Advanced echocardiographic techniques in hereditary cardiac diseases

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Colophon

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Chapter 1

General introduction outline of the thesis

General introduction and outline of the thesis

Hereditary cardiac diseases include all conditions caused by genetic mutations which lead to cardiac abnormalities. Among those, hypertrophic cardiomyopathy (HCM) is the most prevalent inherited cardiomyopathy, characterized by left ventricular hypertrophy > 15 mm and caused - in the majority of patients - by mutations in one of the cardiac sarcomeric protein genes.[1] Patients with HCM are at higher risk for the development of sudden cardiac death (SCD), heart failure, atrial and ventricular arrhythmias and cerebrovascular accidents.[2, 3]

Primary mitral regurgitation (MR) is caused by intrinsic abnormalities of the mitral valve apparatus, in most of the cases represented by mitral valve (MV) prolapse. If left untreated, primary MR is associated with increased morbidity and mortality and is the second most frequent indication for valve surgery.[4, 5]

Whereas the genetic component in HCM has been established and genes have been identified,[1] for primary MR the heritability is still subject of research, although family occurrence has been demonstrated, suggesting an important genetic component.[6-9]

In both conditions, HCM and primary MR, accurate assessment of cardiac chambers size and function, and in particular of the left ventricle (LV), is crucial since it has significant impact on diagnosis, therapeutic decision making (including indication for surgery), and risk stratification. For this purpose, echocardiography is the most used imaging technique in the clinical practice being non-invasive and widely available. Although measuring left ventricular ejection fraction (LVEF) is still the recommended method to evaluate global LV systolic function,[10] several studies have shown that in patients with HCM or primary MR, LVEF remains preserved in most of cases despite subclinical myocardial dysfunction, and does not allow for a proper assessment of LV function.[11-13] Therefore, advanced echocardiographic modalities, particularly based on 2-dimensional speckle tracking imaging, have been developed to provide more sensitive assessment of LV dysfunction and have applied in several cardiovascular diseases.[14]

Two-dimensional speckle tracking echocardiography uses ‘speckle’ artefacts, which are naturally generated due to reflection of the echo beams. By following these speckles frame to frame, the shortening or lengthening of the myocardial segments can be measured throughout the cardiac cycle in longitudinal, radial and circumferential directions.[15] The relative change in myocardial length is defined as strain (%) and can therefore reflect more accurately myocardial contraction. Global

longitudinal strain (GLS) is defined as the average peak longitudinal strain of the LV 17 segments and normal values range from -18 to -20%.[10]

Advanced echocardiographic techniques in patients with hypertrophic cardiomyopathy

Risk stratification is of crucial importance in HCM patients and is mainly focused on SCD. However, it remains a clinical challenge and is currently recommended based on a clinical risk stratification score developed including parameters such as LV thickness, LV outflow tract gradient, positive family history for SCD, non-sustained ventricular tachycardia at Holter-monitoring and unexplained syncope.[2, 3, 16] Nevertheless, the specificity and sensitivity of these parameters are limited, specifically regarding other adverse events rather than SCD, such as heart failure development and death due to other cardiovascular causes. There is therefore an unmet need for additional parameters which may improve risk stratification in these patients. GLS has shown to be able to detect subtle myocardial dysfunction in HCM patients (Figure 1a) probably by reflecting myocardial fibrosis and myocardial disarray and initial studies showed its association with adverse events.[17-21] Also, left atrial (LA) enlargement is a common finding in HCM patients as a result of LV diastolic function, presence of MR and intrinsic atrial myopathy.[22] Increased LA diameter is associated with adverse outcome in HCM patients; however, LAVI is considered more accurate for the assessment of LA size and has shown prognostic value for predicting adverse events in HCM patients.[23-25] Therefore, GLS and LAVI may be promising parameters for risk stratification in HCM patients, but studies evaluating the prognostic value of both parameters in a large HCM population with long-term follow-up are lacking. Moreover, it is unknown how these parameters change over time and whether changes over time may be associated with worse outcome.

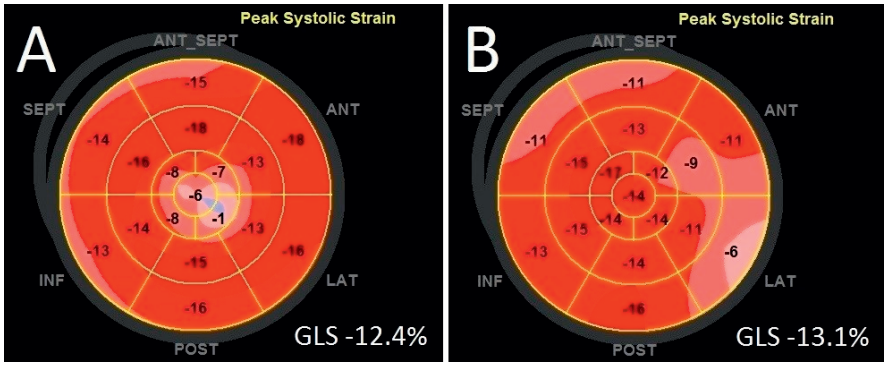

Figure 1. Global longitudinal strain (GLS). **Panel A** presents the bulls-eye plot of a patient with apical hypertrophic cardiomyopathy (HCM), which shows significantly reduced GLS particularly in the apical segments. In **Panel B** the bulls-eye plot of a patient with severe primary mitral regurgitation is presented, which shows reduced GLS in most segments.
ANT anterior; ANT_SEPT anteroseptal; INF inferior LAT lateral; POST posterior; SEPT septal

Although HCM is generally considered as a left-sided heart disease, previous studies demonstrated that the right ventricle (RV) is frequently involved.[26-28] Accurate evaluation of RV function is challenging by standard echocardiographic parameters because of its complex shape and geometry. Initial studies evaluated RV dysfunction in HCM patients, including assessment of RV longitudinal strain as measured by speckle-tracking echocardiography.[29-32] However, these studies used different strain parameters and cut-off values with inhomogeneous results; furthermore, the prognostic value of RV longitudinal strain in HCM patients has not been evaluated yet.

The assessment of GLS does not take into account LV afterload, which can influence significantly myocardial performance. Recently, incorporation of arterial pressure measures have been possible in in LV pressure-strain loops, which can provide different parameters of myocardial work (Figure 2)[33] Initial research has shown that constructive work was impaired in HCM patients and it was associated with LV fibrosis on cardiac magnetic resonance imaging.[34] However, segmental differences in myocardial work parameters in HCM patients and the prognostic value of this new method in these patients are still unknown.

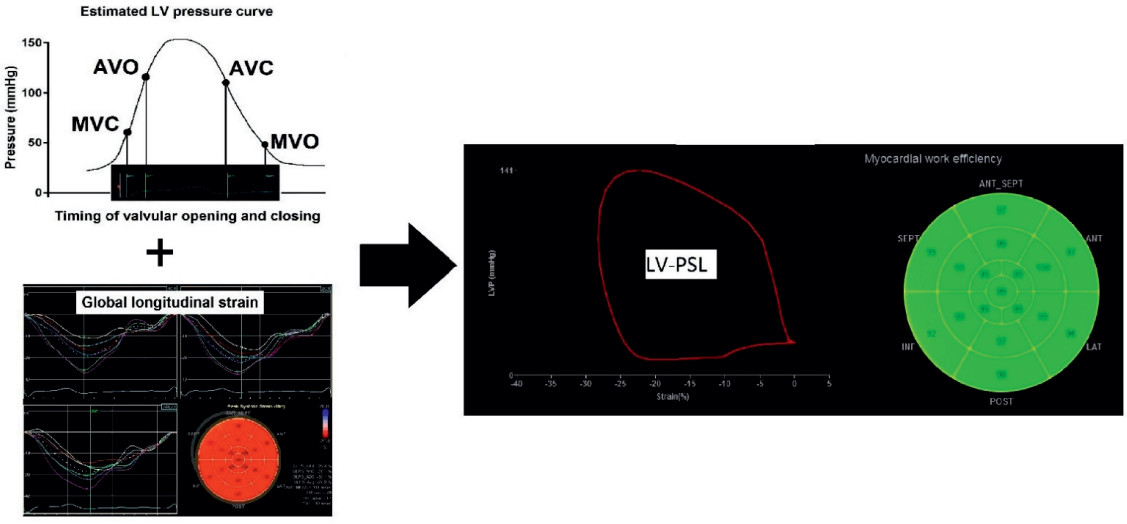

Figure 2. The upper left panel shows the estimated left ventricular (LV) pressure curve, based on the blood pressure measurements and timing of the opening and closing of the mitral and aortic valves. The lower left panel shows the measurement of global longitudinal strain from the 2-, 3- and 4-chamber apical views. The right panel shows the LV pressure strain loop and the bulls-eye plot with cardiac efficiency per segment, as constructed by the specific software.

Etiology of primary mitral valve disease and its genetic background

The most frequent etiology of primary MR is degenerative MV disease, leading to MV prolapse and can be further distinguished in two main forms: Barlow's disease (BD) and fibro-elastic deficiency (FED).[35] BD is generally characterized by thick, redundant leaflets, multi-segmental prolapse and typical MV annular abnormalities, while FED is described as single-segment prolapse, thin leaflets, or thickening limited to the prolapsing segment, and chordal rupture (Figure 3).[36] The underlying cause of MV prolapse in unclear, but several studies demonstrated familial clustering of this disease, suggesting an important genetic component with few pathogenic genes being identified.[6-9, 37-40] Studies evaluating the familial distribution of MV prolapse were so far population based, with a low overall prevalence of MV prolapse, while the prevalence of familial occurrence in a clinical cohort of patients with MV prolapse has not been investigated. Moreover, the exact phenotype of MV prolapse was not specified in previous studies, although BD and FED have different clinical presentations and therefore possibly a different hereditary component.

In patients with BD, the pathophysiologic process which leads to the phenotype of thick and redundant leaflets (and in a later stage to severe MR) is not yet fully understood. It has been hypothesized however that mitral annular abnormalities, such as annular dilatation, mitral annular disjunction (MAD) and the systolic outward motion of the annulus (curling), are probably the primary alterations of the underlying pathology. These annular abnormalities might increase the stress on the whole MV apparatus (already abnormal), leading to thickening and elongation of the MV leaflets and eventually to significant MR.[41-46] Longitudinal echocardiographic studies evaluating changes over time of MV abnormalities could help understanding the pathophysiology of BD and identify these patients in an early phase to improve timing of diagnosis and management. However, no studies evaluated the specific MV characteristics in details over time.

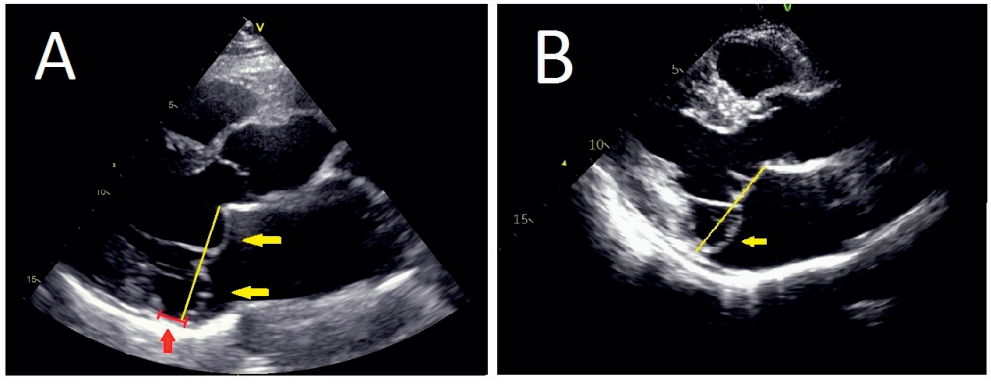

Figure 3. Transthoracic echocardiographic images of parasternal long-axis view of the mitral valve (MV). **Panel A** shows bi-leaflet MV prolapse (yellow arrows) and significant mitral annular disjunction (red arrow) in a patient

with Barlow's disease. In **Panel B** an example of fibro-elastic deficiency is shown, with prolapse of the posterior MV leaflet (yellow arrow), whereas the anterior MV leaflet does not prolapse.

Advanced echocardiographic techniques in patients with primary mitral regurgitation

MV prolapse can lead to severe primary MR and subsequent complications. Prognosis in patients with severe primary MR can be improved significantly with MV surgery.[47, 48] Currently, MV surgery is recommended for symptomatic patients with severe primary MR. In case patients have severe primary MR but are asymptomatic, MV surgery is recommended when there are signs of LV dysfunction or dilatation (LVEF ≤ 60% or LV end-systolic diameter ≥ 45 mm), in case of new onset of atrial fibrillation or of systolic pulmonary artery pressure > 50 mmHg, and when the likelihood of durable repair is high and surgical risk is low.[4, 5] However, appropriate timing of MV surgery is still challenging because LVEF and LV dimension might not timely reflect subtle LV dysfunction. Furthermore, the likelihood of MV repair is highly dependent of MR etiology, being BD MV more difficult to repair and prone to recurrences. LV GLS has been proposed as more sensitive parameter to detect LV dysfunction also in patients with primary MR (Figure 1b) and initial studies demonstrated the association of LV GLS with different adverse events.[49-51] However, whether the association of LV GLS with adverse outcome differs between patients with FED and BD has not been investigated.

Aim and outline of the thesis

The aim of this thesis is to provide new insights in 2 common cardiac diseases with an hereditary base: HCM and primary MR. The thesis focuses specifically on the diagnosis and risk stratification of these patients with advanced echocardiographic techniques.

Part 1 focuses on the potential role of advanced echocardiographic techniques in optimizing risk stratification for patients with HCM. Specifically, in **Chapter 2** the prognostic value of GLS and LAVI are evaluated in a large cohort of HCM patients. **Chapter 3** explores the differences in echocardiographic changes over time between patients with non-obstructive HCM who developed heart failure as compared to patients who did not. In **Chapter 4**, the prevalence and prognostic implications of RV dysfunction, as measured with RV GLS, are evaluated in HCM patients. **Chapter 5** describes the potential (prognostic) value of myocardial work measurements in HCM patients.

In ***Part 2*** of this thesis, patients who underwent MV surgery because of severe primary MR were studied to gain more insights in the heritability and pathophysiology of primary MR. In **Chapter 6,** the familial occurrence and distribution of MV disease in patients with primary MR due to MV prolapse is evaluated. **Chapter 7** describes the echocardiographic changes of MV characteristics over time in patients with BD, before they developed severe MR and underwent MV surgery. Finally, in **Chapter 8**

the value of GLS and of the etiology of MV prolapse is evaluated for risk stratification and surgical timing decision in patients who underwent MV surgery because of severe primary MR.

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Chapter 2

Global longitudinal strain and left atrial volume index provide incremental prognostic value in patients with hypertrophic cardiomyopathy

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Abstract

Background. Current methods for predicting adverse events in patients with hypertrophic cardiomyopathy (HCM) are still limited. Left ventricular global longitudinal strain (GLS) and left atrial volume index (LAVI) have been recently proposed as novel prognostic factors in several cardiovascular diseases. The objective of this study was to evaluate the prognostic value of GLS and LAVI in HCM patients.

Methods and results. 2-dimensional echocardiography was performed in 427 HCM patients (66% men, age 52±15 years) and LAVI and GLS were assessed. During follow-up the primary endpoint of all-cause mortality, heart transplantation, sudden cardiac death (SCD) and/or appropriate implantable cardioverter defibrillator (ICD) therapy was noted. 103 patients reached the primary endpoint during a follow-up of 6.7 (IQR 3.3-10.0) years. Multivariable Cox regression analysis revealed GLS and LAVI to be independently associated with the primary endpoint (HR GLS 1.10 [1.03-1.19],p=0.007; HR LAVI 4.27 [2.35-7.74],p<0.001) after correcting for other clinical variables. When applying the pre-specified cut-off values of 34 mL/m^2 for LAVI and -15% for GLS, Kaplan-Meier survival curves showed significant better survival for patients with LAVI<34 mL/m^2 (p<0.001) and GLS<-15% (p<0.001) as compared with their counterparts. The likelihood-ratio test showed a significant incremental prognostic value of LAVI and GLS (p<0.001), as compared to a model with clinical and standard echocardiographic risk factors. The C-statistic for this model increased from 0.68 to 0.73 when adding GLS and LAVI.

Conclusion. GLS and LAVI are independently associated with adverse outcome in HCM patients and may help to optimize risk stratification in these patients.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most prevalent inherited cardiomyopathy and is associated with increased cardiovascular morbidity and mortality. Particularly, HCM patients experience more frequently sudden cardiac death (SCD) and death due to heart failure, and show an increased risk of stroke-related mortality due to high prevalence of atrial fibrillation.[1, 2] However, risk-stratification in HCM patients remains challenging, mainly due to a large heterogeneity of phenotypes with different prognosis, varying from asymptomatic mild cardiomyopathy throughout life to the occurrence of SCD at young age. Current approach for risk stratification in HCM patients is mainly focused on SCD and advocates for combination of clinical and echocardiographic parameters.[3, 4] However, those parameters are known to have limited sensitivity and specificity particularly in predicting cardiovascular events other than SCD.[5] Therefore, research has focused on identifying potential additional prognosticators to optimize HCM patient management.[6-11] Two-dimensional speckle tracking strain analysis has been recently proposed as a new method to improve assessment of left ventricular (LV) function as compared to conventional echocardiography. In HCM patients, in whom LV ejection fraction (LVEF) is mostly within the normal ranges, global longitudinal strain (GLS) has shown to be able to detect subtle myocardial systolic dysfunction and initial studies have proposed this parameter as a potential novel prognostic factor. [12-16] Similarly, left atrial volume index (LAVI) has been shown to be associated with specific clinical outcomes, such as new onset of atrial fibrillation and SCD, probably reflecting not only LV diastolic dysfunction, but also LV out-flow tract (LVOT) obstruction, mitral regurgitation (MR) and intrinsic atrial myopathy.[17-19] However, the prognostic value of the combination of GLS and LAVI has not been investigated thoroughly. Therefore, the objective of this study was to evaluate the incremental prognostic value of GLS and LAVI for hard adverse clinical outcomes in a large cohort of HCM patients and with a long-term follow-up.

Methods

Patient population

The population consisted of patients with HCM, defined according to current guidelines: a maximal LV hypertrophy (LVH)≥15 mm, in absence of any other cardiac or systemic disease that could cause a similar degree of LVH.[3] Patients were identified from an ongoing clinical registry and excluded if age was <16 years. Patient data were prospectively collected in the departmental cardiology information system (EPD-Vision®; Leiden University Medical Center, Leiden, The Netherlands) and included the

following information: demographic characteristics, New York Heart Association (NYHA) functional class, use of medications, comorbidities and the currently adopted SCD risk factors, such as unexplained syncope, non-sustained ventricular tachycardia (nsVT) on 24 hours electrocardiographic Holter monitoring (≥3 beats at≥120 bpm) and positive family history for SCD at young age (<50 years) in 1st or 2nd degree relatives. Furthermore, an electrocardiogram and echocardiogram were performed in all patients at the moment of the first visit at the out-patient clinic. Interventions, such as percutaneous revascularisation, septal alcohol ablation, myectomy or other cardiac surgery during follow-up or before the first out-patient visit were also recorded. The study complies with the Declaration of Helsinki and was approved by the Institutional Review Board. Due to the retrospective design of this study, the Medical Ethical Committee waived the need of written informed consent.

Echocardiography

Standard transthoracic 2-dimensional echocardiographic studies were performed using commercially available ultrasound machines (Vivid 5, Vivid 7 and E9, GE-Vingmed, Milwaukee, WI). Images were digitally stored and analyzed offline (EchoPAC, version 112, GE Medical Systems, Horten, Norway). LV end-diastolic and end-systolic diameters were measured from the parasternal long-axis view. LV volumes, LVEF and left atrial (LA) volumes were measured using Simpson's method and indexed for body surface area (BSA).[20] LA volume was calculated at end-systole, tracing the LA endocardium in the four and two chamber views. Measurements of septal and posterior wall thickness were obtained in the parasternal long-axis from an M-mode acquisition, while maximal LV wall thickness was assessed from a short-axis view at three different levels (basal, mid and apical). LV diastolic function was assessed mainly using the mitral inflow peak velocities of E divided by the peak early diastolic velocity (E') of the lateral mitral annulus by tissue Doppler imaging, obtaining the E/E' ratio.[21] Assessment of the presence of systolic anterior movement (SAM) of the mitral valve was performed from a parasternal long-axis view and from apical 3- and 5-chamber views. LVOT resting peak gradient was quantified by continuous wave Doppler. The presence and grade of MR was assessed according to a multiparametric approach as recommended.[22]

GLS was measured using speckle tracking analysis on standard apical views (2-, 3- and 4-chamber), acquired with a frame rate of 40-90 Hz (mean 60fps). The region of interest was automatically created and manually adjusted when necessary to fit the entire wall thickness. GLS was then calculated by averaging the peak longitudinal strain in 17 segments from the 3 different views.

Clinical outcome

The primary endpoint was a combined endpoint of all-cause mortality, heart transplantation, aborted SCD and appropriate implantable cardioverter defibrillator (ICD) therapy. Aborted SCD was

defined as a successful resuscitation from cardiac arrest with documented ventricular tachycardia and/or ventricular fibrillation. Appropriate ICD therapy was defined as anti-tachycardia pacing (ATP) and/or shock for ventricular tachycardia and/or ventricular fibrillation. The occurrence of events during follow-up was obtained by medical charts review, retrieval of survival status through the municipal civil registries and by contact with the general practitioner of the patient. The secondary endpoint included (aborted) SCD and appropriate ICD therapy.

Statistical analysis

Continuous variables are expressed as mean±standard deviation, when normally distributed, and as median (interquartile range), when not normally distributed. Categorical variables are presented as absolute numbers and percentages. Differences in baseline characteristics between patients with and without the primary endpoint were assessed using student-t test, Mann-Whitney U test or Chi-square, when appropriate. Univariable Cox regression analysis was performed for all clinical and echocardiographic variables and the variables with a p-value<0.10 were included in a multivariable Cox regression analysis (selecting among the ones highly correlated with each other) to identify independent predictors of the primary and secondary endpoints: hazard ratio (HR) and 95% confidence intervals (CI) were calculated. Kaplan-Meier curves were constructed to estimate the cumulative event-free-survival for the primary endpoint and compared by the log-rank-test. Cut-off value for LAVI (34mL/m2) was defined based on guidelines recommendations, while for GLS (-15%) it was chosen based on the median value of GLS in the current population and on previously suggested cut-off value from the literature in HCM patients[12, 14, 15] To evaluate the incremental value of GLS and LAVI on top of clinical and standard echocardiographic parameters, likelihood-ratio testing was performed as well as calculation of the overall C-statistic as proposed by Harrell et al[23] as an analogue of the area under the ROC for survival analysis for both primary and secondary endpoint. Furthermore, we assessed the impact of adding GLS and LAVI to a basic model using the continuous net reclassification improvement (NRI). A p-value of<0.05 was considered significant. Statistical analysis was performed with the SPSS software package and the R-package survINDRI. (version 20, IBM Corp, Armonk, New York, USA).

Results

Patient population

A total of 427 HCM patients (52±15 years, 66% men) were included (Table 1). A pathogenic or likely pathogenic gene mutation was found in 167 (63%) of the patients who underwent genetic testing (n=264). Mean LVEF was normal in this HCM patient population (65±9%), but mean GLS was impaired (-15±4%) and median LAVI was increased (36(28-47) mL/m^2).

Long-term clinical outcome

During a median follow-up of 6.7 (IQR 3.3-10.0) years, 103 patients reached the primary endpoint: 53 patients experienced aborted SCD or appropriate ICD therapy, 2 patients underwent heart transplantation and 48 patients died. Cause of death was of cardiac origin in 22 patients (11 heart failure, 10 SCD, 1 other cardiovascular cause), non-cardiac in 10 patients (3 sepsis, 6 malignancy, 1 suicide) and unknown in 16 patients. As shown in Table 1, there were no significant differences in demographics, cardiovascular risk factors and symptoms between patients who reached the primary endpoint and those who did not. However, patients who reached the primary endpoint were more likely to undergo a septal intervention, used more frequently beta-blockers and showed a higher incidence of nsVT at 24 hours electrocardiogram Holter monitoring. Furthermore, patients who reached the primary endpoint had a significantly larger maximum wall thickness, worse LV diastolic function (E/E'), more prevalence of SAM, more impaired (less negative) GLS and a larger LAVI (Table 1). The secondary endpoint included 63 events, of which 53 aborted SCD or appropriate ICD therapy and 10 SCD.

Table 1. Clinical and echocardiographic characteristics of the total patient population and dichotomized for patients who reached the primary endpoint versus those who did not.

	Overall N=427	Endpoint No, N=324	Endpoint Yes, N=103	P value
Clinical characteristics				
Age (years)	52±15	51±15	53±15	0.347
Men [n(%)]	282 (66)	214 (66)	68 (66)	1.000
Hypertension [n(%)]	151 (35)	126 (40)	33 (33)	0.239
Previous AF [n(%)]	61 (14)	35 (11)	26 (25)	<0.001
Diabetes mellitus [n(%)]	30 (7)	19 (6)	11 (11)	0.116
NYHA class [n(%)]				0.066
I	333 (80)	258 (82)	75 (73)	
II	69 (17)	49 (15)	20 (20)	
III	15 (3)	8 (3)	7 (7)	
Genetic mutation HCM [n(%)]*	167 (63)	131 (63)	36 (70)	0.192
Septal intervention	56 (13)	34 (11)	22 (21)	0.007
Patients with ICD	150 (35)	86 (27)	64 (62)	<0.001
Medication use [n(%)]				
Beta-blockers	167 (39)	117 (36)	50 (49)	0.028
Calcium-antagonist	93 (22)	66 (21)	27 (27)	0.273
Diuretics	59 (14)	40 (13)	19 (19)	0.142
SCD Risk factors				
Family history of SCD [n(%)]	178 (42)	135 (42)	43 (42)	1.000
Unexplained syncope [n(%)]	38 (9)	26 (8)	12 (12)	0.320
Prior nsVT [n(%)]	110 (26)	70 (22)	40 (39)	0.001
Echocardiography				
LA diameter	41±7	40±7	44±8	<0.001
LVEDD (mm)	44±7	44±6	44±7	0.398
LVEF (%)	65±9	66±9	63±11	0.012
E/E'	10 (8-16)	12 (7-15)	17 (9-25)	<0.001
IVS (mm)	19±5	19±5	21±6	<0.001
PW (mm)	13±3	12±3	13±4	0.019
Max LVH (mm)	21±6	21±5	23±7	<0.001
LVOT gradient (mmHg)	9 (6-19)	19 (6-16)	26 (5-34)	0.555
MR >grade 2 [n(%)]	89 (21)	59 (19)	30 (33)	0.010
SAM [n(%)]	154 (36)	107 (33)	47 (46)	0.024
GLS (%)†	-15±4	-16±4	-13±4	<0.001
LAVI (mL/m²)‡	36 (28-47)	37 (26-43)	51 (35-65)	<0.001

Primary end point: all-cause mortality, heart transplantation, aborted sudden cardiac death, or appropriate ICD therapy. AF atrial fibrillation, GLS global longitudinal strain, HCM hypertrophic cardiomyopathy, ICD implantable cardioverter defibrillator, IVS interventricular septum, LAVI left atrial volume index, LVEDD left ventricular end diastolic diameter, LVEF left ventricular ejection fraction, LVH left ventricular hypertrophy, LVOT left ventricular outflow tract, MR mitral regurgitation, NSVT non-sustained ventricular tachycardia, PW posterior wall, SAM systolic anterior movement, SCD sudden cardiac death

** Only genetically tested patients (N=264)*

† Missing data for 35/427 patients

‡ Missing data for 20/427 patients

Survival analysis

Univariable Cox proportional hazard regression analysis showed that atrial fibrillation, NYHA class, nsVT on 24-hour Holter monitoring, use of beta-blockers, GLS, LVEF, LAVI, maximal LVH, E/E', LA diameter, LVOT resting peak gradient, SAM, MR >2 and septal intervention during follow-up all had a significant association with the primary endpoint. However, multivariable analysis for the primary endpoint revealed only GLS (HR 1.10 (1.03-1.19),p=0.007) and LAVI (HR 4.27, (2.35-7.74),p<0.001) as independent predictors (Table 2).

Table 2. Univariable and multivariable Cox proportional hazard regression analysis to identify independent predictors of the primary endpoint.

Parameter	Univariable HR (95%CI)	P-value	Multivariable HR (95%CI)	P-value
Age	1.01 (0.99-1.03)	0.081	1.00 (0.98-1.01)	0.750
Men	0.97 (0.64-1.45)	0.863		
NYHA class ≥ 2	1.72 (1.11-2.68)	0.016	0.61 (0.30-1.21)	0.261
Previous AF	2.38 (1.52-3.72)	<0.001	1.17 (0.61-2.24)	0.638
Septal intervention	1.82 (1.13-2.94)	0.013	1.79 (0.96-3.35)	0.067
B-blocker	1.58 (1.07-2.32)	0.021		
Family SCD	1.02 (0.69-1.51)	0.928		
Syncope	1.28 (0.70-2.35)	0.417		
nsVT	1.89 (1.27-2.82)	0.002	1.44 (0.87-2.40)	0.156
LA diameter	1.05 (1.03-1.08)	<0.001		
LVEF	0.97 (0.96-0.99)	0.008		
E/E'	2.03 (1.43-2.91)	<0.001	1.38 (0.90-2.12)	0.142
Max LVH	1.04 (1.01-1.07)	0.007	1.00 (0.95-1.05)	0.909
LVOT gradient	1.22 (1.01-1.48)	0.047		
MR grade ≥2	1.81 (1.17-2.80)	0.008		
SAM	1.79 (1.21-2.64)	0.003	1.18 (0.66-2.08)	0.582
GLS	1.13 (1.08-1.19)	<0.001	1.10 (1.03-1.19)	0.007
LAVI	4.23 (2.83-6.31)	<0.001	4.27 (2.35-7.74)	<0.001

AF atrial fibrillation; CI confidence interval, HR hazard ratio, For other abbreviations see Table 1.

When dividing the population according to the pre-specified cut-off value of LAVI, patients with LAVI≥34 mL/m^2 had worse outcome as compared to patients with LAVI<34 mL/m^2. The cumulative

event-free survival at respectively 2 and 6 years was 98% and 93% versus 94%and 81% respectively (log-rank 19.7,p<0.001) (Figure 1a). When dividing the population according to the pre-specified cut-off value of GLS, patients with GLS≥-15% had worse outcome as compared to patients with GLS<-15% (Figure 1b). The cumulative event-free survival at respectively 2 and 6 years was 98% and 91% versus 92%and 76% respectively (log-rank 27.1,p<0.001).

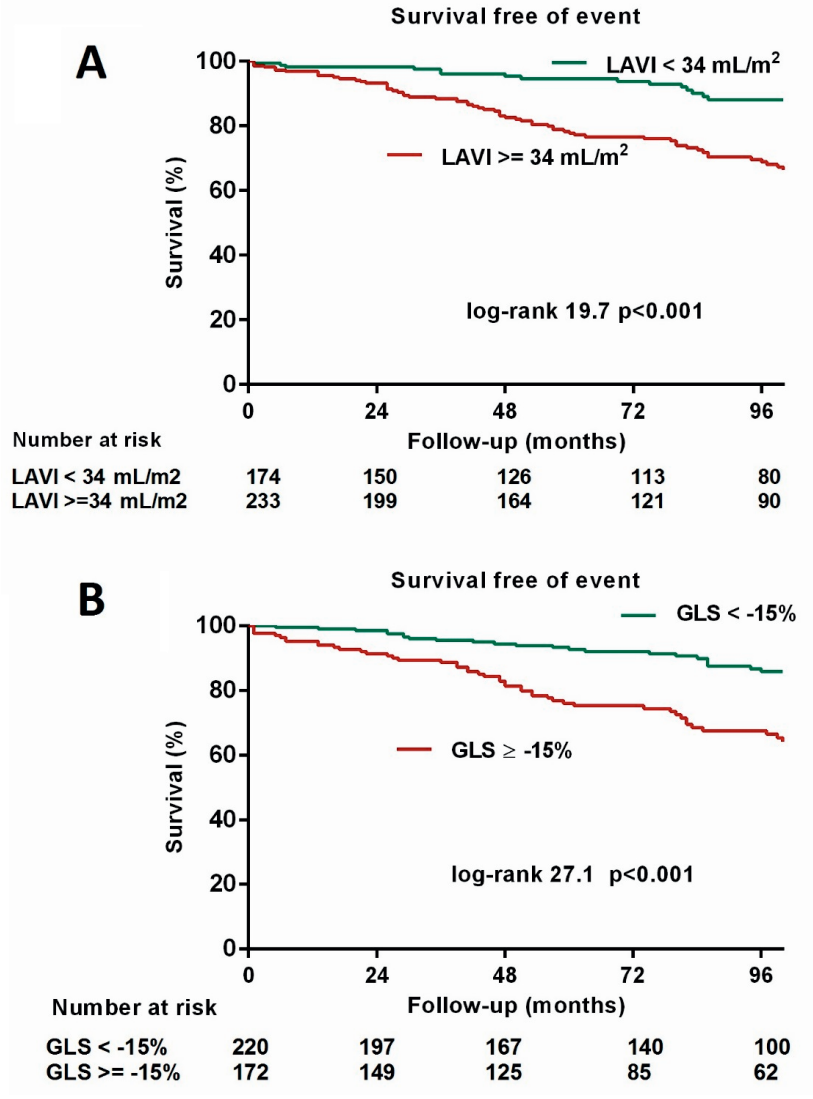

Figure 1. Kaplan-Meier analysis to evaluate the survival free of the primary endpoint of all-cause mortality, heart transplantation, aborted SCD or appropriate ICD therapy. **A.** Left atrial volume index (LAVI). **B.** Global longitudinal strain (GLS).

