) developed moderate to severe FMR after CRT. Patients in whom baseline no or mild FMR progressed to moderate to severe FMR and those with moderate to severe baseline FMR in whom CRT did not improve FMR, had a worse long-term prognosis compared with patients who exhibited no or mild FMR after 6 months of CRT (Figure 5). This association with mortality was independent of LV volume changes and clinical CRT response.

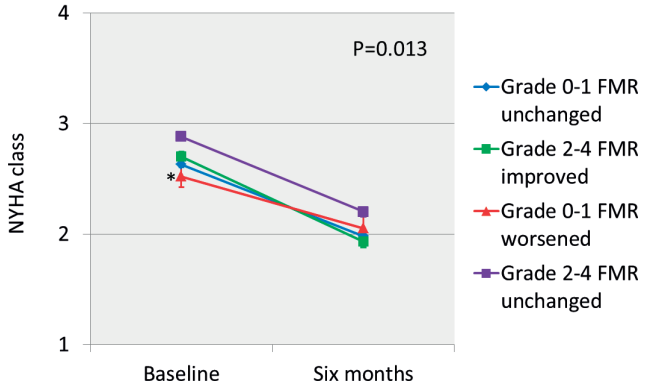


Figure 2: Changes in New York Heart Association (NYHA) class, according to different patterns of evolution of functional mitral regurgitation (FMR). Changes in NYHA class are shown from baseline to 6 months after cardiac resynchronization therapy (CRT), according to the different patterns of evolution of FMR. *P<0.05 vs. other groups. Vertical bars represent standard error of the mean.

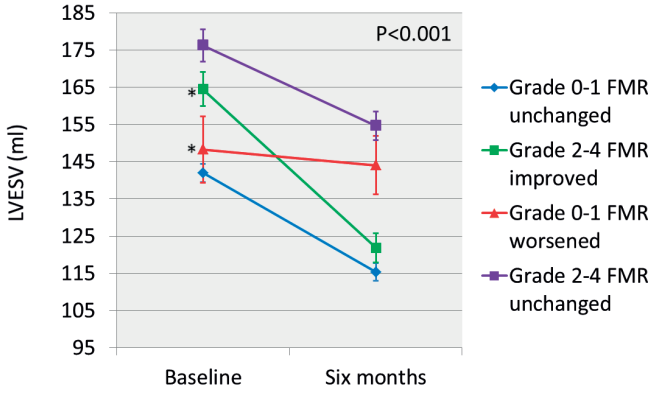
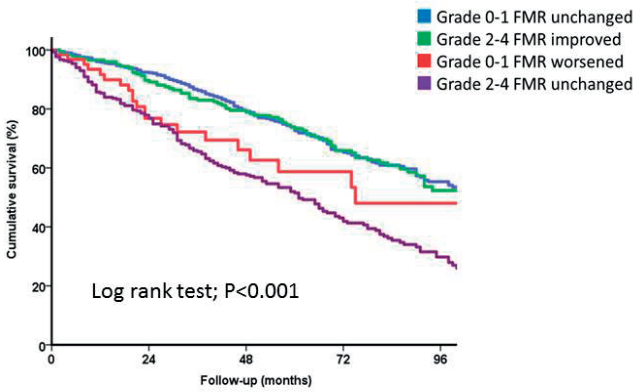


Figure 3: Changes in left ventricular end-systolic volume (LVESV), according to different patterns of evolution of functional mitral regurgitation (FMR). Changes in LVESV from baseline to 6 months after cardiac resynchronization therapy (CRT) are shown, according to different patterns of evolution of FMR. *P<0.01 vs. other groups. Vertical bars represent standard error of the mean.

Prevalence of FMR in HF

The reported prevalence of FMR among patients with HF has varied in prior studies.[4,8,14] In the present study of a large, unselected group of patients, the 43% prevalence of moderate to severe FMR at baseline was similar to the series of Rossi et al.[4] (moderate 49%, severe 24%) and Cipriani et al.[8] (55% moderate to severe).



Number of patients at risk					
Grade 0-1 FMR unchanged	609	495	362	207	96
Grade 2-4 FMR improved	209	167	134	83	38
Grade 0-1 FMR worsened	66	38	19	11	6
Grade 2-4 FMR unchanged	309	210	139	72	34

Figure 4: Kaplan-Meier survival curves for time to cumulative survival in different patterns of functional mitral regurgitation (FMR) evolution. Data are shown for patients with baseline grade 0-1 FMR which remained unchanged at 6 months, baseline grade 2-4 FMR which improved at 6 months, baseline grade 0-1 FMR which worsened at 6 months and baseline grade 2-4 FMR which remained unchanged at 6 months.

Effects of CRT on FMR

Numerous studies have documented the ability of CRT to reduce FMR both acutely, long-term, during rest and exercise.[15-20] CRT addresses various aspects of FMR pathophysiology; by resynchronizing the atrioventricular and inter- and intraventricular contraction, LV preload is optimized and mitral valve closing forces are increased, leading to FMR reduction. By inducing LV reverse remodeling, papillary muscle tethering on mitral leaflets is reduced and mitral annulus dimensions shrink, resulting in improved leaflet coaptation.[19,21-23] In the present study, patients with no or mild FMR at baseline which remained unchanged at 6-month follow-up and patients with moderate to severe FMR at baseline which improved at 6 months after CRT showed the most pronounced LV reverse remodeling, suggesting that CRT ameliorates the underlying pathophysiology of FMR. Interestingly, we found less NYHA functional class improvement and less LVESV reduction in CRT recipients with no or mild FMR at baseline which worsened at 6 months compared to other groups, whereas the worst survival was seen in those with moderate to severe FMR at baseline which remained unchanged. These data demonstrate that mechanisms

underlying symptomatic improvement and LVESV changes after CRT are multifactorial in origin, reflecting more than only changes in FMR.

Table 2: Predictors of all-cause mortality risk, univariable and multivariable Cox proportional hazards models.

	Univariable analysis			Multivariable analysis		
Variable	HR	95% CI	P-value	HR	95% CI	P-value
Baseline grade 0-1 FMR unchanged	-	-	-	-	-	-
Baseline grade 2-4 FMR improved	1.03	0.79-1.34	0.821	1.19	0.89-1.59	0.239
Baseline grade 0-1 FMR worsened	1.58	1.01-2.48	0.046	1.30	0.76-2.23	0.337
Baseline grade 2-4 FMR unchanged	2.16	1.77-2.65	<0.001	1.77	1.41-2.22	<0.001
Age (years)	1.04	1.03-1.05	<0.001	1.03	1.02-1.04	<0.001
Male gender	1.37	1.10-1.71	0.005	1.42	1.09-1.85	0.009
Body mass index (kg/m^2)	0.97	0.95-0.99	0.009	0.98	0.96-1.01	0.131
Diabetes mellitus	1.72	1.42-2.09	<0.001	1.56	1.23-1.99	<0.001
Ischemic etiology of heart failure	1.58	1.32-1.90	<0.001	1.18	0.95-1.47	0.138
Diuretic use	1.77	1.38-2.28	<0.001	1.23	0.91-1.66	0.176
Hemoglobin (g/dl)	0.80	0.73-0.87	<0.001	0.92	0.83-1.03	0.147
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)	2.71	2.28-3.23	<0.001	1.94	1.57-2.40	<0.001
LVEF at 6 months (%)	0.96	0.95-0.97	<0.001	0.98	0.96-0.99	<0.001
Positive echo response*	0.61	0.52-0.73	<0.001	0.82	0.66-1.02	0.080
Positive clinical response	0.82	0.68-0.99	0.040	0.82	0.67-1.01	0.059
Atrial fibrillation	1.76	1.43-2.18	<0.001	1.39	1.08-1.79	0.010

CI: confidence interval, eGFR: estimated glomerular filtration rate, FMR: functional mitral regurgitation, HR: hazard ratio, LVEF: left ventricular ejection fraction. *LVESV reduction of ≥15% at 6 months after cardiac resynchronization therapy.

Association of changes in FMR and outcome

Most important is whether the changes in FMR grade after CRT impact the long-term prognosis of HF patients. In the Cardiac Resynchronization Therapy in Heart Failure (CARE-HF) trial, FMR grade at 3 months' follow-up was an independent predictor of survival.[24] In a study by Verhaert et al.,[25] at 6 months post-CRT both the extent of decrease and the degree of residual FMR were independently associated with survival.[25] More recently, data from the Italian Clinical Service Project (Clinical-Trials.gov Identifier: NCT01007474) reported that at 1 year after CRT implantation, FMR worsened by 1 grade in 42% of patients and remained significant but unchanged from baseline in 58%.[8] The absence of improvement in FMR at 1 year follow-up after CRT was independently associated with increased all-cause mortality. Findings from our large-scale study support the fact that FMR response to CRT during the first 6 months is an important predictor of long-term survival, and provide new insights to this relationship. Moderate to severe FMR at baseline, which remained unchanged at 6 months after CRT implantation, was independently associated with all-cause mortality in HF patients. This association remained significant after adjusting for multiple variables known to impact on HF mortality, including the LV remode-

ling response to CRT. Although FMR and LV volumetric response to CRT are intertwined, the fact that a reduction in FMR was an independent predictor of survival after accounting for LV reverse remodeling demonstrates that the FMR reduction is not merely a reflection of the volumetric response of the LV, but contributes uniquely to long-term survival.

Therapeutic options for residual FMR after CRT

The results of the present study are clinically relevant as they emphasize the unmet treatment need for HF patients in whom FMR persists or worsens after CRT. Therapeutic options for patients with residual moderate to severe FMR after CRT are limited, and they may be considered for percutaneous mitral valve repair. The use of the MitraClip device (Abbott Vascular, Menlo Park, CA) impacted favorably on symptoms, LV remodeling and LV function in the Percutaneous Mitral Valve Repair in Cardiac Resynchronization Therapy (PERMIT-CARE) study of 51 patients with residual moderate to severe FMR after CRT.[26] More recently, the results of the Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) trial, randomizing 152 HF patients to optimal medical therapy (including CRT) and 152 patients to optimal medical therapy and MitraClip implantation, showed similar outcomes in terms of all-cause mortality and unplanned hospitalization for HF.[27] The ongoing Cardiovascular Outcomes for Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional MR (COAPT) trial (Clinical-Trials.gov Identifier: NCT01626079) will provide further evidence on the efficacy of transcatheter mitral valve repair in this high-risk group.

Study limitations

Some limitations should be acknowledged. This was a retrospective, single-center study. FMR severity may be influenced by LV loading conditions, i.e. preload (e.g. diuretics) or afterload (e.g. general anesthesia), which may vary over time. Patients who died before 6 months, underwent mitral valve repair or replacement and those without follow-up echocardiography at 6 months were excluded, potentially introducing selection bias. Nonetheless, medical therapy (with CRT when appropriate) is the accepted standard of care for most HF patients with FMR,[28] and thus the outcomes of the present study are likely representative of what may be expected post-CRT. Finally, although this is currently the largest study to date examining the outcomes of FMR after CRT in HF patients, it was likely under-powered to determine whether FMR worsening from grade 0-1 at baseline to 2-4 at 6 months is an independent predictor of mortality, as this occurred in only 66 patients.

CONCLUSIONS

In the present, large-scale study of HF patients treated with CRT, moderate to severe FMR at baseline, which remained unchanged at 6 months, was strongly associated with increased all-cause mortality independent of LV remodeling and the clinical response to CRT.

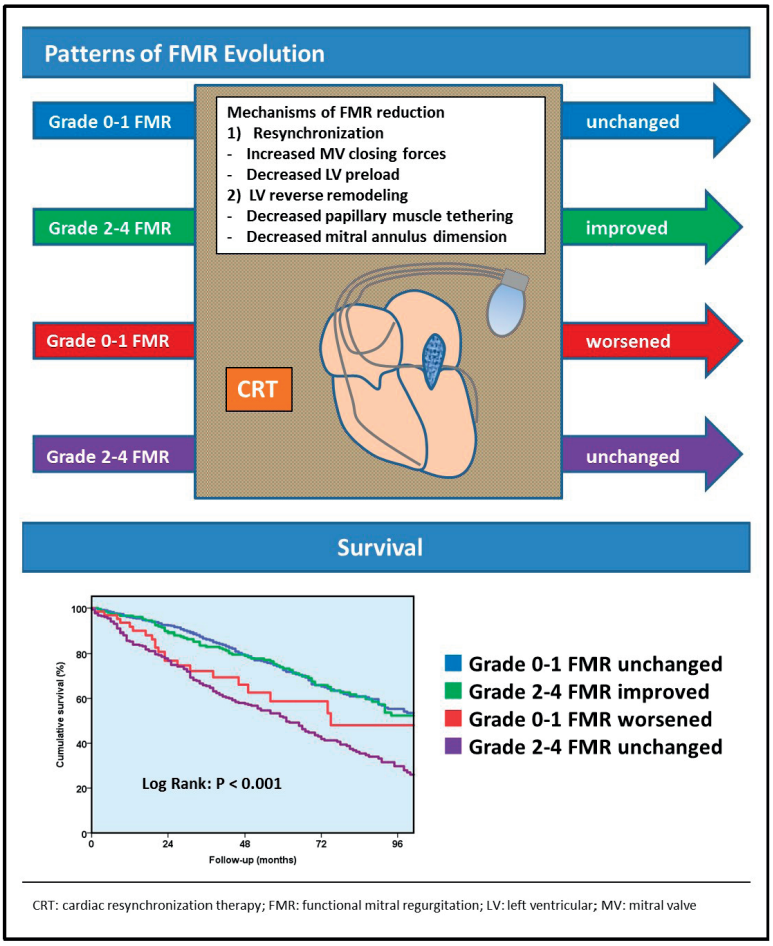


Figure 5: Clinical outcome of different patterns of evolution of functional mitral regurgitation (FMR) after cardiac resynchronization therapy (CRT). Mechanisms of the effect of CRT on FMR are shown for four different patterns of evolution of FMR and their impact on clinical outcomes.

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Impact of atrial fibrillation on improvement of functional mitral regurgitation in cardiac resynchronization therapy

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ABSTRACT

Background: Functional mitral regurgitation (FMR) and atrial fibrillation (AF) are frequent heart failure (HF) complications. Cardiac resynchronization therapy (CRT) can improve FMR; however, little is known about the influence of AF on FMR improvement. The purpose of the current study was to investigate the mechanisms and impact of baseline AF on FMR improvement after CRT.

Methods: CRT recipients with HF, AF or sinus rhythm (SR) at baseline with moderate to severe FMR, were included from an ongoing registry. Left atrial (LA), mitral annular (MA) and left ventricular (LV) dimensions were evaluated echocardiographically. FMR improvement was defined as ≥1 grade decrease from baseline to 6 months' follow-up. Clinical and echocardiographic measurements were performed at baseline and 6 months' follow-up.

Results: 419 patients (mean age 66±8 years, 73% male) were analyzed. At 6 months' follow-up, FMR improved in 145 (45.6%) patients with SR vs. 31 (30.7%) in patients with AF (P=0.011). Despite similar LV reverse remodeling at 6 months after CRT (LV end-systolic volume decreased by 32.1±43.2 ml in the SR group, and by 27.7± 6.3 ml in those with AF; P=0.353), patients with SR exhibited smaller LA volumes (63.0±26.5 ml vs. 103.1±41.0 ml; P<0.001) and MA diameters (42.3±5.6 mm vs. 46.1±5.8 mm; P<0.001), compared to AF patients.

Conclusions: FMR improvement is more common in CRT recipients in SR vs. AF, despite a similar degree of LV remodeling. LA volume and MA diameter are greater in the AF group, causing the negative impact of AF on FMR improvement in CRT, as well as indicating a potential therapeutic target, i.e. AF rhythm control.

INTRODUCTION

Functional mitral regurgitation (FMR) is a frequent complication of heart failure, with a prevalence of 50-65%.[1,2] Global or regional left ventricular (LV) dysfunction or remodeling can cause FMR by tethering of the mitral valve leaflets and impaired closing forces.[3] Atrial fibrillation (AF) is another common manifestation of heart failure (increasing in prevalence from 5% in New York Heart Association (NYHA) class I to 50% in class IV), and it may contribute to the severity of FMR through left atrial (LA) and mitral annular dilatation.[4-6] Both AF and FMR worsen the prognosis of patients with heart failure, although the impact of AF is more controversial.[2,7,8]

Heart failure patients with AF who remain symptomatic despite optimal medical therapy (NYHA class III and ambulatory IV), with wide QRS complex (≥130 ms) and reduced LV ejection fraction (LVEF ≤35%), are candidates for cardiac resynchronization therapy (CRT).[4,9] CRT not only improves LV systolic function, but can also decrease FMR by a variety of mechanisms.[3,9] In addition, CRT has been associated with a reduction of LA dimensions and a decrease in the burden of AF.[10] Since AF may influence the severity of FMR in heart failure patients through LA enlargement and mitral annular dilatation, the purpose of the present study was to investigate if the presence of baseline AF has an impact on the extent of FMR improvement which occurs after CRT.

METHODS

Study population and design

Heart failure patients with moderate to severe FMR at baseline who subsequently received CRT, were selected from an ongoing clinical registry.[11] Patients with heart failure, who remain symptomatic despite receiving maximum tolerated doses of optimal medical therapy, are included in the registry on implantation of a CRT device. The institutional review board approved the study and waived the need for written informed consent for retrospective analysis of clinically acquired data anonymously handled. All data used for the present study were acquired for clinical purposes and handled anonymously. Demographic, clinical, electrocardiographic and echocardiographic data were collected. Patients were divided according to the baseline rhythm: AF vs. sinus rhythm (SR). AF at baseline was classified according to current guidelines: i) paroxysmal ii) persistent iii) long-standing persistent and iv) permanent.[12] Clinical, electrocardiographic and echocardiographic assessment was performed at baseline (before CRT implantation), and repeated at 6 months' follow-up. Ischemic heart failure was defined by the presence of coronary artery disease. The following functional parameters were evaluated: NYHA functional class, quality of life (Minnesota Living with Heart Failure Questionnaire) and (when patients' functional status permits) 6-minute walk test. Patients were excluded if they

underwent mitral valve repair, replacement or percutaneous mitral valve repair at any time, or if the cause of mitral regurgitation was organic.

CRT implantation technique

The right atrial and ventricular leads were placed via a standard subclavian or cephalic vein approach. Coronary sinus venography was used to guide the LV lead implantation. All leads were subsequently connected to a dual-chamber, biventricular CRT device. CRT devices with defibrillator function were implanted in the majority of patients (96%), while 4% received a CRT device without a defibrillator function. Patients were followed up at regular intervals in the heart failure clinic, with concurrent interrogation of device function. Atrioventricular delays were empirically set at 120-140 ms, while interventricular delays were similarly set at 0 ms. CRT device optimization was performed at the discretion of the treating physician during follow-up visits.