When dividing the population in four groups based on the pre-specified GLS and LAVI cut-off values, the group of patients with both GLS<-15% and LAVI<34 mL/m^2 had the best outcome, whereas patients with both GLS≥-15% and LAVI≥34 mL/m^2 had the worst outcome. The cumulative event-free survival at 6 years was 99% for GLS<-15% and LAVI<34 mL/m^2 versus 63% for patients with GLS≥-15% and LAVI≥34 mL/m^2 (log-rank 49.3,p <0.001) (Figure 2).

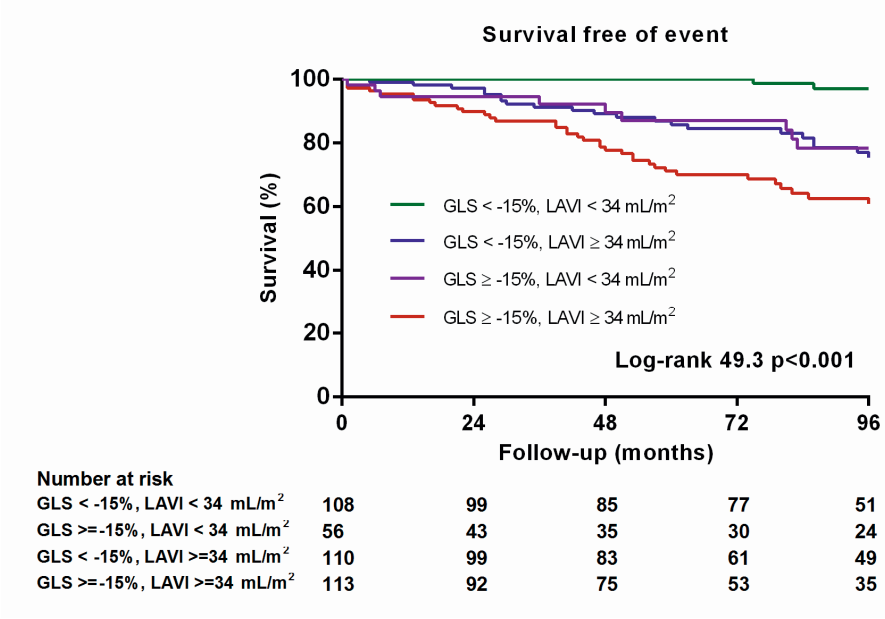

Figure 2. Kaplan-Meier analysis to evaluate the survival free of experiencing the primary endpoint (all-cause mortality, heart transplantation, aborted SCD or appropriate ICD therapy) when combining assessment of global longitudinal strain (GLS) and left atrial volume index (LAVI).

When considering the secondary endpoint, GLS and LAVI showed a significant association with this outcome (HR 1.12 (1.06-1.19),p<0.001 for GLS, HR 3.94 (2.33-6.66),p<0.001 for LAVI) together with gender, nsVT, LA diameter and maximum LVH at the univariable analysis. When corrected for gender, LVH and nsVT, GLS and LAVI remained independently associated with the secondary endpoint at multivariable analysis (HR 1.08 (1.01-1.16),p=0.023 for GLS and HR 3.70 (2.08-6.60),p<0.001 for LAVI).

Incremental value of GLS and LAVI

Figure 3 shows the results of the likelihood-ratio test and the Harrell's C-statistic for LAVI and GLS on top of clinical and standard echocardiographic parameters associated with the primary endpoint at the univariable Cox regression analysis. The addition of LAVI≥34 mL/m^2 to a basic model, provided a

significant improvement (p<0.001), with an increase of the C-statistic from 0.68 to 0.71. The sequential addition of GLS≥-15% further improved the model (likelihood-ratio test p=0.008). Overall, the combined addition of LAVI and GLS to the clinical and standard echocardiographic risk factors provided the best model (likelihood-ratio test p<0.001,C-statistic =0.73). The incremental value of this model was also demonstrated by a NRI of 0.30 (95% CI 0.15-0.42,p<0.001).

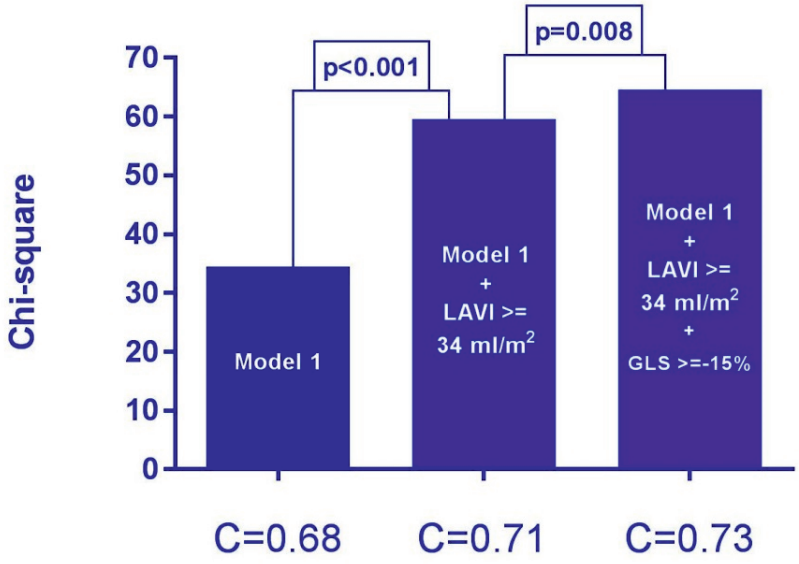

Figure 3. *Likelihood-ratio test.* The bar graphs show the incremental value of GLS and LAVI on top other important clinical risk factors for predicting the primary endpoint. Harrell's C-statistic represents overall adequacy of the risk prediction.
Model 1: age, NYHA class ≥2, previous atrial fibrillation, non-sustained ventricular tachycardia at holter-monitoring, maximum left ventricular wall thickness, maximum left ventricular outflow tract gradient, E/E', systolic anterior movement. GLS global longitudinal strain, LAVI left atrial volume index

Similarly when considering the secondary endpoint, the addition of LAVI≥34 mL/m^2 and GLS≥-15% to a basic model including gender, nsVT and maximum LVH also provided incremental prognostic value: Chi-square increased from 25 to 29 adding GLS (p=0.046) with an improvement of C-statistic from 0.68 to 0.70. More importantly, adding LAVI increased the Chi-square to 39 (p<0.001) with an improvement of C-statistic to 0.79. The NRI was 0.26 (95% CI 0.11-0.41,p<0.001).

Inter- and intra-observer variability

Inter-observer reproducibility for GLS and LAVI was assessed by two independent operators in 15 randomly selected patients. The intra-class correlation coefficient (ICC) between two observers was

0.94(p<0.001) for LAVI and 0.94(p<0.001) for GLS. The ICC for intra-observer agreement was 0.95(p<0.001) for LAVI and 0.91(p<0.001) for GLS.

Discussion

The main findings of the current study can be summarized as follows: 1) in a large cohort of HCM patients, GLS and LAVI demonstrated to be independently associated with the primary endpoint of all-cause mortality, heart transplantation and aborted SCD as well as with the secondary endpoint of (aborted) SCD or appropriate ICD therapy, 2) the presence of both preserved GLS and LAVI showed the highest cumulative event-free survival as compared to patients with impaired GLS and/or LAVI; 3) the addition of GLS and LAVI provided incremental prognostic value on top of other clinical and standard echocardiographic parameters.

Risk stratification in HCM

In HCM patients, risk stratification is a clinical challenge and has been mainly focused on prevention of SCD, for which several risk markers have been proposed, such as family history for SCD, unexplained syncope, nsVT, LV thickness and LVOT gradient. [24] Recently, O'Mahony developed a new risk prediction model to predict SCD in HCM patients, which included the use of continuous variables instead of dichotomized variables [4] and which was implemented in the current European Society of Cardiology guidelines.[3] Although the new risk model improves risk stratification for SCD and subsequently identification of patients who can benefit from an ICD,[25, 26] there are no recommendations in current guidelines for risk stratification for other adverse events such as heart failure-related mortality and other cardiovascular deaths which may occur in HCM patients.[27] Therefore, several studies have tried to identify additional prognostic markers in order to optimize clinical management of HCM patients.

Among these, NT-proBNP, atrial fibrillation, NYHA class and functional exercise capacity were shown to be associated with worse overall prognosis in HCM patients.[9-11] Furthermore, the presence of myocardial fibrosis, as assessed by cardiovascular magnetic imaging with late gadolinium enhancement (CMR-LGE) has been proposed as an important risk marker and showed to be associated not only with SCD but also with adverse cardiovascular events in HCM patients.[6-8, 28] However in clinical practice, ideal prognosticators would be simple and readily available parameters, which should reflect structural abnormalities such as myocardial fibrosis together with myocardial systolic and diastolic dysfunction.

GLS as risk marker

Several studies have shown that GLS, measured by speckle tracking echocardiography, is able to detect subtle myocardial dysfunction in HCM patients probably reflecting the characteristics myocardial fiber disarray, myocardial fibrosis and microvascular dysfunction.[16] A study of Serri et al. showed that GLS can be measured with good reproducibility and is significantly impaired in HCM patients as compared to healthy controls.[29] In a cohort of 32 HCM patients who underwent septal myectomy, GLS significantly correlated with fibrosis in the myocardium samples and could predict arrhythmias better than CMR-LGE.[30]

Initial studies have also assessed the value of GLS to predict adverse events in HCM patients.[12-15] Hartlage et al[12], using a cut-off value for GLS of -16% in 79 HCM patients, found an abnormal GLS to be predictive for a combined endpoint of heart failure hospitalizations, sustained ventricular arrhythmias and all-cause mortality. In a population of 92 high-risk HCM patients that received an ICD, Debonnaire et al[14] demonstrated the value of GLS (with a cut-off of -14%) as potential marker in the prediction of appropriate ICD therapy, which is confirmed for a larger and more heterogeneous HCM population by the current study. Recently, a study by Reant et al[15] showed the association between GLS and the combined endpoint of cardiac death, heart failure admission and appropriate ICD therapy in a large cohort of 472 HCM patients where patients with atrial fibrillation were excluded. Particularly, patients with a GLS>-15.6% showed to have higher risk for cardiac events. In the present study with a similarly large patient population, the prognostic value of GLS was also demonstrated for the hard endpoint of all-cause mortality and appropriate ICD therapy. Particularly, the same cut-off value of -15% for GLS showed significant incremental value over clinical and standard echocardiographic parameters. Furthermore in the current study, patients in atrial fibrillation were not excluded and the multivariable Cox regression analysis corrected for atrial fibrillation, increasing the clinical application of these results considering the potential prognostic value of atrial fibrillation in HCM patients.[31] Finally, the current study evaluated the prognostic value of GLS in combination with LAVI, another potentially important prognosticator.

LAVI as risk marker

Enlargement of LA occurs frequently in HCM patients, reflecting significant LV diastolic dysfunction, LVOT obstruction, presence of MR and intrinsic atrial myopathy.[32] Increased LA diameter is currently implemented in the HCM risk model for SCD.[4] However, LAVI is considered superior as an estimate of LA size[17] and was suggested by initial studies to be of prognostic value for general risk stratification in HCM patients.[18, 19] In the study performed by Yang et al,[18] LAVI was found to be an independent predictor of cardiovascular events in a population of 81 patients with non-apical HCM. Similar results were presented by Losi et al,[19] who evaluated LAVI in 140 HCM patients at baseline

and during follow-up and showed worse prognosis in patients with an enlarged LAVI or a rapid increase in LAVI during follow-up. Debonnaire et al[14] showed that LAVI (with a cut-off of 34ml/m^2) was independently associated with appropriate ICD therapy. Our study not only confirms the association of LAVI with the risk of appropriate ICD therapy or SCD but also shows for the first time the prognostic value of LAVI for a hard mortality outcome, including a large HCM population and with long-term follow-up.

Clinical implications

The present study demonstrated that the combination of GLS and LAVI may improve risk stratification of patients with HCM; for SCD or appropriate ICD therapy, but also for the more general endpoint of all-cause mortality. The prediction model including clinical and standard echocardiographic risk factors showed a C-statistic of 0.68, which is in line with previous literature;[26] the addition of GLS and LAVI increased the C-statistics to 0.73 for the primary endpoint and to 0.79 for the secondary endpoint, suggesting the improvement in predictive value. Such parameters, readily available from a standard echocardiographic screening, might therefore be of great value to improve risk-stratification and therefore potentially to be included in future studies for a more comprehensive risk score for all-cause mortality on top of conventional parameters.

Although the identification of strict cut-off values for these parameters might be debatable, clinical application of GLS and LAVI in the standard management of HCM patients might be stimulated by showing the clinicians how specific values perform in predicting the outcome. In this cohort, a cumulative event-free survival of 99% after 6 years was demonstrated for patients with both preserved GLS and LAVI (as defined using -15% and 34ml/m^2),[12-15, 18] whereas event-free survival was only 63% after 6 years in patients with impaired GLS and LAVI (Figure 4). Therefore, the identification of patients that are considered at low risk could be improved using GLS and LAVI, with important implications for the timing of starting medical therapy, planning follow-up of out-patient visits and SCD screening, as well as decision-making over ICD implantation.

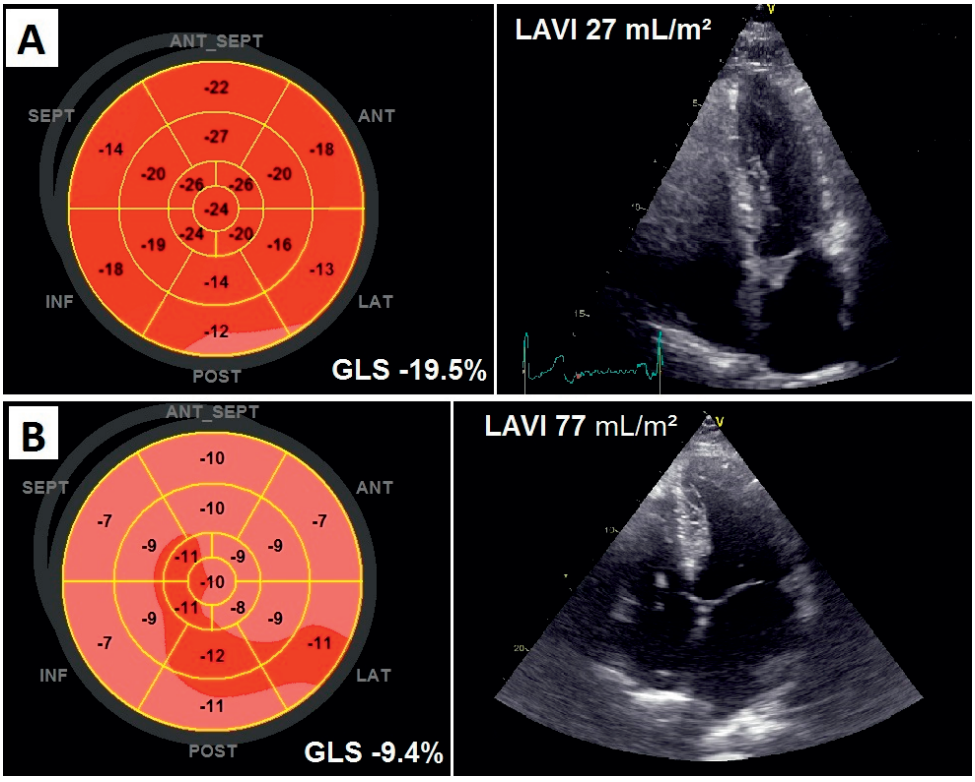

Figure 4. Examples of global longitudinal strain (GLS) displayed in a bull's eye for the 17 left ventricular segments (color coded from dark red, as preserved GLS, to pink as impaired GLS) and left atrial volume index (LAVI) assessment. **Panel A.** A 55-year old patient with normal GLS and LAVI who did not experience an event during 7.5 years of follow-up. **Panel B.** A 42-year old patient with both abnormal GLS and LAVI that experienced appropriate ICD therapy 2.5 years after baseline echocardiography.

Limitations

This study has several limitations that should be mentioned. In this single-center study only echocardiographic equipment of GE was used; therefore the results (and the cut-off value proposed) should be interpreted with caution when compared to other vendors. The European Association of CardioVascular Imaging and the American Society of Echocardiography recently set up a task force to evaluate the inter-vendor variability. From this evaluation, GLS showed a variability below 10% between different vendors, which is comparable to standard echocardiographic measurements currently used.[33] Furthermore, it is known that in HCM patients, appropriate ICD therapy may overestimate the event rate when ATP for ventricular tachycardia that could have been self-terminating are included. In the supplemental file the results of the Cox analysis are provided when ATP was removed as an outcome, which showed similar results (Supplemental table 1 and 2). Other potential prognostic markers, such as CMR-LGE, or NT-pro-BNP were not systematically assessed.

Importantly, further prospective studies in large patient population are needed to validate these data, especially to determine the most appropriate cut-off value for GLS in HCM patients and how these measurements could be implemented in daily clinical practice.

Conclusions

GLS and LAVI are both independently associated with adverse outcome in HCM patients. The combination of these two parameters has incremental value on top of standard clinical and echocardiographic parameters for predicting adverse events and could be considered in a more comprehensive risk score assessment.

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Chapter 3

Development of and Progression of Overt Heart Failure in Non-Obstructive Hypertrophic Cardiomyopathy

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Abstract

Only few studies aimed at identifying predictors of heart failure (HF) in hypertrophic cardiomyopathy (HC) patients. Furthermore, serial echocardiographic analyses are lacking in these patients and little is known about the natural progression of left ventricular (LV) abnormalities and their association with HF development. Aim of this study was to assess the prognostic value of LV global longitudinal strain (GLS) and other clinical and echocardiographic characteristics for the development of HF in patients with non-obstructive HC; furthermore, changes in echocardiographic parameters over time were correlated with HF development. Echocardiography was performed in 236 HC patients (68%male, age50±14 years) at their initial visit and during follow-up (6.5(4.1-9.8)years). The endpoint of new HF development or progression to New York Heart Association (NYHA) class III/IV was noted and echocardiographic changes over time were compared between patients with and without HF using linear mixed model analysis. In total 40 patients reached the HF endpoint. Multivariable cox regression analysis showed that age (HR 1.04(1.01-1.06),p=0.016), NYHA class (HR 2.30(1.07-4.95),p=0.033), GLS (HR 1.15(1.05-1.22),p=0.001) and left atrial volume (LAVI, HR 2.22(1.10-4.50),p=0.027) were independently associated with the HF endpoint. Echocardiographic parameters, including GLS and LAVI, remained stable over time in patients without HF endpoint, but changed significantly in patients who developed HF (group-time interaction, p=0.042 for GLS and p=0.027 for LAVI). In conclusion, LV dysfunction is a progressive phenomenon in non-obstructive HC patients which can be detected by repeated echocardiography. Importantly, GLS and LAVI at baseline as well as their changes over time are associated with HF.

Keywords: Hypertrophic cardiomyopathy; Heart failure; Global longitudinal strain; Left atrial volume

Introduction

Hypertrophic cardiomyopathy (HC) is a common inherited cardiomyopathy with a heterogeneous phenotype and can lead to adverse outcomes, such as sudden cardiac death (SCD) and evolution to overt heart failure (HF).[1-3] Because of improved SCD risk stratification, the natural course of this disease has changed and adverse outcomes are increasingly due to HF development. However, only few studies evaluated predictors specifically of HF outcome in HC patients[3-6] and data on echocardiographic changes over time in left ventricular (LV) function are lacking. It is therefore unknown which parameters are useful to monitor evolution towards HF, especially since LV ejection fraction (LVEF) often remains within normal range.[3, 6] Global longitudinal strain (GLS) has been proposed as a marker for subtle myocardial dysfunction and is associated with adverse outcome in HC patients.[7-11] However, the prognostic value of GLS for HF outcome and its changes over time has not been explored yet.[5, 12] The objectives of this study were therefore to evaluate the association of GLS with HF development or progression and to evaluate echocardiographic changes over time in non-obstructive HC patients.

Methods

Patients with a clinical diagnosis of HC were identified from an ongoing clinical registry in our center. HC was diagnosed according to current guidelines: maximal LV hypertrophy (LVH) ≥ 15mm. (or ≥ 13mm in case of an affected first-degree relative), which could not be explained by abnormal loading conditions.[1] Only patients >16 year and with at least two echocardiograms available were included, with a minimum interval of 1 year in between. This last inclusion criterion was chosen in order to assess changes in echocardiographic characteristics over time and their association with the endpoint. Patients were also excluded if they had LVOT obstruction of >30 mmHg (also after Valsalva provocation manoeuvre), if they were in New York Heart Association (NYHA) functional class III or IV at first evaluation, if LVEF was <50% or if echocardiography was of insufficient quality. Patient data were collected in the departmental cardiology information system (EPD-Vision®; Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analysed. Demographics, comorbidities, NYHA functional class and medication use were reported. In addition, currently known HC SCD risk factors were noted: unexplained syncope, previously documented non-sustained ventricular arrhythmias (nsVT) and a family history of SCD at young age (<50 years) in 1st or 2nd degree relatives. Furthermore, interventions such as ICD implantation and percutaneous coronary intervention (PCI) were noted. Our study complies with the Declaration of Helsinki. Due to the

retrospective design of this study, the Medical Ethical Committee waived the need of written informed consent.

Standard transthoracic echocardiography was performed at rest using commercially available ultrasound systems (Vivid 5, Vivid 7 and E9, GE-Vingmed, Milwaukee, WI). Images were digitally stored and analysed offline using EchoPAC (version 112, GE Medical Systems, Horten, Norway). Two-dimensional, M-mode and Doppler data were acquired according to current recommendations.[13] LV dimensions were measured from the parasternal long-axis view. LV end-diastolic and end-systolic volumes were measured and LVEF was calculated using Simpson's method. Left atrial (LA) dimensions were measured from the parasternal long-axis view and LA volume was calculated from an end-systolic tracing of the LA endocardium in the 4- and 2-chamber views and indexed for body surface area (LAVI). Maximal LV wall thickness was assessed in the short-axis view. LV diastolic function was determined by using the E/E' from the mitral Doppler inflow (E) and tissue Doppler imaging at the lateral wall of the mitral valve (E').[14] LVOT peak gradient was quantified by continuous wave Doppler during rest and during Valsalva provocation manoeuvre and the presence and severity of mitral regurgitation (MR) was assessed as recommended.[15] Global longitudinal strain (GLS) was obtained using speckle tracking analysis on the three apical views (2-, 3- and 4-chamber), acquired at a frame rate >40 fps (mean frame rate 60 fps). The region of interest was automatically created and manually adjusted to the myocardial thickness when necessary. GLS was then defined as the average peak longitudinal strain in 17 segments from the 3 different views, excluding the segments that could not be traced correctly (figure 1). Patients underwent echocardiography at their initial visit in our center and during follow-up. Particularly, the echocardiography at the first visit at our center was considered "baseline", while the "follow-up" echocardiography was chosen as the last available examination, or in case the patient developed the endpoint of HF, as the last available echocardiographic examination before the event date.

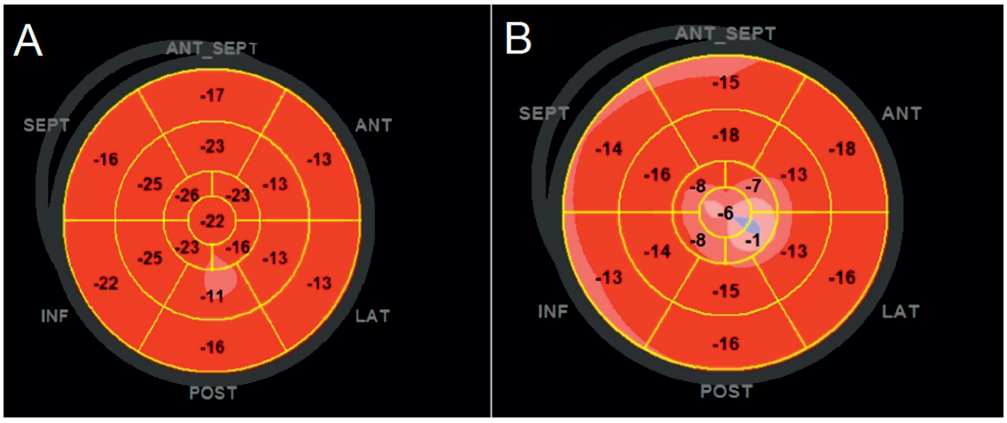

Figure 1. Example of changes in left ventricular global longitudinal strain (GLS) displayed in a bull's eye for the 17 left ventricular segments (color-coded from dark red, as preserved GLS, to pink/blue as impaired GLS). **Panel A.** Echocardiography with preserved GLS (-18.5%) in a 65-year old male patient in 2006. **Panel B**. Echocardiography in the same patients with a decline in GLS (-12.4%) in 2015. In 2016 this patient reached the heart failure endpoint.

As also defined in previous publications,[6] the endpoint of this study included: new onset of any HF symptoms[16], progression of HF symptoms or HF hospitalisation. Specifically, new onset of HF was defined in patients who never had HF symptoms, but developed at least NYHA functional class II during follow-up. Progression of HF was defined when patients were already at NYHA functional class II symptoms at baseline, but progressed to NYHA functional class III or IV at follow-up.

Statistical analysis was performed with the SPSS software package (version 20, IBM Corp, Armonk, New York, USA). Continuous variables are reported as mean±standard deviation, when normally distributed, and as median (interquartile range), when not normally distributed. Categorical variables are presented as absolute numbers and percentages. Differences in baseline characteristics between groups were assessed using student-t test, Mann-Whitney U test or Chi-square, when appropriate. Univariable and multivariable Cox regression analysis was used to identify baseline variables associated with the endpoint. Because of the relatively low number of events, separate models were made including clinical variables and echocardiographic variables separated. Linear mixed model analysis was used to assess echocardiographic changes over time in patients with and without HF endpoint. The outcome, the time of the echocardiography (baseline or follow-up) and the interaction between outcome and time of echocardiography, were incorporated in the model as fixed variables and corrected for age and NYHA class at baseline. An unstructured covariance matrix was applied. The estimated marginal means±standard error were presented. A p-value of <0.05 was considered significant. To evaluate the reproducibility for GLS and LAVI, the intra-class correlation

coefficient (ICC) was calculated for inter-observer agreement (by 2 independent operators) and intra-observer agreement (repeated measurements by the same operator) in 15 randomly selected patients.

Results

A total of 236 patients (50±14 years,68% men) fulfilled the inclusion criteria out of a cohort of 436 HC patients. For 134 patients no follow-up echocardiography was available and were excluded (128 patients were followed-up in another hospital and 6 patients reached the endpoint before the second echocardiography), 9 patients were excluded because of insufficient quality of echocardiography, 15 patients were excluded because already in NYHA class III/IV at baseline evaluation and 42 patients were excluded because of obstructive HC and/or LVEF <50%. Table 1 provides the clinical characteristics at baseline.

Table 1. Baseline clinical characteristics in the overall population and compared between patients who did and did not develop the heart failure endpoint.

	Overall (N=236)	**Event**		**P-value**
		No (N=196)	**Yes (N=40)**	
Clinical characteristics				
Age (years)	50±14	48±14	56±13	0.001
Men	160(68%)	132(67%)	28(70%)	0.853
Hypertension	88(37%)	68(35%)	20(50%)	0.075
AF	31(13%)	22(11%)	9(23%)	0.031
NYHA class I	210(89%)	179(91%)	31(78%)	0.022
PCI	25(11%)	16(8%)	9(23%)	0.020
Genetic mutation*	102(63%)	89(64%)	13(57%)	0.330
Familial SCD	106(45%)	89(45%)	17(43%)	0.862
Unexplained syncope	22(9%)	19(10%)	3(8%)	1.000
nsVT	56(24%)	40(20%)	16(40%)	0.014
**only tested patients(N=163)*				
Medication use				
Beta-blockers	73(31%)	56(29%)	17(43%)	0.093
Calcium-antagonist	39(17%)	28(14%)	11(28%)	0.059

AF atrial fibrillation; nsVT non-sustained ventricular tachycardia; NYHA New York Heart Association; PCI percutaneous coronary intervention; SCD sudden cardiac death

Categorical variables are listed as n(%). Continuous variables are listed as mean ± SD.

Most patients were in NYHA functional class I, whereas 26(11%) patients were in NYHA functional class II. During a median follow-up of 6.5(4.1-9.8) years, 40 patients reached the HF endpoint: 31 patients developed first HF symptoms (NYHA functional class ≥ II) and 9 patients developed progressive HF (to NYHA functional class III/IV). A total of 14 of these patients were also hospitalized for HF. As shown in Table 1, there were no significant differences in gender, cardiovascular risk factors, genetic mutations, family history for SCD or unexplained syncope between patients who reached the endpoint and those who did not. However, patients who reached the endpoint during follow-up were older at baseline, more often presented with NYHA class II symptoms and nsVT on the 24-hour holter-monitoring, and they also had more frequently previous PCI.

Table 2. Baseline echocardiographic variables in the overall population and compared between patients who did and did not develop the heart failure endpoint. Considering the differences in clinical characteristics between the 2 groups (see Table 1), p-values were corrected for age and New York Heart Association functional class.

Variable	Overall N=236	Event		P-value
		No (N=196)	Yes (N=40)	
LA diameter (mm)	40±7	39±6	44±8	0.005
LVEDD (mm)	44±6	44±6	46±6	0.037
LVEF (%)	65±8	66±6	60±9	0.001
E/E'	9(7-13)	9(7-13)	12(9-23)	<0.001
LVH (mm)	20(17-23)	19(17-23)	22(19-25)	0.005
LVOT (mmHg)	7(5-11)	8(5-11)	6(4-8)	0.010
MR ≥ grade 2	34(14%)	25(13%)	9(23%)	0.135
GLS (%)	-16±4	-17±4	-13±5	<0.001
LAVI (mL/m²)	34(26-43)	32(25-40)	45(33-59)	<0.001

GLS global longitudinal strain; LA left atrial; LAVI left atrial volume index; LVEDD left ventricular end diastolic diameter; LVEF left ventricular ejection fraction; LVH left ventricular hypertrophy; LVOT left ventricular outflow tract; MR mitral regurgitation

Categorical variables are listed as n(%). Continuous variables are expressed as mean ± SD or median (interquartile range).

Regarding the baseline echocardiographic variables (Table 2), significant differences between the 2 groups were observed for the following variables (after correcting for age and NYHA class): LA diameter, LVEDD, LAVI, LV wall thickness and E/E' were larger in patients who reached the HF outcome and GLS, LVEF and LVOT gradient were more impaired in patients who reached the HF outcome, although remaining within the normal range. There were no significant differences at baseline for grade >2 MR between both groups.

Univariable Cox proportional hazard regression analysis showed that age, NYHA functional class, nsVT, LV wall thickness, LVEF, LA diameter, E/E', GLS and LAVI (baseline values) were significantly associated with the HF endpoint (Table 3).

Table 3. Univariable Cox proportional hazard regression analysis to identify predictors for the heart failure endpoint.

Parameter	Univariable HR (95% CI)	P-value
Age (per year)	1.06 (1.03-1.09)	<0.001
NYHA class ≥ 2	6.29 (3.45-11.45)	<0.001
AF	2.96 (1.44-6.10)	0.003
Familial SCD	1.30 (0.75-2.25)	0.347
Unexplained syncope	1.27 (0.54-2.97)	0.586
nsVT	1.06 (0.60-1.87)	0.840
LVH max (mm.)	1.04 (0.99-1.08)	0.062
LVEDD (mm.)	1.01 (0.97-1.05)	0.671
LVEF (%)	0.96 (0.93-0.98)	0.001
LA diameter (mm.)	1.07 (1.04-1.10)	<0.001
E/E'	1.90 (1.17-3.09)	0.010
LVOT (mmHg)	0.99 (0.74-1.34)	0.992
GLS (%)	1.12 (1.05-1.19)	<0.001
LAVI (ml/m^2)	3.84 (2.04-7.23)	<0.001

AF atrial fibrillation; CI confidence interval; GLS global longitudinal strain; HR hazard ratio; LA left atrial; LAVI left atrial volume index; LVEDD left ventricular end diastolic diameter; LVEF left ventricular ejection fraction; LVH left ventricular hypertrophy; LVOT left ventricular outflow tract; nsVT non-sustained ventricular tachycardia; NYHA New York Heart Association; SCD sudden cardiac death

Step 1 of the multivariable analysis showed that age, NYHA functional class and nsVT were independently associated with the endpoint. In step 2, the most important baseline echocardiographic variables were tested and the analysis showed that LAVI and GLS were associated with the endpoint. In step 3, the most important significant variables from the previous steps were combined, revealing NYHA functional class, GLS and LAVI to be independently associated with the HF endpoint (Table 4).

Table 4. Stepwise multivariable cox proportional hazard regression analysis to identify independent predictors of the heart failure endpoint.

Parameter	Multivariable HR (95% CI)	P-value
Step 1: clinical variables		
NYHA class 2	2.52(1.17-5.45)	0.019
Age (year)	1.04(1.01-1.06)	0.005
nsVT	2.18(1.15-4.13)	0.018
AF	1.83(0.87-3.87)	0.116
Step 2: echocardiographic variables		
LAVI (ml/m^2)	5.77(2.17-15.36)	<0.001
GLS (%)	1.21(1.10-1.33)	<0.001
E/E'	1.02(0.99-1.04)	0.194
LVH max (mm)	1.04(0.98-1.10)	0.230
Step 3: clinical and echocardiographic variables of importance combined		
NYHA class 2	2.30(1.07-4.95)	0.033
Age (year)	1.04(1.01-1.06)	0.016
GLS (%)	1.13(1.05-1.22)	0.001
LAVI (ml/m^2)	2.22(1.10-4.50)	0.027

AF atrial fibrillation; CI confidence interval; GLS global longitudinal strain; HR hazard ratio; LAVI left atrial volume index; LVH left ventricular hypertrophy; nsVT non-sustained ventricular tachycardia; NYHA New York Heart Association

Figure 2 illustrates the changes over time in the echocardiographic parameters, corrected for follow-up time, age and NYHA functional class, for both groups: patients with and without the HF endpoint. Median time interval between the two echocardiograms was 5.7(3.4-8.8) years and 6.5(4.2-9.8) years for patients with and without the HF endpoint respectively. LVEDD and LV wall thickness did not change over time in patients without the HF endpoint. However, in patients with the HF endpoint, a significant increase in LVEDD (46±6 vs 48±6mm,p=0.047) and a decrease in LV wall thickness (22(19-25) vs 19(16-23)mm, p=0.035) were observed. Also, group-time interaction was significant for LVEDD (p=0.021) and showed a trend for LV wall thickness (p=0.072). Patients who reached the HF endpoint showed an increase in LAVI at follow-up (45(33-59) ml/m^2 vs 50(37-67) ml/m^2), although when corrected for age, NYHA functional class and follow-up time, this difference was not statistically significant (p=0.099). For patients who did not reach the HF endpoint, LAVI remained within the normal range at follow-up (34(26-43) ml/m^2 vs. 31(25-38) ml/m^2,p=0.119). Group-time interaction was significant (p=0.026), demonstrating that LAVI changes differently for patients who reached the HF endpoint, versus patients who did not. Furthermore, patients who reached the HF endpoint, showed a worsening in GLS at follow-up (-13%±5 vs -11%±3,p=0.001). The impairment in GLS for patients who did not reach the HF endpoint was less pronounced over time (-16.5%±4 vs -15.9%±3,p=0.003) compared with the patients with the HF endpoint, which is revealed

by the significant group-time interaction(p=0.042). For the LVOT gradient and E/E' there were no differences observed in group-time interaction.

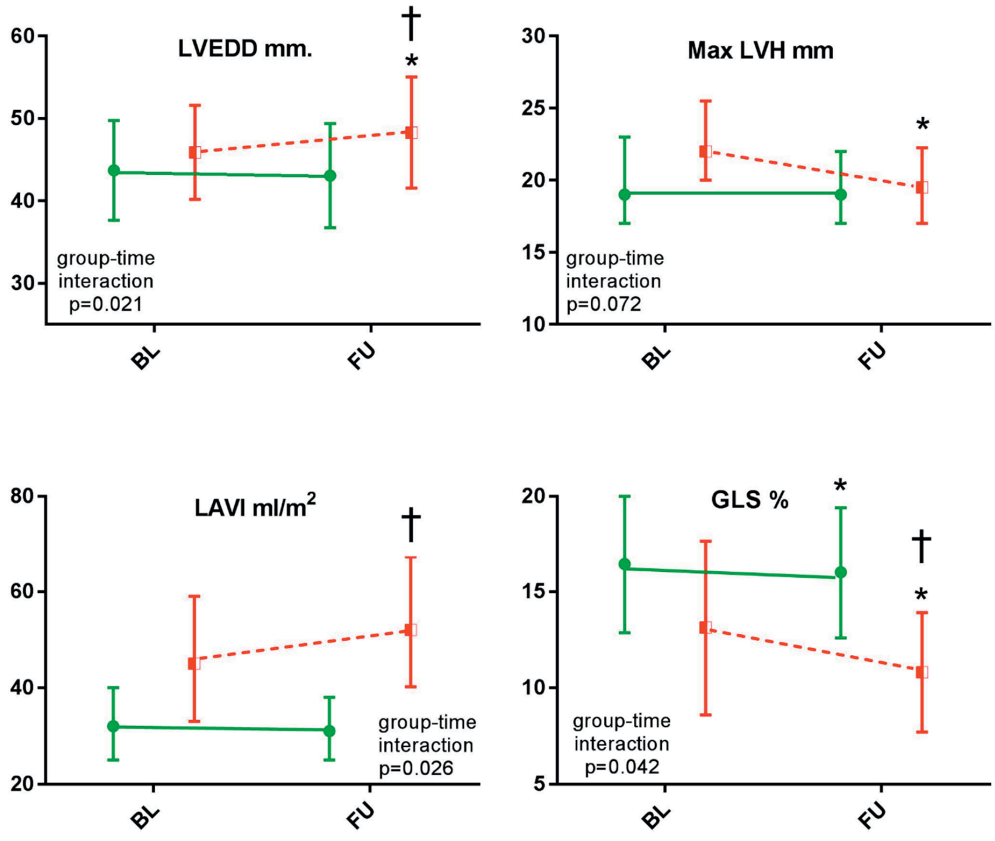

Figure 2. Linear mixed model analysis of echocardiographic changes over time, corrected for the time between the 2 echocardiographic examinations and for age and NYHA class at baseline, for patients who reached the HF endpoint (dotted line) vs. patients who did not reach the HF endpoint (solid line).
BL baseline, GLS global longitudinal strain, FU follow-up, LAVI left atrial volume index, LVEDD left ventricular end diastolic diameter, LVH left ventricular hypertrophy
* $p < 0.05$ compared to baseline within group
† $p < 0.05$ between groups at follow-up

The ICC for measurements between two different observers was 0.94(p<0.001) for LAVI and 0.94(p<0.001) for GLS. The ICC for repeated measurements by the same observer (intra-observer agreement) was 0.95(p<0.001) for LAVI and 0.91(p<0.001) for GLS.

Discussion

The main results of this study can be summarized as follows: 1) GLS at baseline is independently associated with the development or progression of overt HF in non-obstructive HC patients, together with LAVI, NYHA functional class and age, 2) changes over time in GLS, LAVI and LVEDD are associated with the HF endpoint.

Studies in HC patients have mainly focused on the risk for life-threatening arrhythmias and the consequences and management of LVOT obstruction.[1, 2, 17, 18] However, since risk stratification and treatment for both SCD and LVOT obstruction in HC patients improved significantly over the years, HF development has emerged as an important complication in these patients. Olivotto et al.[19] described different patterns of disease progression in HC and showed an ongoing process of LV remodelling which eventually leads to end-stage HF. This progression has been described also in other studies[3, 20, 21] as LV systolic dysfunction, relative wall thinning and LV dilation, which occurs approximately in 5% of patients. Young age at diagnosis, a family history for HC and greater wall thickness were shown to be predictive for the development of end-stage HF.[3] However, the development of significant HF symptoms frequently precedes the occurrence of the end-stage phase. Pasqualucci et al.[21] showed that in a relevant percentage of HC patients mortality can occur within 3 years after HF symptoms onset, despite a preserved LVEF. In this regard, Maron et al.[6] evaluated the natural history of non-obstructive HC patients and showed that, despite the relatively benign course of this disease, still 10% of patients progressed to NYHA class III/IV during follow-up. These observations emphasize the need for parameters that could be used to identify non-obstructive HC patients at risk for HF development before the end-stage phase occur. However, identification of myocardial dysfunction before clinical symptoms appear can be challenging in these patients, since LVEF is mostly preserved. Several potential prognostic markers for HF related outcomes have been studied in HC patients.[4, 22] Recently, GLS has been proposed as a potentially prognostic marker in this patient population. Almaas et al.[7] demonstrated that GLS correlates with fibrosis in myocardial samples of the septum and Saito et al.[23] showed a good correlation between GLS and late gadolinium enhancement (LGE) measured on cardiac magnetic resonance (CMR), reporting also an association with cardiac events. In a previous study of our center,[11] we demonstrated the incremental prognostic value of GLS and LAVI for a combined endpoint of all-cause mortality, heart transplantation, aborted SCD and appropriate ICD therapy in a cohort of 427 HC patients. However, in this study only baseline echocardiography was analysed and HF development was not included in the combined endpoint. In a retrospective study by Reant et al,[5] GLS was found to be independently associated with a combined endpoint of cardiovascular death,

ICD therapy or HF admission in a cohort of 472 HC patients. Additionally, GLS was also associated with an endpoint of HF death and HF admissions, although not tested in a multivariable analysis. The present study confirms the importance of GLS specifically for predicting HF development or progression in non-obstructive HC patients. In addition, the present study showed the independent prognostic value of LAVI for the development or progression of HF symptoms. LA enlargement is a common finding in HC patients, which reflects the atrial remodelling caused by elevated LV filling pressures, MR and is associated with AF and thromboembolic events.[24] Currently, LA diameter is used to evaluate LA enlargement, but LAVI showed to be superior to LA diameter for predicting cardiovascular events.[25] Losi et al[26] found and increased LAVI to be associated with adverse outcome. The current study confirms these results in a large non-obstructive HC population, specifically focusing on the HF endpoint.

Although echocardiography is the most important imaging modality in the diagnosis and monitoring of HC,[1] limited studies describe echocardiographic changes over time in these patients and none included GLS. In the present study LVEDD, LV wall thickness, LAVI and GLS changed significantly over time in patients who developed HF. These findings are in line with the results of Pasqualucci et al.[21], which showed a significant decline in LVEF and LVH and an increase in LA and LV diameter over time in HC patients with severe HF symptoms (NYHA functional class III/IV). Losi et al. showed that patients with an increase in LA volume >3 mL/year had worse outcome compared to patients who did not show this increase.[26] The current study demonstrated that these changes are already detectable before HF symptoms occur and LVEF declines and that repeated echocardiography can be used to identify patients at risk. Particularly, the additional prognostic value of GLS and its changes over time was shown, possibly reflecting also changes in myocardial ultrastructural and functional characteristics. Considering the lack of good prognosticators for HF development in non-obstructive HC, the current study showed that GLS and LAVI may represent new tools to improve risk-stratification in these patients and specifically for HF development and progression. Furthermore, during echocardiographic follow-up a worsening in these parameters could be detected, even before HF symptoms occurred or LVEF declined, suggesting their potential application in patient monitoring and to eventually start early treatment.

Several limitations should be mentioned. Because of the retrospective design of this study, the time interval between the echocardiograms varied among patients. Therefore we corrected for time in the linear mixed model analysis. Since there were only 40 events in the study population, we could not analyse > 4 parameters in one multivariate analysis. Furthermore, the important HF biomarker NT-pro-BNP was not systematically assessed and could not be tested. The echocardiograms were

performed with one vendor; therefore the absolute values of GLS should be interpreted with caution when compared to values obtained by other vendors. However, GLS showed a variability below 10% between different vendors and this is comparable to standard echocardiographic measurements currently used.[27] Further prospective studies in large patient populations are needed to validate these data and to define how GLS measurements could tailor patient management and treatment.

In conclusion, LV dysfunction is a progressive phenomenon in non-obstructive HC patients which can be detected by repeated GLS measurements. Importantly in these patients, GLS and LAVI at baseline as well as their changes over time were independently associated with HF development or progression.

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Chapter 4

Prevalence and Prognostic Implications of Right Ventricular Dysfunction in Patients With Hypertrophic Cardiomyopathy

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Abstract

Right ventricular (RV) dysfunction is a well-known prognostic factor in several cardiac diseases. However, the prevalence of RV dysfunction in hypertrophic cardiomyopathy (HC) is unclear and its prognostic value is unknown. This study aims at addressing these issues assessing RV function with speckle tracking echocardiography. In 267 HC patients (52±15 years, 68% male), standard and advanced echocardiographic measurements of RV function were performed including RV 4-chamber longitudinal strain (RV4CLS) and RV free wall longitudinal strain (RVFWLS). The primary endpoint was all-cause mortality and heart failure development. RV dysfunction was observed in 9% of patients based on tricuspid annular plane systolic excursion (TAPSE ≤17mm), 5% based on fractional area change (FAC<35%), 23% based on RVFWLS ≥-19%, 39% based on RVFWLS ≥-23% and 55% based on RV4CLS ≥-20%. In total 59(22%) patients reached the primary endpoint during a median follow-up of 6.7(IQR 4.2-9.8) years. Kaplan-Meier survival curve showed a significant worse survival free of the endpoint for patients with impaired RV4CLS ≥-20% vs. patients with preserved RV4CLS <-20% (log-rank 7.0,p=0.008) and for patients with impaired RVFWLS ≥-19% vs. patients with preserved RVFWLS <-19% (log-rank 4.4,p=0.037). Multivariable Cox regression analysis showed that E/E' (HR 2.26(1.30-3.92),p=0.004), left ventricular global longitudinal strain LV GLS (HR 1.08(1.01-1.17),p=0.034) and RV4CLS (HR 1.08(1.02-1.15),p=0.007) were independently associated with the primary endpoint. In conclusion, RV dysfunction as measured by longitudinal strain is relatively frequent in HC patients. Impaired RV4CLS is –together with LV GLS and E/E'– associated with adverse outcome, which may indicate a more severe form of HC.

Keywords: Hypertrophic cardiomyopathy; Right ventricular function; Speckle tracking echocardiography; Prognosis

Introduction

Hypertrophic cardiomyopathy (HC) is the most common inherited heart disease, primarily characterised by left ventricular (LV) hypertrophy,[1, 2] but frequently involves also the right ventricle (RV).[3-6] Data on RV function in HC patients is limited, partially because the accuracy of standard echocardiographic measurements is challenged by the complex shape and geometry of the RV. Initial studies showed a low prevalence of RV dysfunction in HC patients, when assessed with conventional RV parameters.[7, 8] RV longitudinal strain measured by two-dimensional (2D) speckle tracking analysis might better reflect RV contractility and few studies demonstrated a subtle, RV dysfunction in a substantial amount of HC patients.[6, 9, 10] However, different parameters with different cut-off values have been proposed, including RV four chamber longitudinal strain (RV4CLS) and RV free wall longitudinal strain (RVFWLS).[11] Importantly, the prognostic value of RV dysfunction assessed by longitudinal strain has not been studied in HC patients. The objectives of this study were therefore to evaluate the prevalence of RV dysfunction in a large cohort of HC patients, including the assessment of RV longitudinal strain parameters and their correlation with LV function and to assess the prognostic value of impaired RV4CLS and RVFWLS for all-cause mortality or heart failure (HF) development.

Methods

Patients with a clinical diagnosis of HC were identified from an ongoing clinical registry in the Leiden University Medical Center (LUMC), Leiden, the Netherlands. HC was defined according to current guidelines: maximal LV thickness ≥15mm (or ≥13mm in case of an affected first-degree relative), which could not be explained by abnormal loading conditions.[1] Clinical evaluation included demographic characteristics, cardiovascular risk factors, New York Heart Association (NYHA) functional class, genetic status, medication use and the parameters of the HC sudden cardiac death (SCD) risk score: family history of SCD at young age, previously documented non-sustained ventricular arrhythmias (nsVT) and unexplained syncope[12]. Also septal interventions and implantable cardioverter defibrillator (ICD) implantation were noted. A complete echocardiographic assessment was performed at the initial evaluation in the LUMC. Patients were excluded when the echocardiogram was of insufficient quality to perform RV measurements. These data were prospectively collected in the departmental cardiology information system (EPD-Vision®; Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analysed. The study complied with the Declaration of Helsinki. Due to the retrospective design of this study, the Medical Ethical Committee declared that no formal ethical approval was needed and waived the need of written informed consent.

A commercially available ultrasound machine (Vivid 5, Vivid 7 and E9, GE-Vingmed, Milwaukee, WI) was used to perform standard 2D transthoracic echocardiography at rest. Images were digitally stored and analyzed offline using EchoPAC (version 112, GE Medical Systems, Horten, Norway). As recommended, LV diameters, LV septal thickness, LV posterior wall thickness and left atrial (LA) diameter were assessed on the parasternal long-axis view. Maximum LV wall thickness (LVWT) was assessed from a short-axis view at different levels from base to apex. LV volumes and LV ejection fraction (LVEF) were measured using Simpson's method and indexed for body surface area (BSA).[13] LV diastolic function was assessed using Doppler mitral inflow peak velocities of E divided by the peak early diastolic velocity (E') of the lateral mitral annulus, calculating the E/E' ratio.[14] The presence of systolic anterior movement (SAM) of the mitral valve was evaluated on the parasternal long-axis view and from apical 3- and 5-chamber acquisitions and grade of mitral regurgitation (MR) was assessed according to current recommendations.[15] LV outflow-tract (LVOT) peak gradient at rest was quantified by continuous wave Doppler. RV function was evaluated from the 4-chamber apical view according to current recommendations[10] and including RV fractional area change (FAC) and tricuspid annular plane systolic excursion (TAPSE). RV wall thickness (RVWT) was evaluated from the subcostal view measuring the RV free wall during end-diastole. Systolic pulmonary artery pressure (sPAP) was calculated by combining the peak velocity of the tricuspid regurgitation jet and the right atrial (RA) pressure estimated by the diameter and inspiratory collapse of the vena cava inferior.[16] 2-D speckle tracking analysis was performed to measure LV global longitudinal strain (LV-GLS), RV4CLS and RVFWLS. For LV-GLS the 2-, 3- and 4-chamber apical views acquired at a frame rate >40 fps were used and the region of interest was automatically created and manually adjusted when appropriate. LV-GLS was then calculated by averaging the peak longitudinal strain in 17 LV segments from the 3 different views. For RV4CLS and RVFWLS, a dedicated RV apical view was used to trace the RV free wall and the RV part of the intraventricular septum at end-systole and the region of interest manually adjusted to secure proper tracking of the myocardium. RV4CLS was then calculated as the average of the 6 segments (figure 1) and RVFWLS was calculated as the average of the 3 segments of the RV free wall.

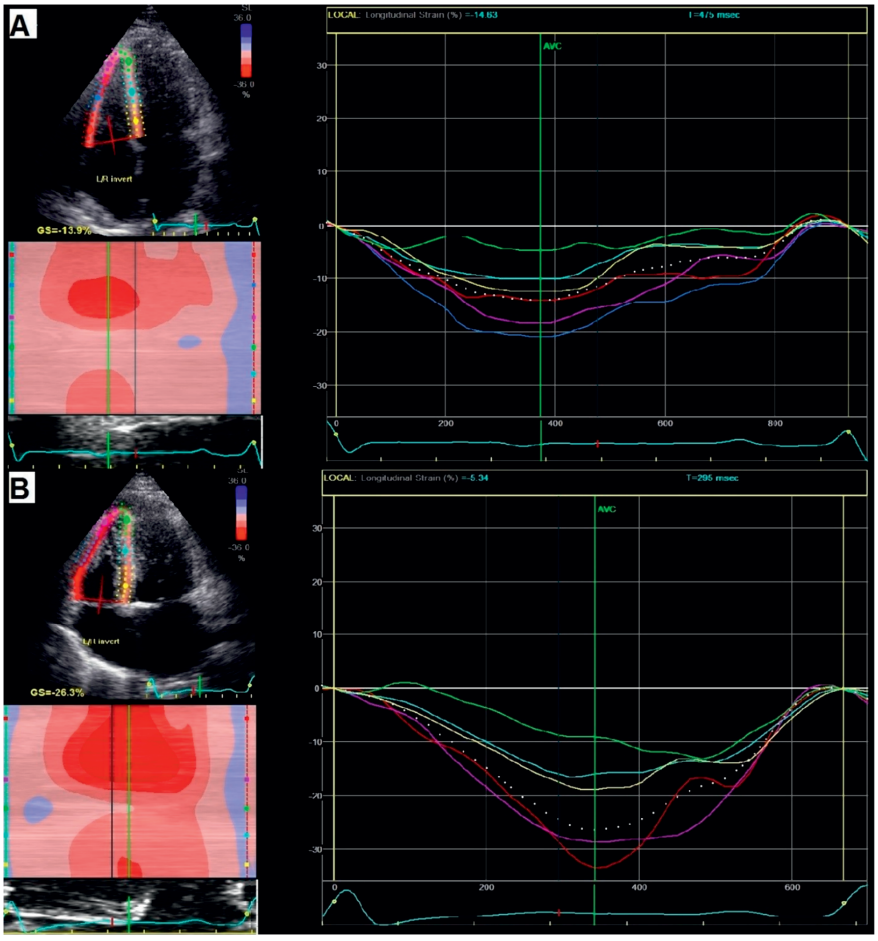

Figure 1. Assessment of right ventricular four chamber longitudinal strain (RV4CLS) by 2D speckle-tracking echocardiography. **Panel A.** 51-year old patient with impaired RV4CLS of -13.9% who developed severe HF symptoms 3 years later. **Panel B.** 56-year old patient with preserved RV4CLS of -26.3% who did not experience an event during 8 years follow-up.

Primary endpoint of the study was a combined endpoint of all-cause mortality or HF development. HF was defined as: new onset of any HF symptoms,[17] progression of HF symptoms to NYHA functional class III/IV or HF hospitalization. Specifically, new onset of HF was defined in patients who never had HF symptoms, but developed at least NYHA functional class II during follow-up. Progression of HF was defined when patients were already at NYHA functional class II symptoms at baseline, but progressed to NYHA functional class III or IV at follow-up. The occurrence of events was obtained by review of medical charts and/or contact with the general practitioner of the patients. Survival status was also retrieved through the municipal civil registries. The secondary endpoint

included (aborted) SCD or appropriate ICD therapy, defined as anti-tachycardia pacing and/or shock for ventricular tachycardia or ventricular fibrillation.

Continuous variables are presented as mean±standard deviation, when normally distributed or as median(interquartile range) when not normally distributed. Categorical variables are presented as absolute numbers and percentages. The relation of RV4CLS and RVFWLS with other clinical and echocardiographic parameters was assessed using Pearson's method or Spearman's method. The percentage of patients with RV dysfunction was calculated according to different cut-off values of RV4CLS and RCFWLS. Current recommendations and the study of Muraru et al.[18] propose RV4CLS ≥ -20% and RVFWLS ≥ -23% as abnormal. However, other studies showed that RVFWLS ≥ -19% was associated with poor prognosis.[19, 20] Therefore, Kaplan-Meier curves were constructed for the different cut-off values to estimate the survival free from the endpoint and compared by log-rank test for patients with RV4CLS <-20% vs. RV4CLS ≥-20%, RVFWLS <-19% vs. RVFWLS ≥-19% and RVFWLS <-23% vs. RVFWLS ≥-23%. For the primary endpoint, univariable and multivariable Cox regression analysis were used to identify predictors of this endpoint and hazard ratios (HR) and 95% confidence interval (CI) were calculated. Because of the relatively low number of events, the multivariable analysis was performed in separate steps including clinical and echocardiographic parameters. To avoid collinearity, 2 separate multivariate analyses were performed to assess the independent prognostic value of RV4CLS and RVFWLS. For the secondary endpoint only univariable analysis was performed. Statistical analysis was performed with the SPSS software package (version 23, IBM Corp, Armonk, NY). P-values <0.05 were considered statistically significant.

Results

A total of 267 HC patients (52±15 years, 68% male) were included out of a cohort of 436 patients; 169 patients were excluded because of insufficient quality or incomplete images for the RV assessment (RV free wall not eligible for strain analysis). Clinical and echocardiographic characteristics of the overall population are summarized in Table 1. Most patients were asymptomatic (81% in NYHA class I) and a known HC genetic mutation was found in 58% of tested patients. Already at baseline evaluation, 7(3%) patients had a septal intervention, 27 (10%) underwent a PCI and 59 (22%) patients had an ICD. Although LVEF was within normal values, LV-GLS was significantly impaired (-15±5%).[13] 15% of the patients showed obstructive HC with a significant LVOT gradient. Interestingly, mean RVWT was 6±1mm, mean RV4CLS was -19±5% and mean RVFWLS was -24±7%.

Table 1. Baseline clinical and echocardiographic characteristics of the overall population.

Clinical characteristics	
Age (years)	52±15
Men	182(68%)
Hypertension	98(37%)
Atrial fibrillation	27(10%)
NYHA class ≥ II	51 (19%)
Septal intervention*	7(3%)
PCI*	27(10%)
ICD implanted*	59(22%)
Genetic mutation†	96(58%)
Beta-blocker	96(36%)
Calcium-antagonist	46(18%)
Family history of SCD	112(42%)
Unexplained syncope	27(10%)
Prior nsVT	70(27%)
Echocardiographic characteristics	
LVEDD (mm)	44±7
LVEF (%)	65±9
LV-GLS (%)	-15±5
Maximum LVH (mm)	20(17-24)
Peak LVOT (mmHg)	9(6-19)
LA diameter (mm)	41±7
E/E'	10(8-15)
MR > grade 2	54(21%)
SAM	94(35%)
RV4CLS (%)	-19±5
RVFWLS (%)	-24±7
TV annulus (mm)	30±5
TAPSE (mm)	24±5
RV FAC (%)	48±7
RV wall thickness (mm)	6±1
TR ≥ grade 2	27(10%)
sPAP (mmHg)	25(22-28)

FAC fractional area change; LA left atrial; LVEDD left ventricular end diastolic diameter; LVEF left ventricular ejection fraction; LV-GLS left ventricular global longitudinal strain; LVH left ventricular hypertrophy; LVOT left ventricular outflow tract; ICD implantable cardioverter defibrillator; MR mitral regurgitation; nsVT non-sustained ventricular tachycardia; NYHA New York Heart Association; PCI percutaneous coronary intervention; RV right ventricular; RV4CLS right ventricular four chamber longitudinal strain; RVFWLS right ventricular free wall longitudinal strain; SAM systolic anterior motion; SCD sudden cardiac death; sPAP systolic pulmonary artery pressure; TAPSE tricuspid annular plane systolic excursion; TV tricuspid valve

** interventions before baseline echocardiography*

† *only genetically tested patients (N=165)*

In Table 2 the correlation of RV4CLS and RVFWLS and other clinical and echocardiographic characteristics are shown. RV4CLS showed a weak but significant correlation with maximum LVWT,

LA diameter, E/E', LVEF, TAPSE, RV FAC and RVWT. The correlation between RV4CLS and LV-GLS was moderate. RVFWLS also showed a correlation with maximum LVWT, LA diameter, LVEF, TAPSE, RV FAC and RVWT, but not with E/E'. The correlation between RVFWLS and LV-GLS was moderate.

Table 2. Correlation of right ventricular four chamber longitudinal strain (RV4CLS) and right ventricular free wall longitudinal strain (RVFWLS) with other echocardiographic parameters.

Variable	RV4CLS		RVFWLS	
	P-value	**R**	**P-value**	**R**
Age	0.264	-0.069	0.302	-0.063
Maximum LVH (mm)	<0.001	0.278	0.003	0.181
LVEDD (mm)	0.197	-0.079	0.441	-0.047
LA diameter (mm)	0.001	0.209	0.041	0.126
E/E'	0.019	0.155	0.414	0.054
Peak LVOT (mmHg)	0.364	-0.056	0.139	-0.091
MR > grade 2	0.173	0.084	0.693	0.025
LVEF (%)	<0.001	-0.223	0.001	-0.198
LV-GLS (%)	<0.001	0.459	<0.001	0.352
TAPSE (mm)	<0.001	-0.349	<0.001	-0.302
RV FAC (%)	<0.001	-0.253	<0.001	-0.243
sPAP (mmHg)	0.065	0.120	0.376	0.058
RV wall thickness (mm)	0.021	0.143	0.010	0.160

FAC fractional area change; LA left atrial; LVEDD left ventricular end diastolic diameter; LVEF left ventricular ejection fraction; LV-GLS left ventricular global longitudinal strain; LVH left ventricular hypertrophy; LVOT left ventricular outflow tract; MR mitral regurgitation; RV right ventricular; RV4CLS right ventricular four chamber longitudinal strain; RVFWLS right ventricular free wall longitudinal strain; sPAP systolic pulmonary artery pressure; TAPSE tricuspid annular plane systolic excursion

Figure 2 presents the percentages of patients with RV dysfunction based on the different echocardiographic parameters and according to different cut-off values.

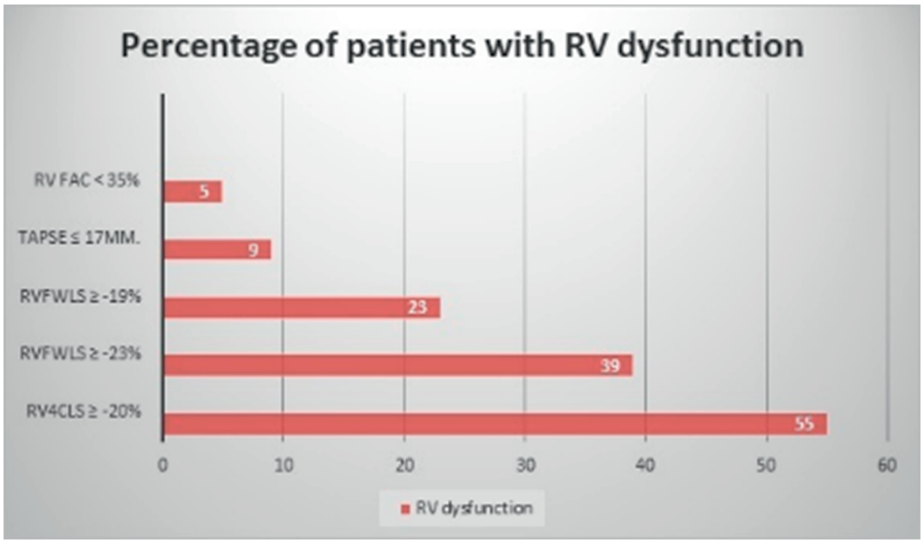

Figure 2. Prevalence of right ventricular dysfunction
RV4CLS right ventricular four chamber longitudinal strain; RV FAC right ventricular fractional area change; RVFWLS right ventricular free wall longitudinal strain; TAPSE tricuspid annular systolic plane excursion

During a median follow-up of 6.7(IQR 4.2-9.8) years, 59 patients reached the primary endpoint of all-cause mortality or HF development. Specifically, 41/59 patients reached the HF endpoint: 22 patients developed HF symptoms (NYHA class ≥2) and 19 patients showed progressive HF (to NYHA class III/IV), 13 of those patients were also hospitalized for HF. A total of 18 patients died and the cause of death was unknown in 7 patients, SCD in 3 patients, 1 patient died of complications after cardiac surgery and cause of death was non-cardiac in 7 patients. 32 patients reached the secondary endpoint: 3 patients experienced SCD, 4 patients had aborted SCD and 25 patients received appropriate ICD therapy (15 ICD shocks and 10 ATP).