Echocardiographic acquisition and data analysis

Transthoracic echocardiograms were performed in the left lateral decubitus position with a commercially available echocardiographic system (E9 or VIVID 7, General Electric Vingmed Ultrasound, Milwaukee, USA). ECG-triggered M-mode, 2-dimensional and Doppler data were collected and digitally stored in order to facilitate off-line analysis (EchoPac 113, General Electric Vingmed Ultrasound, Milwaukee, USA). LV end-systolic (LVESV) and end-diastolic (LVEDV) volumes were measured on 2-dimensional apical 2- and 4-chamber views according to the Simpson's method, whereafter LVEF was calculated.[13] The LA volume was measured during mid-systole in optimized apical 2- and 4-chamber views, while the mitral valve annulus diameter was similarly measured during mid-systole in an apical 4-chamber view and a parasternal long-axis view (Figure 1). Both qualitative and quantitative parameters were employed to grade FMR severity according to contemporary recommendations on an ordinal scale, with none=0, mild=1, moderate=2, moderate to severe=3 and severe=4.[14] Improvement in FMR was defined as ≥1 grade decrease from baseline to 6-month follow-up.

Statistical analysis

Continuous data are presented with means and standard deviations, while categorical data are expressed in numbers and percentages. Independent samples t-tests were used to compare continuous variables and χ^2 tests, as well as Fisher's exact tests (as appropriate) for comparison of categorical variables. A binary logistic regression analysis was performed to investigate the association of rhythm at baseline with improvement of FMR, correcting for left bundle branch block (LBBB), angiotensin-converting enzyme (ACE)-inhibitor use, rhythm at baseline and biventricular pacing >90%. Analyses were performed with SPSS for Windows, version 23.0 (SPSS, Armonk, NY, USA). All statistical tests were two-sided, and a P-value <0.05 was considered statistically significant.

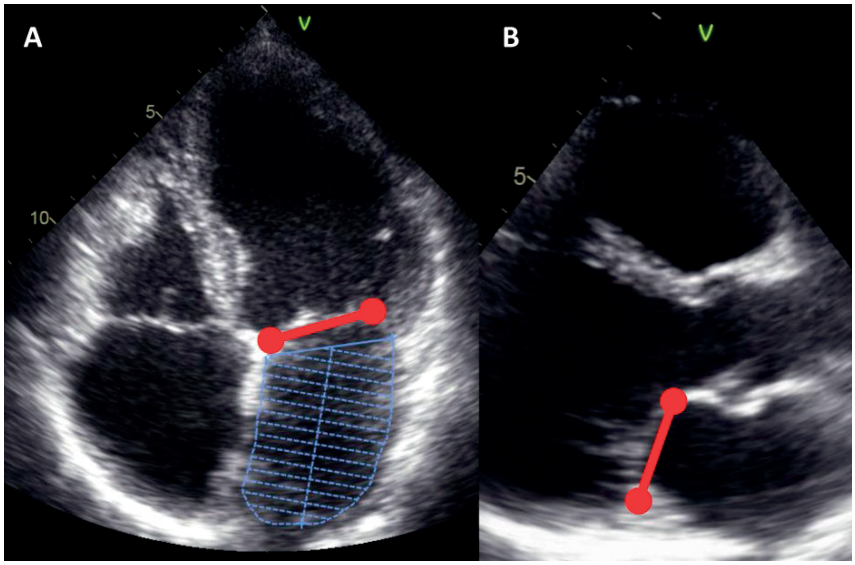

Figure 1: Measurement of mitral annulus diameter. Mitral valve annulus diameter, measured in mid-systole in an apical 4-chamber view (red, dumbbell marker) and left atrial volume, measured in mid-systole in an apical 4-chamber view (blue grid) (A). Mitral annulus diameter, measured in mid-systole in a parasternal, long-axis view (red, dumbbell marker) (B).

RESULTS

Baseline patient characteristics

Of 1 570 heart failure patients treated with CRT, 419 patients (mean age was 66±8 years, 73% male) presented with moderate to severe FMR. Baseline characteristics of patients in AF (n=101) and patients in SR (n=318) are presented in Table 1. Among patients with baseline AF, 52 (51%) had paroxysmal, 44 (44%) permanent, 4 (4%) persistent and 1 (1%) long-standing persistent AF. Thirty-three (33%) patients with baseline AF underwent direct current cardioversion before CRT implantation, 10 (10%) His bundle ablation and 1 (1%) AF catheter ablation.

Improvement in FMR severity after CRT

CRT induced comparable reductions in LVESV (from baseline to 6 months) for patients in SR at baseline and in patients in AF at baseline: a mean LVESV decrease of 32.1±43.2 ml (18.1%) vs. 27.7±36.3 ml (18.6%), was respectively observed; P=0.353 (Figure 2, Table 2). Despite similar extent of LV reverse remodeling, improvement in FMR (from baseline to 6 months) was more frequently observed among patients in SR at baseline as compared to patients in AF at baseline (145 (45.6%) vs. 31 (30.7%), respectively; P=0.011) (Figure 3). Interestingly, after 6 months of CRT, patients in SR at baseline demonstrated a smaller LA volume than those in AF at baseline (63.0±26.5 ml vs. 103.1±41.0 ml, respectively; P<0.001) (Table 2), as well as a greater decrease

in LA size (10.2% vs. 2.3%, respectively; P=0.047) (Table 2). Similarly, patients with SR at baseline evidenced a smaller mitral annulus diameter (measured in the parasternal, long-axis view) (34.5±4.8 mm vs. 39.6±5.2 mm, respectively; P<0.001) and a greater degree of mitral annulus remodeling (4.4% vs. 0.0%, respectively; P<0.001) at 6 months post-CRT, compared to those with AF at baseline (Table 2). On multivariable, logistic regression analysis, SR at baseline remained independently associated with FMR improvement after CRT (adjusted odds ratio (OR) 1.69; 95% confidence interval (CI) 1.02-2.83; P=0.04). These results suggest that the atriogenic component of FMR needs to be corrected in addition to LV reverse remodeling to optimize the rate of FMR improvement after CRT implantation.

Table 1: Patient baseline characteristics according to rhythm (atrial fibrillation or sinus rhythm).

	AF (n=101)	SR (n=318)	P-value
Age (years)	70±8	66±10	<0.001
Male gender, n (%)	85 (84.2)	222 (70.0)	0.004
Ischemic etiology, n (%)	53 (52.5)	185 (58.2)	0.357
LBBB, n (%)	41 (40.6)	225 (70.8)	<0.001
QRS duration at baseline (ms)	157.0±34.0	156.0±29.3	0.768
NYHA class, n (%)			
- I	3 (3.0)	8 (2.5)	0.731
- II	24 (23.8)	83 (26.1)	0.696
- III	63 (62.4)	201 (63.2)	0.906
- IV	11 (10.9)	26 (8.2)	0.422
6 MWT (m)	309.4±106.4	317.9±116.9	0.549
QoL score	33.2±19.1	33.4±19.2	0.949
Diabetes mellitus, n (%)	18 (17.8)	63 (19.8)	0.773
eGFR <60 ml/min/1.73 m^2, n (%)	47 (46.5)	142 (44.7)	0.819
LVEF (%)	26.2±8.4	25.0±7.6	0.173
LVEDV (ml)	198.7±72.4	233.0±83.9	<0.001
LVEDVi (ml/m^2)	101.2±36.0	120.5±41.2	<0.001
LVESV (ml)	149.0±62.9	177.3±74.4	0.001
LVESVi (ml/m^2)	76.0±31.5	91.8±37.7	<0.001
LA volume (ml)	105.5±37.7	70.3±25.8	<0.001
Mitral annular diameter (mm)	47.7±5.4	44.0±5.3	<0.001
Medication, n (%)			
- Diuretic	90 (89.1)	263 (82.7)	0.158
- Digoxin	29 (28.7)	47 (14.8)	0.003
- β-blocker	62 (61.4)	236 (74.2)	0.017
- Mineralocorticoid antagonist	50 (49.5)	152 (47.8)	0.819
- ACE-inhibitor/ARB	81 (80.2)	287 (90.3)	0.013

Continuous variables are mean ± standard deviation. AF: atrial fibrillation, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, eGFR: estimated glomerular filtration rate, LA: left atrial, LBBB: left bundle branch block, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVEDVi: indexed left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVESVi: left ventricular end-systolic volume, 6 MWT: 6-minute walk test, NYHA: New York Heart Association, QoL: quality of life, SR: sinus rhythm.

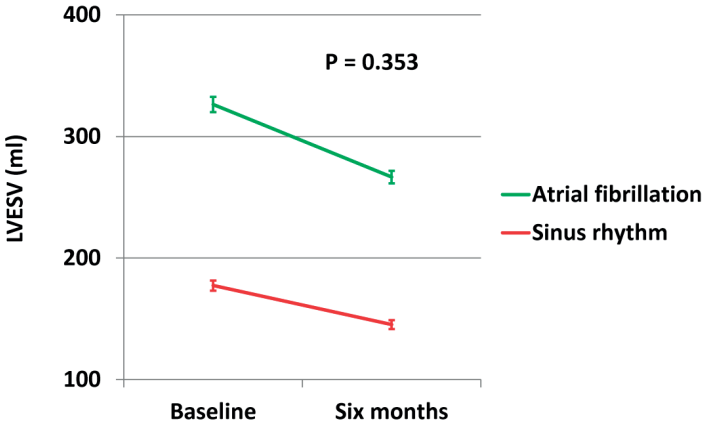

Figure 2: Changes in left ventricular end-systolic volume (LVESV). Change in LVESV from baseline to 6 months after cardiac resynchronization therapy in patients with sinus rhythm vs. atrial fibrillation at baseline. Vertical bars represent standard error of the mean.

DISCUSSION

Heart failure patients with AF before CRT implantation, experienced less improvement in FMR as compared to CRT recipients in SR at baseline. This difference was observed despite a similar extent of LV reverse remodeling after 6 months. Importantly, LA volume and mitral annular dimension were significantly larger in the baseline AF group as compared to the baseline SR group at 6 months after CRT, suggesting an atrial component in the pathophysiology of FMR not fully reversed by CRT.

LV remodeling and FMR improvement in CRT: the impact of AF

LV reverse remodeling defined by a reduction in LVESV has been reported in 62-85% of heart failure patients treated with CRT and is associated with superior survival at follow-up.[15,16] LV reverse remodeling is one of the mechanisms by which CRT improves FMR. However, CRT reduces the amount of FMR by other mechanisms, including resynchronization of atrioventricular, inter- and intraventricular contraction, and an increase in mitral leaflet closing forces which leads to improved leaflet coaptation.[3,17,18]

Table 2: Changes in LVESV, LA volume and mitral annular diameters, according to baseline rhythm.

	AF	SR	P-value
LVESV (ml)			
- Baseline	149.0±62.9	177.3±74.4	0.001
- 6 months	121.4±52.2	145.2±65.4	0.001
- Change	27.7±36.3	32.1±43.2	0.353
- % change	18.6	18.1	0.725
LA volume (ml)			
- Baseline	105.5±37.7	70.3±25.8	<0.001
- 6 months	103.1±41.0	63.0±26.5	<0.001
- Change	2.4±29.4	7.2±22.7	0.133
- % change	2.3	10.2	0.047
Mitral annular diameter (A4C view) (mm)			
- Baseline	47.7±5.4	44.0±5.3	<0.001
- 6 months	46.1±5.8	42.3±5.6	<0.001
- Change	1.6±4.8	1.7±5.2	0.820
- % change	3.4	3.9	0.731
Mitral annular diameter (PSLAX view) (mm)			
- Baseline	39.6±5.2	36.1±4.7	<0.001
- 6 months	39.6±5.2	34.5±4.8	<0.001
- Change	0.0±4.2	1.6±3.7	0.001
- % change	0.0	4.4	<0.001

A4C: apical 4-chamber, AF: atrial fibrillation, LA: left atrial, LVESV: left ventricular end-systolic volume, PSLAX: parasternal long-axis, SR: sinus rhythm.

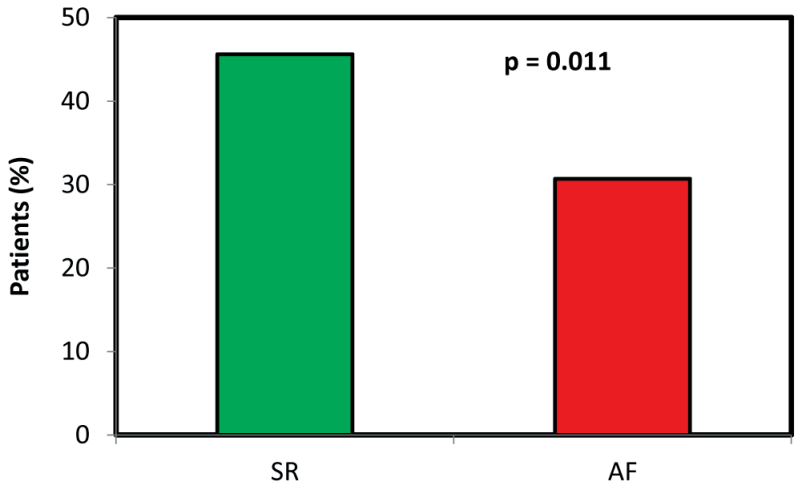

Figure 3: Improvement in functional mitral regurgitation. Percentage (%) of patients demonstrating improvement of functional mitral regurgitation after cardiac resynchronization therapy, according to baseline rhythm. Improvement in FMR (from baseline to 6 months) was more frequently observed among patients in SR at baseline (45.6%), compared to patients in AF at baseline (30.7%). AF: atrial fibrillation, FMR: functional mitral regurgitation, SR: sinus rhythm.

In a study of 673 CRT recipients (162 with AF), no significant difference in the change in LVESV was found between SR and AF groups (P=0.828).[19] Our data confirm that there is no appreciable difference in the amount of LV reverse remodeling between CRT recipients with AF and SR at baseline, while a greater reduction in FMR is noted at 6 months in heart failure patients with SR at baseline who are treated with CRT, compared to AF at baseline. The negative impact of baseline AF on the extent of FMR reduction, can therefore not be ascribed only to a differential effect on LV remodeling, and another mechanism should be considered.

Influence of AF on FMR

It is proposed that AF worsens FMR by means of i) mitral annular dilatation, and ii) atriogenic leaflet tethering (Figure 4).[20,21] Longstanding AF is firmly linked to LA enlargement.[22] Structurally, the mitral annulus is closely related to the LA, and due to the absence of a reinforcing fibrous skeleton, the posterolateral annulus is susceptible to stretching by longitudinal LA muscle fibers when the LA enlarges.[5] Mitral annular dilatation leads to a reduced coaptation area of the mitral leaflets, and subsequent worsening of FMR.[20] AF may worsen FMR by another mechanism, namely atriogenic leaflet tethering, which implies stretching of the posterior mitral leaflet across the LV wall by LA enlargement, with subsequent displacement/tethering of the anterior mitral valve leaflet away from the papillary muscles.[21] Two studies have reported an association between AF on the one hand, and an increased mitral annular area and FMR on the other hand.[23] In the present study we found evidence to support these mechanisms in the context of CRT, namely patients with baseline AF having an enlarged LA, less decrease in LA volume, a larger mitral annulus diameter, less mitral annular remodeling and worse FMR at 6 months' follow-up, compared to patients in SR at baseline. The decrease in mitral annular diameter is much more pronounced when measured in the parasternal long-axis view, compared to the apical 4-chamber view. This likely reflects the fact that long-axis measurement transects the fixed annulus and the unsupported part, while the apical 4-chamber measurement may still transect a second, fixed part of the mitral fibrous skeleton (Figure 5).

Effects of CRT on LA and mitral annular size

LA reverse remodeling has been documented after CRT, especially in responders to CRT.[10,24] The LA volume decreased from 66.8±25.2 cm^3 to 58.4±27.8 cm^3 in CRT responders (defined as a reduction of ≥10% LVESV) (P=0.014) in a study of 107 CRT recipients.[24]

The effect of CRT on the mitral annulus per se, has not been extensively investigated. In a study of 30 patients with heart failure and FMR, CRT led to an improvement of the mitral annulus area deformation (defined as diastolic mitral annulus area minus systolic mitral annulus area divided by diastolic mitral annulus area, percent) in responders (defined as a patient having a reduction of ≥15% LVESV) from 19±10% to 25±8%, while there was no change in non-responders (from 22±9% to 22±9%).[18] Conversely, in another study including 26 patients with FMR undergoing CRT, there was no immediate change in the mitral annulus diameter.[25]

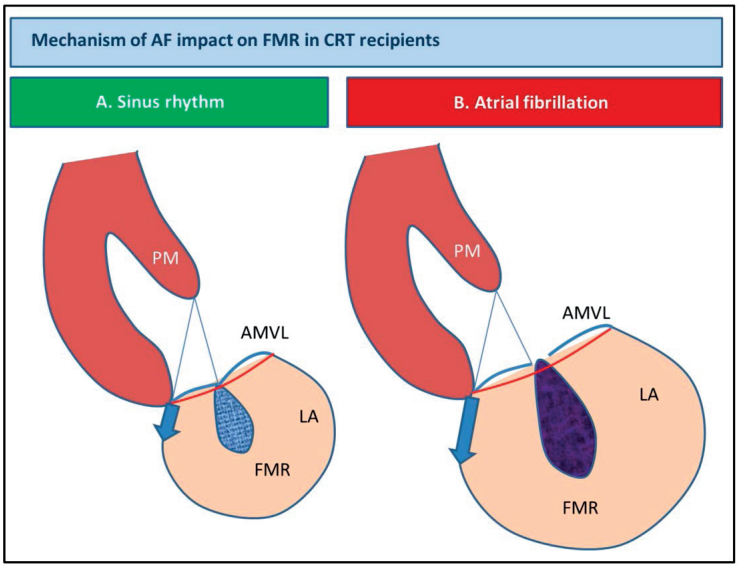

Figure 4: Mechanism of AF impact on FMR in CRT recipients. The mitral annulus (indicated in red) is closely related to the LA, and due to the absence of a reinforcing fibrous skeleton, the posterolateral annulus is susceptible to stretching by longitudinal LA muscle fibers when the LA enlarges (blue arrows indicate stretching forces of the LA on the posterolateral annulus). Mitral annular dilatation leads to a reduced coaptation area of the mitral leaflets (gap between the leaflets in B), and subsequent worsening of FMR. A CRT recipient with SR at baseline is shown in A), and a patient with AF at baseline in B). AF: atrial fibrillation, AMVL: anterior mitral valve leaflet, CRT: cardiac resynchronization therapy, FMR: functional mitral regurgitation, LA: left atrium, PM: papillary muscle, SR: sinus rhythm.

As far as the authors are aware, there are no reports in the literature that describe the differential effect of AF vs. SR at baseline on LA and mitral annulus reverse remodeling after CRT. Our data demonstrate that LA volume and mitral annular dimension are significantly larger after CRT in patients with moderate to severe FMR and AF at baseline, compared to those in SR at baseline.

In summary, baseline AF therefore appears to exert an inhibitory effect on LA and mitral annular reverse remodeling after CRT in patients with FMR. This resulted in less improvement in FMR in CRT recipients with baseline AF as compared to patients in SR at baseline.