In patients with preserved RV4CLS (<-20%), the cumulative survival rates free of the primary endpoint at 2, 5 and 8 years follow-up were 93%, 90% and 84% respectively. In contrast, patients with impaired RV4CLS (≥-20%) showed significantly worse outcome with survival rates free of the primary endpoint of 90% at 2 years, 82% at 5 years and 68% after 8 years (log-rank 8.3,p=0.004) (Figure 3A). When using RVFWLS of -19% as a cut-off value, patients with preserved RVFWLS (<-19%) showed cumulative survival rates of 94%, 88% and 78% at 2, 5 and 8 years follow-up respectively, whereas patients with impaired RVFWLS (≥-19%) showed worse outcome with survival rates of 90% at 2 years, 80% at 5 years and 68% after 8 years (log-rank 4.4, p=0.037) (Figure 3B).

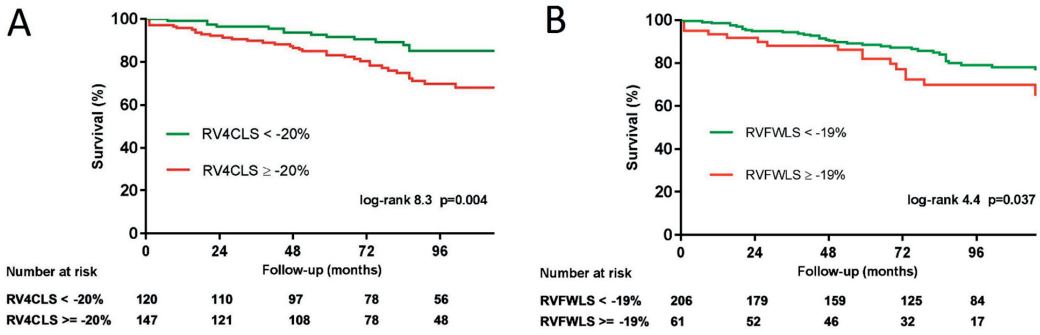

Figure 3. Kaplan-Meier analyses to evaluate the survival free of experiencing the endpoint (all-cause mortality or heart failure (HF) development). **(A)** Patients with right ventricular four chamber longitudinal strain (RV4CLS) <-20% compared to patients with RV4CLS ≥-20% **(B)** Patients with right ventricular free wall longitudinal strain (RVFWLS) <-19% compared to patients with RVFWLS ≥-19%

When using -23% as a cut-off value for RVFWLS, no differences in survival rates were observed between patients with normal RVFWLS (<-23%) as compared to patients with abnormal RVFWLS (≥-23%). Univariable Cox regression analysis showed that age, NYHA class ≥2, nsVT, LA diameter, E/E', MR>grade 2, LVEF, LV-GLS, RV4CLS, RVFWLS, TV annulus, TAPSE, TR≥grade 2 and sPAP were all significantly associated with the primary endpoint. Concerning the secondary endpoint, only unexplained syncope, LA diameter, maximum LVWT and LV-GLS were associated with this endpoint. Specifically, the echocardiographic measurements of the RV were not associated with the secondary endpoint (Table 3).

Table 3. Univariable Cox proportional hazard regression analysis to identify parameters associated with the primary and secondary endpoints.

Univariable analysis	Primary endpoint: all-cause mortality + HF development		Secondary endpoint: (aborted) SCD + appropriate ICD therapy	
Parameter	**HR (95%CI)**	**P-value**	**HR (95%CI)**	**P-value**
Age	1.04(1.02-1.05)	<0.001	0.99(0.97-1.01)	0.431
NYHA class≥2	2.14(1.23-3.73)	0.008	0.97(0.37-2.53)	0.955
Ventricular septal intervention	1.07(0.46-2.49)	0.879	2.04(0.78-5.31)	0.144
Beta-blockers	1.38(0.83-2.31)	0.218	1.29(0.64-2.62)	0.479
nsVT	1.78(1.05-3.00)	0.033	1.81(0.90-3.68)	0.099
Family history of SCD	1.16(0.69-1.93)	0.583	1.79(0.89-3.60)	0.105
Syncope	1.19(0.54-2.63)	0.664	2.57(1.05-6.29)	0.039
LA diameter (mm)	1.06(1.03-1.09)	<0.001	1.07(1.03-1.11)	<0.001
E/E'	3.49(2.15-5.65)	<0.001	1.41(0.69-2.85)	0.344
Maximum LVH (mm)	1.03(0.99-1.07)	0.094	1.06(1.02-1.11)	0.004
Peak LVOT(mmHg)	1.03(0.78-1.38)	0.817	1.28(0.91-1.82)	0.159
MR > grade 2	2.41(1.41-4.11)	0.001	1.01(0.44-2.33)	0.980
LVEF (%)	0.93(0.90-0.95)	<0.001	0.99(0.95-1.02)	0.449
LV GLS (%)	1.16(1.09-1.24)	<0.001	1.12(1.03-1.21)	0.007
RV4CLS (%)	1.11(1.06-1.17)	<0.001	1.05(0.97-1.13)	0.215
RVFWLS (%)	1.05 (1.01-1.09)	0.013	1.01 (0.96-1.06)	0.700
TV annulus (mm)	1.06(1.00-1.11)	0.044	1.07(0.99-1.14)	0.073
TAPSE (mm)	0.93(0.87-0.98)	0.009	1.02(0.94-1.10)	0.653
RV FAC (%)	0.97(0.94-1.00)	0.067	0.97(0.93-1.02)	0.207
RV wall thickness (mm)	1.01(0.81-1.27)	0.916	1.08(0.79-1.47)	0.639
TR ≥ grade 2	2.76(1.46-5.21)	0.002	0.55(0.13-2.32)	0.418
sPAP (mmHg)	1.05(1.02-1.09)	0.003	1.03(0.99-1.09)	0.178

CI confidence interval; FAC fractional area change; HF heart failure; HR hazard ratio; LA left atrial; LVEF left ventricular ejection fraction; LV GLS left ventricular global longitudinal strain; LVH left ventricular hypertrophy; LVOT left ventricular outflow tract; ICD implantable cardioverter defibrillator; MR mitral regurgitation; nsVT non-sustained ventricular tachycardia; NYHA New York Heart Association; RV right ventricular; RV4CLS right ventricular four chamber longitudinal strain; RVFWLS right ventricular free wall longitudinal strain; SCD sudden cardiac death; sPAP systolic pulmonary artery pressure; TAPSE tricuspid annular plane systolic excursion; TV tricuspid valve

In Table 4 the results of the multivariable analysis for the primary endpoint are shown. Step 1, including clinical characteristics, showed that age (HR1.03(1.01-1.05),p=0.011) is independently associated with the primary endpoint. In step 2, the most important left-sided echocardiographic variables were tested and the analysis showed that E/E' (HR 2.39(1.39-4.11),p=0.002) and LV-GLS (HR 1.11(1.03-1.20),p=0.006) were associated with the primary endpoint. Step 3 and 4 were separately performed for RV4CLS and RVFWLS. In step 3a the standard RV parameters were tested combined with RV4CLS and of those only RV4CLS was associated (HR 1.10(1.04-1.17),p=0.002) with the primary endpoint. In step 4a, significant variables from the previous steps were combined,

revealing E/E' (HR 2.26(1.30-3.92),p=0.004), LV-GLS (HR 1.08(1.01-1.17),p=0.034) and RV4CLS (HR 1.07(1.02-1.15),p=0.007) to be independently associated with the primary endpoint.
In step 3b the standard RV parameters were tested combined with RVFWLS and of those, none were significantly associated with the primary endpoint, although RVFWLS was borderline significant (HR 1.04(0.99-1.09), p=0.060). In step 4b RVFWLS was combined with the significant variables from the previous steps, and revealed only E/E' and LV-GLS to be significantly associated with the endpoint, while RVFWLS was not (HR 1.03(0.99-1.08), p=0.121).

Table 4. Step-wise multivariable Cox regression analyses to evaluate whether right ventricular four chamber longitudinal strain (RV4CLS) and right ventricular free wall longitudinal strain (RVFWLS) are independently associated with the primary endpoint.

Parameter	**Multivariable analysis HR (95% CI)**	**P-value**		
Step 1: clinical characteristics				
Age	1.03(1.01-1.05)	0.011		
NYHA ≥ 2	1.54(0.85-2.79)	0.155		
nsVT	1.64(0.96-2.79)	0.068		
Step 2: echocardiographic LV parameters				
LA diameter (mm)	1.03(0.99-1.07)	0.078		
E/E'	2.39(1.39-4.11)	0.002		
MR > grade 2	1.67(0.87-3.19)	0.121		
LV GLS (%)	1.11(1.03-1.20)	0.006		
Parameter	**Multivariable analysis HR (95% CI)**	**P-value**	**Multivariable analysis HR (95% CI)**	**P-value**
Step 3: echocardiographic RV parameters	*Step 3a*		*Step 3b*	
TV annulus (mm)	1.04(0.98-1.10)	0.189	1.04 (0.98-1.10)	0.168
TAPSE (mm)	0.99(0.92-1.06)	0.735	0.96 (0.90-1.03)	0.262
TR ≥ grade 2	1.93(0.89-4.20)	0.096	1.81 (0.85-3.84)	0.125
sPAP (mmHg)	1.02(0.99-1.06)	0.233	1.03 (0.99-1.07)	0.128
RV4CLS (%)	1.10(1.04-1.17)	0.002		
RVFWLS (%)			1.04 (0.99-1.09)	0.060
Step 4: all combined	*Step 4a*		*Step 4b*	
Age	1.01(0.99-1.04)	0.069	1.02 (0.99-1.04)	0.058
E/E'	2.26(1.30-3.92)	0.004	1.04 (1.01-1.07)	0.004
LV GLS (%)	1.08(1.01-1.17)	0.034	1.10 (1.03-1.19)	0.007
RV4CLS (%)	1.08(1.02-1.15)	0.007		
RVFWLS (%)			1.03 (0.99-1.08)	0.121

CI confidence interval; HR hazard ratio; LA left atrial; LV GLS left ventricular global longitudinal strain; MR mitral regurgitation; nsVT non-sustained ventricular tachycardia; NYHA New York Heart Association; RV right ventricular; RV4CLS right ventricular four chamber longitudinal strain; RVFWLS right ventricular free wall longitudinal strain; sPAP systolic pulmonary artery pressure; TAPSE tricuspid annular plane systolic excursion; TV tricuspid valve

Discussion

The present study showed that 1) RV dysfunction, reflected by impaired RV4CLS or RVFWLS, is a common finding in patients with HC and is correlated to LV dysfunction as assessed by LV-GLS, and 2) impaired RV4CLS is independently associated with worse outcome in terms of all-cause mortality and HF development together with LV-GLS and E/E'. Several studies already showed that HC is a biventricular disease although the clinical definition is based on LV thickness and function. McKenna et al.[5] for example showed that RVWT >5-7 mm is commonly observed in HC patients (44%) and associated with presence of HF symptoms and supraventricular arrhythmias. Similarly, Maron et al.[3] used magnetic resonance imaging to study the RV in HC patients and found an increased RVWT (7±2mm), which was significantly correlated with LVWT (R^2=0.4,p<0.001). In the present study, a mean RVWT of 6±1mm was observed, confirming the presence of biventricular hypertrophy. Few other studies focused on RV function assessment in HC patients, using different echocardiographic methods such as TAPSE, RV FAC or tissue Doppler imaging.[7, 8] However, these parameters often remain within the normal range until RV function significantly impairs and therefore might not reflect subtle RV dysfunction. Finocchiaro et al.[7] for example reported a prevalence of RV dysfunction of 6% in 324 HC patients, measured by RV FAC <35%, and 11% defined by TAPSE <17mm; however, an abnormal RV myocardial performance index (>0.4) was found in 71% and sPAP >35 mmHg in 24% of the patients. The low prevalence of RV dysfunction, defined by impaired RV FAC or TAPSE, is comparable to the present study and suggests the limited sensitivity of these parameters to detect subtle RV dysfunction.

GLS has been suggested as more sensitive measure of myocardial dysfunction and several studies evaluated the clinical value of LV-GLS in HC patients.[21-25] However, RV longitudinal strain has been studied less extensively in these patients and there is no consensus on which parameter should be used between RV4CLS and RVFWLS. Recent guidelines suggest to use RVFWLS when assessing RV function, yet this recommendation is not specifically for HC patients and without a clear proposed cut-off value.[11] Muraru et al.[18] evaluated 276 healthy volunteers and defined the reference value as -20% for RV4CLS and -23% for RVFWLS. However, other studies in patients with pulmonary hypertension suggested that a lower cut-off value of RVFWLS (-19%) is associated with prognosis.

Initial studies in HC patients[6] used RV4CLS and showed that this parameter was significantly impaired in patients as compared to controls (-19.4±4.4% vs. -23.8±2.7%), with a significant correlation of RV4CLS with LV mass and LV-GLS. The present study included a larger group of HC patients and showed a relatively high prevalence (55%) of impaired RV4CLS (when using -20% as cut-off value), but also a high prevalence (39%) of impaired RVFWLS (when using -23% as cut-off value),

and still 23% of impaired RVFWLS when applying a more strict cut-off value of -19%. Furthermore, RV4CLS and RCFWLS were both associated mainly with impaired LV-GLS, but also with increased LVWT and RVWT, although not with elevated sPAP. These observations suggest a primary involvement of the RV in HC patients together a significant inter-ventricular dependency.

Current study also evaluated the prognostic value of RV4CLS and RVFWLS in HC patients, while only few studies with small patient populations studied the prognostic value of RV function.[7, 26, 27]. Rosca et al. demonstrated an association between RVWT and ventricular arrhythmias in these patients, while both LV-GLS and RV4CLS were not independently associated with this endpoint probably due to the small sample size.[6] The present study demonstrated in a large group of HC patients the association of RV4CLS and RVFWLS with the endpoint of all-cause mortality and HF development. However in the multivariate analysis, RV4CLS performed better than RVFWLS and showed an independent association with the primary endpoint, together with LV-GLS and E/E', while RVFWLS was only associated on a univariate level. This might be due to the fact that RV4CLS better reflects the interventricular dependence, still remaining associated with the outcome after correction for LVGLS in the multivariate analysis and therefore not being explained solely by LV (septal) dysfunction). With the secondary endpoint of appropriate ICD therapy, both RV4CLS and RVFWLS showed no significantly association, which partially confirms the findings by Rosca et al.[6] These results suggest that echocardiographic evaluation of RV function including RV longitudinal strain should be considered in the standard assessment of HC patients and might be helpful in risk stratification. Particularly, impaired RV4CLS seems to identify patients with a more severe HC profile with important biventricular systolic and diastolic dysfunction, who might deserve closer monitoring and/or more aggressive treatment to avoid HF development. In turn, the use of RV4CLS and RVFWLS for risk prediction of SCD in HC patients has not been proven.

Several limitations of this study need to be mentioned. Due to the retrospective design, a relatively large group of patients was excluded because RV longitudinal strain could not be measured or a dedicated view was not available. Furthermore, RV longitudinal strain measurements were performed only with GE software and therefore the absolute values of RV longitudinal strain might not be generalizable to other vendors. Particularly, the software used in this study was originally developed to measure LV-GLS and still has to be validated for RV longitudinal strain measurements. However, several studies showed the accuracy of this parameter to assess RV dysfunction in patients with different cardiomyopathies.[9, 28, 29] Also, when using the septal segments in the calculation of RV4CLS, an accurate distinction of the LV part from the RV part is not possible and therefore the correlation between LV-GLS and RV4CLS might have been overestimated. Finally, prospective studies

with comprehensive assessment of the RV function are needed to validate these results and to define which parameter – RV4CLS or RVFWLS – and which cut-off values should be used to identify HC patients at risk for adverse outcome.

In conclusion, RV dysfunction is relatively common in HC patients either assessed by RV4CLS or RVFWLS. Importantly, an impaired RV4CLS is associated with all-cause mortality and HF development together with LV-GLS and E/E', possibly identifying patients with a more severe form of HC.

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Chapter 5

Myocardial work in non-obstructive hypertrophic cardiomyopathy: implications for outcome

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Abstract

Aims. Non-invasive left ventricular (LV) pressure-strain loop (PSL) analysis is emerging as a new echocardiographic method to evaluate LV function, integrating longitudinal strain by speckle-tracking analysis and sphygmomanometrically-measured blood pressure to estimate myocardial work. Aims of this study were:1) to describe global and segmental myocardial work in HCM patients;2) to assess the correlation between myocardial work and other echocardiographic parameters;3) to evaluate the association of myocardial work with adverse outcomes.

Methods and results. 110 non-obstructive HCM patients (55±15 years,66% male), with different phenotypes (apical, concentric and septal hypertrophy), and 35 age- and sex-matched healthy controls were included. The following myocardial work indices were included: myocardial work index (MWI), constructive work (CW), wasted work (WW), cardiac efficiency (CE). The combined endpoint included all-cause mortality, heart transplantation, heart failure hospitalizations, aborted sudden cardiac death and appropriate implantable cardioverter defibrillator therapy. Mean global CW (1722±602 vs. 2274±574mmHg%, p<0.001), global CE (93(89-95) vs. 96(96-97)%, p<0.001) and global MWI (1534±551 vs. 1929±473mmHg%) were significantly reduced, while global WW (104(66-137) vs. 71(49-92)mmHg%,p<0.001) was increased in HCM patients compared to controls. Segmental impairment in CW co-localized with maximal wall thickness (HCM phenotype) and global CW correlated with LV wall thickness (r=-0.41,p<0.001), diastolic function (r=-0.27,p=0.001) and QRS duration (r=-0.28,p=0.001). Patients with global CW>1730 mmHg% (median value) experienced better event-free survival than those with global CW<1730 mmHg%(p<0.001).

Conclusion. Myocardial work, assessed non-invasively with echocardiography and blood pressure measurement, is reduced in non-obstructive HCM patients; it correlates with maximum LV wall thickness, and is significantly associated with worse long-term outcome.

Keywords: hypertrophic cardiomyopathy; myocardial work; left ventricular pressure strain loop; echocardiography

Introduction

Hypertrophic cardiomyopathy (HCM) is the most prevalent inherited cardiomyopathy and is characterized by increased myocardial wall thickness, accompanied by myocardial fiber disarray and interstitial fibrosis. These alterations lead to subtle myocardial systolic and diastolic dysfunction which are not always detectable by standard echocardiographic parameters.[1, 2] Previous studies have shown that left ventricular (LV) global longitudinal strain (GLS), measured by speckle-tracking echocardiography, is often impaired in HCM patients, despite a normal LV ejection fraction (LVEF), and is significantly correlated with the presence of myocardial fibrosis as assessed by cardiac magnetic resonance (CMR) imaging.[3] Moreover, impaired LV GLS has been associated with adverse outcomes in HCM patients, such as all-cause mortality, sudden cardiac death (SCD), heart failure and ventricular arrhythmias.[4-8] LV GLS however, remains a load-dependent measure of LV function, which might limit the assessment of LV performance under certain hemodynamic conditions, and when performing follow-up evaluations. A non-invasive technique of myocardial work estimation has been introduced as a novel method to evaluate myocardial performance. This approach takes into account both LV deformation and afterload by constructing a LV pressure-strain loop (PSL) which integrates non-invasively measured arterial blood pressure and longitudinal strain acquired by echocardiographic speckle-tracking analysis.[9-11] A first study showed that constructive work (CW) is impaired in patients with HCM and is associated with LV fibrosis as assessed by CMR.[12] However, segmental analysis of myocardial work has not been performed in these patients, despite the frequently heterogenous distribution of LV hypertrophy, and importantly, the potential prognostic value of these novel cardiac work measures is currently unknown. Therefore, the aims of this study were: 1) to describe global and segmental indices of myocardial work in HCM patients compared to healthy individuals; 2) to assess the correlation of myocardial work with other echocardiographic parameters; 3) to evaluate the association of myocardial work with adverse outcomes.

Methods

Study population

Patients with a diagnosis of HCM were identified from an ongoing clinical registry. HCM was diagnosed according to current guidelines: maximal LV hypertrophy (LVH) ≥15 mm (or ≥13 mm in case of affected first-degree relatives), which could not be explained by abnormal loading conditions.[1] Patients with obstructive HCM, defined as an LV outflow tract (LVOT) gradient ≥30 mmHg at rest or during provocation, were excluded. Patients were also excluded when speckle tracking was not feasible, or when non-invasive blood pressure values were not available at the time of the echocardiogram used for the calculation of myocardial work. Clinical data were collected from the departmental cardiology information system (EPD-Vision®; Leiden University Medical Center, Leiden, The Netherlands) and the first echocardiogram available was used for analysis. In addition, 35 healthy individuals with structurally normal hearts were selected from the echocardiography database as controls, and matched for age, sex and LVEF. The study complies with the Declaration of Helsinki. Due to the retrospective design of this study, the local ethics committee waived the need of individual, written informed consent.

Echocardiography

A commercially available ultrasound machine (Vivid E9, GE-Vingmed, Milwaukee, WI, USA) was used to perform standard 2-dimensional transthoracic echocardiography (TTE). Images were digitally stored and analyzed offline using proprietary software (EchoPac 202, General Electric Vingmed Ultrasound, Milwaukee, WI, USA). The LV dimensions, LV septal thickness, LV posterior wall thickness and left atrial (LA) diameter were measured from the parasternal long-axis view. Maximum LV wall thickness was assessed from short-axis views at different levels from base to apex to ascertain the different patterns of LVH. Septal HCM was diagnosed in the presence of asymmetric LVH, isolated to the septal and/or anteroseptal segments of the LV, while apical HCM was defined when LVH was limited to the apical segments of the LV. Concentric HCM was defined as symmetric LVH in all LV segments. LV volumes, LVEF and LA volume were measured using Simpson's method and indexed for body surface area (BSA).[13] LV diastolic function was assessed using Doppler mitral inflow peak E-wave velocity, divided by the peak early diastolic velocity (E') of the lateral mitral annulus, expressed as the E/E' ratio.[14] The grade of mitral regurgitation (MR) was assessed by using a multiparametric approach, according to current recommendations.[15] LVOT peak gradient at rest was quantified by continuous wave Doppler. Peak systolic pulmonary artery pressure was estimated by adding the peak velocity of the tricuspid regurgitation jet on continuous wave Doppler to the right

atrial pressure (estimated by the diameter and percentage inspiratory collapse of the inferior vena cava).[16]

Myocardial Work

LV myocardial work was calculated by integrating longitudinal strain and sphygmomanometrically-measured blood pressure, as previously described by Russell et al.[10] LV longitudinal strain was measured using speckle-tracking analysis on the standard 2-, 3- and 4-chamber apical views. The region of interest was automatically created and manually adjusted when necessary. LV GLS was then calculated by averaging the peak longitudinal strain in 17 segments from the 3 apical views. The peak systolic LV pressure was assumed to be equal to the peak arterial systolic pressure, based on the brachial cuff blood pressure measurements. A non-invasive LV pressure-strain curve was then constructed by proprietary software (EchoPac 202, General Electric Vingmed Ultrasound, Milwaukee, WI) and adjusted according to the duration of the ejection and isovolumetric phases which were defined by the opening and closure of the mitral and aortic valves.

During the LV ejection period - defined as the period between mitral valve closure and mitral valve opening - the total work within the area of the LV PSL represented the global myocardial work index (GMWI), myocardial work performed during segmental shortening represented constructive work (CW), whereas myocardial work performed during segmental elongation represented wasted work (WW). During isovolumetric relaxation, this definition was reversed such that myocardial work during shortening was considered as WW and myocardial work during lengthening was considered CW. CW and WW were calculated for each LV segment, according to the 17-segment model, and the global CW and WW were calculated as the averages of the segmental values. Cardiac efficiency (CE) was then expressed as CW / (CW+WW) x 100% per segment and the global CE as an average of all segmental values (Figure 1). To evaluate segmental differences, the mid and basal segments were combined, as well as the apical segments, resulting in 7 segments: septal, antero-septal, inferior, lateral, posterior, anterior and apical.

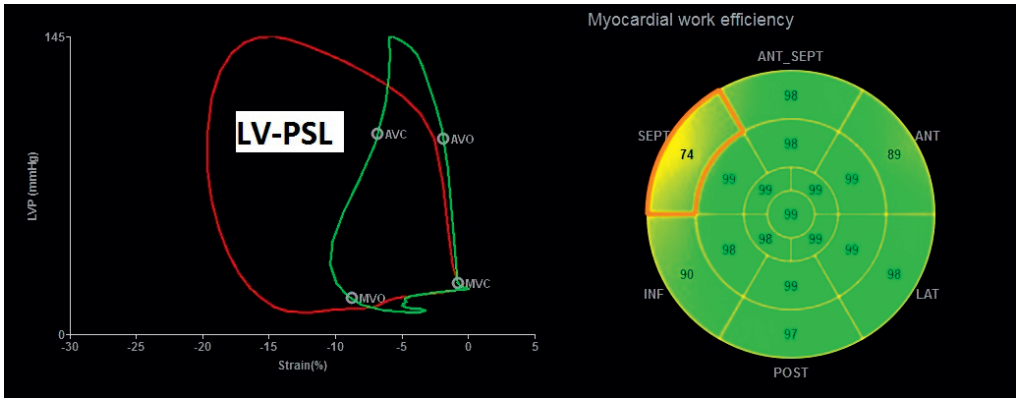

Figure 1. Examples of a left ventricular pressure strain loop (LV-PSL) and cardiac efficiency (CE). The red curve represents a normal LV-PSL, while the green curve reflects the deviating PSL of a septal segment in a HCM patient. The bulls-eye plot on the right, shows a significantly decreased CE in the septal segment.

Clinical outcomes

The endpoint of this study was a combined endpoint of all-cause mortality, heart transplantation, heart failure hospitalizations, aborted SCD and appropriate implantable cardioverter defibrillator (ICD) therapy. Aborted SCD was defined as a successful resuscitation from cardiac arrest with documented ventricular arrhythmias, while appropriate ICD therapy was defined as shock or anti-tachycardia pacing for ventricular arrhythmias. The occurrence of events during follow-up was obtained from survival status in municipal civil registries, review of medical charts and liaison with general practitioners.

Statistical analysis

Continuous variables are presented as mean ± standard deviation when normally distributed or as median (interquartile range) when not normally distributed. Categorical variables are presented as absolute numbers and percentages. Differences in clinical and echocardiographic characteristics between HCM patients and controls were compared using the Student t test, Mann-Whitney U test or χ^2 test, as appropriate. Receiver operating characteristic (ROC) curves were constructed to determine which myocardial work parameter had the highest area under the curve (AUC) to predict outcome. A Kaplan-Meier curve was then constructed to estimate the cumulative survival free of the endpoint and compared by log-rank test between patients with CW above the median (>1730 mmHg) and patients with CW below the median (<1730 mmHg). The correlation of CW with other clinical and echocardiographic parameters was assessed using Pearson's method or Spearman's method for continuous normally distributed, and ordinal and continuous non-normally distributed

parameters, respectively. Segmental differences between the various HCM phenotypes were analysed with the ANOVA and Kruskal Wallis tests. Intra-class correlation coefficients (ICC) were calculated for inter-observer and intra-observer agreement in 10 randomly selected patients, in order to evaluate reproducibility. Statistical analysis was performed with SPSS (version 23, IBM Corp, Armonk, NY, USA). P-values <0.05 were considered statistically significant.

Results

Study population

The study population consisted of 145 individuals: 110 patients diagnosed with HCM (55±15 years, 66% male) and 35 healthy controls (52±16 years, 51% male). Clinical characteristics of both groups are presented in Table 1. By definition, no differences were observed between the 2 groups regarding age and sex. Compared to controls, HCM patients showed slightly higher systolic blood pressure values and longer QRS duration. Previous atrial fibrillation was reported in 19 HCM patients (17%); 22 patients (20%) had heart failure symptoms (NYHA class II or more) and 21 patients (19%) had received an ICD.

Table 1. Clinical and ECG characteristics of HCM patients and controls.

	Controls N=35	**HCM patients N=110**	**p-value**
Clinical characteristics			
Age (years)	52±16	55±15	0.450
Men [n(%)]	18 (51)	73 (66)	0.159
Systolic BP (mmHg)	126±18	135±19	0.016
Diastolic BP(mmHg)	77±9	80±12	0.124
(Previous) Atrial fibrillation [n(%)]	0 (0)	19 (17)	0.007
NYHA class [n(%)]			0.002
I	35 (100)	88 (80)	
II	0 (0)	19 (17)	
III/IV	0 (0)	3 (3)	
ICD [n(%)]	0 (0)	21 (19)	0.002
ECG characteristics			
Heart rate (bpm)	66±11	66±11	0.964
QRS duration (ms)	94±10	109±25	0.001
LBBB/ RBBB [n(%)]	0 (0)	14 (13)	0.022
Ventricular pacing [n(%)]	0 (0)	11 (10)	0.066

BP blood pressure; ECG electrocardiography; HCM hypertrophic cardiomyopathy; ICD implantable cardioverter defibrillator; LBBB left bundle branch block; NYHA New York Heart Association; RBBB right bundle branch block

Standard echocardiographic characteristics

In Table 2 the echocardiographic characteristics are compared between HCM patients and healthy controls. HCM patients had a thicker interventricular septum and posterior wall, as well as a greater maximum LV wall thickness (19±5 mm vs 9±2 mm, p<0.001). Regarding different patterns of LVH, the majority expressed a septal phenotype (66%), followed by concentric HCM (24%), while apical HCM was observed in 10% of patients. LV dimensions were smaller in patients with HCM when compared to controls, while LA dimensions and volumes were higher in patients with HCM compared to controls. No differences were observed between HCM patients and controls regarding LVEF, although LV volumes were slightly lower in HCM patients and LV diastolic function was more often impaired. LV GLS was significantly impaired in HCM patients compared to controls (-14±5 vs -19±2%, p<0.001). Furthermore, MR grade ≥2 was observed in 17(16%) of the HCM patients and the LVOT gradient was within the normal range (as per inclusion criteria).

Table 2. Echocardiographic characteristics of HCM patients and controls.

	Controls N=35	**HCM patients N=110**	**p-value**
IVS (mm)	8 ± 2	18 ± 4	<0.001
PW (mm)	9 ± 1	12 ± 2	<0.001
Max LVH (mm)	9 ± 2	19 ± 5	<0.001
HCM phenotype [n(%)]			n/a
Septal	-	73 (66)	
Concentric	-	26 (24)	
Apical	-	11 (10)	
LVESV (ml)	45 ± 14	39 ± 15	0.032
LVEDV (ml)	116 ± 31	103 ± 29	0.039
LVEF (%)	61 ± 6	63 ± 10	0.331
LV GLS (%)	-19 ± 2	-14 ± 5	<0.001
LA diameter (mm)	34 ± 4	40 ± 6	<0.001
LAVI (ml/m²)	22 ± 6	36 ± 13	<0.001
E/E'	8 (6-9)	10 (7-14)	<0.001
Resting LVOT gradient (mmHg)	5 (3-5)	7 (5-11)	<0.001
MR ≥ grade 2 [n(%)]	0 (0)	17 (16)	0.013
sPAP (mmHg)	22 (18-26)	25 (21-31)	0.003

IVS interventricular septum; LA left atrial; LAVI left atrial volume index; LVEDV left ventricular end-diastolic volume; LVEF left ventricular ejection fraction; LVESV left ventricular end-systolic volume; LV GLS; left ventricular global longitudinal strain; LVOT left ventricular outflow tract; MR mitral regurgitation; PW posterior wall; sPAP systolic pulmonary artery pressure;

Myocardial work: global indices

Global myocardial work indices are summarized in Fig. 2. HCM patients showed significantly lower values of GMWI (1534±551 vs. 1929±473mmHg%, p<0.001) and global LV CW compared to controls (1722±602 mmHg% vs 2274±574 mmHg%, p<0.001) as well as higher values of global LV WW (104(66-137) mmHg% vs 71(49-92) mmHg%, p<0.001). This resulted in a lower global LV CE with a median of 93(89-95)% for HCM patients, compared to 96(96-97)% for controls (p<0.001).

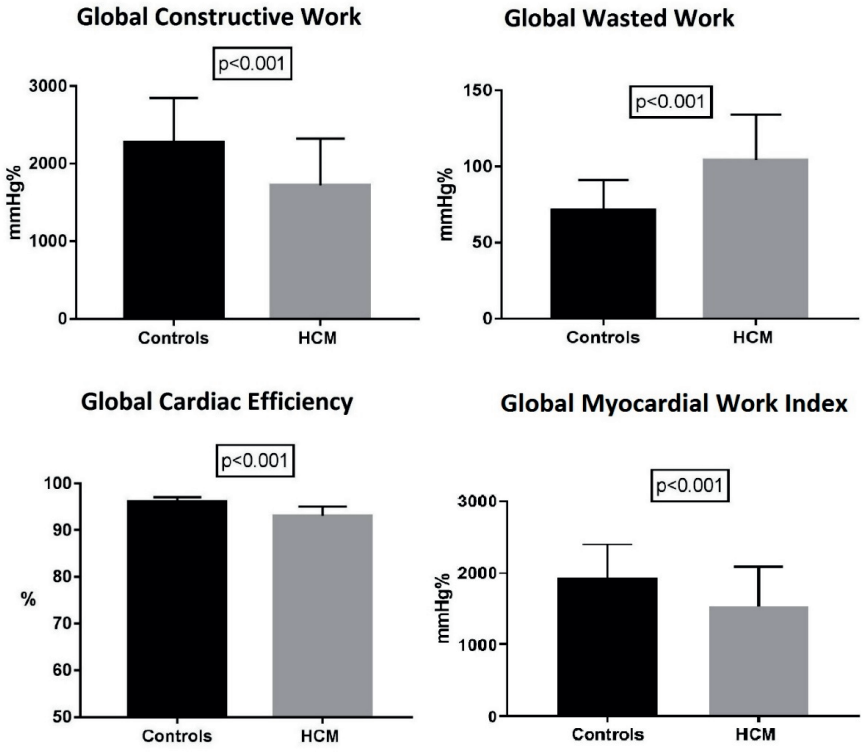

Figure 2. Myocardial work parameters in controls and hypertrophic cardiomyopathy (HCM) patients.

Correlation of global constructive work with other parameters

Global CW showed significant correlation with LA volume index (LAVI, r= -0.37, p<0.001), maximum LV wall thickness (r= -0.41, p<0.001), LV diastolic function (r= -0.27, p=0.001) and QRS duration (r= -0.28, p=0.001). Global CW showed also a high correlation with LV GLS (r=0.85, p<0.001). However, global CW was not significantly related with LV volumes (LVEDV, r= 0.034, p=0.681; LVESV, r= -0.11, p=0.187)

Association of global constructive work with outcomes

During a median follow-up of 5.4 (3.0-7.8) years, 24 patients (22%) reached the combined endpoint: 1 patient underwent a heart transplant, 1 patient experienced aborted SCD, 10 patients had appropriate ICD therapy, 1 patient was admitted for heart failure and 11 patients died. The cause of death was cardiac in 4 patients, non-cardiac in 3 patients and unknown in the remaining 4 patients. In order to assess which of the global myocardial work parameters had the strongest association with the endpoint, ROC curves were constructed. LV GLS showed an AUC of 0.74 (95% 0.63-0.85, p<0.001) and GMWI also showed a good association with the endpoint with an AUC of 0.77 (95% CI 0.66-0.87, p<0.001). However, global LV CW had the largest AUC of 0.78 (95% CI 0.68-0.88, p<0.001), while global LV WW showed no significant association with the endpoint with an AUC of 0.53 (95% CI 0.39-0.68, p=0.61) and global CE showed a borderline association with the endpoint with an AUC of 0.63 (95% CI 0.48-0.77, p=0.06). Subsequently, survival analysis was performed using global LV CW. When using the median value of the study population, patients with more impaired global LV CW (< 1730mmHg%) had a significantly worse survival free of the endpoint compared to patients with more preserved global LV CW (> 1730 mmHg%) (log-rank 11.2, p<0.001), as shown in Figure 3.

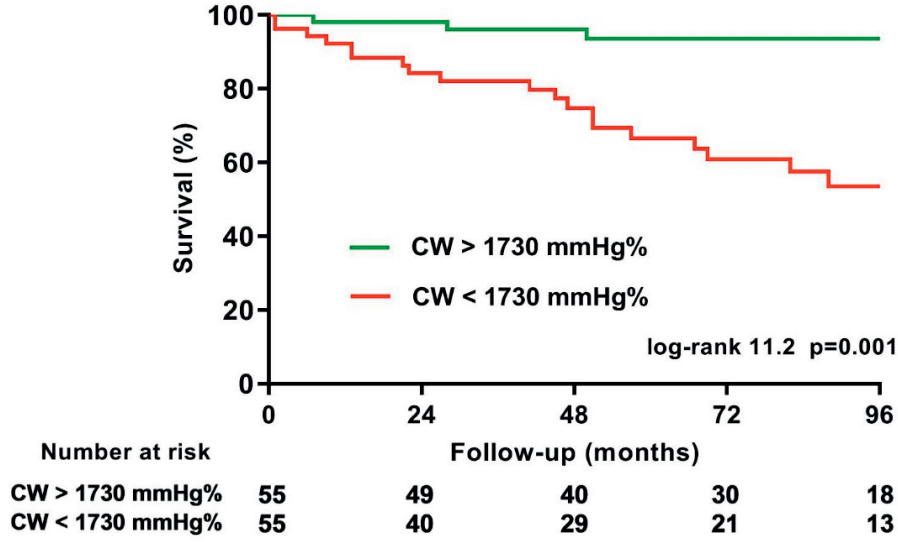

Figure 3 Kaplan-Meier survival curves depicting time to cumulative, event-free survival (all-cause mortality, aborted sudden cardiac death, heart failure hospitalizations and appropriate implantable cardioverter-defibrillator therapy) in patients with hypertrophic cardiomyopathy. Data are shown according to left ventricular constructive work (CW) >1730 mmHg% and CW <1730 mmHg% (median value).

Intra- and inter-observer variability of myocardial work parameters

The ICC for repeated measurements by the same observer (intra-observer agreement) was excellent for GLS (0.98(0.92-0.99), p<0.001), GMWI (0.97 (0.92-0.97), p<0.001) and global CW (0.99(0.96-0.99), p<0.001) and good for global WW (0.82 (0.27-0.96), p=0.009) and global CE (0.86(0.43-0.97), p=0.004); the ICC for measurements between two different observers (inter-observer agreement) was also excellent for GLS (0.97(0.88-0.99), p<0.001), GMWI (0.96 (0.89-0.97), p<0.001) and global CW (0.97(0.89-0.99),p<0.001) and good for global WW (0.76(0.05-0.94),p=0.022) and global CE (0.91(0.65-0.98), p=0.001)

Myocardial work: segmental analysis

Segmental values of myocardial work parameters are presented in Table 3 and compared between HCM patients and healthy controls. In LV all segments, CW was lower in patients with HCM as compared to controls. Interestingly, differences in WW were less evident. Only in the apical and anterior segments, WW was higher in HCM patients compared to controls, while in the other segments no differences in WW were observed between the two groups. The segmental CE was significantly lower for HCM patients in the apical, anteroseptal, posterior, lateral and anterior segments compared to controls. Regarding the septal segments, CE was not significantly different between HCM patients (94(90-98)%) and controls (95(93-97)%).

Table 3. Segmental analysis of myocardial work parameters in HCM compared to controls. * p-value < 0.05

	Constructive work (mmHg%)		Wasted Work (mmHg%)		Cardiac efficiency (%)	
	Controls	**HCM**	**Controls**	**HCM**	**Controls**	**HCM**
Apical	2670 ± 792	2068 ± 922*	43 (24-77)	102 (54-188)*	98(96-99)	94(90-97)*
Septal	1813 ± 472	1354 ± 606*	77 (50-103)	60 (22-119)	95(93-97)	94(90-98)
Anteroseptal	2107 ± 575	1521 ± 613*	56 (30-103)	73 (32-148)	97-94-98)	94(86-98)*
Inferior	2050 ± 500	1652 ± 669*	70 (35-133)	61 (21-139)	96(93-98)	96(90-98)
Posterior	2246 ± 729	1676 ± 758*	88 (40-207)	111 (49-223)	94(92-98)	93(85-96)*
Lateral	2160 ± 559	1625 ± 666*	55 (27-102)	80 (31-151)	97(95-98)	95(89-98)*
Anterior	2077 ± 684	1466 ± 733*	35 (21-72)	76 (29-134)*	98(96-98)	94(85-98)*

Figure 4 shows the segmental CW in the different HCM phenotypes. In patients with apical HCM, CW of the apical segments (1123±747 mmHg%) was significantly lower compared to patients with septal HCM (2255±860 mmHg%) and concentric HCM (1946±920 mmHg%), p<0.001. Similarly, septal CW was lower in patients with septal HCM (1385±579 mmHg%) and concentric HCM (1126±479

mmHg%) compared to patients with apical HCM (1693±860 mmHg%, p=0.025). In patients with concentric HCM, all segments (except for the apical segments) tended to have lower values of CW, although this difference was statistically significant only for the inferior segments (1408±584 mmHg% in concentric HCM vs. 1691±636 mmHg% in septal HCM and 1980±905 mmHg% in apical HCM, p=0.040).

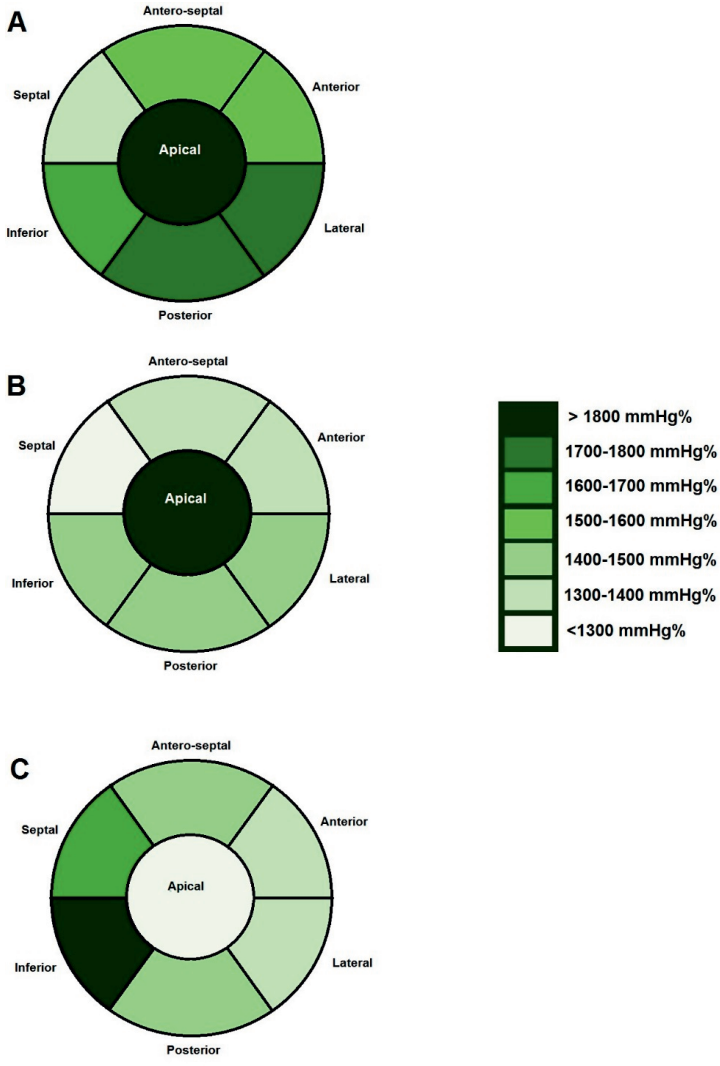

Figure 4. Segmental analysis of left ventricular constructive work for different hypertrophic cardiomyopathy (HCM) phenotypes.
Panel A septal HCM, ***Panel B*** concentric HCM, ***Panel C*** apical HCM

Discussion

The main findings of the present study can be summarized as follows: 1) HCM patients showed impaired values of global LV myocardial work parameters – GMWI, CW, WW and CE – when compared to healthy individuals, 2) global LV CW showed a correlation with maximum LV wall thickness, diastolic function and QRS duration and was significantly associated with adverse outcomes; 3) segmental differences of CW were observed in different HCM phenotypes.

Myocardial work in HCM

HCM is characterized by LV hypertrophy, myocardial fiber disarray and interstitial fibrosis, which can all significantly affect LV diastolic and systolic function, without an overt impairment of LVEF.[17] Consequently, several echocardiographic measurements have been proposed to better assess LV function in HCM patients. Over the past few years, LV GLS, as derived from speckle-tracking analysis, has emerged as a promising measure of LV function in patients with HCM and has shown a good correlation with histologically-proven myocardial fibrosis.[18] Moreover, several studies have demonstrated the prognostic value of LV GLS for predicting adverse outcomes in HCM patients.[3-8] However, LV GLS remains load-dependent, which might represent a limitation in case of changes in the hemodynamic conditions.[19] Myocardial work has been introduced as a new parameter of LV function, that takes into account the LV deformation as well as the LV afterload by constructing a LV-PSL based on non-invasive LV pressure (sphygmomanometric blood pressure) measurements. Russell et al.[10] validated this method against invasive LV pressure measurements and the LV-PSL area demonstrated a robust correlation with myocardial metabolism when assessed with positron emission tomography.

Several studies have already applied myocardial work measurements to various cardiac conditions.[12, 20-25] A study by Chan et al.[24] evaluated GMWI in patients with different loading conditions (i.e. with hypertension or ischemic and non-ischemic cardiomyopathies). In this study, patients with hypertension showed higher GWI compared to controls, whereas global CE was preserved due to a proportional increase in global CW and global WW. In a study by Van der Bijl et al,[23] the prognostic value of global CE in patients referred for cardiac resynchronization therapy (CRT) was evaluated. Lower values of global CE were associated with better outcome after CRT, likely reflecting the potential correction of LV dyssynchrony and recruitment of contractile reserve obtained with CRT in these patients. Only a single study evaluated myocardial work in HCM patients: Galli et al.[12] showed that global CW was reduced in 82 HCM patients as compared to controls (1599 ± 423 vs 2248 ± 249 mmHg%, p<0.001), while global WW was similar between HCM patients and controls (141±125 vs 101±88 mmHg%, p=0.18). The present study found similar values of global CW, which were

significantly reduced in HCM patients compared to controls. The values of global WW in HCM patients observed in the present study were also similar to the ones reported by Galli et al,[12] but we measured lower values of global WW in controls, accentuating the difference of global WW between HCM patients and. Galli et al.[12] demonstrated that a global CW of <1623 mmHg% was predictive of myocardial fibrosis on CMR, which might also explain the correlation of CW with diastolic dysfunction and LV thickness observed in the current study. In addition, a correlation between global CW and QRS duration was found probably reflecting the influence of (mild) LV dyssynchrony on myocardial work parameters. However, the association of myocardial work to clinical outcomes has never been evaluated in HCM patients, and the current results demonstrate a significant association of global CW with clinical outcomes.

Moreover, the present study evaluated segmental differences of myocardial work in HCM patients. CW was impaired in all myocardial segments when compared with healthy individuals. Interestingly, WW was only significantly impaired in the apical and anterior segments, whereas it was comparable to controls in the remaining segments. Since WW is mostly affected by dyssynchrony[9] and the prevalence of left or right bundle branch block was low in the current population (13%), relatively preserved values of WW were observed, in line with the findings of Galli et al.[12] Similarly, CE (defined as the ratio of CW divided by CW+WW), showed only mildly impaired values in most myocardial segments. Thus, CW was the most impaired myocardial work parameter in HCM patients, on both a global and segmental level. Moreover, differences of CW were also observed in different HCM phenotypes: patients with apical HCM had the most impaired CW in the apical segments, while in patients with septal and concentric HCM the CW was preserved the in apical segments, but impaired in the other segments. Segmental CW might therefore also be helpful to identify the specific HCM phenotype.

Clinical implications

The introduction of myocardial work parameters in the routine assessment of HCM patients might improve our understanding of cardiac performance in these patients, at both global and segmental levels, overcoming the load-dependency of other echocardiographic parameters by incorporating afterload. This is particularly relevant in patients with HCM, since afterload might change with medication use or geometrical changes and increase of wall thickness over time. This would provide clinicians a more sophisticated tool to refine follow-up of LV function in these patients, when blood pressure might vary between visits, and to assess the potential effect of different therapies. Furthermore, it might also represent a new risk-stratification tool to assess prognosis in HCM patients. Global CW might help especially in identifying 'low-risk' patients since a cumulative event-

free survival of 97% after 5 years was observed for patients with global CW >1730 mmHg%, whereas event-free survival was only 64% after 5 years in patients with global CW <1730 mmHg%.

Limitations

Several limitations of the current study should be mentioned. Some patients were excluded since blood pressure measurements were not available at the same the time of echocardiography; few patients were excluded when speckle-tracking analysis failed. Therefore we cannot exclude that this issue introduced a bias in the assessment. Furthermore, patients with obstructive HCM were excluded, since the estimated LV PSL based on the non-invasive measured blood pressure, does not reflect accurately LV pressure in these patients.[10] Further prospective research is required to confirm our results and establish the clinical utility of myocardial work parameters in HCM.

Conclusion

Myocardial work, assessed non-invasively with echocardiography and blood pressure measurement, is impaired in HCM. Global LV CW is correlated with maximum LV wall thickness, diastolic function and QRS duration and is significantly associated with adverse outcomes. Characteristic segmental patterns of CW can be depicted in different HCM phenotypes.

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Chapter 6

Familial occurrence of mitral regurgitation in patients with mitral valve prolapse undergoing mitral valve surgery

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Abstract

Background. Initial studies have suggested the familial clustering of mitral valve prolapse (MVP), but most of them were either community-based among unselected individuals or applied non-specific diagnostic criteria. Therefore little is known about the familial distribution of mitral regurgitation (MR) in a referral-type population with a more severe MVP phenotype.

The objective of this study was to evaluate the presence of familial MR in patients undergoing surgery for MVP, differentiating patients with Barlow's disease (BD), Barlow forme fruste (FF) and fibro-elastic deficiency (FED).

Methods. 385 patients (62±12 years, 63% male) who underwent surgery for MVP were contacted to systematically assess cardiac family history. Only documented presence of MR was considered to define "familial MR". In the probands, aetiology of MVP was defined by surgical observations.

Results. A total of 107 (28%) probands were classified as BD, 85 (22%) as Barlow FF and 193 (50%) patients as FED. In total, 51 patients (13%) reported a clear family history for MR; these patients were significantly younger, more often diagnosed with BD and also reported more sudden death in their family as compared to "sporadic MR". In particular, "familial MR' was reported in 28 patients with BD (26%), 15 patients (8%) with FED and 8 (9%) with Barlow FF ($p<0.001$).

Conclusions. In a large cohort of patients operated for MVP, the self-reported prevalence of familial MR was 26% in patients with BD and still 8% in patients with FED, highlighting the importance of familial anamnesis and echocardiographic screening in all MVP patients.

Keywords: organic mitral regurgitation, mitral valve prolapse, genetics, epidemiology

Introduction

Mitral valve prolapse (MVP) affects 2-5% of the general population and is the most common cause of primary mitral regurgitation (MR).(1) Presence of MVP and MR may result in left ventricular (LV) dysfunction, heart failure, atrial fibrillation and less frequently sudden cardiac death[1]. Surgery is so far the only therapeutic option for MVP with severe MR and early diagnosis and close monitoring of these patients is recommended to identify the most appropriate timing for operation.(2,3) The underlying cause of MVP is unclear, but a genetic basis has been suggested by demonstrating familial clustering of this disease and by identifying few pathogenic genes.(4-8) Familial screening of MVP patients may therefore represent an important tool to identify these patients at an early stage of the disease and to improve their management and risk stratification. However, collection of family history specific for valvular heart disease is not yet adopted in the current practice and systematic family screening is rarely performed in these patients. This lack of awareness may be due to the limited evidence available so far, since studies evaluating the familial occurrence of MVP were either small and observational,(4,7) or community-based with a low overall prevalence of MVP and significant MR.(5,6) Therefore, little is known about the actual prevalence of familial MR in a referral-type population with a severe MVP phenotype. Moreover, previous studies did not characterize the phenotype of familial MVP with complete echocardiographic analysis, although MVP presents with very different forms, such as Barlow's disease (BD), where the whole valve is affected by excessive leaflet and annular abnormalities, or fibro-elastic deficiency (FED), where the disease is limited to a single-scallop prolapse or flail (9). Therefore, it has not been evaluated whether the inheritance differs among BD as compared to FED, although they might have different aetiology. Accordingly, the aims of the present study were three-fold: 1) to evaluate the familial occurrence of MR based on self-reported family history in a large cohort of MVP patients with a severe phenotype requiring MV surgery 2) to assess whether familial occurrence is different for patients with BD compared to patients with FED and 3) to evaluate the accuracy of self-reported family history.

Methods

Patient selection

All patients who underwent MV surgery for severe MR due to MVP in our center from 2000 to 2017 were identified. Patients with congenital valve disease, connective tissue disorder, endocarditis, rheumatic valve disease and non-ischemic and ischemic cardiomyopathy were excluded. Also, patients who died during follow-up were excluded, since their family history could not be retrospectively obtained. The remaining patients received a letter to ask permission to be contacted

by phone; those who objected were excluded. The other patients were contacted and underwent a thorough structured interview on their cardiovascular family history. In case of a positive family history for valvular heart disease and/or in case of BD (considered in this study as most likely secondary to genetic or developmental alterations), patients were referred to the clinical geneticist. The study complies with the Declaration of Helsinki and was approved by the Institutional Review Board and Medical Ethical Committee. The Medical Ethical Committee waived the need of written informed consent for collecting patient family history. If patients were referred to the clinical geneticist, written informed consent was obtained.

Clinical characteristics

Clinical data were collected from the departmental cardiology information system (EPD-Vision®; Leiden University Medical Center, Leiden, The Netherlands). The aetiology of MV disease was defined according to the surgical observations and patients were classified in 3 groups(9): 1) FED, defined when thin leaflets or thickening limited to a single prolapsing MV segment were observed, mostly with chordal rupture/ flail; 2) BD, defined when bi-leaflet prolapse with generalized excess tissue, elongated chordae and severe annular dilatation were observed; 3) forme fruste (FF) Barlow, defined when myxomatous changes in more than one segment of a single leaflet were observed, and with moderate annular dilatation. Other clinical data included: demographics, cardiovascular risk factors, medication use and concomitant procedures at the time of MV surgery.

Self-reported family history

To evaluate the familial prevalence and distribution of MR in MVP patients, cardiovascular family history was systematically obtained (see Supplemental file). First, the contacted patients ('probands'), were asked whether they had any relatives known with MR. Only patients who were completely sure their relative had MR were classified as having 'familial MR'. In order to apply only a very restrictive definition for familial MR, patients were classified as having 'sporadic MR' in case the family history was negative, unknown or if patients were unsure (e.g. if they only reported 'valve regurgitation' or 'valve surgery'). Second, presence of other cardiovascular disease in the family was asked: other valvular pathology, coronary artery disease (CAD), arrhythmias, cardiomyopathy, congenital heart disease, aortic pathology, cerebrovascular accident (CVA)/ transient ischemic attack (TIA) and unexplained sudden death (SD) at young age (<65 years). Other valvular pathology was defined as valvular heart disease other than MR, or if the patient reported unspecified valvular pathology in the family. CAD was defined when myocardial infarction, prior percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or medical treatment for stable angina pectoris was reported in a relative <65 years. Presence of arrhythmias in a relative was defined in

case of specific treatment for either atrial or ventricular arrhythmias (e.g. medications or implantable cardiac defibrillator (ICD)). Family history was considered positive for cardiomyopathy only if the proband could report a specific diagnosed cardiomyopathy. Aortic pathology included reported aortic aneurysms/dissections. SD was defined as unforeseen and unexplained SD in a relative <65 years. For all reported cardiac diseases, the relation of the affected relative to the proband was noted.

Genetic consultation and evaluation of affected relatives

The probands who were referred to the clinical geneticist, underwent consultation according to standard practice. The family history was reviewed in detail and a pedigree was constructed. If the patient reported any relevant cardiac family history, the involved relative was asked for consent to retrieve their medical information in order to confirm the exact diagnosis. Familial MR was defined in a relative if the echocardiographic report was available and described MR ≥ grade 2 and/or a specific description of primary MR, such as BD, FED or MVP in general. The pedigrees were also evaluated to suggest possible patterns of inheritance. However, considering the lack of data on the penetrance of primary MR and the incomplete familial screening, no definite conclusions could be drawn.

Echocardiography

Standard transthoracic echocardiography was performed in all probands before operation with a commercially available ultrasound device (Vivid 5, Vivid 7 and E9, GE-Vingmed, Milwaukee, WI). Left atrial (LA) diameter and LV dimensions were acquired from the parasternal long-axis view. LV volumes, LV ejection fraction (LVEF) and LA volumes were measured using Simpson method and indexed for body surface area (BSA).(10) MVP was defined based on the Carpentier classification and the severity of MR was quantitatively assessed using a multi-parametric approach. Systolic pulmonary artery pressure (sPAP) was estimated from the tricuspid regurgitant jet velocity as recommended.(11) Image analysis was performed with EchoPAC (version 112, GE Medical Systems, Horten, Norway).

Statistical analysis

Continuous variables are presented as mean±standard deviation, when normally distributed and as median(interquartile range) when not normally distributed. Categorical variables are expressed as absolute numbers and percentages. Differences in clinical and echocardiographic characteristics between patients with familial MR and sporadic MR were assessed using Student T-test, Mann Whitney U test or Chi-square test, when appropriate. The agreement between self-reported and confirmed family history was assessed with Cohen's Kappa. Statistical analysis was performed using

SPSS version 23.0 (IBM Corp., Armonk, NY, USA). A p-value <0.05 was considered statistically significant.

Results

Patient population

A total of 385 patients (62±12 years, 63% male) were included for final analysis from a cohort of 693 patients who underwent surgery for severe primary MR between 2000-2017 (Figure 1). 185 patients were excluded because they died, 92 patients declined to participate and 31 could not be contacted. Based on the surgical observations, 193(50%) patients were diagnosed with FED, 107(28%) with BD and 85(22%) with FF Barlow (Table 1).

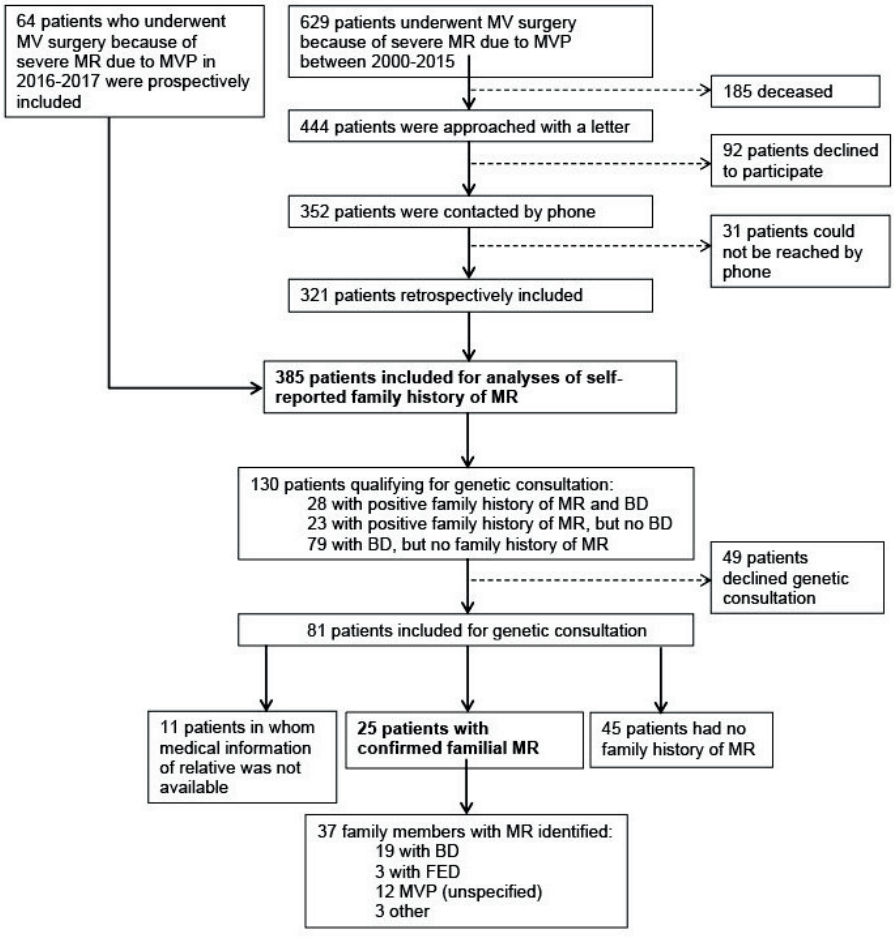

Figure 1. Flow-chart of patient selection.

Table 1. Clinical and echocardiographic characteristics of patients with and without self-reported familial primary mitral regurgitation (MR).

	All patients (n=385)	Familial MR (n=51)	Sporadic MR (n=334)	P-value
Clinical characteristics				
Age (years)	62±12	58±11	62±12	0.006
Men [n(%)]	241(63)	29(57)	212(64)	0.437
Hypertension [n(%)]	167(43)	22(43)	145(43)	1.000
Diabetes [n(%)]	13(3)	3(6)	10(3)	0.545
NYHA class [n(%)]				0.163
I	138(36)	21(41)	117(35)	
II	191(50)	27(53)	164(49)	
III/IV	56(14)	3(6)	53(16)	
Surgical Diagnosis [n(%)]				<0.001
FED	193(50)	15(29)	178(53)	
Barlow	107(28)	28(55)	79(24)	
FF Barlow	85(22)	8(16)	77(23)	
Echocardiographic parameters				
LVEDD (mm.)	55±7	56±6	55±6	0.255
LVESD (mm.)	34±6	35±7	34±6	0.548
LVEF (%)	65±8	64±8	65±8	0.540
LA diameter (mm.)	45±7	44±8	45±7	0.305
LAVI (ml/m^2)	47(38-61)	45(36-57)	47(38-62)	0.222
sPAP (mmHg)	32(25-40)	32(25-35)	32(26-40)	0.567
TR grade ≥ 2 [n(%)]	84(23)	9(19)	75(20)	0.581
Concomitant procedures				
CABG [n(%)]	67(17)	5(10)	62(19)	0.164
TVP [n(%)]	192(50)	25(49)	167(50)	1.000
MAZE [n(%)]	94(24)	13(26)	81(24)	0.862

MR, mitral regurgitation; NYHA, New York Heart Association; FED, fibroelastic deficiency; FF, forme fruste; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVEF, left ventricular ejection fraction; LA, left atrial; LAVI, left atrial volume index; sPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation; CABG, coronary artery bypass grafting; TVP, tricuspid valve annuloplasty

Prevalence of familial MR and family history of other cardiovascular disease in MVP patients

Self-reported family history for MR was positive in 51 MVP patients (13%). Table 1 shows the clinical and echocardiographic characteristics of patients with familial MR as compared to patients with sporadic MR. No differences between the two groups were observed regarding cardiovascular risk factors, concomitant surgical procedures and echocardiographic parameters. However, patients with familial MR were significantly younger and more often diagnosed with BD (55%) compared to patients with sporadic MR (24%). Figure 2a presents the prevalence of familial MR per MR aetiology and shows that patients with BD more often reported a positive family history (26% vs 8% in FED and 9% in FF Barlow patients, p<0.001). In figure 2b the self-reported prevalence of other cardiovascular

diseases is presented. No differences were observed between patients with familial MR and with sporadic MR regarding most diseases; however, SD in <65 year family members was significantly more frequent in patients with familial MR (29% vs. 14%,p=0.007). No significant differences were observed when comparing the prevalence of SD per MR aetiology: 20% of BD patients reported unexplained SD <65 years vs 14% of FF Barlow and FED patients (p=0.29).