Clinical implications

Since FMR response to CRT is of prognostic importance, and this response is impaired by AF, mitigating the negative influence of AF on FMR is an attractive therapeutic strategy. In 330 patients with permanent AF who received CRT, 34 (10.3%) spontaneously recovered SR at 4 months.[26] In contrast, in a study of 74 patients (27% with persistent AF and 73% with permanent AF), CRT did not induce spontaneous conversion to SR in any patient at 6 months of follow-up.[27] With the current findings, it is unclear if awaiting a spontaneous return to SR after CRT is the optimal strategy. Various additional treatment options could be considered

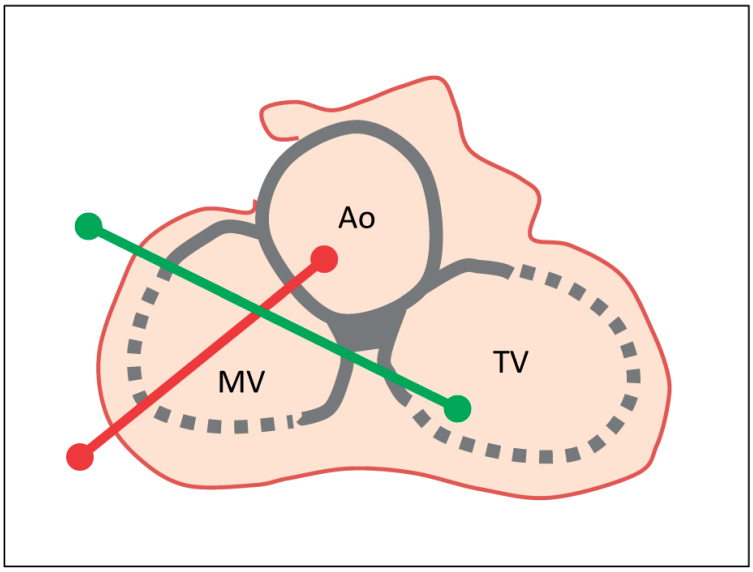

Figure 5: Differences in mitral annular remodeling, when measured in apical 4-chamber view and parasternal, long-axis view. The decrease in mitral annular diameter is much more pronounced when measured in the parasternal long-axis view, compared to the apical 4-chamber view. This likely reflects the fact that long-axis measurement (red line) transects the fixed annulus (solid grey line) and the unsupported part (dashed, grey line), while the apical 4- chamber measurement (green line) may still transect a second, fixed part of the mitral fibrous skeleton (solid grey line) in some patients. This will therefore underestimate the effect of cardiac resynchronization therapy on mitral annular remodeling. Ao: aorta, MV: mitral valve, TV: tricuspid valve.

to restore SR in AF patients, including pharmacological and electrical cardioversion, as well as catheter ablation. In a study by Gertz et al. 53 patients with moderate to severe FMR who underwent AF catheter ablation, the mitral annular dimension was significantly larger in those with recurrent AF compared to patients who remained in SR (3.48±0.34 cm vs. 3.24±0.32 cm, respectively; P=0.06) at one year.[28] In the same study, the LA volume was larger in patients with recurrent AF as compared to patients who remained in SR (66.4±18.4 ml vs. 52.4±12.7 ml, respectively; P=0.02) at one year follow-up.[28] Moreover, significant FMR at one year follow-up was observed in 24% of patients in SR as compared to 82% in patients with AF at one year follow-up (P=0.005).[28] Although this study was not performed in patients undergoing CRT, the results suggest that AF ablation has the potential to reduce FMR in CRT recipients by reducing LA volume and mitral annular diameter.

Currently, one trial investigated AF recurrence after radiofrequency catheter ablation in patients who previously underwent CRT; Di Biase et al. randomized CRT recipients to AF ablation or amiodarone use, with a minimum follow-up of 2 years.[6] The recurrence of AF was significantly lower in the patients undergoing ablation as compared to the patients using amiodarone (30% vs. 66%, respectively; P<0.001) and a significant mortality difference was observed in favour of ablation (8% vs. 18%; P=0.037).[6] The concept of an atrial myopathy has gained

attention in recent years, with those having more advanced electromechanical atrial disease (e.g. fibrosis, visualized with cardiac magnetic resonance imaging) responding less well to catheter ablation.[29] It is not inconceivable that patients with advanced atrial myopathy and/or long-standing AF will also respond suboptimally to ablative therapy in terms of FMR reduction. Even though the success rate of AF ablation is more variable in persistent and long-standing AF, mitral annular reverse remodeling and a decrease in AF recurrence in CRT patients were seen in those studies where such patients were included.[6, 28]

Recently, the Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial demonstrated lower all-cause mortality and heart failure hospitalization in heart failure patients with AF who underwent catheter ablation, when compared to medical therapy.[30] Of the patients who underwent ablation, 27% had a CRT device in situ.[30] Although reduction in FMR was not reported, this trial provides further support for the role of catheter ablation in the management of AF in heart failure patients, including those with CRT.

Study limitations

This was a single-center, retrospective study. The severity of FMR can be influenced by different hemodynamic conditions, although only hemodynamically stable patients were included in the current analysis. The differences between the amount of change in chamber dimensions (Table 2) of CRT recipients with SR and AF at baseline, have to be interpreted cautiously due to fairly large standard deviations.

CONCLUSIONS

Improvement of FMR is more often observed in CRT recipients in SR at baseline, as compared to patients with AF at baseline, despite a similar degree of LV reverse remodeling at 6 months after CRT. LA volume and mitral annular diameter are larger at 6 months in the patients with AF at baseline, suggesting that these mechanisms may relate to the adverse effect of AF on FMR improvement following CRT. AF rhythm control (especially by means of catheter ablation) is therefore a potential therapeutic target to improve FMR after CRT in patients with AF, although the response in those with permanent AF may be variable, compared to paroxysmal AF.

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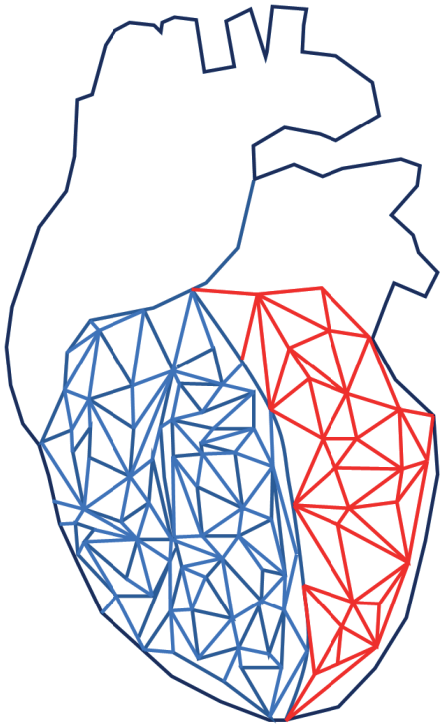
Part II:

Imaging approaches to risk-stratification of cardiac disease



8

Sudden cardiac death: the role of imaging

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Int J Cardiol 2017;237:15-18.

ABSTRACT

Sudden cardiac death (SCD) is defined as “a non-traumatic, unexpected, fatal event occurring within one hour of the onset of symptoms in an apparently healthy subject”, and it causes a fifth of all deaths worldwide. It often occurs in individuals not previously known with cardiac disease, which makes prevention challenging. The mechanism underlying SCD is thought to be a trigger (e.g. ischemia) acting upon a substrate (e.g. scar), causing a lethal arrhythmia. Primary prevention refers to patients at high risk of SCD and secondary prevention to those who have had an aborted episode of SCD. Insertion of an implantable, cardioverter-defibrillator (ICD) is the most effective approach to primary prevention; currently ICD candidate selection is based on a left ventricular ejection fraction (LVEF) ≤35%. The LVEF is neither sensitive nor specific in identifying individuals who will benefit from ICD therapy, and therefore alternative strategies are required. The present review article summarizes the evidence on various non-imaging (e.g. microvolt T-wave alternans, signal-averaged ECG, QRS fragmentation and measures of autonomic function) and imaging (echocardiography, cardiac magnetic resonance and radionuclide) modalities showing incremental value over LVEF to identify the patients who will benefit from an ICD.

INTRODUCTION

Sudden cardiac death (SCD) is defined as "a non-traumatic, unexpected, fatal event occurring within one hour of the onset of symptoms in an apparently healthy subject" in the guideline on management of patients with ventricular arrhythmias (VA) and the prevention of SCD of the European Society of Cardiology.[1] An unwitnessed death can be still be considered a SCD if the individual in question was in good health 24 hours before the event.[1] SCD accounts for more than 4 million deaths per year globally, which translates into one fifth of all recorded deaths.[1] About half of SCDs occur in individuals who are not known to have underlying heart disease before the fatal event, thus presenting a significant challenge to effective prevention.[1]

SCD: CAUSES, MECHANISMS AND PREVENTION

The most common cause of SCD is coronary artery disease, which accounts for up to 50% of SCD in white males. Other causes of SCD are: cardiomyopathies, cardiac hypertrophy, valvulopathies, myocarditis and primary electrical disorders.

The underlying mechanism of SCD is currently understood as a trigger which acts on a substrate, thereby causing a lethal arrhythmia (ventricular tachycardia or ventricular fibrillation) and subsequent hemodynamic instability. A typical example of such an interaction is myocardial ischemia (trigger) interacting with post-infarct myocardial scar (substrate) in the so-called peri-infarct zone. This zone represents a transition between the infarct core and healthy myocardium, and contains scar tissue which is interspersed with normal cardiomyocytes. Slow conduction of electrical impulses occurs in the peri-infarct zone, allowing the establishment of re-entry circuits and arrhythmias.

Prevention of SCD is twofold: primary, i.e. in patients deemed to be at high risk of SCD, or secondary, i.e. who have had an episode of SCD aborted spontaneously or by resuscitation efforts. The most effective strategy for both primary and secondary prevention of SCD is the implantable, cardioverter-defibrillator (ICD). Evidence for the use of the ICD in primary prevention arose from the Multicenter Automatic Defibrillator Implantation Trial (MADIT II) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).[2,3] The rate of SCD was decreased by more than 30% in patients with a myocardial infarction and a left ventricular ejection fraction (LVEF) of ≤30% in MADIT II.[2] Similarly, all-cause mortality was reduced by more than 20% in heart failure patients with LVEF ≤35% in SCD-HeFT.[3]

SELECTION OF ICD CANDIDATES: CURRENT PRACTISE

The decision to implant an ICD for primary prevention is currently based primarily on the LVEF. An LVEF ≤35% is a class Ia indication for ICD according to current European Society of Cardiology guidelines.[1] An exception to this recommendation are the patients with LVEF ≤35% within the first 6 weeks after myocardial infarction. This is based on the results of the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) showing that prophylactic ICD therapy within 40 days post-infarction failed to reduce all-cause mortality.[4]

However, LVEF ≤35% may not be sensitive enough to select ICD candidates for primary prevention. In the Oregon Sudden Unexpected Death Study (2 093 patients with SCD and 448 with echocardiographic data) only 20.5% of patients had LVEF ≤35%. Furthermore, a number of studies have demonstrated that appropriate therapy occurs in less than a third of ICD recipients with LVEF ≤35% (while still exposing them to potential complications of the device) (Table 1).[3,5-10] Accordingly, relying on LVEF alone for guiding selection of ICD candidates for primary prevention, may not be the ideal strategy.

Table 1: Summary of studies reporting the characteristics of patients with appropriate ICD therapy.

Study	Year published	No. of patients	LVEF (%)*	Duration of follow-up	Appropriate therapy (%)
Sabbag et al.[5]	2015	2 349	<40% in 66% of patients	2.5 years	2.6 (shock)
Weeke et al.[6]	2013	1 609	25 (20-30)	Mean 1.9±1.3 years	13.4 (shock & ATP) 7.8 (shock)
MacFadden et al.[7]	2012	3 822	29±11 (women) 31±14 (men)	1 year	15.3 (women) 21 (men) (shock & ATP)
Huikuri et al.[8]	2009	312	30±6	2 years	8 (VT/VF on loop recorder)
Chow et al.[9]	2008	575	24±4.8	Mean 2.1±0.9 years	11.1 (shock & ATP)
Bardy et al.[3]	2005	829	24 (19-30)	Median 3.8 years	21 (shock)
Moss et al.[10]	2004	720	23±5	3 years	35 (shock & ATP)

ATP: antitachycardia pacing, LVEF: left ventricular ejection fraction, VF: ventricular tachycardia, VT: ventricular fibrillation. *LVEF is presented as mean ± standard deviation or median and interquartile range.

PATIENT SELECTION BASED ON NON-IMAGING TECHNIQUES

Investigation of non-imaging approaches for SCD risk-stratification has been directed mainly at electrophysiological parameters, e.g. microvolt T-wave alternans (MTWA), signal-averaged ECG (SAECG), QRS fragmentation and measures of autonomic function (e.g. heart rate variability (HRV)).

MWTA is the consequence of abnormal handling of intracellular calcium and has been associated with increased risk of SCD in a study of 768 patients with ischemic cardiomyopathy (hazard ratio 2.29; P=0.049).[11] Late potentials, recorded in the terminal QRS complex, are the basis for an abnormal SAECG. VA and death occurred in 28% and 17% (P=0.0001) of patients with an abnormal and normal SAECG, respectively, after 5 years of follow-up in 1 925 patients with coronary artery disease.[12] Conversely, no clear link was established with VA or SCD in 313 patients referred for an electrophysiology study.[13] QRS fragmentation can be measured non-invasively with magnetocardiography, which records cardiac electromagnetic activity with detectors placed close to the thoracic wall. QRS fragmentation was significantly increased in patients with VA, compared to those without (67.8±24.3 vs. 55.4±26.3; P=0.006) in a study of 158 post-infarct patients.[14]

PATIENT SELECTION BASED ON NOVEL IMAGING TECHNIQUES

Strain echocardiography, late gadolinium contrast-enhanced (LGE) cardiac magnetic resonance (CMR) and nuclear imaging techniques have provided measures with incremental value over LVEF to identify the patients who may benefit from an ICD. These imaging modalities permit visualization of both triggers (e.g. myocardial ischemia) and substrates (e.g. scar) for SCD in ischemic and non-ischemic cardiomyopathy.

With speckle tracking echocardiography, the active deformation (strain) of the myocardium can be assessed as a measure of LV systolic function and as an indirect reflector of myocardial fibrosis/scar. Global longitudinal strain (GLS) has been independently associated with SCD, appropriate ICD therapy and VA in ischemic cardiomyopathy patients (Figure 1A-B), cardiac systemic sclerosis and in repaired tetralogy of Fallot.[15] In patients with myocardial infarction, the value of longitudinal strain in the peri-infarct zone predicts appropriate ICD therapy.[15] In addition, by measuring the time to peak longitudinal strain in 17 LV segments, LV mechanical dispersion can be assessed. A large LV mechanical dispersion suggests the presence of slow and heterogeneous electrical conduction of the LV myocardium (e.g. due to areas of scar) (Figure 1C). Each 10 ms increase in LV mechanical dispersion has been associated with increased risk of VA in 988 patients after acute ST-segment elevation myocardial infarction (hazard ratio 1.15; P=0.032).[15]

The presence and burden of myocardial scar detected with LGE-CMR relates to SCD, appropriate ICD therapy and VA in patients with ischemic and non-ischemic cardiomyopathies (Figure 1D-E).[16,17] Most importantly, quantification of the peri-infarct zone area with LGE-CMR has shown incremental prognostic value over the extent of myocardial scar, suggesting that the peri-infarct zone better reflects the substrate susceptible to develop VA. The size of the peri-infarct zone remains independently associated with all-cause mortality when corrected for LVEF (hazard ratio 1.42; P=0.002) and for scar burden (hazard ratio 1.25; P<0.001).[18]

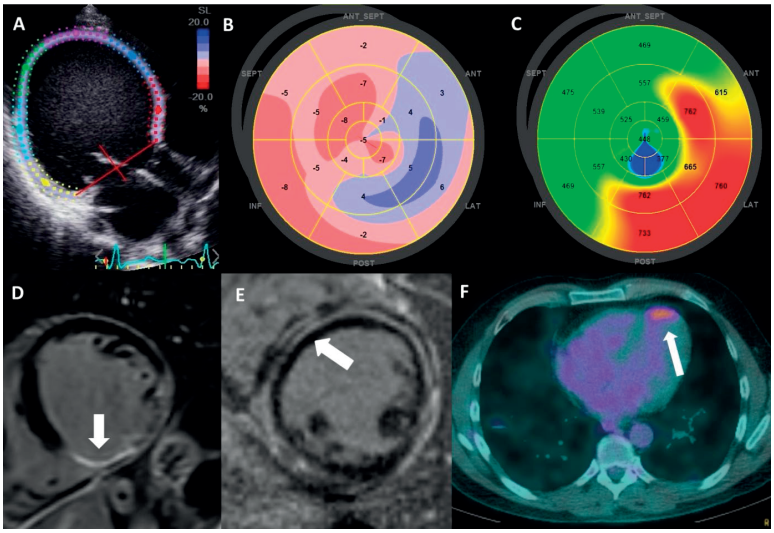

Figure 1: Imaging modalities to assess the risk of ventricular arrhythmias and sudden cardiac death. With speckle tracking echocardiography (A) left ventricular (LV) global longitudinal strain (B) and mechanical dispersion (C) can be assessed. Ischemic heart failure patient with dilated left ventricle (A) and significantly impaired LV global longitudinal strain, with LV segments coded in blue (signifying lengthening) and shades of red (signifying better shortening) (B) and large mechanical dispersion with the latest activated segments in the posterolateral regions (C). Thinned, inferoseptal and inferior, basal segments post-infarct, delineated by late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) imaging (D, arrow). Midwall-fibrosis of the interventricular septum in a patient with dilated cardiomyopathy, indicated by LGE-CMR imaging (E, arrow). Increased apical uptake of ^{18}F-fluorodeoxyglucose on a fused, positron emission tomography and computed tomography scan, indicating the location of cardiac inflammatory activity in a patient with sarcoidosis (F, arrow).

The use of radionuclide imaging for SCD assessment has focused on cardiac innervation. SCD and appropriate ICD therapy is more common in heart failure patients (ischemic and non-ischemic) with a high washout rate or a decreased heart/mediastinum uptake ratio (H/M) of Iodine-123 (^{123}I) metaiodobenzylguanidine (MIBG), an analogue of noradrenaline which indicates areas of myocardial denervation.[19] An H/M ratio ≥1.6 was independently associated with less SCD and VA in heart failure patients when taking LVEF into account (hazard ratio 0.36; P=0.006).[19]

Similarly, ^{123}I-MIBG imaging has proven useful to identify patients with hypertrophic cardiomyopathy and arrhythmogenic, right ventricular cardiomyopathy who are at risk of VA.[17] Using the radiopharmaceutical carbon-11-metahydroxyephedrine, positron emission tomography (PET) permits detection of sympathetic denervation in ischemic heart disease, which has been associated with increased risk for SCD. The presence of perfusion defects (rubidium-82) and inflammation (increased ^{18}F-fluorodeoxyglucose (FDG) uptake) on PET are predictive of VA in patients with cardiac sarcoidosis. Integrated PET-computed tomography scans identify the location of cardiac inflammation with ^{18}F-FDG uptake, and can diagnose extra-cardiac disease and thoracic lymphadenopathy (Figure 1F).

CONCLUSIONS

Although contemporary selection of ICD candidates for primary prevention is based on an LVEF ≤35%, novel non-imaging and imaging-based strategies have demonstrated incremental value over using LVEF in isolation. Prospective trials are required to validate the benefit of imaging techniques in the appropriate selection of ICD candidates.