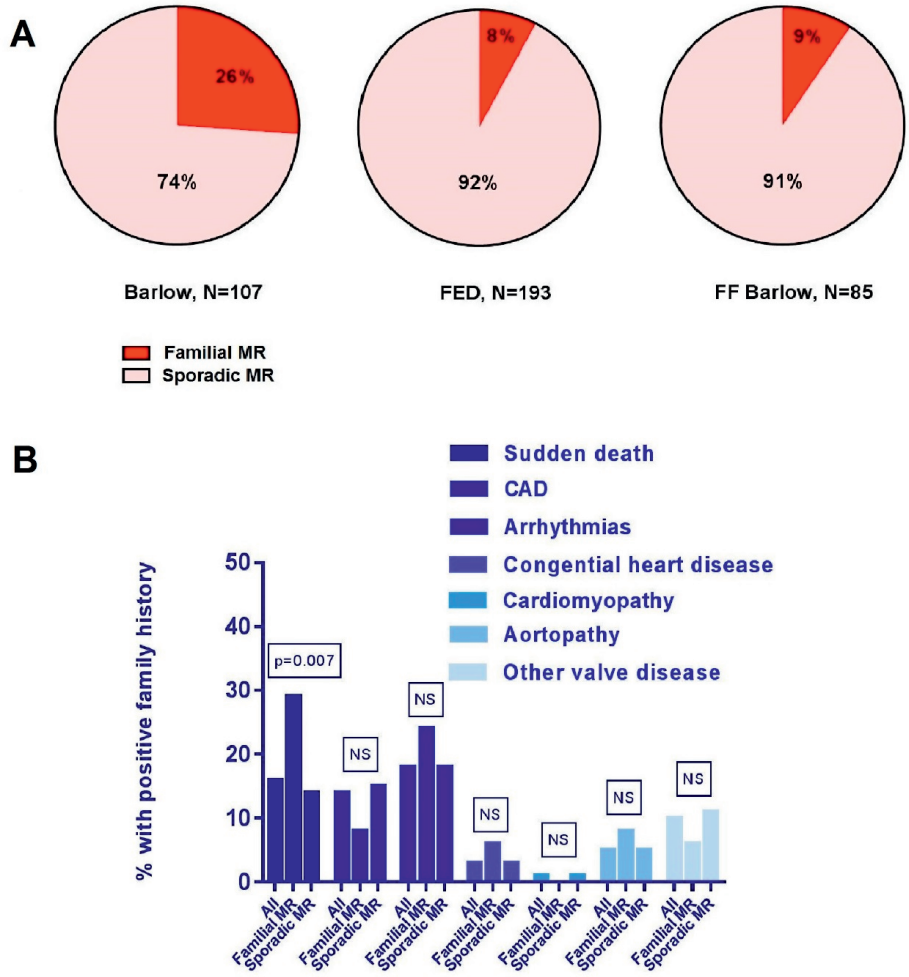

Figure 2. (a) Prevalence of self-reported familial mitral regurgitation (MR) among different MR aetiologies. (**b)** Prevalence of family history for other cardiovascular disease in all patients and compared between patients with familial MR and sporadic MR.

Confirmed familial MR by clinical geneticist

A total of 81 probands were referred for genetic consultation (Figure 1). Of those, 36 had a positive family history for MR (15 patients with a positive family history for MR declined genetic consultation) and the remaining 45 probands did not report familial MR, but were referred because of BD. For 11 relatives who were reported by the probands to have MR, this could not be confirmed, because the information was no longer available (n=4) or because the consent was not obtained from the affected relative (n=7). Eventually, the presence of primary MR was confirmed by echocardiographic and/or surgical reports in 37 relatives from 25 different probands. In 19(52%) relatives the echocardiographic report described the presence of BD, while in 3(8%) relatives FED and in 12(32%) relatives a MVP (not further defined) was reported. In 3 relatives the aetiology was not completely clear (i.e. calcified MV with significant MR). Interestingly, different aetiologies of MR were observed within the same family. Particularly, for 10 relatives (53%) with BD, the diagnosis of the proband was discordant (i.e. FED).

Patterns of inheritance

For the 36 probands with familial MR who were referred to the clinical geneticist, the pedigrees were evaluated and suggested different possible patterns of inheritance. Figure 3 shows examples of pedigrees from the study cohort with different distribution of affected family members.

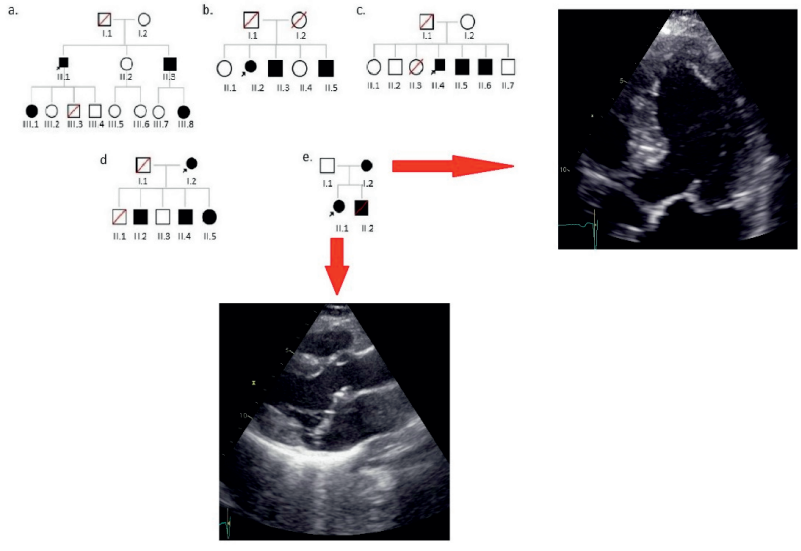

Figure 3. Pedigrees from different families with different distribution of affected family members. **(a)** affected male and female in 2 generations **(b)** 2 brothers and a sister affected
(c) 3 affected brothers **(d)** mother and 2 sons and 1 daughter affected **(e)** mother and both of her children, daughter and son, affected: both mother and daughter show severe mitral valve prolapse at echocardiography

Accuracy of self-reported family history

Medical information was received from 37 relatives who were reported by the probands to have primary MR. In 34 of these patients, diagnosis of primary MR was confirmed by the echocardiographic or surgical report. In 3 relatives, primary MR could not be confirmed due to: a functional MR secondary to LV dilatation (n=2); no clear prolapse or MR but a sclerotic MV in the context of an aortic valve replacement (n-=1).

Furthermore, during the genetic consultation 3 more relatives appeared to be affected but were not reported during the first contact with the proband. In all of these 3 relatives, the presence of primary MR was confirmed. The agreement of self-reported and confirmed family history was therefore overall good with $\kappa=0.80$, $p<0.001$.

Discussion

The main results of the present study can be summarized as follows: 1) In a large cohort of patients who underwent MV surgery because of severe MR due to MVP, the prevalence of self-reported familial MR was 26% in patients with BD and 8% in patients with FED; 2) patients with familial MR were younger as compared to patients with sporadic MR and also reported more frequently SD in their family; 3) a self-reported family history of primary MR showed good agreement with the assessment during genetic counselling.

Heritability of MVP and MR

MVP is a relatively common valve abnormality and its heritability was already suggested in 1966 by Hancock et al. who observed a systolic click and murmur in multiple relatives from different families.(12) Since then, other studies demonstrated the familial clustering of MVP.(4-8) In 1982, Devereux et al(4) evaluated 45 probands and 179 first degree relatives and using M-mode echocardiography found MVP in 30% of them. In 2 large community-based studies by the group of Delling et al,(5,6) familial clustering of MR was demonstrated in non-selected individuals and the authors showed that familial MVP was associated with higher prevalence of MVP and MVP-related MR in the offspring. These studies also suggested higher heritability of MVP based on the severity of the disease, with a magnitude comparable to other complex disease such as CAD and atrial fibrillation, and advocated the need for further studies in a referral-type population with more severe phenotype. Therefore, the present study evaluated the self-reported family history in a large referral-type population of patients requiring MV surgery and demonstrated that familial clustering is also present in this cohort. In the last years, several genetic studies were also performed in patients with familial MR due to MVP and identified 3 possible loci for autosomal-dominant MVP on chromosomes 16 (MMVP1), 11 (MMVP2) and 13 (MMVP3).(13-15) Furthermore, DCHS1 and PLD1

have been linked to autosomal MVP(16,17) and mutations in the filamin A (FLNA) gene have been identified to cause a X-linked form of MVP.(18) In line with these findings, the present study observed different distributions of affected family members between families (figure 3). However, no final conclusions regarding the pattern of inheritance could be made, since 100% penetrance is unlikely and the familial screening was not complete.

Differences in familial MR between BD and FED

Previous studies evaluating the heritability and familial distribution of MVP mainly distinguished the presence of MVP from non-diagnostic morphology of MVP, as prodromal phenotype of the disease. However, these studies did not explore the difference in heritability between different aetiologies of MVP, such as BD and FED. It is well known that BD and FED differ in many characteristics, such as age of diagnosis, clinical presentation, and morphology of the valve, suggesting different pathophysiological mechanisms.(9) Differences in heritability are therefore plausible among these phenotypes, considering also recent findings suggesting that MV abnormalities in BD might be secondary to developmental alterations at the annular junction and leaflets.(19)

The present study showed a significantly higher prevalence of familial MR in BD patients (26%), but still a prevalence of 8% familial MR in FED and of 9% in FF Barlow. Interestingly, when studying the phenotype of MVP within families, patients with FED and BD were observed within the same family, suggesting that in some cases more limited involvement of the MV might be a form of mild phenotype of the same disease, although it might be confused for FED when based on echocardiographic morphological definition (such as the single scallop involvement). These findings suggest that although BD is associated with higher magnitude of heritability, thorough family history should be performed also in patients with FED and FF Barlow and more in depth studies on the morphological characteristics of familial MR in MVP should be performed.

Family history of other cardiovascular disease

It has been reported that MVP may be associated with other cardiovascular disease, such as cardiomyopathies, congenital heart disease, CAD, ventricular arrhythmias and sudden cardiac death.(1,2) Therefore, the present study aimed at collecting a complete family history including also other cardiovascular diseases. No differences were observed for most cardiovascular diseases when comparing familial versus sporadic MR. However, 29% of patients with familial MR, compared to 14% in patients with sporadic MR, reported SD at <65 year of age in their family. Previous studies showed that MVP is significantly associated with sudden cardiac death in young adults, especially in women, and that specific characteristics, such as fibrosis of the papillary muscle and mitral annular disjunction, were associated with ventricular arrhythmias.(20-23) In the present study, additional

information about the relatives who experienced SD was lacking and it is therefore unknown whether SD was of cardiac origin and whether they also had MVP; however, the fact that SD was more prevalent in patients with familial MR underlines the importance of better characterization of these patients and of obtaining an extensive family history in MVP patients.

Clinical implications

The present study showed that familial MR is a common finding in a large cohort of patients who underwent MV surgery for severe MR due to MVP, and should be considered regardless of the aetiology of primary MR. Familial screening for MVP and MR is currently seldom performed but it could represent an important tool for early diagnosis and therefore strict monitoring of the relatives. This approach might be helpful considering the increasing evidence that patients benefit the most from MV surgery when the LV function is still preserved and symptoms have not yet occurred,(24,25) and also to improve risk stratification for sudden cardiac death in this patient population. However, further studies are needed to demonstrate the cost-effectiveness of family screening in MVP. The present study also showed that clinicians can rely with sufficient confidence on the family information the patient provides, at least about the 1st degree affected relatives (positive family history). Therefore, the present study strongly suggests to collect family history as part of standard clinical practice in MVP. In turn, the value of self-reported negative family history could not be evaluated in the present study, since a systematic screening with echocardiography was not performed in all relatives.

Limitations

The present study has several limitations that should be mentioned. Firstly, self-reported family history was used to estimate familial distribution and the accuracy of this information can vary since not all patients are aware of the medical histories of their relatives and is more susceptible to ascertainment bias. However, the importance of family history has been recognized for several other (cardiac) diseases and showed to be reliable at least in first-degree relatives.(26-28) Also for the family history of other cardiovascular diseases, recall-bias might exist in a family, since patients with already known familial MR might be more aware of other cardiac diseases in their family. However, this bias was minimized by asking the cardiac family history systematically and thoroughly in all patients. Second, patients who died after the operation or refused to participate were excluded; if excluding these patients might influence the results cannot be proven. Also, non-diagnostic morphologies of MVP were not systematically evaluated(6) since probands were by definition characterized by a severe phenotype and not all family members were screened with echocardiography (only when they gave consent). Because of the mentioned limitations and the

strict definition applied, the prevalence shown in this study is probably underestimated. A systematic echocardiographic screening of all family members is needed to assess the real prevalence and to identify characteristics associated with familial MR.

Conclusion

In a large cohort of patients operated for MVP with severe MR, a significant prevalence of self-reported familial MR was observed, reaching 30% in patients with BD and almost 10% in patients with FED. Familial MR was also associated with higher incidence of SD. Self-reported family history of MVP is reliable and can be used by physicians to perform further family screening.

Authors contributions

All authors contributed to the conception and design of the study. YH, AW, MW, DB and NA contributed to acquisition of the data. YH and NA analyzed the data, all authors contributed to interpretation of the data. Drafting of the manuscript was done by YH, DB and NA, the manuscript was critically revised by JB and VD. Finally, all authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Chapter 7

Evolution from mitral annular dysfunction to severe mitral regurgitation in Barlow's disease

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Abstract

Objectives Barlow's disease (BD) is characterized by thick, redundant mitral valve (MV) leaflets which can lead to prolapse and significant mitral regurgitation (MR). MV annular abnormalities are also commonly observed and increasingly recognized as possible primary pathology, with leaflet thickening being secondary to increased stress on the MV apparatus. To provide more insights into this hypothesis, the evolution over time of MV abnormalities in BD patients was assessed.

Methods A total of 64 patients (54±12 years,72% male) with BD who underwent MV surgery and had multiple transthoracic echocardiograms (TTE) before surgery, were included. In total 186 TTE were analysed (median time interval 4.2, IQR 2.2-6.5 years) including specific MV characteristics.

Results At baseline, MV leaflet length, thickness, billowing height and annular diameter were larger in BD patients compared to 59 healthy subjects. Systolic outward motion (curling) of the annulus was observed in 77% and severe mitral annular disjunction (≥5mm) in 38% of BD patients. Forty (63%) patients had MR grade I-II and 24 (37%) MR grade III-IV; at baseline the 2 groups only differed in left atrial volume and in thickness and billowing height of the posterior leaflet, showing comparable MV annular abnormalities and dilatation despite different grade of MR. Over time, MV annulus diameter, leaflet length and billowing height increased significantly along with MR grade.

Conclusions In BD patients, MV annulus abnormalities are present at an early stage and precede the development of significant MR, suggesting their substantial role in the pathophysiology of this disease and as important target for surgical treatment.

Keywords: mitral valve prolapse; Barlow's disease; echocardiography; longitudinal changes

Introduction

Current classifications of primary mitral regurgitation (MR), and particularly of mitral valve (MV) prolapse, distinguish mainly between Barlow's disease (BD) and fibro-elastic deficiency (FED). BD is characterized by myxoid infiltration and collagen alterations of the MV, resulting in thick and redundant leaflets with elongated chordae and a bi-leaflet prolapse. FED is characterized by single-segment prolapse/flail with thin leaflets or thickening limited to the prolapsing segment.[1] Although the redundant and prolapsing MV leaflets are considered the hallmark of BD, specific MV annular abnormalities, such as annular dilatation, mitral annular disjunction (MAD) and systolic outward motion (curling) of the annulus, are also commonly observed in these patients.[2-5] These annular abnormalities are increasingly recognized as a primary component of the underlying pathology of BD, which might increase the mechanical stress on the MV apparatus, with further thickening and elongation of leaflets and chordae, and possibly also development of ventricular arrhythmias.[6,7] However, whether these annular abnormalities are concomitant to the leaflet alterations, secondary to the development of MR or might precede them is not known yet. Longitudinal echocardiographic studies could help understanding the pathophysiology of BD and identifying the main morphological and functional alterations underlying this complex MV pathology, improving timely diagnosis, and eventually identifying the main target of surgical repair. However, follow-up studies are cumbersome in this population, since patients often present to clinical attention at a late stage, when severe MR has already developed, or the echocardiographic assessment is not systematically performed. Few studies reported on the echocardiographic characteristics related to the progression of MR in patients with MV prolapse,[8-10] but focussed on leaflet alterations without assessing the specific MV annular abnormalities more typically associated with BD. Therefore, the aim of the present study was to evaluate changes in MV morphology and function over time, particularly focusing on annular abnormalities, using echocardiography in a relatively large group of BD patients who eventually developed a severe MR requiring surgery.

Methods

Patient population

Patients who underwent MV surgery for severe primary MR due to BD between 2000-2017 were identified in two different centers: Leiden University Medical Center, Leiden, the Netherlands and Centro Cardiologico Monzino, IRCCS, Milan, Italy. The diagnosis of BD was based on echocardiographic findings and confirmed by intraoperative observations:[1,11] a bi-leaflet MV prolapse due to excessive tissue and elongated chordae, with annular abnormalities such as annular dilatation with or without calcification and systolic outward motion (curling). Patients with other forms of MV prolapse (such as FED and BD forme fruste), with hypertrophic cardiomyopathy, with Marfan's syndrome and with endocarditis were excluded. Furthermore, in order to study the echocardiographic changes over time before MV surgery, patients were included in this study when there were ≥2 complete transthoracic echocardiograms (TTE) available before MV surgery with ≥2 years in between. Patient data were collected at the time of the first TTE from the departmental cardiology information systems (EPD-Vision® at Leiden University Medical Center, and W-Hospital at Centro Cardiologico Monzino), and included age, gender and cardiovascular risk factors. In addition, 59 healthy controls having structural normal hearts, were selected from the echocardiography database. These controls were matched based on age, gender and cardiovascular risk factors. The study complies with the Declaration of Helsinki and was approved by the Institution Review Boards. Due to the retrospective design of this study, the Medical Ethical Committee waived the need for written informed consent.

Echocardiographic analysis

Standard TTE was performed with commercially available ultrasound systems and the same machine was used during follow-up (Vivid 7 and E9, GE-Vingmed, Milwaukee, WI and ie33 and EPIQ system, Philips Medical System, Andover, MA). Images were digitally stored and analyzed offline using EchoPAC (version 112, GE Medical Systems) and QLAB (Philips Medical System). All available TTE performed before MV surgery were analyzed. Left ventricular (LV) end-diastolic diameter (EDD) and end-systolic diameter (ESD) were measured from the parasternal long-axis view and LV ejection fraction (EF) and left atrial volume were calculated using Simpson's biplane method. Left atrial volume was indexed (LAVI) for body surface area.[12] MR severity was graded according to current recommendations using a multi-parametric approach and MR was classified as mild (grade I), mild-moderate (grade II), moderate-severe (grade III) and severe (grade IV).[13] Systolic pulmonary artery pressure was estimated by measuring maximal tricuspid regurgitant jet velocity with the simplified Bernoulli equation in combination with an estimation of the right atrial pressure, as recommended.[14]

Tricuspid valve annular diameter was measured from a right ventricular focused apical 4-chamber view.[13]

Mitral valve morphology and function assessment

All measurements of MV morphology and function were performed on the parasternal long-axis view according to current recommendations and applying the definition used by previous studies:[7,15,16] MV annular diameter was determined in the end-systolic phase, just before opening of the MV leaflets (Figure 1a). Leaflet length was measured as the distance from the hinge point to the free edge and was measured by slowly reviewing the cardiac cycle to identify the hinge point and the free edge, without including the chordae (Figure 1b). Leaflet thickness was defined as the maximum distance from atrial to ventricular surface, considering the entire leaflets (Figure 1c). Leaflet billowing height was defined as the maximum prolapse of the leaflet into the left atrium, measured as the maximum height above the annular level (Figure 1d).[17] Furthermore, presence of annular curling, defined as unusual hypermobile outward and downward systolic motion of the posterior mitral annulus on the adjacent myocardium, was noted.[2] MAD was measured as the separation between the insertion of the posterior leaflet into the left atrial wall and the base of the LV posterior wall (Figure 1e); MAD ≥ 5 mm was considered significant.[18-20]

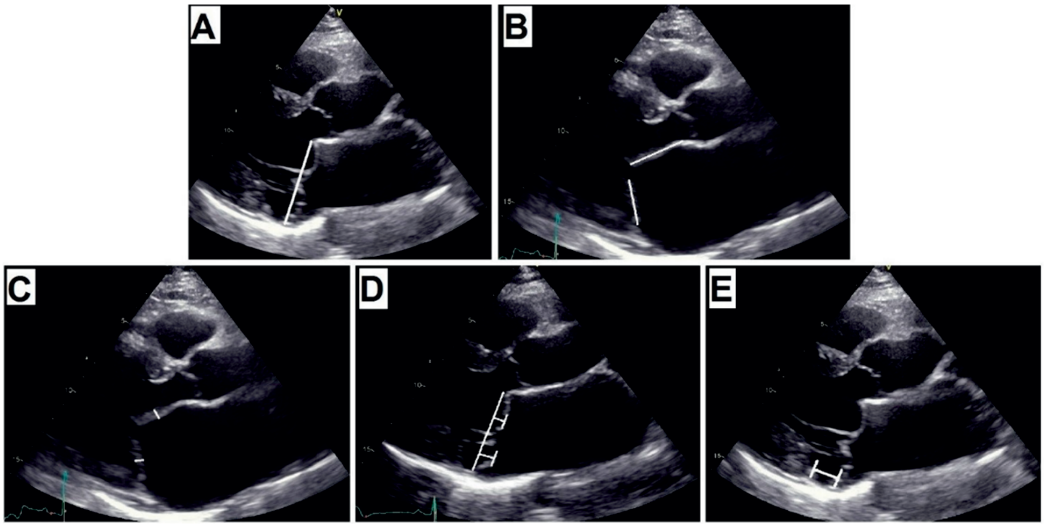

Figure 1. Transthoracic echocardiography showing the specific mitral valve measurements: **(A)** mitral annular diameter **(B)** Length of mitral valve leaflets **(C)** Thickness of mitral valve leaflets **(D)** Billowing height of mitral valve leaflets **(E)** Mitral annular disjunction

Statistical analysis

Statistical analysis was performed with the SPSS software package (version 20, IBM Corp, Armonk, New York, USA) and R version 3.6.0. Continuous variables are reported as mean±standard deviation, when normally distributed, and as median (interquartile range), when not normally distributed. Categorical variables are presented as absolute numbers and percentages. Differences in clinical and echocardiographic characteristics between control subjects and patients with BD were assessed using Student-T test, Mann-Whitney U-test or Chi-square, when appropriate. BD patients were further divided based on MR grade (patients with MR grade I/II vs. MR grade III/IV) at first TTE, in order to evaluate whether changes in MV morphology were correlated to the severity of MR. Changes over time within these 2 groups were analysed by comparing the median change per year with a one-sample Wilcoxon test. Furthermore, a linear mixed model with a fixed interaction between time and MR grade, and random intercept and time slope per patient, was used to assess echocardiographic changes over time for all patients and for patients with MR grade I/II at baseline compared to patients with MR grade III/IV at baseline. Intra-class correlation coefficients were calculated for inter-observer and intra-observer agreement in 10 randomly selected patients, to evaluate reproducibility. A p-value of <0.05 was considered significant.

Results

Patient population

A total of 64 BD patients (54±12 years,72% male) were included in the analysis according to the inclusion and exclusion criteria. Clinical and echocardiographic characteristics (at the time of the first TTE) of these patients were compared with the 59 controls (Table 1). Regarding conventional echocardiographic measurements, patients with BD showed larger LVEDD (54±6mm vs. 49±6mm,p<0.001) and slightly higher LVEF (63±5% vs. 61±6%,p=0.026). Furthermore, patients with BD showed LA dilatation with a larger median LAVI (37(29-48)ml/m^2 vs 24(17-28) ml/m^2,p<0.001). All BD patients showed some degree of MR: 40(63%) had MR grade I or II and 24(37%) had MR grade III or IV. In 49 patients (77%), annular curling of the MV was observed. Furthermore, in BD patients mean MAD was 2.9±3 mm and 24 patients (38%) showed significant MAD(≥5 mm). Both annular curling and MAD were not observed in the controls. In BD patients, the MV annulus was significantly dilated (already at first TTE) compared to controls (36±5mm vs. 27±3mm,p<0.001). Moreover, length, thickness and billowing height of the posterior and anterior MV leaflets were significantly larger in patients with BD compared to controls.

Table 1. Clinical and echocardiographic characteristics of patients with BD disease (at the first echocardiographic assessment) as compared to age- and gender-matched healthy subjects.

	Controls (N=59)	BD (first TTE, N=64)	p-value
Clinical characteristics			
Age (years)	54±11	54±12	0.816
Male [n(%)]	42(71)	46(72)	1.000
Hypertension [n(%)]	21(36)	24(38)	0.603
Hypercholesterolemia [n(%)]	7(12)	14(22)	0.158
Diabetes [n(%)]	2(3)	1(2)	0.511
Echocardiographic characteristics			
LVEDD (mm)	49±6	54±6	<0.001
LVESD (mm)	32±7	34±7	0.071
LVEF (%)	61±6	63±5	0.026
LAVI (ml/m^2)	24(17-28)	37(29-48)	<0.001
sPAP (mmHg)	24(19-27)	24(23-31)	0.015
TV annulus (mm)	29±5	34±5	<0.001
MR grade [n(%)]			<0.001
none	59 (100)	0(0)	
I-II	0(0)	40 (63)	
III-IV	0(0)	24 (37)	
MV annular curling [n(%)]	0(0)	49(77)	<0.001
MAD height (mm)	0	2.9±3	<0.001
Significant MAD [n(%)]	0 (0)	24(38)	<0.001
MV annulus (mm)	27±3	36±5	<0.001
Length AML (mm)	17±2	23±3	<0.001
Length PML (mm)	11±2	16±3	<0.001
Thickness AML (mm)	2±0.5	4±1	<0.001
Thickness PML (mm)	2±0.5	4±1	<0.001
Billowing height AML (mm)	0	4±2	<0.001
Billowing height PML (mm)	0	5±2	<0.001

AML anterior mitral leaflet, LAVI left atrial volume index, LVEDD left ventricular end-diastolic diameter, LVEF left ventricular ejection fraction, LVESD left ventricular end-systolic diameter, MAD mitral annular disjunction, MR mitral regurgitation, MV mitral valve, PML posterior mitral leaflet, sPAP systolic pulmonary artery pressure, TTE trans-thoracic echocardiography, TV tricuspid valve

Barlow's disease: changes in mitral valve morphology over time

Of the 64 patients with BD, a total of 186 echocardiograms were assessed (range 2-11 echocardiograms per patient). In Table 2 the differences between the first and last echocardiogram are presented. The median time interval between the first and last echocardiogram was 4.2(2.2-6.5) years. At the time of the first TTE, 40 patients (63%) had MR grade I or II, while at the time of the last TTE (before surgery) all patients progressed to MR grade III-IV. Between first and last TTE, LVESD and LVEF remained stable over time, while LVEDD and LAVI showed significant increase. The tricuspid

valve annular diameter showed a trend towards increase, however this was not significantly different. No significant changes in annular curling and presence of significant MAD were observed over time, although the MAD height slightly increased. All other MV characteristics changed significantly during follow-up: in particular, MV annulus dilatation progressed over time and the length as well as thickness of both anterior mitral leaflet (AML) and posterior mitral leaflet (PML) increased.

Table 2. Changes in echocardiographic parameters over time in patients with BD. P-value corrected for time in between the echocardiograms.

Parameter	First TTE	Last TTE	P-value
LVEDD (mm)	54±6	57±7	0.008
LVESD (mm)	34±7	35±7	0.195
LVEF (%)	63±5	63±7	0.436
LAVI (ml/m^2)	37(29-48)	51(38-63)	<0.001
sPAP (mmHg)	24(23-31)	30(25-37)	<0.001
TV annulus (mm)	29±5	35±5	0.101
MR grade [n(%)]			<0.001
I-II	40 (63)	0 (0)	
III-IV	24 (37)	64 (100)	
Annular curling [n(%)]	49 (77)	52(81)	0.250
MAD height (mm)	2.9±3	3.1±3	0.004
Significant MAD [n(%)]	24(38)	26(41)	0.500
MV annulus (mm)	36±5	39±5	<0.001
Length AML(mm)	23±3	24±4	<0.001
Length PML(mm)	16±3	17±3	<0.001
Thickness AML(mm)	4±1	5±1	<0.001
Thickness PML(mm)	4±1	5±1	<0.001
Billowing height AML(mm)	4±2	5±3	0.010
Billowing height PML(mm)	5±2	7±3	<0.001

AML anterior mitral leaflet, LAVI left atrial volume index, LVEDD left ventricular end-diastolic diameter, LVEF left ventricular ejection fraction, LVESD left ventricular end-systolic diameter, MAD mitral annular disjunction, MR mitral regurgitation, MV mitral valve annulus, PML posterior mitral leaflet, sPAP systolic pulmonary artery pressure, TV tricuspid valve

Furthermore, the prolapse became more evident with an increase of the billowing height of the AML and PML. In Figure 2, results of the mixed model analysis of some of the individual MV measurements over time are shown. All available MV measurements of the echocardiograms between the first and last TTE are taken into account in this analysis and further show that MV annular dilation (slope 0.44, p<0.001), leaflet length (slope for AML 0.27, p<0.001; slope for PML 0.27, p<0.001) and billowing height (slope for AML 0.13, p=0.01; slope for PML 0.35, p<0.001) increased over time.

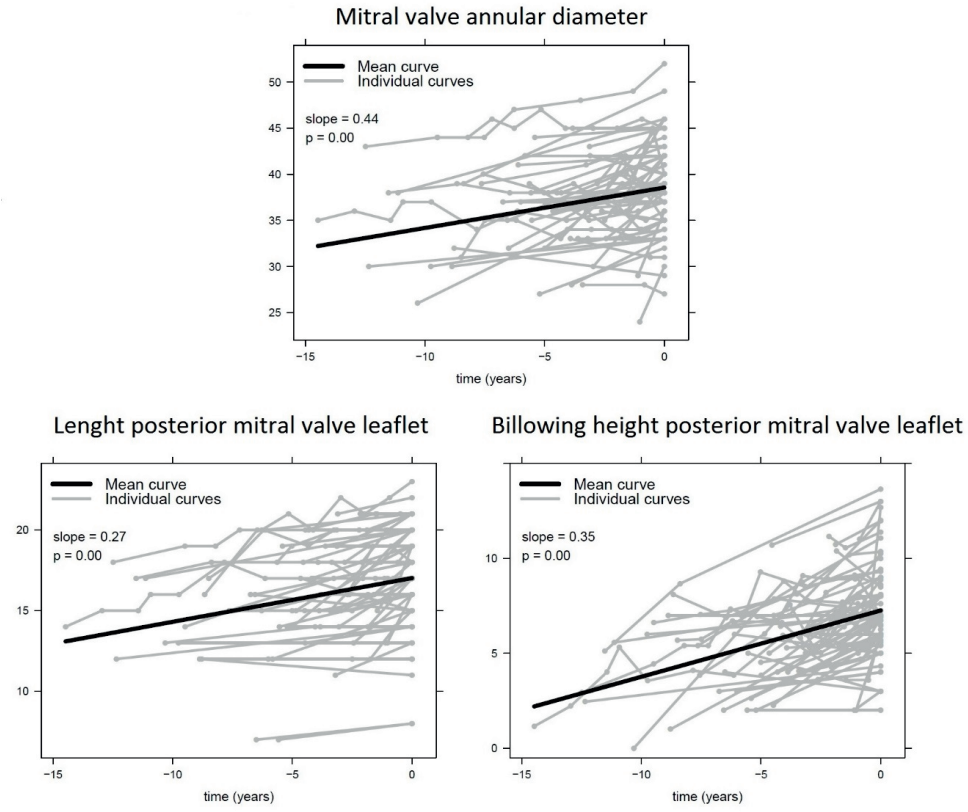

Figure 2. Changes over time in some of the mitral valve characteristics. The grey lines represent the individual measurements per patient, the black lines present the mean curve of all patients. Values on y-axis in millimeters. Patients underwent MV surgery at time point '0'.

Differences between MR grade I/II and MR grade III/IV

In Table 3, differences between patients with MR grade I/II and patients with already MR grade III/IV at the first TTE are presented. The echocardiographic measurements at first and last TTE are shown for each group and compared between the 2 groups as well as within groups over time. At the time of the first TTE, LAVI, thickness of the PML and billowing height of the PML were significantly larger in patients with MR grade III/IV compared to patients with MR grade I/II. All other measurements were not significantly different between the 2 groups at the time of the first TTE.

Table 3. Echocardiographic changes over time between BD patients with MR grade I/II vs. MR grade III/IV (at the time of the first echocardiography).

Parameter	MR grade I/II (N=40)	MR grade III/IV (N=24)	p-value between groups	p-value group-time interaction
LVEDD (mm)				0.94
First TTE	54±7	56±6	0.26	
Last TTE	57±7*	56±6	0.64	
LVESD (mm)				0.70
First TTE	33±7	36±7	0.16	
Last TTE	35±8*	36±6	0.63	
LVEF (%)				0.08
First TTE	64±5	63±6	0.63	
Last TTE	62±8	64±6	0.19	
LAVI (ml/m^2)				0.50
First TTE	33(17-43)	46(35-54)	0.005	
Last TTE	50(37-60) *	53(42-66)	0.23	
sPAP (mmHg)				0.58
First TTE	25(22-31)	25(23-31)	0.66	
Last TTE	29(25-37) *	31(27-33)*	0.76	
MV annulus (mm)				0.65
First TTE	36±5	37±4	0.36	
Last TTE	38±5*	39±4*	0.66	
Length AML (mm)				0.014
First TTE	23±3	24±4	0.25	
Last TTE	24±3*	25±4*	0.12	
Length PML (mm)				0.49
First TTE	15±3	16±3	0.15	
Last TTE	17±3*	18±1*	0.35	
Thickness AML (mm)				0.88
First TTE	4±1	4±1	0.16	
Last TTE	5±1*	5±1*	0.37	
Thickness PML (mm)				0.19
First TTE	4±1	5±1	0.003	
Last TTE	5±1*	6±2*	0.063	
Billowing height AML (mm)				0.99
First TTE	4±2	5±2	0.076	
Last TTE	5±3*	5±3	0.64	
Billowing height PML (mm)				0.46
First TTE	5±2	6±3	0.016	
Last TTE	7±2*	8±3*	0.16	

* p-value <0.05 within group: first vs. last measurement, corrected for time between echocardiograms

AML anterior mitral leaflet, LAVI left atrial volume index, LVEDD left ventricular end-diastolic diameter, LVEF left ventricular ejection fraction, LVESD left ventricular end-systolic diameter, MR mitral regurgitation, MV mitral valve, PML posterior mitral leaflet, sPAP systolic pulmonary artery pressure, TTE transthoracic echocardiography

In the group of patients with MR grade I/II at baseline, all echocardiographic measurements showed an increase over time, except for LVEF which remained stable. In the group of patients with MR grade III/IV at baseline, LV dimensions, LVEF and LAVI remained stable, while parameters of MV morphology (annular diameter, leaflet length, thickness and billowing height) increased over time, except for billowing height of the AML. Additionally, the group-time interaction showed whether the echocardiographic variables changed differently over time between the 2 groups: most parameters showed similar changes over time in the 2 groups except for the length of the AML, which showed a slightly higher increase (24±4mm to 25±4mm) for patients with MR grade III/IV as compared to patients with MR grade I/II (23±3mm to 24±3mm,p=0.010).

Inter- and intra-observer variability

The intra-class correlation coefficients for repeated measurements by the same observer (intra-observer agreement) was excellent for all parameters; the intra-class correlation coefficients for measurements between two different observers (inter-observer agreement) was generally good or excellent (Supplemental file 1).

Discussion

The present study provides novel insights in the pathophysiology of specific MV abnormalities in patients with BD who eventually developed severe MR. In particular, MV annular abnormalities, such as dilatation, systolic curling and disjunction, represent a common feature of these patients and are present already before development of significant MR, which is in turn associated to increasing leaflet thickness and billowing height over time.

Mitral valve morphology in patients with BD

The MV apparatus is a complex structure, whose proper function is guaranteed by normal leaflet morphology and attachment to papillary muscles and to the MV annulus. Particularly, the MV annulus contributes significantly to valve competence not only being the anchoring point of the leaflets but also by active systolic contraction. Normally, the MV annulus has a saddle shape and is attached posteriorly to the LV myocardium; therefore, when systolic LV contraction occurs, MV annulus also contracts along its antero-posterior diameter enhancing the coaptation of the AML and PML and preventing MR.[21] Significant abnormalities of MV annulus morphology and function have been observed in BD, including hypermobility of the posterior annulus (systolic curling), attachment of the PML above the LV myocardium (MAD) and annular dilatation.[2-5] From histological samples, Hutchins et al.[18] were the first recognizing MV annular abnormalities in patients with MV prolapse

and also introduced the term MAD, defined as a separation between the LV myocardium and the attachment of the PML in the atrial wall. The authors also suggested for the first time that a defect in the annulus fibrosus could be the primary abnormality in BD and that the other morphologic and functional alterations of the leaflets might be secondary. Since then, several studies have described MV annular abnormalities in patients with MV prolapse using echocardiography or magnetic resonance imaging, but interestingly with some variation in the definition and in the reported prevalence.[7,15,19-24] Lee et al.[20] defined MAD when ≥5mm displacement was observed and reported a prevalence of 42% in patients who underwent MV surgery because of degenerative MR. Eriksson et al.[19] evaluated 109 patients who underwent MV surgery, with transesophageal echocardiography and reported a prevalence of MAD, defined as any displacement, of 98% in patients with advanced MV degeneration and 9% in patients with mild MV degeneration. In contrast, Konda et al.[23] reported MAD (defined as ≥2mm displacement) also in healthy subjects and therefore questioned the pathological significance of this finding. Of note, most articles did not describe the presence of systolic curling of the MV annulus, although these two abnormalities are considered to reflect similar annular alterations.[6] Furthermore, the discrepancies in the prevalence of annular abnormalities between studies might be explained by the difference in patient populations included (i.e. any type of MV prolapse or organic MR in general). Studies evaluating differences in annular dynamics between patients with FED and BD have demonstrated that the MV annulus in FED patients has relatively normal function and is mildly dilated compared to BD.[3,5] These observations also contribute to the hypothesis that the diffuse thickening and elongation of MV leaflets, not observed in FED, are probably partially a primary alteration in BD but partially also compensatory to altered stress on the MV apparatus due to the abnormal annular dynamics. However, only studies including serial echocardiographic examinations focusing on MV annular abnormalities, could help supporting this hypothesis. Therefore, the present study selected only patients with a clear phenotype of BD and showed that MV annular abnormalities are detectable with TTE at an early stage, before significant MR develops.

Evolution of mitral valve abnormalities in BD

Few studies assessed changes in MV morphology and function over time in patients with MV prolapse. Avierinos et al.[10,25] evaluated the natural history of asymptomatic MV prolapse and showed that age and MR grade at baseline were independent predictors of MR progression. The rate and determinants of MR progression were evaluated by Enriquez-Sarano et al.[9] in 74 patients with organic MR and showed that MR progressed over time which was correlated with an increase in MV annular diameter. However, the progression of MR was poorly predictable using baseline characteristics and it was unclear which MV alterations preceded development of MR. Furthermore,

more specific MV abnormalities, like leaflet characteristics, MAD and systolic curling of the annulus, were not evaluated. In another study, by Delling et al,[8] longitudinal changes in MV characteristics were evaluated in patients from the Framingham Offspring, including 63 patients with MV prolapse, 60 patients with 'non-diagnostic MV prolapse morphologies' and 138 healthy subjects. They showed that a large proportion of patients from both groups, MV prolapse and 'non-diagnostic MV prolapse morphologies', showed changes over time with increasing leaflet thickness, displacement and progression of MR, demonstrating that also patients with mild MV abnormalities can progress to a more severe phenotype of MV prolapse. MV prolapse and LV diameter were identified as predictors of progression of MR. However, the MV alterations that preceded the development of MR and specific annular abnormalities were not evaluated. The present study is the first to describe the longitudinal changes of specific MV characteristics in a population of patients with a clear BD phenotype. At the time of the first TTE, MV annular dilatation, (any) disjunction and curling were observed in the majority of patients, even in the absence of significant MR and signs of LV or LA remodeling, whereas elongation and thickening of the MV leaflets were also observed, but to less extent. Over time, leaflet elongation, thickening and prolapsing height progressed, leading to impaired leaflet coaptation and severe MR and to LV and LA dilatation. In Figure 3 these phases are presented schematically. These results support the hypothesis that MV annular abnormalities might play a primary role in the primary pathology of BD leading to secondary alterations in the whole MV apparatus. Correction of these abnormalities should be therefore a crucial target of the surgical treatment.

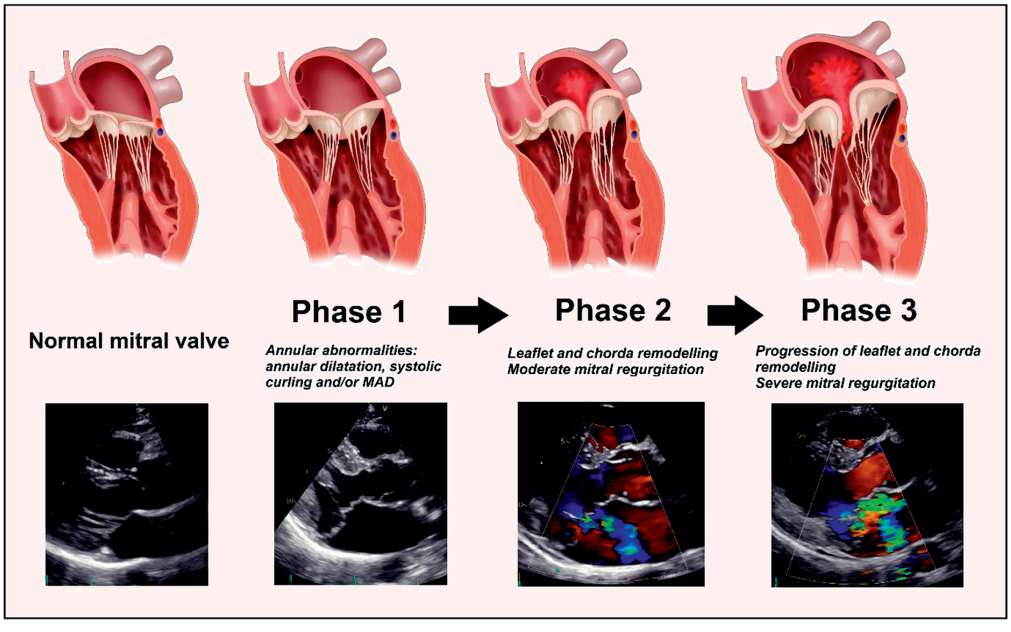

Figure 3. Evolution of mitral valve abnormalities in patients with BD over time.
Left panel: normal MV; *'***Phase 1'***:* Annular abnormalities, including annular dilatation, mitral annular disjunction and systolic curling, without mitral regurgitation (MR); *'***Phase 2'***:* Remodelling of leaflets and chordae, including elongation, thickening and prolapse of the MV leaflets with moderate MR; **'Phase 3'***:* Progression of leaflet and chorda remodelling and development of severe MR and left atrial dilatation.

Clinical implications

The observations of the present study may be relevant in the choice of surgical strategy for these patients. Annular remodelling and stabilization should represent the cornerstone of surgical treatment in BD, in order to correct the dilatation and abnormal annulus movement, which in some cases is the main cause of anterior leaflet prolapse.[26] Furthermore, proper annuloplasty reduces the stress applied to native valvular leaflet, preventing further leaflet degeneration and possible recurrence of mitral regurgitation. The results of the current study underline also the importance of recognizing MV annular abnormalities in patients with BD at the time of first diagnosis. When assessing these patients echocardiographically, complete assessment of the MV should be performed, including MV annular dynamics. Since the present study suggested annular abnormalities to be the early sign of BD, assessment of MV abnormalities could be particularly important when screening family members in the setting of familial BD.[27] Patients without significant MV prolapse or MR but important annular dysfunction might be considered for regular follow-up, also considering the recently suggested association between MAD and ventricular arrhythmias.[7,22] More studies with larger population are needed to confirm these results and demonstrate the prognostic value of these MV annular abnormalities and how and when to intervene.

Limitations

Because of the retrospective design of this study, longitudinal follow-up was not standardized and therefore the amount and time in between echocardiograms varied among patients. Therefore, the mixed model analysis was corrected for time and included all available echocardiograms, instead of only 'first' and 'last'. Although all patients had severe MR at the last echocardiogram, at the time of the first echocardiogram, the stage of the disease differed among patients. To minimize bias regarding the heterogeneity in disease stage at baseline, we compared patients with MR grade I/II with patients with MR grade III/IV and the changes in echocardiographic characteristics over time. In this study, only two-dimensional TTE was used, although other imaging techniques like cardiac magnetic resonance and three-dimensional and/or transoesophageal echocardiography could have

better accuracy; however, TTE is more readily available and likely to be used in clinical practice and showed to be able to accurately detect MV abnormalities.[15,22,23]

Conclusion

In patients with BD, abnormalities of the MV annulus are present at an early stage and precede the development of significant MR, suggesting a substantial role in the pathophysiology of this disease and an important target for surgical treatment.

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Chapter 8

Prognostic value of global longitudinal strain and etiology after surgery for primary mitral regurgitation

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Abstract

Objective: to investigate whether left ventricular (LV) global longitudinal strain (GLS) is associated with long-term outcome after mitral valve (MV) surgery for primary mitral regurgitation (MR) and to assess the differences in outcome according to MR etiology: Barlow's disease (BD), fibro-elastic deficiency (FED) and forme fruste (FF).

Background: Appropriate timing of MV surgery for primary MR is still challenging and may differ according to the etiology. In these patients, LV-GLS has been proposed as more sensitive measure to detect subtle LV dysfunction as compared to LV ejection fraction.

Methods: Echocardiography was performed in 593 patients (64% male,age 65±12years) with severe primary MR who underwent MV surgery, including assessment of LV-GLS. The etiology (BD, FED or FF) was defined based on surgical observation. During follow-up, primary endpoint was all-cause mortality and a secondary endpoint included cardiovascular death, heart failure hospitalizations and cerebro-vascular accidents.

Results During a median follow-up of 6.4(3.6-10.4) years, 146 patients died (16 within 30 days after surgery), 46 patients were hospitalized for heart failure, and 13 patients had a cerebro-vascular accident. Age (hazard ratio (HR)=1.08 [1.05-1.11],p<0.001) and LV-GLS (HR=1.13 [1.06-1.21],p<0.001) were independently associated with all-cause mortality. Patients with LV-GLS>-20.6% (more impaired) showed significant worse survival than patients with LV-GLS≤-20.6%; of interest, patients with BD showed similar prognosis compared to FED and FF. In addition, previous atrial fibrillation (HR=1.70 [1.012.86],p=0.045) and LV-GLS (HR=1.01 [1.01-1.15],p=0.019) were independently associated with the secondary endpoint.

Conclusions LV-GLS is independently associated with all-cause mortality and cardiovascular events after MV surgery for primary MR and might be helpful to guide surgical timing. Importantly, patients with BD showed similar prognosis when corrected for age, compared to patients with FED or FF.

Introduction

Untreated severe primary mitral regurgitation (MR) is associated with increased morbidity and mortality, but prognosis in these patients can be significantly improved with mitral valve (MV) surgery (1,2). However, timing of surgery is still a matter of debate. According to most recent guidelines(3,4), MV surgery is recommended for symptomatic patients with severe primary MR, or in asymptomatic patients with severe primary MR when left ventricular (LV) systolic dysfunction or dilatation occurs (based on LV ejection fraction (EF) and LV diameters), in the presence of pulmonary arterial hypertension or in case of new-onset atrial fibrillation (AF) and when the likelihood of repair is high and the surgical risk is low. Despite these recommendations, appropriate timing of surgery remains a clinical challenge, since identification of symptoms might be difficult, LVEF and LV dimension may not reliably reflect LV dysfunction and the likelihood of MV repair is dependent of MR etiology and expertise of the surgical center. LV global longitudinal strain (GLS) has been introduced as a more sensitive and accurate measurement of LV function(5) and current guidelines mention the potential incremental value of LV-GLS over LVEF for risk stratification in patients with severe primary MR(3). Although few studies have shown the association of LV-GLS with outcome after surgery for primary MR, evidence of the prognostic value of LV-GLS in these patients remains limited(6-8). Therefore, the present study aimed at further investigating the prognostic value of preoperative LV-GLS in a large contemporary population of patients who underwent MV surgery for primary MR and with a long-term follow-up. Additionally, despite the fact that the likelihood of MV repair plays a significant role in the management of these patients, only a very limited number of studies reported long-term outcome after MV surgery systematically differentiating the MR etiology, including Barlow's disease (BD) and fibro-elastic deficiency (FED), which are characterized by different MV lesions.(9) Therefore, the present study also aimed at investigating the impact of MR etiology over the long-term outcome after MV surgery(10).

Methods

Patient population

Patients who underwent MV surgery for severe primary MR in our center between 2000-2015 were identified. Patients were excluded if transthoracic echocardiography was not available before surgery. Furthermore, patients with rheumatic valve disease, active endocarditis, connective tissue disorders or hypertrophic cardiomyopathy were excluded. Included patients were divided in 3 groups according to the etiology of MR, based on echocardiographic findings and surgical observations(11,12): 1) FED, defined when thin leaflets or thickening limited to a single prolapsed

segment of the MV were observed, with or without chordal rupture/ flail; 2) BD, defined when a bi-leaflet prolapse with excess tissue, elongated chordae and annular abnormalities, such as annular displacement and curling of the annulus, were observed; 3) forme fruste (FF), defined when myxomateous changes in more than one segment of a single leaflet were observed, but without significant annular abnormalities. All patients underwent clinical and echocardiographic evaluation before MV surgery. Patient data were prospectively collected in the departmental cardiology information system (EPD-Vision®; Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analysed. Clinical data included demographic characteristics, cardiovascular risk factors, New York Heart Association functional class, comorbidities and EUROSCORE II. Duration of cardio-pulmonary bypass and aortic cross-clamp time were noted, as were other concomitant surgical procedures. The study complies with the Declaration of Helsinki and was approved by the Institutional Review Board. Due to the retrospective design of this study, the Medical Ethical Committee waived the need of written informed consent.

Echocardiography

Standard transthoracic echocardiography was performed with commercially available ultrasound machines (Vivid 7 and E9, GE-Vingmed, Milwaukee, WI). Images were digitally stored and analysed offline using EchoPAC (version 112, GE Medical Systems, Horten, Norway). LV end-diastolic (EDD) and end-systolic (ESD) diameters and left atrial (LA) diameter were measured from the parasternal long-axis view. LV volumes, LVEF and LA volumes were measured using Simpson's method and indexed for body surface area(13). Stroke volume was measured by determining the velocity time integral at the level of the LV outflow tract and the LV outflow tract diameter (π x (LV outflow tract diameter/2)^2 x velocity time integral). MR severity was quantitatively assessed according to current recommendations using a multi-parametric approach and including the effective regurgitant orifice area (using proximal isovelocity surface area method) and regurgitant volume measurements, when feasible(14). Systolic pulmonary artery pressure was estimated by measuring maximal tricuspid regurgitant jet velocity with the simplified Bernoulli equation in combination with an estimation of the right atrial pressure, as recommended(15).

Speckle tracking analysis was performed from the apical views (two-, three- and four-chamber) at a frame rate >40 fps (mean 60 fps) to assess LV-GLS. The region of interest was automatically created and manually adjusted to the myocardial thickness when necessary. LV-GLS was then calculated by averaging the peak longitudinal strain values of the 17 segments, excluding segments that could not be traced correctly.

Outcome analysis

The date of MV surgery was set as the beginning of the observational period. The primary endpoint of this study was all-cause mortality >30 days after surgery. The occurrence of death during follow-up was obtained by medical charts review and through the municipal civil registries for survival status. In case cause of death was unclear from the medical charts, the general practitioner or local hospital was contacted. The secondary endpoint was a combined endpoint of cardiovascular events, including cardiac death, heart failure hospitalization and cerebrovascular accidents. Heart failure hospitalization was defined when the patient was admitted because of signs and symptoms of decompensated heart failure. Patients who underwent re-operation were censored at that time.

Statistical analysis

Continuous variables are reported as mean±standard deviation, when normally distributed, and as median(interquartile range), when not normally distributed. Categorical variables are presented as absolute numbers and percentages. Differences in baseline clinical and echocardiographic characteristics between the groups based on etiology were assessed using ANOVA, Kruskal-Wallis or Chi-square tests, when appropriate. To evaluate which variables were associated with the endpoints, univariable Cox proportional hazard regression analysis was performed and hazard ratios (HR) with 95% confidence interval were calculated. To identify independent prognosticators of the primary and secondary endpoint, separate multivariable analysis was performed including all variables with a $p<0.10$ at univariable analysis.

Survival curves were constructed according to the Kaplan-Meier method to estimate cumulative survival and compared using log-rank tests. The cut-off value for LV-GLS was based on the median value (-20.6%) of the study population which is in concordance with previously suggested cut-off value for normal range(6,7). To provide more insight into the relation between LV-GLS and mortality, also Kaplan-Meier curves according to tertiles of LV-GLS were constructed. To assess the additional prognostic value of LV-GLS on top of other clinical variables, likelihood-ratio testing was performed and Harrell's C-statistic(16) was calculated. A p-value<0.05 was considered significant. The SPSS software package (version 20, IBM Corp, Armonk, New York, USA) was used for statistical analysis.

Results

Patient population

A total of 593 patients were included (65±12 years,64% male) out of a cohort of 684 patients who underwent surgery for organic MR in our center. Of these, 91 patients were excluded due to the lack of echocardiographic examinations (or of sufficient quality) before surgery. A total of 365 patients were classified as FED, 164 were classified as BD and 64 as FF. Baseline clinical characteristics and

the differences between the 3 groups are shown in Table 1. Patients with BD were significantly younger than patients with FF or FED (59±13 years vs. 64±11 years and 68±10 years, respectively). No differences were observed for cardiovascular risk factors and the incidence of AF (either paroxysmal or persistent) between the 3 groups. However, patients with BD were more often asymptomatic which was shown by the percentage of patients in New York Heart Association class I (39% vs. 28% and 24%,p<0.001). Furthermore, patients with BD had a better renal function and a lower EUROSCORE II. However, patients with BD had longer surgery times, as reflected by a longer cardio-pulmonary bypass time and longer aortic cross-clamp time, but they underwent less frequently concomitant coronary artery bypass grafting, whereas no differences were observed for concomitant tricuspid valve annuloplasty (table 1).

Table 1. Baseline clinical characteristics of the total population and divided in 3 groups according to the MR etiology.

	All patients (N=593)	FED (N=365)	Barlow (N=164)	Forme Fruste (N=64)	P-value
Clinical characteristics					
Age (years)	65 ± 12	68 ± 10	59 ± 13	64 ± 11	<0.001
Men [n(%)]	380 (64)	233 (64)	102 (62)	45 (70)	0.729
Hypertension [n(%)]	259 (46)	150 (44)	83 (52)	26 (43)	0.203
Diabetes [n(%)]	23 (4)	13 (4)	9 (5)	1 (2)	0.572
Atrial fibrillation [n(%)]	219 (37)	131 (36)	61 (37)	27 (42)	0.627
NYHA class: [n(%)]					<0.001
I	169 (29)	87 (24)	64 (39)	18 (28)	
II	282 (48)	163 (45)	82 (50)	37 (58)	
III	133 (22)	107 (30)	17 (10)	9 (14)	
IV	7 (1)	6 (2)	1 (1)	0 (0)	
Serum creatinine (µmol/L)	89 ± 26	92 ± 29	83 ± 17	89 ± 29	0.002
eGFR (ml/min/1.73m^2)	79 ± 27	74 ± 25	88 ± 27	83 ± 31	<0.001
EUROSCORE II (%)	2.0 (1.1-3.8)	2.4 (1.3-4.5)	1.4 (0.9-2.7)	2.1 (1.0-3.6)	<0.001
MV surgery					
Type of surgery: [n(%)]					0.240
MV repair	584 (98)	360 (99)	160 (97)	64 (100)	
MVR (mechanical)	4 (1)	1 (0.3)	3 (2)	0(0)	
MVR (bioprosthetic)	5 (1)	4 (1)	1 (0.6)	0(0)	
Aortic cross-clamp time (min)	200 ± 67	188 ± 63	217 ± 62	222 ± 85	<0.001
CPB time (min)	151 ± 52	142 ± 51	167 ± 49	167 ± 54	<0.001
Concomitant procedures					
CABG [n(%)]	121 (20)	85 (23)	17 (10)	19 (30)	0.003
TVP [n(%)]	274 (46)	161 (44)	87 (53)	26 (47)	0.103
MAZE [n(%)]	168 (28)	90 (25)	54 (33)	24 (38)	<0.001
Aortic surgery [n(%)]	45 (8)	37 (10)	6 (4)	2 (3)	<0.001

CABG coronary artery bypass grafting; CPB cardio-pulmonary bypass; eGFR estimated glomerular filtration rate; FED fibro-elastic deficiency; MR mitral regurgitation; MV mitral valve; MVR mitral valve replacement; NYHA New York heart association; TVP tricuspid valve annuloplasty

Echocardiographic characteristics

Baseline echocardiographic characteristics and differences between the 3 groups are shown in Table 2. Median time between the echocardiography and MV surgery was 40(7-135) days, which was not significantly different between groups. Mean LVEF was 65±8%, and only 113(19%) patients had LVEF between 50-60%; no differences in LVEF were noted between groups. Patients with BD had slightly larger LVEDD compared to patients with FF and FED (55±7 vs. 54±7 and 54±7 for LVEDD,p=0.034); however when LVEDD was indexed for body surface area, it was not significantly different among the groups. Similarly, LVESD, LA dimension and LV and LA volumes were not significantly different between groups. The effective regurgitant orifice area was not significantly different between the 3 groups, but the regurgitant volume was slightly lower in patients with BD compared to FED and FF (51±28ml for BD, vs 60±22ml and 60±23ml for FF and FED,p=0.004). Of interest, the systolic pulmonary artery pressure was significantly higher in FED patients compared to FF and BD (35(28-48)mmHg vs 32(27-43) and 30(25-35)mmHg,p<0.001). Furthermore, mean LV-GLS was within the normal ranges in the overall population(-20.7%±4). Interestingly, LV-GLS was better in BD patients as compared to FF and FED (-22%±4 vs -21%±4 and -20%±4,p=0.003).

Table 2. Echocardiographic characteristics of the total population and divided in 3 groups according to MR etiology.

	All patients (N=593)	FED (N=365)	Barlow (N=164)	Forme Fruste (N=64)	P-value
Echocardiography					
LV EDD (mm)	54 ± 7	54 ± 7	55 ± 7	54 ± 7	0.034
LV EDD index (mm/m^2)	29 ± 4	28 ± 4	29 ± 4	28 ± 4	0.190
LV ESD (mm)	33 ± 7	33 ± 7	34 ± 7	33 ± 7	0.481
LV ESD index (mm/m^2)	18 ± 4	18 ± 4	18 ± 4	17 ± 4	0.752
LV EDV (ml)	135 ± 42	132 ± 42	141 ± 41	135 ± 42	0.082
LV EDV index (ml/m^2)	71 ± 20	69 ± 20	73 ± 17	70 ± 19	0.144
LV ESV (ml)	45 (34-59)	44 (32-58)	48 (37-60)	44 (36-61)	0.055
LV ESV index (ml/m^2)	23 (19-30)	23 (18-30)	25 (20-31)	23 (19-31)	0.064
LV EF (%)	65 ± 8	65 ± 8	64 ± 8	64 ± 8	0.742
Forward SV (ml)	59 (48-72)	59 (48-73)	58 (45-71)	62 (48-74)	0.849
LA diameter (mm)	45 ± 8	45 ± 7	45 ± 9	47 ± 8	0.153
LAVI (ml/m^2)	51 (39-63)	48 (38-61)	53 (42-69)	52 (41-70)	0.063
MR grade [n(%)]					0.014
III	186 (31)	98 (27)	67 (40)	21 (33)	
IV	407 (69)	267 (73)	97 (60)	43 (67)	
EROA (mm^2)	41 (29-54)	41 (31-55)	38 (28-53)	42 (28-55)	0.186
RVol (mL)	57 ± 24	60 ± 22	51 ± 28	60 ± 23	0.004
TR grade [n(%)]					0.851
0	66 (12)	41 (12)	18 (11)	7 (11)	
1-2	468 (81)	286 (81)	131 (80)	51 (84)	
3-4	38 (7)	26 (7)	9 (5)	3 (5)	
sPAP (mmHg)	32 (27-43)	35 (28-48)	30 (25-35)	30 (25-42)	<0.001
LV GLS (%)	-21 ± 4	-20 ± 4	-22 ± 4	-21 ± 4	0.003

EROA effective regurgitant orifice area, FED fibro elastic deficiency, GLS global longitudinal strain, LA left atrial, LAVI left atrial volume index; LV left ventricular; EDD end diastolic diameter, EDV end diastolic volume, EF ejection fraction, ESD end systolic diameter, ESV end systolic volume; MR mitral regurgitation, RVol regurgitant volume, sPAP systolic pulmonary artery pressure; SV stroke volume

Outcome

During median follow-up of 6.4(3.6-10.4) years, 146 deaths occurred, of which 16 occurred <30 days after surgery (1 gastro-intestinal bleeding, 7 multi-organ failure, 2 acute myocardial infarction, 5 heart failure and 1 ventricular arrhythmia). A total of 31 patients underwent second MV surgery, of whom 10 died during further follow-up, they were censored at time of re-surgery. For the remaining 120 deaths, cause of death was cardiac in 28 patients, unknown in 36 patients and non-cardiac in 56 patients. Furthermore, 46 patients were admitted to the hospital because of heart failure and 13 patients had a cerebro-vascular accident.

Survival analysis

Univariable Cox hazard regression analysis showed that age, New York Heart Association class ≥2, previous AF, eGFR, LVEDD, LVEF, systolic pulmonary artery pressure, LV-GLS and MR etiology (BD being protective) were associated with the all-cause mortality endpoint. However, multivariable analysis showed that only age and LV-GLS were independently associated with all-cause mortality (HR 1.08(1.05-1.11),p<0.001 for age; HR 1.13(1.06-1.21),p<0.001 for LV-GLS (table 3)).

Table 3. Univariable and multivariable Cox regression analysis to identify independent predictors for all-cause mortality after MV surgery (primary endpoint).

Variable	Univariable HR (95% CI)	p-value	Multivariable HR (95% CI)	p-value
Age (years)	1.09 (1.07-1.11)	<0.001	1.08 (1.05-1.11)	<0.001
NYHA class≥2	2.12 (1.32-3.39)	0.002	1.20 (0.70-2.06)	0.504
Atrial fibrillation	1.77 (1.24-2.53)	0.002	0.92 (0.56-1.50)	0.726
eGFR (ml/min/1.73m^2)	0.97 (0.96-0.98)	<0.001	0.99 (0.98-1.01)	0.447
LVEDD (mm.)	0.96 (0.93-0.99)	0.005	0.98 (0.95-1.02)	0.389
LVESD (mm.)	1.01 (0.98-1.03)	0.571		
LVEF (%)	0.97 (0.95-0.99)	0.009	1.00 (0.97-1.03)	0.891
LA diameter (mm)	1.02 (1.00-1.04)	0.081	1.01 (0.98-1.04)	0.614
EROA (mm^2)	1.00 (0.99-1.01)	0.729		
LV-GLS (%)	1.16 (1.11-1.21)	<0.001	1.13 (1.06-1.21)	<0.001
sPAP (mmHg)	1.02 (1.00-1.03)	0.016	0.99 (0.98-1.01)	0.530
TVP	0.88 (0.61-1.27)	0.494		
CABG	1.03 (0.66-1.61)	0.901		
MVR	0.91 (0.13-6.51)	0.203		
Diagnosis:				
Forme fruste		<0.001		0.257
FED	1.14 (0.65-2.00)	0.655	0.58 (0.29-1.15)	0.117
Barlow	0.41 (0.21-0.83)	0.013	0.56 (0.25-1.24)	0.557

CABG coronary artery bypass grafting, CI confidence interval, eGFR estimated glomerular filtration rate, EROA effective regurgitant orifice area, FED fibro elastic deficiency, GLS global longitudinal strain, HR hazard ratio, LA left atrial, LVEDD left ventricular end diastolic diameter, LVEF left ventricular ejection fraction, LVESD left ventricular end systolic diameter, MVR mitral valve replacement, NYHA New York heart association, sPAP systolic pulmonary artery pressure, TVP tricuspid valve annuloplasty

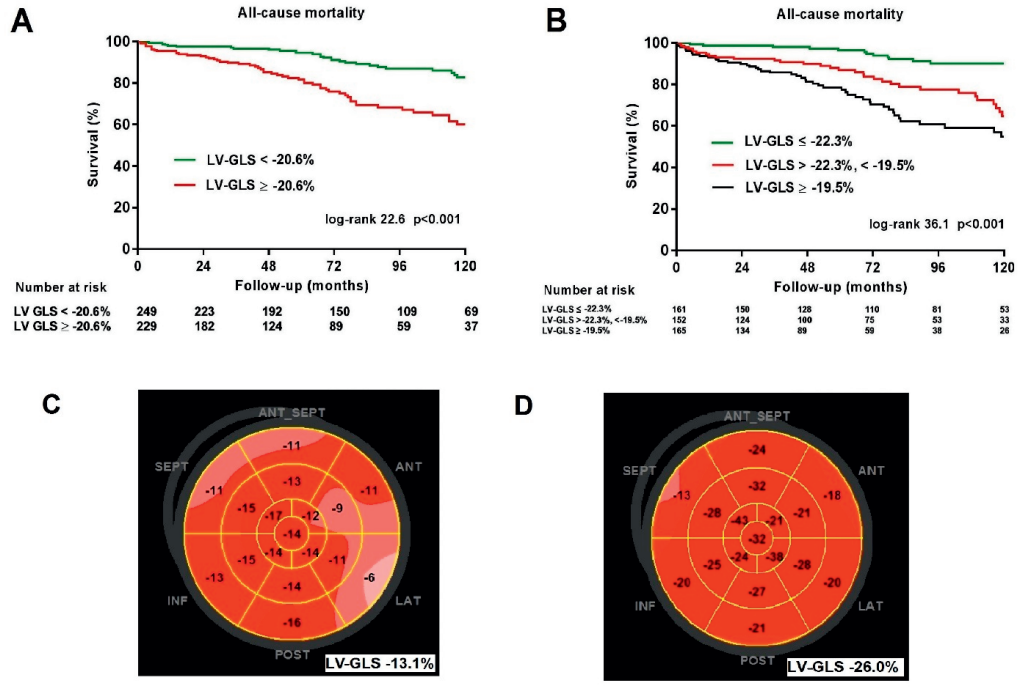
In table 4 the results of the Cox cause-specific hazard analysis are shown for the secondary endpoint. The multivariable analysis showed that previous AF and LV-GLS were independently associated with cardiovascular events (HR 1.08(1.01-1.15),p=0.019 for LV-GLS and HR 1.70(1.01-2.86),p=0.045) for previous AF).