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9

Risk stratification of genetic, dilated cardiomyopathies associated with neuromuscular disorders: role of cardiac imaging

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ABSTRACT

The etiology of dilated cardiomyopathy (DCM) can be grouped as either genetic or non-genetic. More than 50 pathogenic genes have been described, with sarcomeric and lamin A/C mutations being the most common. Mutation carriers for genetic DCM are often asymptomatic until cardiac disease manifests with heart failure, arrhythmias or sudden cardiac death. Preventive strategies are promising, but can only be applied and tested adequately if genetic DCM can be diagnosed at an early stage. Early diagnosis of mutation carriers that may develop overt DCM requires advanced imaging techniques that can detect subtle structural and functional abnormalities. Advanced echocardiographic techniques such as tissue Doppler imaging and speckle tracking strain analysis permit early detection of functional abnormalities, whereas cardiovascular magnetic resonance (CMR) techniques provide information on tissue characterization and myocardial energetics that may be altered at an early stage. Furthermore, nuclear imaging techniques provide information on cellular function (metabolism, perfusion). Once the diagnosis of overt DCM has been established, various imaging parameters such as echocardiography-based myocardial mechanics and CMR-based tissue characterization have shown incremental benefit to left ventricular ejection fraction in risk-stratification. Further research is required to understand how imaging techniques may help to choose management strategies which could delay progression when instituted early in the course of the disease. The present article reviews the role of imaging in the risk-stratification of genetic DCM in general, with specific emphasis on DCM associated with neuromuscular disorders.

INTRODUCTION

Dilated cardiomyopathy (DCM) is defined as "left ventricular (LV) or biventricular systolic dysfunction and dilation that are not explained by abnormal loading conditions or coronary artery disease".[1] Ischemic heart disease is therefore excluded by definition, and etiologies of DCM are divided into two major groups: genetic and non-genetic.[1] The distinction between genetic and non-genetic DCM is sometimes less clear, since the likelihood of certain non-genetic etiologies (e.g. chemotherapy) of causing DCM can be superimposed on the genetic susceptibility of an individual.[1]

More than 50 pathogenic genes have been described, with sarcomeric and lamin A/C mutations being the most common, but defects of the desmosome, nucleus, mitochondrion, lysosome and ion channels are also associated with the development of DCM.[2,3] More than one pathogenic mutation may be present in a single individual, and this may be (at least in part) responsible for the large variation in penetrance of many of the genetic defects causing DCM.[4]

The clinical manifestations of a genetic defect can vary from being "preclinical" (mutation carrier without clinical manifestations, LV dilation without hypokinesia or arrhythmias) to "clinical" (hypokinetic but non-dilated cardiomyopathy or DCM).[1] The entity of hypokinetic but non-dilated cardiomyopathy has recently been formally defined as "hypokinesia without significant LV dilation".[1]

Early diagnosis of mutation carriers who may develop overt DCM requires advanced imaging techniques that detect subtle structural and/or functional abnormalities. Advanced echocardiographic techniques such as tissue Doppler imaging and speckle tracking strain analysis permit early detection of functional abnormalities, whereas cardiovascular magnetic resonance (CMR) techniques provide information on tissue characterization and myocardial energetics that may be altered at an early stage. Furthermore, nuclear imaging techniques provide information on cellular function (metabolism, perfusion). The evidence supporting these imaging techniques in the diagnosis and risk-stratification of patients with DCM is accumulating, specifically in DCM associated with neuromuscular disorders (genetics and extracardiac features: Table 1).[5-7] The present article reviews the role of imaging in the early diagnosis and risk-stratification in established disease of patients with DCM associated with neuromuscular disorders.

EARLY DIAGNOSIS OF VENTRICULAR DYSFUNCTION IN DCM ASSOCIATED WITH NEUROMUSCULAR DISORDERS

Early diagnosis is integral to the process of risk-stratification in DCM, since patients often remain asymptomatic until cardiac disease manifests with heart failure, life-threatening arrhythmias or sudden cardiac death.[8,9] The onset or progression of ventricular systolic dysfunction and the development of myocardial fibrosis may be slowed by early initiation of therapy resulting eventually in improved prognosis.

Examples include: the early use of systemic steroids, angiotensin-converting enzyme (ACE)-inhibitors or beta-blockers in patients with Duchenne muscular dystrophy (DMD).[10-16] Barber et al.[16] demonstrated in 462 patients with DMD that every year of steroid treatment decreased the probability of developing cardiomyopathy (defined by abnormal LV fractional shortening or ejection fraction (EF)) by 4%. Additionally, in a randomized, double-blind study of 56 DMD patients with normal LVEF, ACE-inhibitors delayed the onset of LV systolic dysfunction (P=0.02).[11] In a similar fashion, either an ACE-inhibitor or a beta-blocker improved LV fractional shortening in patients with DMD and Becker muscular dystrophy and cardiac involvement (P<0.05).[15] Experimental therapies hold promise of influencing disease processes when initiated early, e.g. the membrane sealant poloxamer (which repairs damaged biologic membranes), growth hormone treatment or gene therapy in DMD.[17-19] Approaches to early diagnosis have focused on advanced imaging techniques to demonstrate abnormalities of cardiac structure, and mechanical as well as cellular function.

Table 1: Neuromuscular diseases which are associated with genetic, dilated cardiomyopathies (DCM).[5-7]

Disorder	Abnormal gene/ protein; chromosome	Mode(s) of transmission	Clinical features (extracardiac)
Duchenne muscular dystrophy	Dystrophin; Xp21	X-linked recessive	• Proximal, skeletal muscle weakness • Respiratory failure
Becker muscular dystrophy	Dystrophin; Xp21	X-linked recessive	Similar to Duchenne muscular dystrophy, but more benign course
Emery-Dreifuss muscular dystrophy	• Emerin; Xq28, Xq26 • Lamin A/C; 1q21	• X-linked recessive • Autosomal dominant • Autosomal recessive	• Contractures, e.g. Achilles tendons and elbows • Humero-peroneal muscle weakness & wasting
Limb-girdle muscular dystrophy	• FKRP, 19q • Lamin A/C; 1q22	• Autosomal recessive • Autosomal dominant	Weakness of shoulder and pelvic girdles
Myotonic dystrophy	• DMPK; 19q13 (type I) • ZNF9; 3q21 (type II)	Autosomal dominant	• Skeletal muscle weakness, e.g. facial, sternocleidomastoid and intrinsic muscles of hand • Myotonia (slow relaxation after contraction) • Non-muscular, e.g. cataracts, insulin resistance
Friedreich ataxia	FXN; 9q13	Autosomal recessive	• Ataxia of gait and limbs • Abnormal reflexes: absence of deep tendon reflexes and extensor plantar responses • Loss of position and vibration sense in lower limbs

DMPK: myotonic dystrophy protein kinase, FKRP: fukutin-related protein, FXN: frataxin, ZNF9: zinc finger protein 9.

Cardiac structure

Increased extracellular matrix and fibrosis of the myocardium are the hallmark of changes in the cardiac structure in DCM. Myocardial late gadolinium enhancement (LGE) allows the non-invasive detection of replacement myocardial fibrosis with CMR imaging.[20] Segmental LGE has been demonstrated in individuals with DMD and Becker muscular dystrophy before the onset of LV or right ventricular systolic dysfunction, and may therefore indicate early disease (Figure 1).[20-24] Similarly, segmental LGE has been visualised in carriers of lamin A/C mutations and in patients with myotonic dystrophy and preserved LVEF.[25-28] Segmental LGE has also been detected in mitochondrial diseases with cardiac involvement (chronic progressive external ophthalmoplegia and Kearns-Sayre syndrome) but normal LV systolic function.[29]

However, in early phases of DCM, reactive fibrosis (increase of interstitial space by deposition of collagen) rather than replacement fibrosis is present. This reactive fibrosis is detected with T1 mapping CMR imaging techniques. For example, longitudinal relaxation is described by a T1 recovery curve, and the time constant (when 63% of recovery has occurred) of such a curve can be represented by a pixelwise, colour-coded map (a T1 map).[30] Increased reactive fibrosis will result in long T1 times in native T1 maps (acquired without the use of a gadolinium-based contrast agent). In contrast, when T1 maps are registered after gadolinium-based contrast media administration, the T1 times are shorter in segments with increased fibrosis as compared to normal myocardium.[31]

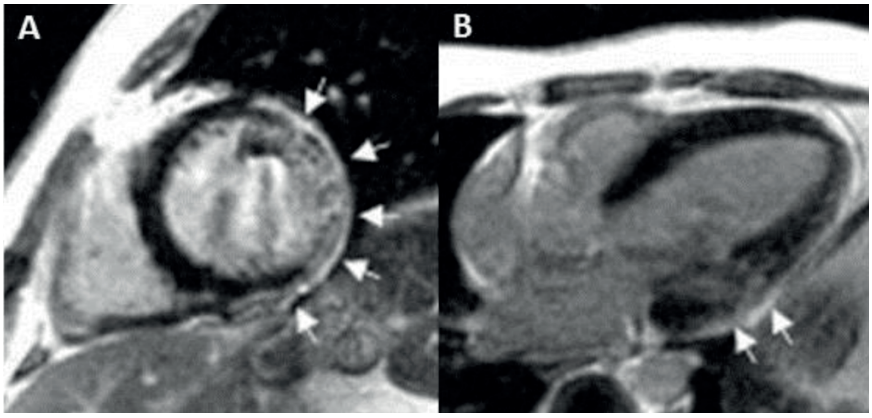

Figure 1: Cardiac magnetic resonance with late gadolinium enhancement (LGE) in a patient with Becker muscular dystrophy. Transmural fibrosis in the lateral free wall of the left ventricle in a short-axis view (indicated by arrows) (A) and a horizontal long-axis view (B). Adapted with permission from Yilmaz et al.[21]

Different CMR sequences are employed in T1 mapping, e.g. modified Look-Locker Inversion (MOLLI) recovery and shortened MOLLI (ShMOLLI).[30] The extracellular volume fraction (ECV) of the myocardium, which is a measure of the size of the extracellular space, can be calculated from the native myocardial and precontrast blood T1 values, the post-contrast myocardial and blood T1 values, as well as the haematocrit.[32] Interstitial, reactive myocardial fibrosis, re-

presenting an early form of myocardial damage, can be both diagnosed and quantified by T1 mapping and ECV calculation.[33] An elevated ECV was found in lamin A/C mutation carriers with normal LV systolic function, and even in some individuals without LGE. ECV may therefore be an even more sensitive marker of early disease than LGE.[34] An elevated ECV and native T1 values have also been documented in patients with DMD and normal LV systolic function (including some without LGE) (Figure 2).[35-37] T1 mapping may be particularly suited to the investigation of cardiac involvement in myotonic dystrophy, since fibrosis is most frequently diffuse, rather than localised, in this condition.[38] Postcontrast T1 values were significantly lower in a group of individuals diagnosed with type 1 and type 2 myotonic dystrophy and normal LV systolic function, compared to controls.[38] Segmentally-increased ECV and focal lipid deposits have been described in patients affected with type 2 myotonic dystrophy and preserved LV systolic function – including regions without LGE – supporting the concept that reactive, diffuse fibrosis is a very sensitive marker of cardiac involvement.[28]

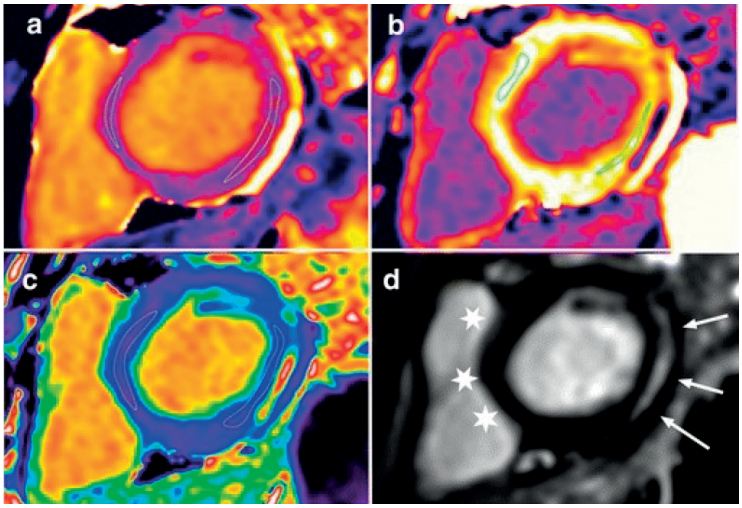

Figure 2: Cardiac magnetic resonance T1 mapping in a patient with Duchenne muscular dystrophy, demonstrating fibrosis of the lateral wall in short-axis views. The images show a native T1 map of the left ventricle (a) a post-contrast T1 map, (b) an extracellular volume (ECV) map, and (c) late gadolinium enhancement (LGE), with arrows indicating LGE of the lateral wall and stars denoting normal, septal myocardium (d). Reproduced with permission from Olivieri et al.[35]

Myocardial tissue characterization can also be performed with echocardiography by analysis of the reflected ultrasound signal, which is known as integrated backscatter (IBS). Two parameters are generally measured in the anteroseptal and posterior walls of the left ventricle which include the magnitude of cyclical variation and the IBS intensity (both expressed in dB).[39,40] A decrease in the magnitude of cyclical variation denotes an increase in myocardial collagen content, even though it can be influenced by myocardial water content, myofibril architecture and contractility, while the degree of IBS intensity shows a correlation with myocardial fibrosis.[39,40]

In a study of 25 patients with DMD, the IBS intensity was higher, and the magnitude of cyclical variation lower, in the outer half of the LV myocardium compared to controls, suggesting epicardial fibrosis.[39] Similarly, a lower magnitude of cyclical variation and a higher IBS intensity were noted in 20 children with DMD, compared to age-matched controls (Figure 3).[41]

Mechanical function

Although LVEF is the measure of choice to characterize LV systolic function, subtle changes in myocardial function can be detected with more sensitive measures based on deformation and tissue velocity imaging. Myocardial deformation can be quantified by strain, which reflects a unitless measure of change in dimension.[42] Echocardiographic strain imaging is most commonly performed with speckle tracking echocardiography. Myocardial "speckles", which arise from the interaction of ultrasound and myocardium, are identified by imaging software and their displacement followed from frame to frame.[42] Strain is most commonly reported in the longitudinal, radial or circumferential directions of LV deformation and can be reported at segmental level (pertaining only to one segment of the ventricle) or global level (reflecting all segments of the ventricle).[43] Global LV longitudinal strain is the deformation parameter which has been most extensively studied, and demonstrates the best reproducibility. Myocardial strain imaging has demonstrated value in both the early diagnosis and risk-stratification of various cardiac diseases, including genetic and non-genetic cardiomyopathies.[43] Different CMR techniques can also be employed to measure strain, e.g. myocardial tagging and feature tracking.[44,45]

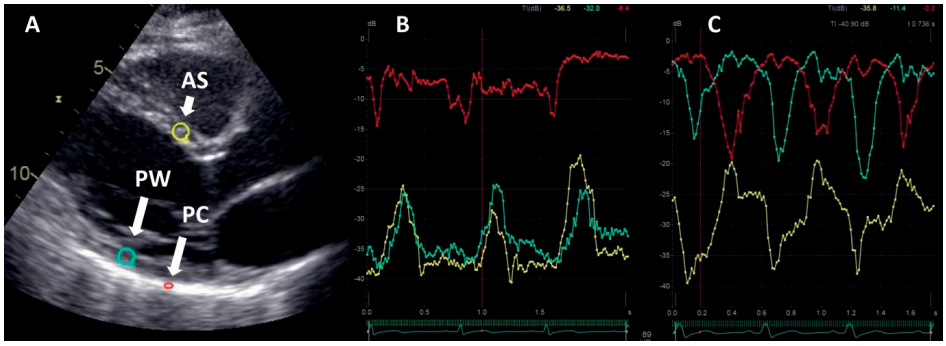

Figure 3: Integrated backscatter (IBS) in a patient with Duchenne muscular dystrophy. Assessment of the basal anterior septum (AS), basal posterior wall (PW) and pericardium (PC) by placement of regions of interest on a parasternal, long-axis view (A). Tracking of IBS during three cardiac cycles with color coding: anterior septum (yellow curve), posterior wall (blue curve) and pericardium (red curve) in a normal individual (B). The cyclic variations of IBS are clearly visible. IBS values of the posterior wall (blue curve) are similar to the pericardium (red curve) in a patient with Duchenne muscular dystrophy, suggesting myocardial fibrosis (C).

Impaired LV longitudinal, circumferential and radial strain, as well as reduced longitudinal and radial strain rates (using speckle tracking echocardiography) have been reported in individuals with DMD and normal LVEF on echocardiography or CMR.[46-51] Impaired segmental LV systolic

and diastolic radial strain rates were noted in patients with Becker muscular dystrophy and a normal LVEF.[52] Reduced LV segmental, circumferential strain (despite normal LVEF) was observed in patients with Emery-Dreifuss muscular dystrophy due to lamin A/C mutations.[53] An abnormal transmural LV strain pattern (comparing endo-, mid- and epicardial strain values) was identified in patients with DMD and preserved LVEF.[54]

The myocardial tissue velocity can be determined by tissue Doppler echocardiography during both systole and diastole.[55,56] Systolic myocardial tissue velocity is a reflection of longitudinal LV function, which is caused by endocardial fibre shortening, while diastolic myocardial tissue velocity is a surrogate of early diastolic, LV relaxation.[57] Impaired LV systolic and diastolic myocardial tissue velocities are markers of early cardiac disease and have been associated with outcome in various cardiac disorders.[57-60] Systolic and diastolic LV tissue velocities are reduced in patients with DMD and Friedreich ataxia who display a normal LVEF.[47,48,61-63] Similarly, systolic and diastolic LV tissue velocities are impaired in patients with myotonic dystrophy with a normal LVEF.[64,65]

In a normal heart, LV endocardial velocity (measured with tissue Doppler imaging) is greater than epicardial velocity, which reflects the rate of increase in wall thickening with contraction. The myocardial velocity gradient is the difference in myocardial velocity between the endo- and epicardium, divided by the myocardial wall thickening, and is an index of regional myocardial function.[66] Abnormal myocardial velocity gradients were identified in the interventricular septum, as well as the posterior wall of the left ventricle, in patients with Friedreich ataxia, DMD and Emery-Dreifuss muscular dystrophy (in the presence of a lamin A/C mutation) and preserved LV systolic function.[53,67,68]

Cellular function

Phosporus-31 magnetic resonance spectroscopy (^{31}P-MRS) allows non-invasive examination of cardiac energetics by quantification of high-energy phosphate metabolites.[69] Altered cardiac energetics are early markers of cardiomyopathy, often preceding morphological and overt functional abnormalities. Evaluation of LV myocardial metabolism can be obtained on a cellular level with ^{31}P-MRS.[70] Current 1.5T and 3T scanners do not allow voxel sizes with a spatial resolution which is high enough to produce spectra of individual myocardial segments (according to the American Heart Association 17-segment model) and subsequently, a volume of interest is placed in either the anterior LV wall or the interventricular septum.[71,72] Peaks in the ^{31}P-MR spectra reflect the concentrations of the three phosphorous atoms of adenosine triphosphate (ATP), i.e. γ-ATP, α-ATP and β-ATP, as well as phosphocreatine (PCr) (Figure 4).[69] From the ATP and PCr concentrations, the ratio of PCr to ATP can be calculated, which is influenced by abnormal cardiac metabolism in disease states. The reaction equilibrium of the creatine kinase reaction favours the synthesis of ATP rather than PCr, leading to a reduction in PCr when ATP demand is in excess of ATP supply – the consequence of which is a decrease in the PCr:ATP ratio.[69]

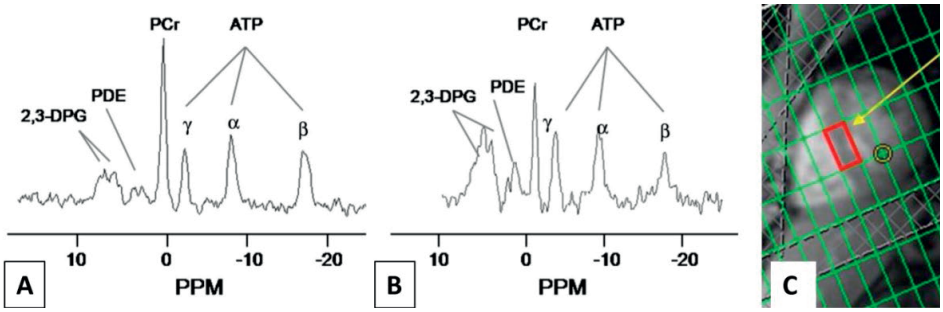

Figure 4: ^{31}P-magnetic resonance spectroscopy. The spectrum of a healthy individual, demonstrating peaks for 2,3-diphosphoglycerate (2,3-DPG), phosphodiesters (PDE), phosphocreatine (PCr), γ-adenosine triphosphate (ATP), α-ATP and β-ATP (A). Reduced PCr:ATP ratio in a patient with dilated cardiomyopathy (B). Region of interventricular septum in a short-axis view (red box, indicated by yellow arrow) for which quantification of myocardial metabolites is performed with ^{31}P-magnetic resonance spectroscopy (C). PPM: parts per million. Adapted with permission from Holloway et al.[71]

Some carriers of Xp21 mutations (the gene encoding dystrophin, causing DMD and Becker muscular dystrophy) with normal LV wall thickness, systolic and diastolic function, nevertheless manifest a reduced PCr/ATP.[73] Abnormal cardiac energetics, diagnosed with ^{31}P-MRS, may therefore also be a signal of early cardiac involvement in such patients. Similarly, a reduced myocardial PCr/ATP has been detected in patients with myotonic dystrophy, Friedreich ataxia and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome – all without evident structural or functional heart disease.[7,70,74] Additionally, ^{31}P-MRS can be used to interrogate skeletal muscle energetics, thereby allowing a comprehensive assessment of cardio-neuromuscular disorders.[70]

Nuclear imaging can also evaluate the cellular integrity and function. Global and regional myocardial perfusion can be visualised with gated imaging with single-photon emission computed tomography (SPECT).[75] Dystrophin-deficient myocardium is more vulnerable to pressure overload than normal myocardium, particularly in the LV inferior wall which is exposed to greater wall stress than other segments of the left ventricle.[8] Patients with DMD and Becker muscular dystrophy may show myocardial perfusion defects in the LV inferior wall on ^{99m}technetium SPECT imaging.[8] In addition, the myocardial cells of the LV apical segments are rich in dystrophin protein and may also show myocardial perfusion defects (Figure 5). This technique has not only shown potential for the early identification of cardiac involvement, but also for monitoring treatment response to systemic steroid therapy in DMD.[8] After a follow-up period of two years in patients with DMD who received systemic steroids, a significant improvement in myocardial perfusion was detected while no change was evident in LV dimensions or LVEF.[8] Positron emission tomography (PET) imaging, using ^{13}N-ammonia as tracer, can image myocardial perfusion, as well as ^{99m}technetium SPECT; the advantage of PET over SPECT is that PET permits absolute quantification of processes, whereas SPECT provides semiquantitative measurements.[75] Furthermore, myocardial metabolism can be investigated with ^{18}F-fluorodeoxyglucose

(FDG) PET.[75] Patients with DMD and normal LVEF have shown reduced myocardial perfusion in the LV posterobasal and posterolateral segments on ^{13}N-ammonia PET, whereas the uptake of ^{18}F-FDG was increased, suggesting the presence of regional metabolic alteration in uptake and trapping, a reduction in regional blood flow or both.[76]

RISK-STRATIFICATION IN ESTABLISHED DISEASE

Once a diagnosis of genetic DCM has been established, risk-stratification is of paramount importance. Risk may entail ventricular arrhythmias, incident heart failure or sudden cardiac death. Various imaging parameters of myocardial structure and function have been identified which may be useful in risk-stratification.

Cardiac structure

LGE of the interventricular septum (denoting myocardial fibrosis), was associated with ventricular arrhythmias in a cohort of lamin A/C mutation carriers with a normal LVEF (LGE was present only in patients experiencing ventricular arrhythmias, P=0.007), and may therefore help to risk-stratify these individuals, who are at high risk of ventricular arrhythmias and sudden cardiac death.[27] Patients with Friedreich ataxia and cardiac involvement experienced more frequent cardiac symptoms in the presence of LGE: after 12 months of follow-up, 3 of 14 (20%) patients with LGE experienced cardiac events, while no events were recorded in LGE-negative patients (P=0.1).[77] Not only the presence of LGE, but also the extent thereof may be important in the quantification of risk: transmural LGE in patients with DMD or Becker muscular dystrophy was an independent predictor of ventricular tachycardia and hospitalization for heart failure (hazard ratio (HR) 2.89; 95% confidence interval (CI) 1.09-7.68; P=0.033) regardless of preserved or reduced LVEF.[78]

The presence of LGE in patients with DMD has been associated with the development of heart failure symptoms and impaired LVEF (64±6% in LGE-negative patients vs. 57±7% in LGE-positive patients; P=0.014), while the extent of LGE has been correlated with the degree of decline in LVEF over time (2.2±0.31% decline per year in LGE-positive patients vs. 0.21±0.22% decline per year in LGE-negative patients; P=0.34).[79,80] LGE is therefore a potential marker of not only the presence of heart failure, but also of its progression.[79,80]

An increased ECV has been associated with arrhythmias (odds ratio (OR) 1.97; 95% CI 1.21-32.22; P=0.032) in patients with Becker muscular dystrophy, while the presence of LGE per se (considered in a binary fashion) was not.[81] While the presence of LGE is useful in the diagnosis of cardiac involvement in Becker muscular dystrophy, quantification of ECV may have more utility in risk-stratification.[81]

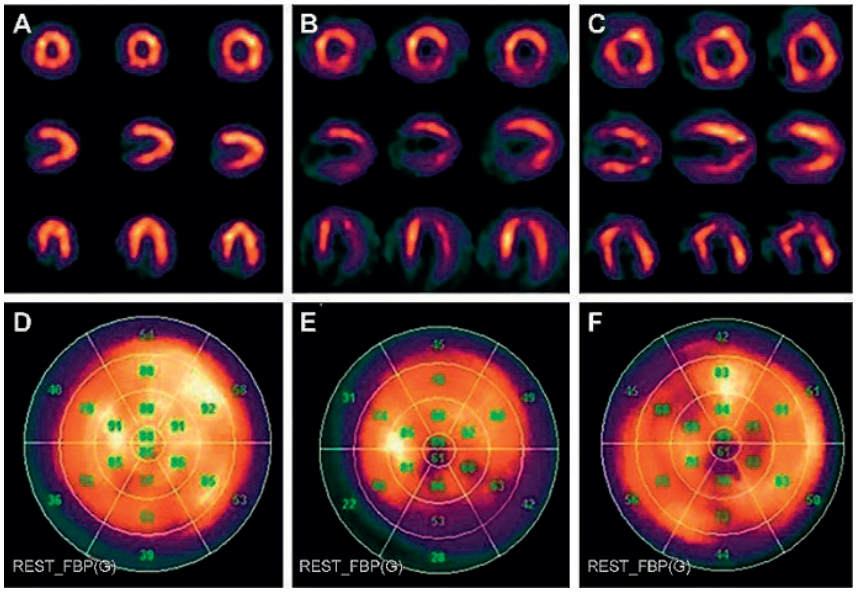

Figure 5: Myocardial perfusion defects at rest assessed with ^{99m}technetium single-photon emission computed tomography in three patients with Duchenne muscular dystrophy. Cross-sectional myocardial perfusion images are displayed in A-C panels (short-axis, horizontal long-axis and the vertical long axis from top to bottom) and the polar maps are presented in panels D-F. The patient presented in panels A and D shows normal myocardial perfusion whereas the patients in panels B/E and C/F show perfusion defects in the inferior and apical segments. REST_FBP: filtered back projection images acquired at rest, (G): gated. Reproduced with permission from Zhang et al.[8]

Mechanical function

In 88 patients with DMD or Becker muscular dystrophy and cardiac involvement, an LVEF <45% independently predicted ventricular tachycardia and hospitalization for heart failure (HR 0.94; 95% CI 0.89-0.97; P=0.001).[78] Similarly, an LVEF <45% was associated with appropriate implantable cardioverter-defibrillator therapy and sudden cardiac death (HR 4.4; 95% CI 1.7-11.0; P=0.021) in lamin A/C mutation carriers.[82]

However, in patients with preserved LVEF, strain imaging may refine the risk-stratification of these patients. Longitudinal, septal (averaged from four septal segments) strain, measured with speckle tracking echocardiography, was reduced when compared to longitudinal strain in non-septal segments of the LV in 41 lamin A/C mutation carriers (Figure 6).[27] In the same study, reduced septal strain correlated with the PR-interval on electrocardiography (R=0.41, P=0.03), while a prolonged PR-interval was associated with ventricular arrhythmias (P<0.001).[27]

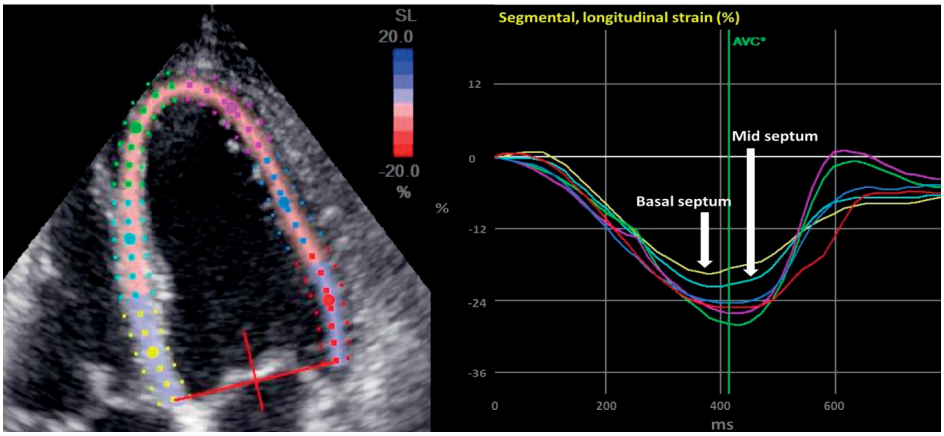

Figure 6: Impaired septal strain in a patient with lamin A/C mutation. Longitudinal strain is assessed with 2-dimensional speckle tracking echocardiography in the apical 4-chamber view. Different myocardial segments are indicated by different colours. White arrows identify impaired strain curves from the inferoseptal basal and midventricular myocardial segments. AVC: aortic valve closure.

In addition, LV mechanical dispersion measures the standard deviation of the time to peak systolic deformation of 16-17 segments of the left ventricle, and is an application of strain imaging performed with speckle tracking echocardiography.[83,84] LV mechanical dispersion is an indicator of the degree of mechanical heterogeneity, and has been associated with ventricular arrhythmias in a number of different cardiac pathologies.[83,85,86] Increased mechanical dispersion has been reported in lamin A/C mutation carriers with ventricular arrhythmias as compared with mutation carriers without ventricular arrhythmias (49±14 ms vs. 38±10 ms; P=0.02), while LVEF alone could not distinguish between individuals with and without ventricular arrhythmias (Figure 7).[87]

CLINICAL INTEGRATION OF CARDIAC IMAGING IN RISK-STRATIFICATION OF GENETIC DCM ASSOCIATED WITH NEUROMUSCULAR DISORDERS

Position statements on the diagnosis, risk-stratification and treatment of DCM (including the role of genetic testing) have been published by the American Heart Association and the European Society of Cardiology.[1,9,88] Based on the abovementioned position statements, an algorithm can be proposed which integrates cardiac imaging modalities into the risk-stratification of genetic DCM (Figure 8).

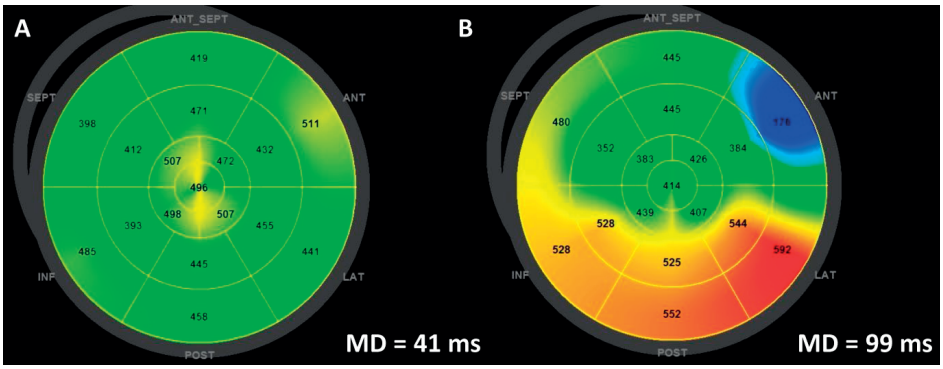

Figure 7: Segmental mechanical dispersion (MD) displayed in a parametric map of the left ventricle. In a lamin A/C mutation carrier without ventricular arrhythmias, all segments are activated simultaneously (panel A). A patient with a lamin A/C mutation and ventricular arrhythmias, in whom late activation of the inferior and posterior and segments (orange-red areas) is present, resulting in increased mechanical dispersion (MD) (panel B).

Although there are no specific position statements for genetic DCM associated with neuromuscular disorders, the principles are similar, and therefore, it can be applied to these genetic conditions. This algorithm (Figure 8) includes both early diagnosis and risk-stratification of established disease. In general, it is not recommended to screen children before the age of 10-12 years.[88] There are two approaches to screening family members of an index patient (the proband) with genetic DCM: genetic and clinical cascade screening. Genetic cascade screening involves testing family members for the specific mutation present in the proband. If the result is negative, no risk exists for development of the specific, genetic DCM, and further screening is not required.[88] If: i) genetic screening is not available, ii) the mutation is present, or iii) no disease-causing mutation can be found in the proband, clinical cascade screening is indicated. This involves history-taking, physical examination, a 12-lead ECG and transthoracic echocardiography.

If the LVEF is reduced (≤50%) or the LV end-diastolic diameter or volume is increased, the presence of disease is established.[1] Genetic testing to risk-stratify patients with established disease is of limited utility, except in lamin A/C mutations, which portend a high risk.[88] Advanced cardiac imaging can be used to further risk-stratify these individuals by means of early diagnosis: LV longitudinal strain and mechanical dispersion can be derived from routinely-acquired, 2-dimensional echocardiographic data without additional cost. When echocardiography does not provide a definitive answer regarding the presence/absence of disease, or when the echocardiographic window is suboptimal, CMR can be considered.

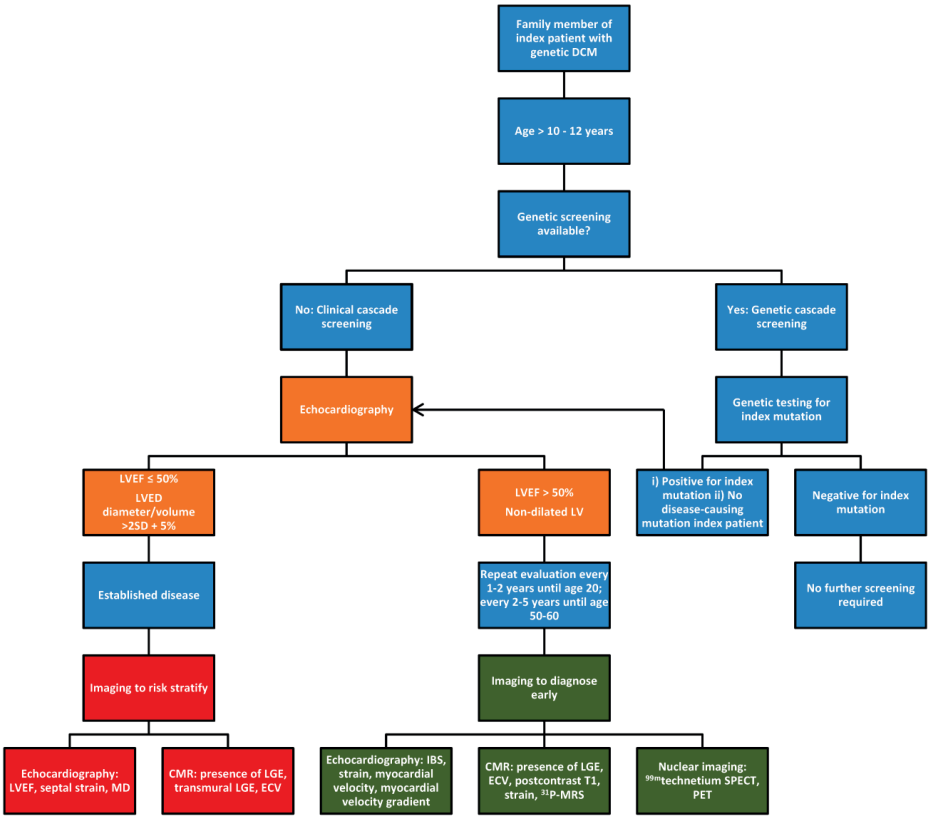

Figure 8: Proposed algorithm for integration of cardiac imaging in risk-stratification of genetic, dilated cardiomyopathy (DCM). Color coding denotes the following: blue = guideline-directed approach for risk-stratification, orange = guideline-based role for imaging, red = suggested role of imaging in risk-stratification for established disease, green = suggested role of imaging for early diagnosis.

If the LVEF is preserved (>50%) and/or the left ventricle is not dilated, clinical cascade screening has to be repeated at 1-2 yearly intervals until the age of 20 years, and every 2-5 years until the age of 50-60 years.[88] Transthoracic echocardiography is included in each screening event. For the risk-stratification of established disease, assessment of IBS, strain and myocardial velocities on clinically acquired echocardiographic data could help identify patients with increased risk of progression of the disease or ventricular arrhythmias. However, the impact of these measures on the clinical management of the patients is still being evaluated. Similar to risk-stratification for established disease, CMR can be performed when uncertainty remains. If contrast is administered for LGE, post-contrast T1 maps and ECV calculation can be performed. Strain imaging and ^{31}P-MRS are promising but still considered investigational techniques. Nuclear imaging techniques can be considered if requested for additional indications, e.g. exclusion of coronary artery disease as potential cause of cardiomyopathy.

The clinical applicability of various imaging techniques is summarized in Table 2. In general, the reproducibility of imaging parameters is good in genetic DCM (Table 3). In the absence of studies comparing different imaging modalities and parameters for risk-stratification of genetic DCM, a specific order of testing cannot be recommended currently, and the sequence of imaging modalities will depend more on the availability, cost and concomitant indications, as discussed above.

Table 2: Summary of imaging techniques and their clinical applicability.

Substrate	Imaging modality	Imaging technique	General use
Cardiac structure	**CMR**	LGE	Routine
		Native T1 mapping	Investigational
		Post-contrast T1 mapping	Investigational
		ECV	Investigational
	Echocardiography	IBS	Investigational
Mechanical function	**Echocardiography**	LVEF	Routine
		LV global longitudinal strain	Investigational
		LV global circumferential strain	Investigational
		LV systolic myocardial tissue velocity	Investigational
		LV diastolic myocardial tissue velocity	Investigational
		LV myocardial velocity gradient	Investigational
		Mechanical dispersion	Investigational
	CMR	CMR circumferential strain	Investigational
Cellular function (metabolism, perfusion)	**CMR**	^{31}P-MRS (metabolism)	Investigational
	Nuclear imaging	^{99m}technetium SPECT (perfusion)	Routine
		PET (perfusion, metabolism)	Routine

CMR: cardiac magnetic resonance imaging, ECV: extracellular volume fraction, IBS: integrated backscatter, LGE: late gadolinium enhancement, LV: left ventricular, LVEF: left ventricular ejection fraction, PET: positron emission tomography, ^{31}P-MRS: phosphorous-31 magnetic resonance spectroscopy, SPECT: single-photon emission computed tomography.

CURRENT STATE OF KNOWLEDGE AND FUTURE PERSPECTIVES

Even though the diagnostic role of cardiac imaging is well defined for genetic DCM, there are two evident research opportunities, where imaging will play a pivotal role: the prediction of outcome with imaging parameters and the benefit of early therapy in the prevention (or inhibition of progression) of genetic DCM. Lack of data regarding early therapy may be partly ascribed to the absence of effective, directed therapies. Prospective trials will be required to obtain evidence that any directed therapy or standard heart failure therapy (e.g. ACE-inhibitors)

improves patient outcomes when started early in the course of the disease. Treatment effects have generally been evaluated with only conventional functional imaging parameters (e.g. LV fractional shortening or LVEF), although LV global longitudinal strain has been employed to measure the effect of enalapril and carvedilol in patients with DMD and Becker muscular dystrophy.[15]

Despite various imaging parameters providing data on risk-stratification in established disease, prospective studies are also necessary to determine if these data will translate into improved outcomes, e.g. when used for guidance of primary prevention implantable cardioverter defibrillator (ICD) placement.

Few studies have systematically studied multimodality imaging in a single mutation or disease entity in order to compare their relative usefulness in early diagnosis or risk-stratification, or to compare a single technique between different etiologies of genetic DCM.

In summary, the following steps are required before cardiac imaging parameters can guide therapy for genetic DCM. Both conventional (LVEF) and novel (LV strain) parameters have to be evaluated for their ability to predict long-term outcome (development of symptoms, decrease in LV systolic function, ventricular arrhythmias and mortality), especially in asymptomatic mutation carriers. Furthermore, a variety of therapies (ACE-inhibitors and ICD) have to be evaluated for their abilities to influence the course of disease, either when instituted early in asymptomatic mutation carriers or in established disease that has been risk-stratified with imaging techniques. Moreover, the impact of such therapies can be measured by imaging (for example change in ECV) or mortality endpoints and, finally, multicentre studies will be required.

Employing imaging markers as therapeutic targets may prove especially useful, since obtaining long-term follow-up of uncommon cardiomyopathies in multicentre studies, will be challenging. Two lines of evidence suggest that imaging parameters could be useful as therapeutic targets. First, pharmacotherapy (beta-blockers and systemic steroids) has been shown to reverse LV remodeling in genetic DCM (DMD and Becker muscular dystrophy).[13,14] This likely reflects an inhibitory effect on myocardial fibrosis, and T1 mapping CMR techniques (including calculation of myocardial ECV) have the potential to reflect a treatment effect. In addition, early therapy has been proven to delay the onset or slow the progression of systolic dysfunction in some types of genetic DCM, e.g. systemic steroids and ACE-inhibitors in patients with DMD.[10,11] Parameters from imaging techniques could therefore be used to guide therapy.

Table 3: Reproducibility of various imaging techniques.

Substrate	Imaging modality	Imaging technique	Reproducibility for genetic DCM
Cardiac structure	**CMR**	LGE	K=0.75; P<0.001
		Native T1 mapping	-
		Post-contrast T1 mapping	ICC for inter-observer agreement=0.997; 95% CI 0.994-0.999
		ECV	• ICC for intra-observer agreement=0.957; P<0.001 • ICC for inter-observer agreement=0.963; P<0.001
	Echocardiography	IBS	-
Mechanical function	**Echocardiography**	LVEF	• ICC for intra-observer agreement=0.80; 95% CI 0.47-0.94 • ICC for inter-observer agreement=0.77; 95% CI 0.48-0.93
		LV global longitudinal strain	• ICC for intra-observer agreement=0.72 • ICC for inter-observer agreement=0.78
		LV global circumferential strain	• ICC for intra-observer agreement=0.91 • ICC for inter-observer agreement=0.88
		LV systolic myocardial tissue velocity	• Intra-observer mean percentage variation=6.7-9.2% for systolic indices • Inter-observer mean percentage variation=3.8-6.8% for systolic indices
		LV diastolic myocardial tissue velocity	• Intra-observer mean percentage variation=5.6-11.8% for diastolic indices • Inter-observer mean percentage variation=6.6-9.9% for diastolic indices
		LV myocardial velocity gradient	• Mean intra-observer difference=8.2±5.3% (interventricular septum) and 8.0±6.9% (posterior wall) • Mean inter-observer difference=9.3±44% (interventricular septum) and 8.8±3.8% (posterior wall)
		Mechanical dispersion	-
	CMR	CMR circumferential strain	-
Cellular function	**CMR**	^{31}P-MRS	-
	Nuclear imaging	^{99m}Tc-MIBI/SPECT (perfusion)	-
		PET	-

CI: confidence interval, CMR: cardiac magnetic resonance, ECV: extracellular volume fraction, IBS: integrated backscatter, ICC: intraclass correlation coefficient, LGE: late gadolinium enhancement, LV: left ventricular, LVEF: left ventricular ejection fraction, PET: positron emission tomography, ^{31}P-MRS: phosphorous-31 magnetic resonance spectroscopy, ^{99m}Tc-MIBI/SPECT: technetium 99m-methoxyisobutylisonitrile single-photon emission computed tomography.

CONCLUSIONS

Genetic DCM represents a substantial proportion of DCM. Affected individuals are at high risk of complications, and strategies to identify disease early and effectively risk-stratify these patients are needed. A variety of cardiac imaging modalities have proven their ability to identify disease early and they have shown promise in risk-stratification. Further research is required to apply imaging techniques to the evaluation of management strategies which could delay progression when instituted early in the course of disease.

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10

Left ventricular 2D speckle tracking echocardiography for detection of systolic dysfunction in genetic, dilated cardiomyopathies

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ABSTRACT

Background: Genetic, dilated cardiomyopathy (DCM) can be caused by a large variety of mutations. Mutation carriers are often asymptomatic until DCM is well established, presenting with heart failure, arrhythmias or sudden cardiac death. Preventive strategies can only be applied if DCM is detected early. Echocardiographic, left ventricular (LV) global longitudinal strain (GLS) is a promising tool for early diagnosis, i.e. before a decrease in LV ejection fraction (EF) has occurred. We therefore investigated the role of LV GLS as an early disease marker in genetic DCM.

Methods: Genetic DCM patients and genotyped family members were evaluated. The study population was grouped as: i) genotype-positive, phenotype-positive patients (GPFP) with a pathogenic mutation and LVEF<55%, ii) genotype-positive, phenotype-negative (GPFN) individuals with a pathogenic mutation and LVEF≥55%, and iii) genotype-negative, phenotype-negative (GNFN) individuals without a pathogenic mutation and LVEF≥55%.

Results: A total of 115 individuals (mean age 53±15 years, 51% male) were analyzed: 28 (24%) were classified as GNFN, 50 (44%) as GPFN and 37 (32%) as GPFP. Various mutations were represented: 39 (34%) titin, 14 (12%) lamin A/C, 13 (11%) sarcomeric and 21 (18%) less frequent mutations (grouped together). The mean LVEF was 58±14% for all subjects. The mean LV GLS in the GNFN group was -21.7±1.5% vs. -19.7±3.5% for the GPFN group (P=0.036). The mean LV GLS was -12.9±4.3% for the GPFP category (P<0.001 vs. GPFN and GNFN).

Conclusions: Decreased LV GLS discriminates GPFN individuals from normal controls, which may permit early institution of therapy for genetic DCM.

INTRODUCTION

Dilated cardiomyopathy (DCM) is defined as "left ventricular (LV) or biventricular systolic dysfunction and dilation that are not explained by abnormal loading conditions".[1] There are two main etiological groups, i.e. genetic and non-genetic.[1] A broad variety of mutations underlie genetic DCM, with sarcomeric, lamin A/C (LMNA) and titin (TTN) mutations being most frequent.[2,3] Mutation carriers often remain asymptomatic until cardiac disease is well established, and then present clinically with advanced heart failure and depressed LV ejection fraction (LVEF), life-threatening arrhythmias or sudden cardiac death.[4] In order to institute effective preventive therapies for these serious complications, clinicians will require the ability to diagnose genetic DCM early.

Echocardiographic strain imaging is most commonly performed with 2-dimensional (2D) speckle tracking strain echocardiography and LV global longitudinal strain (GLS) is the most frequently used measure of LV systolic (dys)function. LV GLS has proven useful for diagnosing early phases of both genetic and non-genetic cardiomyopathies, as well as in risk-stratification.[5] The utility of LV GLS in the early diagnosis of genetic DCM has not been thoroughly investigated. The purpose of the present study is therefore to investigate LV GLS as a potential marker of early LV systolic dysfunction in individuals who are mutation carriers for genetic DCM.

METHODS

Study population and data collection

Clinical and echocardiographic data from genotyped patients with DCM, as well as genotyped family members of probands, were analyzed from an ongoing clinical registry of genetic DCM. For retrospective analysis of data collected for clinical purposes and handled anonymously, the institutional review board waived the requirement for patient written informed consent. Mutation screening was clinically performed in family members with a cardiomyopathy-related gene panel. Patients gave consent for mutation screening. LV dysfunction (phenotype positive) was defined as an LVEF<55%.[6] Mutations were considered pathogenic or likely pathogenic (genotype positive) if associated with DCM in the literature or in the local population, as described previously.[2,7] Individuals were excluded if a mutation was considered of uncertain significance, likely benign or benign.[7] In addition, significant valvular and coronary artery disease were exclusion criteria.

The study population was divided into three categories: i) genotype-positive, phenotype-positive (GPFP) ii) genotype-positive, phenotype-negative (GPFN) and iii) genotype-negative, phenotype-negative (GNFN). Patient groups were compared in terms of LV systolic function as assessed with conventional (LVEF) and 2D speckle tracking echocardiography (LV GLS) to

investigate whether LV GLS is more sensitive than LVEF to identify the patients with subclinical DCM.

Echocardiographic data acquisition

Transthoracic echocardiography was performed in the left lateral decubitus position, using a commercially available system (E9 or VIVID 7, General Electric Vingmed Ultrasound, Milwaukee, USA) equipped with either a 3.5 MHz or a M5S transducer and with adjustment of the depth and gain settings as appropriate. M-mode, 2D and Doppler data were stored digitally after acquisition to allow for off-line analysis (EchoPac 113, General Electric Vingmed Ultrasound, Milwaukee, USA).

Chamber quantification, i.e. LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), left atrial volume and calculation of the LVEF, was performed on 2- and 4-chamber apical views, according to contemporary guidelines.[6] LV GLS was measured with 2D speckle tracking echocardiography and averaged from standard apical views (2-, 4- chamber, and long-axis).[6,8]

Statistical analysis

Continuous variables are presented as means and standard deviations, and categorical data as numbers and percentages. Independent samples t-tests, as well as one-way analysis of variance (ANOVA), were employed for the comparison of continuous variables. The χ^2 and Fisher's exact tests (as appropriate) were used to compare categorical variables. Post-hoc analyses were utilized for inter-group comparisons, where appropriate. All analyses were conducted with SPSS for Windows, version 23.0 (SPSS, Armonk, NY, USA). All statistical tests were two-sided, and a P-value of <0.05 was considered statistically significant.

RESULTS

Clinical, genetic and electrocardiographic characteristics

A total of 115 persons (mean age 53±15 years, 51% male) were analyzed. Thirty-seven (32%) patients were GPFP, 50 (44%) individuals were GPFN and 28 (24%) individuals were classified as GNFN. The distribution of specific, pathogenic mutations is presented in Table 1. Mutations of TTN and LMNA were the most common: 39 (34%) and 14 (12%), respectively. Baseline characteristics of individuals, according to their genotype-phenotype classification, are summarized in Table 2. Use of heart failure medication (diuretics, mineralocorticoid antagonists, angiotensin-converting enzyme (ACE)-inhibitors and beta-blockers) was significantly higher in patients who were classified as GPFP, compared to GPFN and GNFN individuals (P<0.05 for both interactions). Patients in the GPFP group were less frequently in sinus rhythm, and more often paced, compared to GPFN and GNFN groups (P<0.05 for both comparisons).

Conventional and 2D speckle tracking echocardiographic parameters in genotype-phenotype groups

GPFP patients had larger LV volumes and lower LVEF as compared with the other groups, but there were no differences between GNFN and GPFN groups (Table 2). The mean LV GLS for all study subjects was -18.0±4.9%. Measurement of LV GLS was feasible in all 115 (100%) of patients. Interestingly, LV GLS was significantly more impaired in GPFN patients than in GNFN individuals, whereas the GPFP group showed the most impaired LV GLS (Figures 1 and 2). Therefore, in contrast to conventional echocardiographic parameters, GPFN individuals could be distinguished from GNFN controls using LV GLS.

Table 1: Distribution of mutations in genotype-positive, phenotype-negative (GPFN) and genotype-positive, phenotype-positive (GPFP) categories.

	GPFN (n=50)	GPFP (n=37)
TTN	24	15
LMNA	10	4
MYH7	0	4
MYH6	1	0
TPM1	1	1
TNNT2	0	2
MYPN	1	0
MYBPC3	2	1
ANKRD1	1	1
VCL	1	2
DSP	0	2
PLN	2	0
LAMA4	1	0
SCN5A	1	2
PKP2	1	0
PSEN1	2	2
DES	1	1
ANO5	1	0

TTN: titin, LMNA: lamin A/C, ANKRD1: cardiac ankyrin repeat protein, MYH7: β-myosin heavy chain, MYH6: α-myosin heavy chain, VCL: metavinculin, TPM1: α-tropomyosin, TNNT2: cardiac troponin T, MYBPC3: myosin-binding protein C, DSP: desmoplakin, PLN: phospholamban, LAMA4: laminin-α-4, SCN5A: sodium channel type V, PKP2: plakophilin 2, PSEN1: presenillin 1, MYPN: myopalladin, DES: desmin, ANO5: anoctamin-5.

DISCUSSION

The principal result of this study, is that LV GLS is substantially more impaired in GPFN individuals as compared to controls. Therefore, LV GLS may identify mutation carriers for genetic DCM with a normal LVEF (GPFN) at an early (subclinical) stage.

Clinical and genetic characteristics of DCM

Even though more than 50 pathogenic genes have been identified in genetic DCM, sarcomeric, LMNA and TTN mutations are the most frequent.[2,3] In the study by Van Spaendonck et al. (which did not include TTN mutations), LMNA mutations represented 23% of the mutation-positive patients, while sarcomeric mutations accounted for another 16%.[2] The corresponding percentages in our study are 16% and 14%, respectively, and are comparable. Despite the fact that TTN mutations are commonly found in genetic DCM, it is still not completely clear what percentage of these mutations is truly pathogenic.[1] In a Finnish study of 145 patients with DCM, TTN mutations were identified in 20.6% of these patients.[9] In our study, TTN mutations were present in 45% of mutation-positive (i.e. GPFN and GPFP) individuals.

Table 2: Clinical characteristics.

	GNFN (n=28)	GPFN (n=50)	GPFP (n=37)
Age (years)	52.1±13.8	50.0±14.5	56.2±16.7
Male gender, n (%)	12 (42.9)	22 (44.0)	25 (67.6)
NYHA class, n (%)			
- I	27 (96.4)	48 (96.0)	30 (81.1)
- II	1 (3.6)	1 (2.0)	3 (8.1)
- III	0 (0.0)	1 (2.0)	1 (2.7)
- IV	0 (0.0)	0 (0.0)	3 (8.1)
Medical therapy, n (%)			
- Diuretic	0 (0.0)	4 (8.0)	16 (43.2)*†
- Mineralocorticoid antagonist	0 (0.0)	3 (6.0)	12 (32.4)*†
- ACE-inhibitor	3 (10.7)	3 (6.0)	14 (37.8)†
- AII antagonist	2 (7.1)	5 (10.0)	13 (35.1)
- Beta-adrenoreceptor antagonist	5 (17.9)	9 (18.0)	20 (54.1)*†
- Amiodarone	0 (0.0)	0 (0.0)	4 (10.8)
- Sotalol	0 (0.0)	1 (2.0)	3 (8.1)
- Digoxin	0 (0.0)	1 (2.0)	3 (8.1)
- Anticoagulation	1 (3.6)	4 (8.0)	15 (40.5)*†
Heart rhythm, n (%)			
- Sinus rhythm	26 (92.9)	49 (98.0)	22 (59.5)†
- Paced rhythm	0 (0.0)	1 (2.0)	14 (37.8)*†
- Atrial fibrillation	2 (7.1)	0 (0.0)	1 (2.7)
AV block, n (%)			
- 1st degree	0 (0.0)	2 (4.0)	3 (8.1)
- 2nd degree	0 (0.0)	2 (4.0)	0 (0.0)
- 3rd degree	0 (0.0)	0 (0.0)	1 (2.7)
LA volume (ml)	34.7±13.4	36.8±12.5	51.0±26.2*†
LVEF (%)	66.8±5.7	64.3±6.7	42.2±11.0*†
LVEDV (ml)	77.9±23.2	80.2±25.0	106.3±51.3*†
LVESV (ml)	26.2±9.3	29.3±12.4	65.7±48.8*†

Values are mean ± standard deviation. AII: angiotensin II receptor antagonist, ACE: angiotensin converting enzyme inhibitor, AV: atrioventricular, GNFN: genotype-negative phenotype-negative, GPFN: genotype-positive phenotype-negative, GPFP: genotype-positive phenotype-positive, LA: left atrial, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, NYHA: New York Heart Association, *P<0.05 vs. GNFN, †P<0.05 vs. GPFN.

The identification of a pathogenic mutation does not necessarily imply the presence of clinically-relevant cardiac disease, nor does it aid in risk-stratification. Alternative strategies are therefore required for identifying cardiac involvement and predicting the risk of complications.

Conventional echocardiographic parameters in genetic DCM

Lakdawala et al. compared 21 patients with overt, genetic DCM, 12 asymptomatic genotyped family members with disease-causing mutations (subclinical DCM) and 29 normal controls.[10]

"Overt" genetic DCM was defined as an LVEF <55% and/or LV enlargement (according to published reference values).[10] The LV end-diastolic diameter (LVEDD) was not found to be significantly different between the subclinical group (4.3±0.7 cm) and the controls (4.3±0.6 cm) (P=0.65).[10] Neither the LV end-systolic diameter (LVESD) in individuals with "subclinical

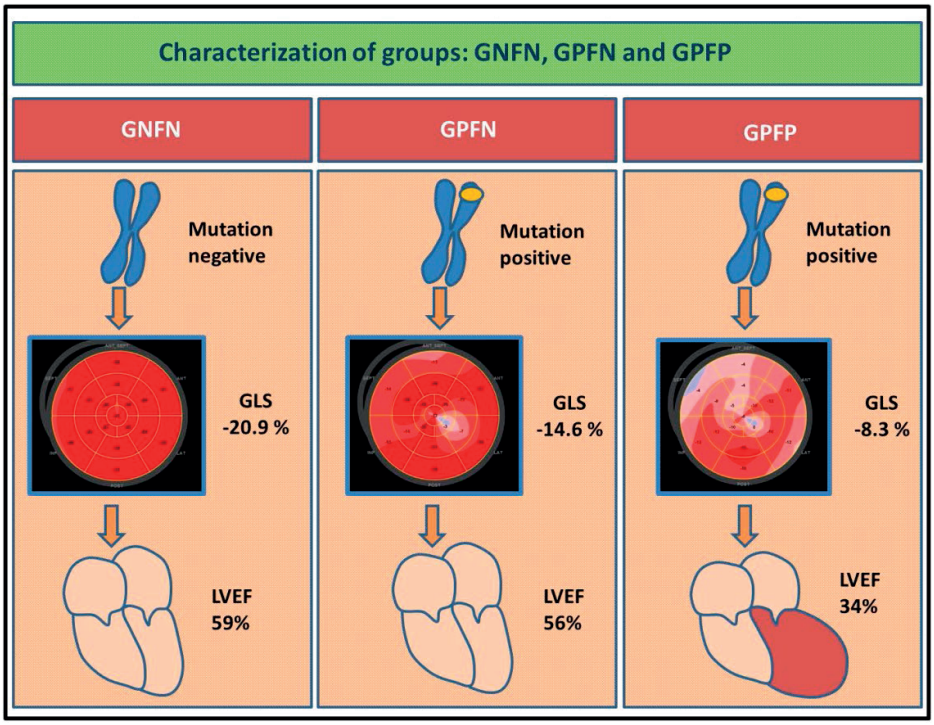

Figure 1: Characterization of groups: GNFN, GPFN, GPFP. The genotype status, global longitudinal, left ventricular strain (GLS) and left ventricular ejection fraction (LVEF) of three different individuals are shown to illustrate the following groups: genotype-negative, phenotype-negative (GNFN), genotype-positive, phenotype-negative (GPFN) and genotype-positive, phenotype-positive (GPFP). On the left-sided panel, a GNFN individual is shown, without a genetic mutation, with a normal GLS of -20.9% and a normal LVEF of 59%. The patient in the middle panel has a titin mutation, an impaired GLS of -14.6% and a normal LVEF of 56%, and is therefore GPFN. In the right-hand panel, a GPFP patient is shown, with a lamin A/C mutation, an impaired GLS of -8.3% and a depressed LVEF of 34%. Despite a normal LVEF of ≥55%, reduced GLS distinguishes the individual in the middle panel from a normal control (left-sided panel).

DCM" (3.1±0.6 cm) and controls (2.8±0.5 cm) (P=0.09) nor the LVEF (59±3% and 62±5%, respectively; P=0.07) could discriminate individuals with "subclinical DCM" from controls.[10] In a study of 674 first-degree relatives of patients with familial DCM, only 50 (7%) demonstrated evidence for cardiac involvement by either LV dilatation or reduced LVEF on echocardiographic screening.[11] Baig et al. interrogated a cohort of 225 family members of patients with familial DCM on echocardiography, and also found only a small percentage (3%) with reduced LVEF.[12] Therefore, conventional echocardiographic parameters (LVEDD, LVESD, LVEF) are unable to reliably distinguish GPFN patients from GNFN controls. Our data are in agreement with these findings, and argue in favor of exploring novel echocardiographic parameters with which to diagnose genetic DCM early.

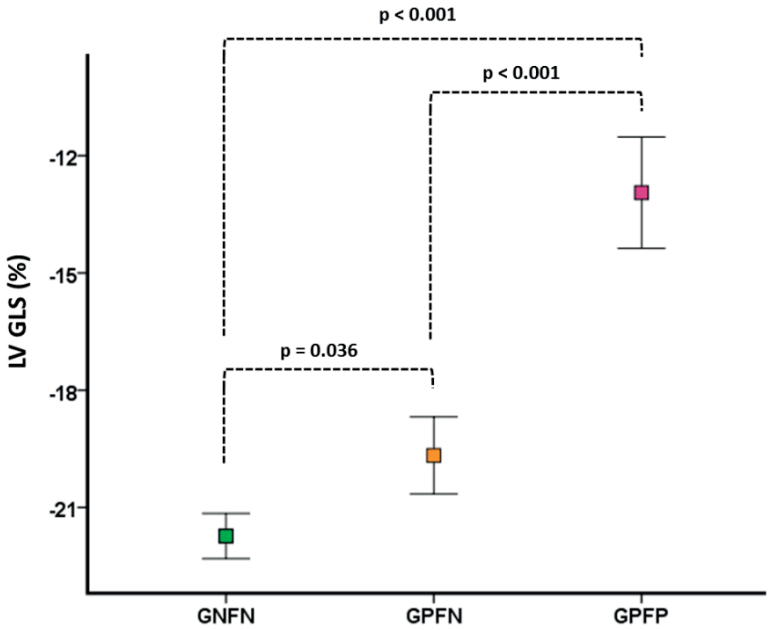

Figure 2: Left ventricular strain, according to genotype-phenotype group. Mean left ventricular global longitudinal strain (LV GLS), stratified according to the following groups: genotype-negative, phenotype-negative (GNFN), genotype-positive, phenotype-negative (GPFN) and genotype-positive, phenotype-positive (GPFP). Color-coded squares indicate mean values of GLS, while horizontal bars represent 95% confidence intervals.

The role of 2D speckle tracking strain echocardiography to assess LV longitudinal strain in genetic DCM

Early diagnosis is integral to the process of risk-stratification in genetic DCM, since affected individuals are often asymptomatic until established heart failure, life-threatening arrhythmias or sudden cardiac death occurs.[4] Effective, preventive strategies can only be implemented if genetic DCM can be reliably diagnosed at an early stage of the disease process.

Structural signs of early genetic DCM have been described with cardiac magnetic resonance (CMR) imaging. In a cohort of 41 LMNA mutation carriers, late gadolinium enhancement (LGE)

on CMR was visualized in the basal septum only in individuals who experienced ventricular arrhythmias, while LVEF was similar in those with and without ventricular arrhythmias (56±13% vs. 53±14%; P=0.55).[13] In the same study, there were also no significant differences in LVEDD (51±9 mm vs. 54±9 mm; P=0.34) or LVESD (36±10 mm vs. 39±9 mm; P=0.29) between subjects with and without ventricular arrhythmias.[13] Basal, septal LGE therefore appears to be a sign of early disease, which could not be diagnosed with conventional echocardiographic parameters.[13] The myocardial extracellular volume fraction, determined by CMR imaging, was increased in 19 LMNA mutation carriers (28.0±3.2%) compared to controls (22.7±3.0%) (P<0.001).[14] Even though the indexed LVEDV was slightly higher in mutation carriers than in controls (87±20 ml/m^2 vs. 76±12 ml/m^2, respectively; P<0.05), LVEF was normal in both groups.[14] Although arrhythmia risk was not specifically addressed, 3 LMNA mutation carriers (16%) had sustained ventricular tachycardia on ECG monitoring, while another 3 (16%) manifested non-sustained ventricular tachycardias.[14] Reverse LV remodeling has been documented with early therapy in selected subgroups of genetic DCM, e.g. beta-blockers and systemic steroids in patients with Duchenne and Becker muscular dystrophy, probably reflecting an effect on myocardial fibrosis.[15,16]

Impaired LV GLS (partially) reflects myocardial fibrosis in patients with heart failure, and is more accurate in this regard than LVEF or other deformation parameters (e.g. LV global circumferential strain).[17] The functional impairment seen in early genetic DCM (impaired LV GLS) therefore most likely follows structural abnormalities, such as myocardial fibrosis, although the contribution of a purely functional (e.g. sarcomeric dysfunction) component cannot be excluded. In the study by Lakdawala et al., LV GLS was significantly decreased in individuals with "subclinical" genetic DCM, compared to normal controls, and LV GLS was lower in patients with "overt" genetic DCM, compared to the "subclinical" group (P<0.001 for all interactions).[10] Of note, all mutations were sarcomeric, and >90% of individuals were female.[10] In contrast, TTN, LMNA, sarcomeric and other mutations were represented in our study, with about half of the individuals being male. This is in agreement with published mutation and gender distributions for genetic DCM.[2,9] The key finding of our study is that LV GLS is substantially lower in GPFN individuals than in normal controls (GNFN) in a representative cohort. Therapy which is instituted early, has already been proven to delay the onset or slow the progression of systolic dysfunction in some types of genetic DCM, e.g. systemic steroids and ACE-inhibitors in patients with Duchenne muscular dystrophy.[18,19]

It is therefore clear that GPFN individuals who cannot be reliably identified by conventional echocardiographic parameters, demonstrate structural and functional cardiac abnormalities on different imaging modalities (CMR and 2D speckle tracking strain echocardiography). The results of the present study support the validity of identifying GPFN persons with 2D speckle tracking strain echocardiography, using LV GLS.

The true value of early diagnosis in patients with genetic DCM can only be addressed by prospective studies, investigating both the predictive value of imaging markers (e.g. LV GLS) for the development of a positive phenotype (decreased LVEF, dilated LV, arrhythmias, heart

failure, sudden cardiac death), as well as the efficacy of early initiation of preventive measures, e.g. standard heart failure therapy with ACE-inhibitors or primary prevention and implantable cardioverter defibrillator implantation.

Study limitations

This was a retrospective, single-center study. Nonetheless, all the major groups of mutations associated with genetic DCM are well represented. Subgroup analyses were not conducted on different mutation groups, due to the limited study population. In addition, the association between LV GLS and hard endpoints, such as arrhythmic events, was not evaluated since this was beyond the scope of the present study and the follow-up was relatively short (median follow-up was 4 months (interquartile range (IQR) 1-25)) to observe a significant number of events that can lead to clinically meaningful conclusions. Likewise, LV diastolic function was not evaluated. Measurements of LV GLS are not vendor-independent, and the threshold for reduced LV GLS may vary among different echocardiographic vendors, although the amount of variation is acceptable for clinical use.[8] Finally, CMR data were not systematically available in this population to perform tissue characterization analysis.

CONCLUSIONS

Mutation carriers in genetic DCM (GPFN) often remain asymptomatic until presenting with advanced cardiac disease. Decreased LV GLS can help to discriminate GPFN individuals from normal controls (GNFN). This may allow early disease detection in genetic DCM. Larger, prospective studies are required to confirm these findings.

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SUMMARY, CONCLUSIONS AND FUTURE PERSPECTIVES

SUMMARY Part I: The role of echocardiography in predicting outcome after CRT

Cardiac resynchronization therapy (CRT) is an established treatment for heart failure patients who remain symptomatic despite optimal medical therapy (New York Heart Association functional class II-III and ambulatory class IV) with a wide QRS complex (≥130 ms) and reduced left ventricular ejection fraction (LVEF) ≤35%. The benefits of CRT, however, may differ according to the QRS complex duration and morphology. In **chapter 2**, the effect of baseline QRS duration and morphology on LV reverse remodeling and LVEF improvement after CRT was investigated. Patients with a baseline QRS ≥150 ms demonstrated more LV reverse remodeling (mean reduction in LV end-systolic volume (LVESV) of 34.3 ml vs. 14.8 ml; P<0.001) and a greater LVEF improvement (mean increase 6.8% vs. 5.2%; P<0.001), compared to those with QRS <150 ms. Similarly, CRT recipients with left bundle branch block (LBBB) at baseline, evidenced more LV reverse remodeling (P<0.001) and LVEF improvement (P<0.001) than those with non-LBBB QRS morphology. LBBB QRS morphology and increasing QRS duration therefore translated into a greater degree of LV reverse remodeling and systolic function improvement than non-LBBB morphology and a lesser QRS duration, which is supportive of contemporary guidelines for CRT placement.

In **chapter 3**, different CRT response definitions were compared. An LV volumetric response to CRT is conventionally defined as a ≥15% reduction in LVESV at 6 months post-CRT. An improvement in global longitudinal strain (GLS) on speckle tracking echocardiography may also be seen in response to CRT. A CRT volumetric response and an improvement in LV GLS are not always seen in the same patient, and the prognostic impact of seeing: i) an improvement in GLS or a reduction in LVESV or ii) an improvement in GLS and a reduction in LVESV, was subsequently investigated. CRT recipients with an improvement in LV GLS and a reduction in LVESV, had significantly lower all-cause mortality compared to those who had either: i) an improvement in LV GLS or a reduction in LVESV, but not both and ii) no improvement in either LV GLS and no reduction in LVESV (P<0.001). This reflects the fact that these two parameters (LV GLS and LVESV) represent different mechanisms, and supports the use of LV GLS as a meaningful parameter in defining CRT response, in addition to the more commonly used definition which is based on a reduction in LVESV.

Chapter 4 examines the role of LV mechanical dispersion (LVMD) in the long-term outcome of CRT recipients. LVMD is a novel, echocardiographic parameter which quantifies mechanical heterogeneity of the LV, and is defined as the standard deviation of the time from the onset of the QRS complex on the triggered ECG to the peak longitudinal myocardial strain (measured with speckle tracking echocardiography) in a 17-segment model of the LV. LVMD has been associated with ventricular arrhythmias in a number of cardiac diseases. Risk stratification of patients after CRT implantation remains a clinical challenge, and LVMD was calculated in a

cohort of heart failure CRT recipients post-implant. They were divided into groups according to the median LVMD at 6 months after CRT implantation. Those with less LVMD (≤84 ms) experienced fewer ventricular arrhythmias and lower all-cause mortality than those with LVMD >84 ms, and a greater LVMD was independently associated with a higher mortality risk (hazard ratio (HR) 1.002; confidence interval (CI) 1.000-1.005; P=0.037) and more frequent ventricular arrhythmias (HR 1.003; CI 1.000-1.005; P=0.026).

CRT restores mechanical efficiency to the failing LV by resynchronization of contraction. In **chapter 5**, global, LV myocardial work efficiency was measured with a recently introduced, non-invasive technique, synthesizing data from speckle tracking strain echocardiography and sphygmomanometric blood pressure recordings. Patients with class I indications for CRT were dichotomized according to the baseline, mean global LV myocardial work efficiency before CRT implantation. Those recipients with less efficient myocardial energetics at baseline (global, LV myocardial work efficiency <75%), experienced lower mortality rates than those with more efficient left ventricles (log-rank test, P=0.029). On multivariable analysis, global LV myocardial work efficiency <75% was associated with a decreased risk of all-cause mortality (HR 0.48; 95% CI 0.25-0.92; P=0.027). Global, LV myocardial work efficiency at baseline therefore holds promise to risk-stratify heart failure patients before CRT implantation, and may help to refine selection criteria in those who already have class I indications for CRT implantation.

Functional mitral regurgitation (FMR) is a common complication of heart failure, which worsens prognosis, but is also amenable to improvement with CRT. In **chapter 6**, the prognostic impact of FMR evolution in CRT patients was evaluated. Moderate or severe FMR at baseline, which remained unchanged at 6 months after the institution of CRT, was independently associated with long-term mortality (HR 1.77; 95% CI 1.41-2.22; P<0.001). The prognostic implication of moderate or severe FMR, which did not improve with CRT at 6 months, was independent of LV volumetric response to CRT, indicating that FMR evolution is not merely a reflection of the LV volumetric change, but contributes uniquely to long-term survival. **Chapter 7** focuses on the impact of atrial fibrillation (AF) on FMR improvement after CRT. FMR improved in 45.6% of CRT recipients with sinus rhythm (SR) before implantation, compared to 30.7% with AF (P=0.011). Despite a similar degree of LV reverse remodeling at 6 months post-CRT, patients with SR at baseline had smaller left atrial volumes (63.0±26.5 ml vs. 103.1±41.0 ml; P<0.001) and mitral annular diameters (42.3±5.6 mm vs. 46.1±5.8 mm; P<0.001) in comparison to those with AF. This suggests an inhibitory effect of AF on left atrial and mitral annular reverse remodeling, leading to less FMR improvement after CRT.

SUMMARY Part II: Imaging approaches to risk-stratification of cardiac disease

Chapter 8 provides a brief review of the role of multimodality imaging in the risk-stratification of sudden cardiac death (SCD). Since SCD is the cause of up to one-fifth of global deaths, and often occurs in individuals who have not previously been diagnosed with cardiac disease, primary prevention remains a challenge. The most effective strategy for primary and secondary

prevention of SCD is insertion of an implantable, cardioverter-defibrillator (ICD). Currently, the decision to implant an ICD is predicated mainly on an LVEF ≤35%; however, this approach is known to lack sensitivity and specificity. Multimodality imaging has shown incremental value over LVEF to identify patients who stand to benefit from ICD implantation, e.g. speckle tracking strain echocardiography, late gadolinium contrast enhanced (LGE) cardiac magnetic resonance (CMR) imaging and radionuclide imaging (e.g. iodine-123 metaiodobenzylguanidine uptake).

The role of cardiac imaging techniques in the risk-stratification of genetic, dilated cardiomyopathy (DCM) is extensively reviewed in **chapter 9**. Mutation carriers for genetic DCM are often asymptomatic until cardiac disease manifests with heart failure, arrhythmias or SCD. Risk-stratification of such individuals encompasses both early diagnosis and the phenotyping of established disease. Various imaging modalities are able to demonstrate early functional and structural abnormalities in genetic DCM mutation carriers, e.g. tissue Doppler imaging, speckle tracking strain echocardiography, integrated backscatter echocardiography, CMR LGE and phosphorous-31 magnetic resonance spectroscopy. Functional, cellular abnormalities can be probed with nuclear techniques, e.g. myocardial perfusion by means of single-photon emission computed tomography. In the case of established disease, echocardiography-based methods and CMR have demonstrated incremental benefit to LVEF for effective risk-stratification.

Chapter 10 investigates the use of GLS speckle tracking echocardiography in the early diagnosis of genetic DCM patients. Three groups were compared: i) genotype-positive, phenotype-positive (GPFP) patients, with a pathogenic mutation and an LVEF <55%, ii) genotype-positive, phenotype-negative (GPFN) individuals, with a pathogenic mutation and an LVEF ≥55% and iii) genotype-negative, phenotype-negative (GNFN) controls. Decreased LV GLS distinguished GPFN individuals from normal controls (P<0.001), in contradistinction to LVEF. Such early diagnosis of cardiac involvement in genetic DCM mutation carriers may permit the timely institution of therapy to delay or prevent disease progression.

CONCLUSIONS AND FUTURE PERSPECTIVES

Characterization and risk-stratification of CRT candidates remain a clinical challenge. Reducing the percentage of CRT non-responders, as well as optimizing management of recipients of CRT, continue to be priorities in cardiology practice. Novel cardiac imaging parameters are expected to play a pivotal role in refining the characterization of heart failure patients who are considered for CRT, as well as in the risk-stratification of those who have already received such therapy. The EuroCRT study will prospectively evaluate various cardiac imaging markers (including LVMD and global, LV myocardial work efficiency) for their prognostic value.[1]

The effect of FMR treatment on outcome, is currently under scrutiny. The recently published Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR)[2] and Cardiovascular Outcomes Assessment of the MitraClip Percuta-

neous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT)[3] studies investigated the impact of transcatheter mitral valve repair on outcome in heart failure patients with FMR. Both these trials, however, included patients with and without CRT. The COAPT trial demonstrated a lower rate of hospitalization for heart failure and lower all-cause mortality in the device treatment group (HR 0.53; 95% CI 0.40-0.70; P<0.001), while the MITRA-FR trial failed to show a decrease in the composite primary outcome of all-cause mortality and heart failure hospitalization (odds ratio 1.16; 95% CI 0.73-1.84; P=0.53). Clearly, more data are required to resolve the question of prognostic benefit in the treatment of FMR. AF rhythm control (especially by means of catheter ablation) is a potential therapeutic target to improve FMR in CRT recipients with AF at baseline, and warrants further study.

Although the diagnostic role of multimodality cardiac imaging is well defined for genetic DCM, further research will inform on its ability to predict long-term outcome (e.g. the development of symptoms, decrease in LVEF, ventricular arrhythmias and mortality) in asymptomatic mutation carriers. Additionally, the utility of imaging in effectively guiding the early institution of therapy (e.g. angiotensin converting enzyme (ACE)-inhibitors or ICDs) which may delay or prevent disease progression in genetic DCM mutation carriers, remains to be explored. Adequately defining the role of multimodality cardiac imaging in both the prediction of long-term outcome and the guidance of early therapy, will require prospective studies. Since long-term follow-up in uncommon cardiomyopathies in prospective, multicenter studies will no doubt be challenging, employing imaging biomarkers as therapeutic targets in themselves, may prove especially useful.

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SAMENVATTING, CONCLUSIES EN TOEKOMSTPERSPECTIEVEN

SAMENVATTING DEEL I: DE ROL VAN ECHOCARDIOGRAFIE IN HET VOORSPELLEN VAN DE UITKOMSTEN NA CRT IMPLANTATIE

Cardiale resynchronisatietherapie (CRT) is een bekende behandeling voor patiënten met hartfalen die symptomatisch blijven ondanks optimale medicamenteuze therapie (New York Heart Association functionele klasse II-III en ambulante klasse IV) met een breed QRS-complex (≥130 ms) en een verminderde linkerventrikel ejectiefractie (LVEF) van ≤35%. De voordelen van CRT kunnen echter verschillen afhankelijk van de duur en morfologie van het QRS-complex.

In **hoofdstuk 2** wordt het effect van baseline QRS-duur en QRS-morfologie op LV *reverse remodeling* en verbetering van LVEF na CRT onderzocht. Patiënten met een baseline QRS van ≥150 ms vertoonden meer LV *reverse remodeling* (gemiddelde vermindering van het LV eindsystolisch volume (LVESV) van 34.3 ml vs. 14.8 ml; P<0.001) en een grotere LVEF verbetering (gemiddelde toename 6.8% vs. 5.2%; P<0.001), vergeleken met diegenen met een QRS duur van <150 ms. Evenzo vertoonden ontvangers van CRT, met bij baseline een aanwezig linkerbundeltakblok (LBBB), meer LV *reverse remodeling* (P<0.001) en meer LVEF verbetering (P<0.001) dan patiënten met een niet-LBBB QRS-morfologie. LBBB QRS-morfologie en toenemende QRS-duur leidde tot meer LV *reverse remodeling* en verbetering van LV systolische functie dan niet-LBBB morfologie en een lagere QRS-duur, hetgeen de huidige richtlijnen voor CRT-plaatsing ondersteunt.

In **hoofdstuk 3** worden verschillende definities voor CRT-respons in kaart gebracht. Een LV volumetrische respons op CRT wordt conventioneel gedefinieerd als een ≥15% vermindering in LVESV 6 maanden na CRT. Een verbeterde globale longitudinale *strain* (GLS) op *speckle tracking* echocardiografie, kan ook worden waargenomen met CRT. Een CRT volumetrische respons en een verbetering in LV GLS wordt niet altijd bij dezelfde patiënt gezien. Het prognostisch impact van: i) een verbetering van GLS óf een verlaging van LVESV, óf ii) een verbetering van GLS en een verlaging van LVESV werd onderzocht. CRT-patiënten met een verbetering in LV GLS en een verlaging van LVESV, hadden een lagere algemene sterftekans in vergelijking met diegenen met: i) een verbetering in LV GLS óf een verlaging van LVESV, maar niet beiden, en ii) geen verbetering in LV GLS én geen vermindering van LVESV (P<0.001). Voorgenoemde weerspiegelt het feit dat deze twee parameters (LV GLS en LVESV) verschillende mechanismen vertegenwoordigen. Dit ondersteunt het eventuele gebruik van LV GLS als een waardevolle parameter bij het definiëren van CRT-respons – naast de meer algemeen gebruikte definitie, die is gebaseerd op een verlaging van het LVESV.

Hoofdstuk 4 beschrijft de rol van LV *mechanical dispersion* (LVMD) in de lange termijn uitkomsten van CRT-patiënten. LVMD is een nieuwe echocardiografische parameter die de mechanische heterogeniteit van de LV kwantificeert en wordt gedefinieerd als de standaardafwijking van de tijd vanaf het begin van het QRS-complex op het getriggerde ECG tot de piek longitudinale myocardiale *strain* (gemeten met *speckle tracking* echocardiografie) in

een 17-segmentmodel van de LV. LVMD wordt geassocieerd met ventriculaire aritmieën bij verschillende hartaandoeningen. Risicostratificatie van patiënten na CRT-implantatie blijft een klinische uitdaging. Wij berekenden daarom LVMD na implantatie van CRT in een cohort van patiënten met hartfalen. Ze werden verdeeld in groepen volgens de LVMD mediaan 6 maanden na de CRT-implantatie. Diegenen met een lagere LVMD (≤84 ms) hadden minder ventriculaire aritmieën en een lagere algemene sterftekans dan die met LVMD >84 ms. Een hogere LVMD had een onafhankelijk voorspellende waarde voor sterfterisico (*hazard ratio* (HR) 1.002; betrouwbaarheidsinterval (*confidence interval* (CI)) 1.000-1.005; P=0.037) en voor ventriculaire aritmieën (HR 1.003; CI 1.000-1.005; P=0.026).

CRT herstelt de mechanische efficiëntie van een falende LV door resynchronisatie. In **hoofdstuk 5** werd *global LV myocardial work efficiency* gemeten met een recent geïntroduceerde niet-invasieve techniek, waarbij gegevens werden gesynthetiseerd van *speckle tracking strain* echocardiografie en sphygmomanometrische bloeddrukmetingen. Patiënten met klasse I indicaties voor CRT werden gedichotomiseerd volgens de baseline gemiddelde *global LV myocardial work efficiency* (vóór CRT-implantatie). De CRT-ontvangers met een minder efficiënte myocard-energetica bij baseline (*global LV myocardial work efficiency* <75%) hadden een lagere mortaliteit dan diegenen met efficiëntere linkerventrikels (log-rank test, P=0.029). Via multivariabele analyse was *global LV myocardial work efficiency* <75% voorspellend voor een verlaagd risico op mortaliteit (HR 0.48; 95% CI 0.25-0.92; P=0.027). Baseline *global LV myocardial work efficiency* geeft de mogelijkheid om patiënten met hartfalen vóór CRT-implantatie te risico stratificeren, en kan mogelijk een rol spelen bij het bepalen van fijnere selectiecriteria van diegenen die reeds klasse I-indicaties hebben voor CRT-implantatie.

Functionele mitralisklepinsufficiëntie (*functional mitral regurgitation* (FMR)) is een veel voorkomende complicatie van hartfalen, die de prognose verergert, maar ook te verbeteren valt met CRT. In **hoofdstuk 6** wordt de prognostische impact van de evolutie van FMR bij CRT-patiënten geëvalueerd. Matige of ernstige FMR bij baseline, die 6 maanden na CRT implantatie onveranderd bleef, had een onafhankelijk voorspellende waarde voor mortaliteit (HR 1.77; 95% CI 1.41-2.22; P<0.001). De prognostische implicatie van matige of ernstige FMR die niet verbeterde na 6 maanden CRT, was onafhankelijk van de LV volumetrische respons op CRT. Dit geeft aan dat de evolutie van FMR niet alleen een weerspiegeling is van de verandering in LV-volume, maar ook op unieke wijze bijdraagt tot de overleving op langere termijn. **Hoofdstuk 7** richt zich op de invloed van atriumfibrilleren (AF) op de verbetering van FMR na CRT. FMR verbeterde na de implantatie in 45.6% van CRT-patiënten met sinusritme (SR), vergeleken met 30.7% met AF (P=0.011). Ondanks een vergelijkbare mate van LV *reverse remodeling* 6 maanden na CRT, hadden patiënten in SR bij baseline kleinere linker atrium volumes (63.0±26.5 ml vs. 103.1±41.0 ml; P<0.001) en kleinere mitralisklepannulus diameters (42.3±5.6 mm vs. 46.1±5.8 mm; P<0.001) in vergelijking met de patiënten met AF. Dit suggereert dat de aanwezigheid van AF een negatief effect heeft op de linker atrium en mitralisklepannulus *reverse remodeling*, wat weer op hun beurt leidt tot minder FMR-verbetering na CRT.

SAMENVATTING DEEL II: BEELDVORMING IN DE RISICO STRATIFICEREN VAN CARDIALE AANDOENINGEN

Hoofdstuk 8 geeft een kort overzicht van de rol van multimodale beeldvorming in de risicostratificatie van plotselinge hartdood (*sudden cardiac death* (SCD)). Aangezien SCD de oorzaak is van tot wel één vijfde van de sterfgevallen wereldwijd en vaak voorkomt bij personen die niet eerder zijn gediagnosticeerd met een hartaandoening, blijft primaire preventie een uitdaging. De meest effectieve strategie voor primaire en secundaire preventie van SCD is het inbrengen van een implanteerbare *cardioverter defibrillator* (ICD). Momenteel wordt de beslissing om een ICD te implanteren voornamelijk gebaseerd op een LVEF ≤35%. Het is echter bekend dat deze benadering weinig sensitief en specifiek is. Multimodale beeldvorming levert een toegevoegde waarde aan LVEF om patiënten te identificeren die baat zullen hebben bij een ICD-implantatie. Voorbeelden hiervan zijn: *speckle tracking strain* echocardiografie, aankleuring (*late gadolinium contrast-enhanced* (LGE)) cardiale magnetische resonantie (CMR) *imaging* en nucleaire beeldvorming (bijvoorbeeld 123-jood metaiodobenzylguanidine opname).

De rol van cardiale beeldvormingstechnieken in de risicostratificatie van genetische, dilaterende cardiomyopathie (DCM) wordt uitgebreid besproken in **hoofdstuk 9**. Mutatiedragers voor genetische DCM zijn vaak asymptomatisch totdat ze zich presenteren met hartfalen, aritmieën of SCD. Risicostratificatie van dergelijke individuen omvat zowel vroege diagnostiek als de fenotypering van aangetoonde ziekte. Verschillende beeldvormende technieken zijn in staat om vroeg functionele en structurele abnormaliteiten in genetische DCM-mutatiedragers aan te tonen, bijv. *tissue Doppler*, *speckle tracking strain* echocardiografie, *integrated backscatter* echocardiografie, CMR LGE en fosfor-31 magnetische resonantie spectroscopie. Functionele, cellulaire abnormaliteiten kunnen worden onderzocht met nucleaire technieken, bijv. myocard perfusie d.m.v. *single-photon emission computed tomography*. In het geval van aangetoonde hartziekte, hebben echocardiografie en CMR een toegevoegde waarde tot LVEF in het kader van risicostratificatie.

Hoofdstuk 10 beschrijft het gebruik van GLS *speckle tracking* echocardiografie bij de vroege diagnostiek van genetische DCM-patiënten. Drie groepen werden vergeleken met elkaar: i) genotype-positieve, fenotype-positieve (GPFP) patiënten, met een pathogene mutatie en een LVEF <55%, ii) genotype-positieve, fenotype-negatieve (GPFN) individuen, met een pathogene mutatie en een LVEF ≥55%, en iii) controles die genotype-negatief, fenotype-negatief (GNFN) waren. Een verlaagde LV GLS onderscheidde GPFN-individuen van normale controles (P<0.001) – in tegenstelling tot LVEF. Een dergelijk vroege diagnose van cardiale betrokkenheid bij genetische DCM-mutatiedragers kan mogelijk resulteren in de tijdige instelling van therapie die de voortgang van de ziekte vertraagt of zelfs voorkomt.

CONCLUSIES EN TOEKOMSTPERSPECTIEVEN

Karakterisering en risicostratificatie van CRT-kandidaten blijven klinische uitdagingen. Het verminderen van het aantal *non-responders* op CRT en het optimaliseren van CRT, zijn prioriteiten in de dagelijkse praktijk. Nieuwe cardiale beeldvormingstechnieken zullen naar verwachting een cruciale rol spelen bij zowel het karakteriseren van patiënten met hartfalen bij wie CRT wordt overwogen, alsook bij de risicostratificatie van diegenen die reeds dergelijke behandeling hebben ontvangen. Het doel van het EuroCRT-onderzoek is om de verschillende cardiale beeldvormingsmarkers prospectief te evalueren (inclusief LVMD en *global LV myocardial work efficiency*) met betrekking tot hun prognostische waarde.[1]

Het effect van de behandeling van FMR op prognose wordt momenteel onderzocht. De recentelijk gepubliceerde *Percutaneous Repair with the MitraClip Device for Severe Functional/ Secondary Mitral Regurgitation* (MITRA-FR)[2] en *Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation* (COAPT)[3] trials onderzochten de invloed van percutane mitralisklepreparatie op de uitkomst van patiënten met hartfalen en FMR. In beide onderzoeken waren echter patiënten met én zonder CRT geïncludeerd. De COAPT-studie liet een lager aantal ziekenhuisopnamen voor hartfalen zien en een lager sterftecijfer in de MitraClip groep (HR 0.53; 95% CI 0.40-0.70; P<0.001), terwijl de MITRA-FR-studie geen afname toonde in het samengestelde, primaire eindpunt van mortaliteit en hospitalisatie voor hartfalen (*odds ratio* 1.16; 95% CI 0.73-1.84; P=0.53). Het is duidelijk dat verder onderzoek nodig is om het prognostisch voordeel van de behandeling van FMR, te helpen verklaren. AF ritmecontrole (vooral d.m.v. katheterablatie) is mogelijk een therapeutisch doelwit voor het verminderen van FMR bij CRT-patiënten die bij baseline al AF hebben.

Hoewel de diagnostische rol van multimodale cardiale beeldvorming goed gedefinieerd is voor genetisch DCM, zal verder onderzoek opheldering moeten leveren over het vermogen ervan om ongunstige lange termijn uitkomsten (bijv. de ontwikkeling van symptomen, vermindering van LVEF, ventriculaire aritmieën en sterfte) bij asymptomatische mutatiedragers te voorspellen. Bovendien moet de specifieke waarde van beeldvorming bij therapie (bijv. *angiotensin converting enzyme* (ACE)-remmers of ICDs, die de progressie van de ziekte in genetische DCM-mutatiedragers vertragen of zelfs voorkomen) nog worden onderzocht. Voor het definiëren van de rol van multimodale cardiale beeldvorming bij zowel de voorspelling van uitkomsten op lange termijn, alsook de begeleiding van therapie, zullen prospectieve studies noodzakelijk zijn. Aangezien langetermijn *follow-up* bij zeldzame cardiomyopathieën in prospectieve, multicentrum studies ongetwijfeld uitdagend zullen zijn, zou het gebruik van beeldvormende-*biomarkers* als therapeutisch doelwit op zichzelf, bijzonder nuttig kunnen zijn.

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CURRICULUM VITAE

Pieter van der Bijl werd geboren op 13 november 1981 te Kaapstad, Zuid-Afrika (ZA). In 1999 behaalde hij zijn middelbare schooldiploma te Kaapstad en in 2000 begon hij met zijn opleiding geneeskunde aan de Universiteit Stellenbosch. Tijdens zijn studie verrichte hij als student onderzoek bij de vakgroepen Farmacologie en Microbiologie van de Universiteit Stellenbosch, onder begeleiding van dr. A.D. van Eyk en prof. dr. E. Wasserman. In 2005 behaalde Pieter cum laude zijn artsexamen (MB,ChB) en werd beloond met een medaille als de meest uitstekende student van de faculteit geneeskunde aan de Universiteit Stellenbosch die afstudeerde in dat jaar. In 2006 en 2007 was hij werkzaam als arts-assistent niet in opleiding, op diverse afdelingen van het Dihlabeng ziekenhuis (Betlehem, ZA) en het Kimberley ziekenhuis (Kimberley, ZA). In 2007 behaalde Pieter tevens het diploma anesthesiologie van het anesthesiologen college van Zuid-Afrika. Van 2008 tot en met 2011 was hij arts-assistent interne geneeskunde aan de Universiteit Stellenbosch en het Tygerberg Academisch ziekenhuis (Kaapstad, ZA), en in 2011 behaalde hij de 4-jarige Master interne geneeskunde (M.Med) van de Universiteit Stellenbosch (opleider: prof. dr. M.R. Moosa). In 2011 werd Pieter lid van het college van internisten van Zuid-Afrika als specialist interne geneeskunde. In 2012 startte hij met zijn opleiding tot cardioloog in het Tygerberg Academisch ziekenhuis (Kaapstad, ZA), en ronde het af in 2014 met certificering van het college van geneeskunde van Zuid-Afrika (opleider: prof. dr. A.F. Doubell). Tevens verrichtte hij ook onderzoek op de afdeling cardiologie, onder leiding van dr. M.J. Heradien, prof. dr. P.A. Brink en prof. dr. A.F. Doubell. Pieter was werkzaam als cardioloog in een particulier ziekenhuis in Kaapstad (Kuilsrivier, ZA) in 2015, en ontving ook het Boston Scientific R.C. Fraser International Fellowship gedurende datzelfde jaar. Tijdens dit fellowship ontving hij een opleiding in het St. Thomas ziekenhuis in Londen (opleider: prof. dr. S. Redwood). In 2016 startte Pieter zijn promotieonderzoek aan het Leids Universitair Medisch Centrum onder leiding van prof. dr. J.J. Bax en dr. V. Delgado. In 2017 werd hij toegelaten as Fellow of the European Society of Cardiology (FESC). Als Imaging Fellow volgde Pieter tevens cursussen en ontving hij opleiding in cardiale beeldvorming: echocardiografie, CT (Leids Universitair Medisch Centrum) en MRI (Bronovo ziekenhuis, Den Haag en Ikazia ziekenhuis, Rotterdam). Hij voldeed in 2017 en 2018 aan de nodige beroepseisen en werd gecertificeerd voor cardiale CT (British Society of Cardiovascular Imaging (BSCI)) en cardiale MRI (European Association of Cardiovascular Imaging (EACVI)). Gedurende zijn promotieonderzoek aan het Leids Universitair Medisch Centrum richtte Pieter zich voornamelijk op het onderzoek van verschillende aspecten van geavanceerde beeldvorming met betrekking tot hartfalen en plotselinge hartdood. Een selectie van deze onderzoeksresultaten zijn opgenomen in dit proefschrift.