Table 4. Univariable and multivariable Cox cause-specific hazard analysis to identify independent predictors for cardiovascular events (secondary endpoint including cardiac death, HF hospitalizations and CVA) after MV surgery.

Variable	Univariable HR (95% CI)	p-value	Multivariable HR (95% CI)	p-value
Age (years)	1.06 (1.03-1.08)	<0.001	1.03 (0.99-1.07)	0.076
NYHA class≥2	1.85 (1.07-3.19)	0.027	1.01 (0.55-1.85)	0.971
Atrial fibrillation	2.57 (1.66-3.96)	<0.001	1.70 (1.01-2.86)	0.045
eGFR (ml/min/1.73m^2)	0.98 (0.97-0.99)	<0.001	0.99 (0.98-1.01)	0.621
LVEDD (mm.)	0.98 (0.94-1.00)	0.129		
LVESD (mm.)	1.02 (0.99-1.05)	0.261		
LVEF (%)	0.98 (0.96-1.01)	0.115		
LA diameter (mm)	1.02 (0.99-1.05)	0.153		
EROA (mm^2)	1.00 (0.99-1.02)	0.909		
LV-GLS (%)	1.12 (1.06-1.19)	<0.001	1.08 (1.01-1.15)	0.019
sPAP (mmHg)	1.02 (1.00-1.03)	0.016	1.01 (0.99-1.02)	0.452
TVP	1.10 (0.72-1.69)	0.665		
CABG	1.39 (0.85-2.26)	0.187		
MVR	1.97 (0.27-14.16)	0.502		
Diagnosis:				
Forme fruste		0.013		0.208
FED	1.19 (0.59-2.39)	0.629	0.72 (0.33-1.56)	0.403
Barlow	0.48 (0.21-1.13)	0.094	0.44 (0.17-1.12)	0.085

CABG coronary artery bypass grafting, CI confidence interval, eGFR estimated glomerular filtration rate, EROA effective regurgitant orifice area, FED fibro elastic deficiency, GLS global longitudinal strain, HR hazard ratio, LA left atrial, LVEDD left ventricular end diastolic diameter, LVEDV left ventricular end diastolic volume, LVEF left ventricular ejection fraction, LVESD left ventricular end systolic diameter, MVR mitral valve replacement, NYHA New York heart association, sPAP systolic pulmonary artery pressure, TVP tricuspid valve annuloplasty

Patients with more preserved LV-GLS showed significant better survival in terms of all-cause mortality than patients with more impaired LV-GLS, when divided based on the median LV-GLS of -20.6% (log-rank 22.6,p<0.001) (Central Illustration, panel A). In particular, cumulative survival for all-cause mortality was 94% and 85% at 5 and 10 years respectively for patients with preserved LV-GLS <-20.6% and 81% and 60% for patients with impaired LV-GLS (≥-20.6%). In addition, when dividing the population in 3 groups according to tertiles of LV-GLS, patients with most preserved LV-GLS (≤-22.3%) showed better outcome in terms of all-cause mortality than patients with mildly impaired LV-GLS (between -22.3% and -19.5%), while patients with most impaired LV-GLS (≥-19.5% showed worst survival (log-rank 36.1,p<0.001) (Central Illustration, panel B).



Central illustration. Kaplan-Meier survival curves according to LV-GLS.
In the upper panel survival curves for all-cause mortality are shown according to the median LV-GLS (-20.6%, **Panel A**) and according to the tertiles of LV-GLS (≤-22.3%; -22.3% to -19.5%; ≥-19.5%, **Panel B)**. In the lower panel examples of bulls-eye plot of LV-GLS are shown: **Panel C.** A 69-year old patient, with impaired LV-GLS (-13.1%), who died of heart failure 1.5 year after the echocardiography. **Panel D.** A 46-year old patient, with preserved LV-GLS (-26.0%) who did not experience an event during 12.3 years of follow-up.

Incremental value of LV-GLS

Figure 1 shows the incremental value for predicting all-cause mortality of LV-GLS on top of other clinical and echocardiographic variables evaluated by the likelihood-ratio testing and the Harrell's C-statistic. The addition of LV-GLS to a clinical model (including: age, AF, New York Heart Association class≥2, eGFR, LVEDD, LVEF, systolic pulmonary artery pressure), provided significant improvement of the prognostic model (p<0.001) with an increase of C-statistic 0.74 to 0.77.

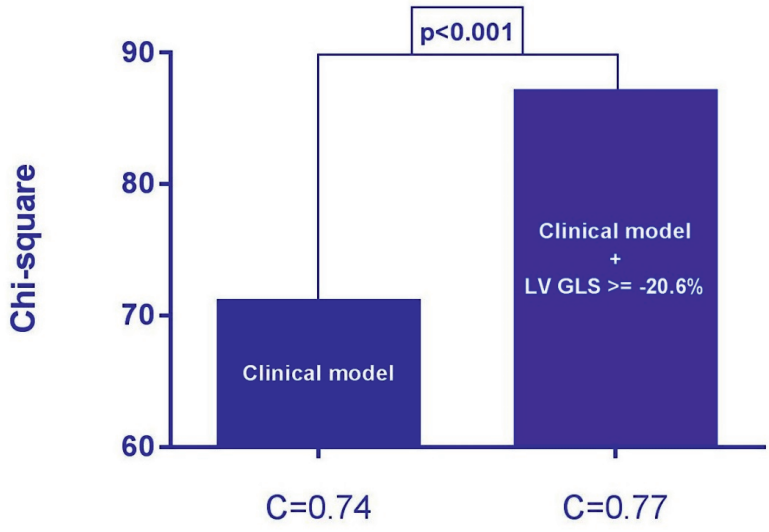


Figure 1. Likelihood-ratio test for the incremental prognostic value of LV-GLS.
The bar graphs show the incremental value of LV-GLS to the standard clinical and echocardiographic variables associated with all-cause mortality. Harrell's C statistic represent overall adequacy of risk prediction.

Discussion

The main findings of this study can be summarized as follows: 1) LV-GLS is independently associated with all-cause mortality and cardiovascular events in patients undergoing MV surgery for severe primary MR; 2) LV-GLS has incremental prognostic value over clinical risk factors for long-term survival; 3) when corrected for age, patients with BD showed similar prognosis compared to FED and FF despite more complex MV involvement and challenging MV repair.

Prognostic markers for long-term outcome after mitral valve surgery

Development of LV dilatation and dysfunction is one of the most important factors considered in current guidelines to refer patients with severe primary MR for surgery. In particular, current European guidelines recommend MV surgery(3), even when patients are asymptomatic, if LVEF is ≤60% and/or LVESD≥45 mm. Most recent American guidelines(4) consider MV surgery also reasonable in these patients when a decrease in LVEF or increase in LVESD is observed during serial echocardiographic examinations, based on the increasing evidence that patients benefit most from surgery when LV function is still preserved. It is however challenging to measure LV systolic function accurately in these patients since LVEF might not properly reflect LV function in the presence of severe MR and, importantly, structural and functional alterations of LV myocardium may occur before a decline in LVEF can be detected(17). Therefore, studies have focused on identifying other

parameters which are able to better detect subclinical LV systolic dysfunction. Brain natriuretic peptide is one of the parameters proposed as a marker of LV dysfunction in these patients. Pizarro et al. showed that elevated plasma brain natriuretic peptide levels were associated with the combined endpoint of heart failure symptoms, LV dysfunction or death in patients with severe organic MR and LVEF >60%(18). Mentias et al. demonstrated that higher levels of plasma brain natriuretic peptide are associated with worse survival in a cohort of 548 patients with asymptomatic severe organic MR(19). In addition, GLS has been proposed as a sensitive and reliable marker of subtle LV dysfunction in patients with severe primary MR and initial studies showed that in these patients, impaired LV-GLS at baseline was associated with worse LV function after MV surgery(20,21,22). The prognostic value of LV-GLS was shown in 2 studies which showed that LV-GLS was associated with long-term mortality together with reduced exercise capacity and elevated brain natriuretic peptide in asymptomatic patients with severe MR and preserved LVEF(6,7). However, current guidelines emphasize the potential limitation of inter-vendor differences in the software algorithms for LV-GLS measurement(3) and in these studies only vector velocity imaging was applied to measure LV-GLS. The present study confirmed the independent prognostic value of LV-GLS when measured with another widely available speckle tracking-based software and in a large population of patients undergoing MV repair with a long-term follow-up. Recently, also Kim et al.(8) studied the prognostic value of LV-GLS after MV surgery in 506 patients with severe primary MR and showed that LV-GLS, measured with another widely used software, was associated with worse outcome in terms of cardiac events and all-cause mortality with a median follow-up of 3.5 years; however more than 10% of the patients had rheumatic or congenital MR and more than 40% in the outcome group underwent MV replacement (instead of repair), which was also significantly associated with the outcome. The present study confirms these results in a more homogenous population of 593 patients with only degenerative MR, underwent solely MV repair and with longer follow-up duration.

Differences between aetiologies: Barlow's disease vs. fibro-elastic deficiency

BD and FED are the most common forms of primary MR(14). BD is characterized by thickened MV leaflets, multi-segmental prolapse, chordal elongation or rupture, and typical annular abnormalities, such as dilatation, abnormal motion and posterior displacement of the annulus. In turn, patients with FED typically show thin, or normal thickened, MV leaflets, single segment prolapse or chordal rupture(11). The correct aetiologic classification is important for patient management, having an impact in the decision-making for timing of surgery and surgical approach. Several studies showed that MV repair surgery for BD is usually longer, more complex and has a lower success rate than in FED if not performed in experienced centers. On the other hand, patients with BD are normally

younger, with less comorbidities and less symptoms at first presentation(11). Although the clinical need for differentiation between BD and FED has already been recognized in current guidelines(3,9), there are only few data available focused on the prognostic value of MR etiology for patients undergoing MV surgery. A study by Coutinho et al.(23) evaluated long-term outcome (re-operation and mortality) after MV surgery in patients with FED or myxomatous valves: no differences were observed in mortality or re-operation between those groups. However, the study analysed only patients with anterior or bi-leaflet prolapse. The present study showed, in line with previous literature, that patients with BD are usually younger, have less comorbidities and a lower logistic Euroscore II, compared to patients with FED or FF. When corrected for age, patients with BD showed similar prognosis as compared to FED and FF despite more complex MV involvement and challenging MV repair. In addition, MR etiology was included in the multivariate analysis when assessing the prognostic value of LV-GLS in primary MR but was not independently associated with long-term mortality or with cardiovascular events.

Clinical implications

Appropriate timing for surgery and risk stratification in patients with severe primary MR is still challenging and therefore research has focused on identifying new and reliable prognostic parameters. The present study confirmed the prognostic value of LV-GLS in patients with severe primary MR and specifically showed that patients with normal LV-GLS have a significantly better outcome. Particularly in asymptomatic patients with severe primary MR, without signs of LV dysfunction according to conventional criteria, or any other clinical indications for surgery according to current guidelines, presence of impaired LV-GLS could possibly lead to early surgery in experienced centres, instead of watchful waiting until overt LV dysfunction develops. In these patients, MV surgery at this early stage might protect for developing LV dysfunction, possibly irreversible, and subsequent adverse events during the follow-up after surgery. This hypothesis however, needs to be demonstrated in a prospective study. Also, in patients who already have indication for surgery according to current guidelines based on other parameters, LV-GLS can optimize risk stratification reflecting more accurately myocardial dysfunction. Furthermore, the present study showed that complex MV lesions, as seen in BD, do not influence the long-term outcome specifically in patients with normal LV-GLS, and therefore absence of myocardial dysfunction.

Limitations

This study has several limitations that should be mentioned. Because this study has been performed in a tertiary referral center, highly experienced in MV surgery, the results from this cohort might not

be generalizable to other centers. Similarly, recurrence of MR during follow-up was not considered, being the aim of the study to identify baseline characteristics associate with the long-term outcome after surgery. Furthermore, although relatively large, patient population was not large enough to perform robust multivariable analyses separately for the 3 MR aetiologic groups. Also, brain natriuretic peptide was not routinely measured and could therefore not be included in this analysis. Finally, further large prospective studies are needed to confirm the results and to assess how LV-GLS can tailor treatment and optimize surgical management for the different aetiologies of primary MR.

Conclusions

LV-GLS, as a sensitive marker of LV systolic dysfunction, is independently associated with long-term all-cause mortality and cardiovascular events after MV surgery for primary MR and can therefore be helpful in optimizing timing of surgery and risk stratification. Importantly, despite more complex involvement of the MV apparatus and therefore surgical operation, patients with Barlow's disease showed similar prognosis compared to patients with FED or FF.

Competency in medical knowledge

The present study confirms the independent association of LV-GLS and long-term adverse events in a large cohort of patients who underwent MV surgery for severe primary MR. In addition, it shows that MR etiology does not have a significant influence on outcome in an experienced surgical center.

Translational Outlook

Complex MV lesions should not delay surgery when patients could be operated in an experienced surgical center. Furthermore, LV-GLS could be used as a new parameter to optimize timing for surgery in these patients, but large prospective studies are needed to evaluate how this could be implemented in daily practice.

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Chapter 9

Summary, conclusions and future perspectives

Summary

In this thesis we evaluated the use of advanced echocardiographic techniques in patients with hereditary cardiac disease, focussing on patients with hypertrophic cardiomyopathy (HCM) and primary mitral regurgitation (MR). Furthermore, the familial occurrence and pathophysiology of mitral valve (MV) alterations in patients with primary MR were assessed.

The general introduction (**Chapter 1**) described the rationale and background of this thesis. The potential role of different echocardiographic measurements, including 2-dimensional speckle-tracking echocardiography, in risk stratification of patients with HCM and primary MR, is discussed. The introduction also elaborated on the pathophysiological process leading to the mitral valve (MV) abnormalities as seen in primary MR and it discussed the possible genetic component of MV prolapse.

Part I: Hypertrophic cardiomyopathy

In the first part of this thesis, the value of different echocardiographic parameters and in particular of strain measures derived from speckle-tracking echocardiography was assessed in HCM patients, particularly for risk stratification purpose.

Predicting adverse outcome in HCM patients is still challenging and the currently used risk score is mainly focused on sudden cardiac death (SCD), although other adverse events may also occur in these patients. In **Chapter 2,** different echocardiographic characteristics, including left ventricular (LV) global longitudinal strain (GLS) and left atrial volume index (LAVI) were assessed in a large cohort of 427 HCM patients. The combined endpoint of all-cause mortality, heart transplantation, SCD and appropriate implantable cardioverter defibrillator (ICD) was noted after long-term follow-up. LV GLS < -15% and LAVI > 34 ml/m^2 were independently associated with the combined endpoint and showed incremental prognostic value on top of currently used risk factors; these echocardiographic parameters may therefore be helpful in overall risk stratification of these patients.

Because risk stratification and treatment of SCD has improved significantly over the last decades, the natural course of HCM has changed and adverse outcomes are increasingly related to heart failure development, but predictors for heart failure development in HCM patients are largely unknown. In **Chapter 3** of this thesis, the association of LV GLS and LAVI with heart failure development was evaluated and its echocardiographic changes over time were assessed in a cohort of 236 patients with non-obstructive HCM. Forty patients developed heart failure during 6.5 (4.1-9.8) years of follow-up

and the multivariable analysis showed that age, New York Heart Association functional class, LV GLS and LAVI were independently associated with the development of heart failure. Moreover, LV dysfunction was a progressive phenomenon as was demonstrated by a worsening of LV GLS and increase of LAVI over time in all patients.

HCM is primarily characterized by LV hypertrophy, but also frequently involves the right ventricle (RV). Although RV dysfunction is known as a prognostic factor in several cardiovascular diseases, data on RV function in HCM patients is limited. Considering the limitation of standard echocardiographic parameters for the assessment of RV size and function, in **Chapter 4** RV function was analysed in 267 HCM patients, including RV four chamber longitudinal strain (RV4CLS) and RV free wall longitudinal strain (RVFWLS). RV dysfunction as measured by RV longitudinal strain was relatively common in HCM patients and correlated to LV dysfunction. Furthermore, an impaired RV4CLS (cut-off value -20%) or impaired RVFWLS (cut-off value -19%) was associated with a combined endpoint of all-cause mortality and heart failure development, which may indicate a more severe form of HCM.

LV GLS appears to be a promising measurement to detect LV dysfunction in HCM patients, however, it remains partially (after)load-dependent and loading condition can vary over time in the same patient and between patients. A new method has been developed to evaluate LV function, which incorporates not only LV GLS, but also the afterload based on non-invasively blood pressure measurements. In **Chapter 5** this new technique was assessed in HCM patients to evaluate global and segmental differences compared to healthy individuals and the association with adverse outcome. Global constructive work, global wasted work and global cardiac efficiency were all impaired in HCM patients compared to controls and an impaired global constructive work (<1730 mmHg%) was associated with adverse outcome. Lastly, segmental differences in myocardial work parameters were observed between different HCM phenotypes.

Part II: Primary mitral regurgitation

In the second part of this thesis, patients with primary MR were studied. Barlow's disease (BD) and fibro-elastic deficiency (FED) are the two dominant etiologies of primary MR due to MV prolapse. Although a genetic basis has been recognized for MV prolapse , familial screening is not systematically performed in current practice and whether there is a possible difference between BD and FED is unknown. The aim of **Chapter 6** was to assess the familial occurrence of MR due to MV prolapse based on self-reported family history. In a large cohort of 629 patients who underwent MV surgery because of severe primary MR due to MV prolapse, 51 patients (13%) reported a clear family history for MR. In particular, a family history positive for primary MR was reported by 26% of patients with BD, but also in 8% of patients with FED. These results suggest that familial screening should be considered in

all patients with primary MR and that patients with familial occurrence could be referred to the clinical geneticist for genetic counselling.

BD is characterized by thick and redundant MV leaflets and mitral annular abnormalities. In **Chapter 7**, MV characteristics were studied over time, by 2-dimensional echocardiography, in patients with BD who developed significant MR requiring surgery. An abnormal MV annular outward motion (curling), mitral annular disjunction and MV annular dilatation were present in an early phase of the disease, even when MR was not severe; significant leaflet alterations, such as thickening and elongation, were also co-existent but significantly progressed later on in the disease. These findings suggest that identification of mitral annular abnormalities should be part of echocardiographic assessment in patients with primary MR and their family members, even when MR is not significant. Furthermore, these findings are relevant in the choice of surgical strategy and highlight the importance of annular remodelling and stabilization.

If left untreated, severe primary MR is associated with increased morbidity and mortality, but can be treated successfully with MV surgery. However, timing of surgery remains a clinical challenge since LV ejection fraction (LVEF) and LV dimension may not be sensitive enough to detect subtle LV dysfunction; furthermore, the likelihood of good repair is dependent of the etiology of MR and the expertise of the surgeon. In **Chapter 8** an impaired LV GLS (> -20.6%) was demonstrated to be independently associated with all-cause mortality in a large cohort of patients who underwent MV surgery because of primary MR and might represent therefore a novel parameter to be taken into consideration when giving indication for surgery. Importantly, patients with BD showed similar prognosis after surgical operation as compared to patients with FED when corrected for age, despite the more complex repair.

Conclusions and future perspectives

The natural course of hereditary cardiac diseases is very heterogenous varying from a asymptomatic benign course with normal life expectancy, to the occurrence of SCD at young age or the need of heart transplant because of severe heart failure. Identifying patients at risk for adverse events is therefore crucial and advanced echocardiography can help to identify patients who should be monitored closely and benefit of early treatment.

In HCM patients, GLS has shown to be a sensitive marker for subtle myocardial dysfunction, for both LV and RV dysfunction, and is related to prognosis. How GLS can be incorporated in daily practice and used for optimizing risk stratification of these patients should be further investigated by prospective studies. As there are ongoing efforts in optimizing echocardiographic techniques, recently myocardial work has been developed and introduced as novel parameter for assessing LV myocardial performance, which takes into account not only GLS but also LV afterload. The first results of the use of myocardial work in HCM patients are promising, however, more research and experience is needed to determine its role in clinical management of HCM patients.

In primary MR, the pathophysiology leading to the MV abnormalities is not fully understood. A genetic component has been described and is further supported by the findings of this thesis, which shows that the prevalence of familial MR in patients with primary MR due to MV prolapse is relatively high and a genetic component should therefore be considered in all these patients. Furthermore, the results of this thesis support the hypothesis that mitral annular abnormalities are crucial components of this MV pathology, probably present very early in the staging of the disease and also responsible for the progressive leaflet alterations leading in a later phase to the development of severe MR. This hypothesis underlines the importance of identifying annular abnormalities, especially when assessing family members of patients with primary MR, since familial screening could represent an important tool for early diagnosis and close monitoring, to identify patients at risk for SCD and to improve timing of surgery. Prospective studies with systematic and complete family screening could determine the exact prevalence of familial MR, reveal the associated genes and provide more insight in the development of MV abnormalities over time.

Finally, when MR progresses in patients with primary MR, LV GLS can be helpful to identify patients at risk for adverse outcome and might therefore represent a new tool for optimizing timing of surgery. Prospective studies should explore how LV-GLS can tailor treatment and surgical management, considering also the different etiologies of primary MR.

Chapter 10

Samenvatting, conclusies en toekomstperspectieven

Samenvatting, conclusies en toekomstperspectieven

Samenvatting

In dit proefschrift hebben we het gebruik van geavanceerde echocardiografische technieken geëvalueerd bij patiënten met erfelijke hartziekten: hypertrofische cardiomyopathie (HCM) en primaire mitralisinsufficiëntie (MI). Daarnaast werden het familiair voorkomen en de pathofysiologie van mitralisklep afwijkingen bij patiënten met primaire MI onderzocht.

In de introductie (**Hoofdstuk 1**) werd de achtergrond van dit proefschrift beschreven. De potentiële rol van verschillende echocardiografische metingen, zoals de 2-dimensionale 'speckle-tracking' echocardiografie, bij het verbeteren van risico stratificatie bij patienten met HCM en primaire MR wordt besproken. In de introductie wordt ook verder ingegaan op de pathofysiologische processen die leiden tot mitralisklep afwijkingen zoals die gezien worden bij primaire MI en tevens werd de mogelijke genetische component van mitralisklepprolaps besproken.

Deel I: Hypertrofische cardiomyopathie

In het eerste deel van dit proefschrift werden de toegevoegde waarde van verschillende echocardiografische parameters, met name 'speckle-tracking-strain' metingen, onderzocht bij HCM patiënten, met name voor het doel van risico stratificatie.

Het voorspellen van een negatieve uitkomst bij HCM patiënten is nog steeds uitdagend en de risicoscore die momenteel gebruikt wordt, is met name gericht op plotse hartdood, terwijl ook andere negatieve uitkomsten kunnen voorkomen bij deze patiënten. In **Hoofdstuk 2** werden verschillende echocardiografische karakteristieken onderzocht in een groot cohort van 427 HCM patiënten , inclusief linker ventrikel (LV) 'global longitudinal strain' (GLS) en linker atrium volume index (LAVI). Na een lange follow-up werd gekeken naar het gecombineerde eindpunt van mortaliteit (door elke oorzaak), harttransplantation, plotse hartdood en terecht implantable cardioverter defibrillator (ICD) therapie.

LV GLS < -15% en LAVI > 34 ml/m^2 waren onafhankelijk geassocieerd met dit eindpunt en gaven een toegevoegde prognostische waarde bovenop de huidige risicofactoren; deze parameters zouden daarom kunnen helpen bij algemene risico stratificatie bij deze patiënten.

Omdat risico stratificatie en de behandeling van plotse hartdood de laatste decennia significant verbeterd is, is ook het natuurlijke beloop van HCM veranderd en zijn negatieve uitkomsten steeds

vaker gerelateerd aan het ontwikkelen van hartfalen. Voorspellers voor het ontwikkelen van hartfalen bij HCM patiënten zijn echter grotendeels niet bekend. In **Hoofdstuk 3** van dit proefschrift, werd de associatie tussen LV-GLS en LAVI en het ontwikkelen van hartfalen geëvalueerd en de echocardiografische veranderingen in de loop van de tijd werden onderzocht in een cohort van 236 patiënten met niet-obstructief HCM. Tijdens een follow-up van 6.5 (4.1-9.8) jaar, ontwikkelden 40 patiënten hartfalen en multivariate analyse liet zien dat dit geassocieerd was met leeftijd, New York Heart Association (NYHA) klasse, LV-GLS en LAVI. Bovendien was LV dysfunctie een progressief fenomeen wat werd aangetoond met een verslechtering van LV-GLS en LAVI in de loop van de tijd voor alle patiënten.

HCM wordt met name gekarakteriseerd door LV hypertrofie, maar vaak is ook de rechter ventrikel (RV) aangedaan. Hoewel RV dysfunctie bekend is als prognostische factor bij verschillende cardiovasculaire aandoeningen, is er niet veel bekend over RV dysfunctie bij HCM patiënten.

Gezien de beperkingen van standaard echocardiografische parameters voor het evalueren van RV grootte en functie, werd in **Hoofdstuk 4** de RV functie bij 267 HCM patiënten geanalyseerd middels RV 4-kamer longitudinale strain (RV4CLS) en de RV vrije wand longitudinale strain (RVFWLS). RV dysfunctie gemeten met RV longitudinale strain was relatief veel voorkomend bij HCM patiënten en gecorreleerd aan LV dysfunctie. Daarnaast waren een verminderde RV4CLS (cut-off waarde -20%) of een verminderde RVFWLS (cut-off waarde -19%) geassocieerd met het gecombineerde eindpunt van mortaliteit (door elke oorzaak) en het ontwikkelen van hartfalen, wat een indicatief is voor een ernstigere vorm van HCM.

Hoewel LV GLS een veelbelovende meting is om LV dysfunctie te detecteren bij HCM patiënten, is het gedeeltelijke afterload-afhankelijk en deze afterload kan variëren bij dezelfde patiënt op verschillende momenten. Daarom is een nieuwe methode ontwikkeld om LV functie te evalueren, waarbij niet alleen LV GLS, maar ook de afterload wordt meegenomen, welke hierbij is gebaseerd op niet-invasieve bloeddrukmetingen. In **Hoofdstuk 5** wordt deze nieuwe methode onderzocht bij HCM patiënten en werden globale en segmentale verschillen vergeleken met gezonde individuen en werd de associatie met een negatieve uitkomst onderzocht. ‘Global constructive work’, ‘global wasted work’ en ‘global cardiac efficiency’ waren allen verminderd bij HCM patiënten in vergelijken met de controle groep. Een verminderde ‘global constructive work’ (<1730mmHg%) was tevens geassocieerd met een negatieve uitkomst. Tenslotte werden segmentale verschillen in de ‘myocardial work’ parameters geobserveerd tussen de verschillende HCM fenotypes.

Deel II: Primaire mitralis insufficiëntie

In het tweede deel van dit proefschrift werden patiënten met primaire MI bestudeerd. De ziekte van Barlow en 'fibro-elastic deficiency' (FED) zijn de 2 meest voorkomende etiologieën van primaire MI ten gevolge van mitralisklepprolaps. Hoewel een genetische aanleg voor mitralisklepprolaps beschreven is, wordt er in de huidige praktijk geen systematische familiaire screening verricht, bovendien is niet bekend of er verschillen zijn tussen de ziekte van Barlow en FED wat betreft erfelijkheid. Het doel van **Hoofdstuk 6** was daarom om het familiair voorkomen van MI als gevolg van mitralisklepprolaps te onderzoeken, gebaseerd op zelf-gerapporteerde familie anamnese. In een groot cohort van 629 patiënten die in het verleden mitralisklep chirurgie hebben ondergaan vanwege ernstige MI door mitralisklepprolaps, waren 51 patiënten (13%) welke een duidelijke positieve familie anamnese hadden voor MI. In het bijzonder was de familie anamnese voor primaire MI positief bij 26% van de patiënten met de ziekte van Barlow, maar ook bij 8% van de patiënten met FED. Deze resultaten suggereren dat familiaire screening overwogen moet worden bij alle patiënten met primaire MI en dat patiënten met een familiair voorkomen van MI verwezen zouden kunnen worden naar de klinisch geneticus voor verder genetisch onderzoek.

De ziekte van Barlow wordt gekarakteriseerd door verdikte mitralisklep bladen en afwijkingen van de mitralisklep annulus. In **Hoofdstuk 7** werden deze karakteristieken bestudeerd in het verloop van de tijd middels 2-dimensionale echocardiografie, bij patiënten met de ziekte van Barlow die uiteindelijk significante MI ontwikkelden welke chirurgie behoefde. Een afwijkende beweging van de mitralisklep annulus (curling), mitralisklep annulus disjunctie en mitralisklep annulus dilatatie waren te zien in de beginfase van de aandoening, ook wanneer er nog geen significante MI was. Significante klepblad veranderingen, zoals verdikking en verlenging waren ook te zien en verergerden in het verloop van de tijd. Deze bevindingen tonen dat de identificatie van mitralisklep annulus afwijkingen standaard deel zou moeten uitmaken van echocardiografisch onderzoek bij patiënten met primaire MI en hun familieleden, ook wanneer er (nog) geen significante MI is. Bovendien zijn deze bevindingen relevant in de keuze van chirurgische strategie en benadrukken deze het belang van remodellering en stabilisatie van de annulus.

Wanneer ernstige primaire MI niet behandeld zou worden, is dit geassocieerd met een verhoogde morbiditeit en mortaliteit, maar dit kan succesvol behandeld worden met mitralisklepchirurgie.

De timing van deze chirurgie is echter een klinische uitdaging, mede omdat LV ejectiefractie (LVEF) en LV dimensie niet sensitief genoeg zijn om subtiele LV dysfunctie te detecteren; bovendien is een goede mitralisklepplastiek afhankelijk van de etiologie van MI en de expertise van de chirurg. In **Hoofdstuk 8** werd aangetoond dat een verminderde LV GLS (> -20.6%) onafhankelijk geassocieerd was met mortaliteit (door elke oorzaak) in een groot cohort van patiënten die mitralisklep chirurgie hadden

ondergaan vanwege primaire MI. Daarom zou dit een nieuwe parameter kunnen zijn waarmee rekening gehouden kan worden bij het stellen van een chirurgische indicatie. Daarnaast was de prognose na chirurgie bij patiënten met de ziekte van Barlow vergelijkbaar met FED patiënten, gecorrigeerd voor leeftijd, ondanks een complexere mitralisklepplastiek.

Conclusies en toekomstperspectieven

Het natuurlijke beloop van erfelijke hartziekten is heterogeen en loopt uiteen van een asymptomatische benigne beloop met normale levensverwachting, tot een plotse hartdood op jonge leeftijd of een harttransplantatie vanwege ernstig hartfalen. Het identificeren van patiënten met zulke negatieve uitkomsten is daarom cruciaal en geavanceerde echocardiografische technieken kunnen helpen om patiënten te identificeren die regelmatig gecontroleerd moeten worden en baat kunnen hebben bij vroegtijdige behandeling.

Bij HCM patiënten werd aangetoond dat GLS een sensitieve marker is om subtiele myocardiale dysfunctie te detecteren, zowel LV als RV dysfunctie, en is tevens gerelateerd aan prognose. Hoe GLS precies gebruikt zou moeten worden in de dagelijkse praktijk en bij het optimaliseren van risicostratificatie bij deze patiënten, moet verder onderzocht worden middels prospectieve studies.

Omdat er voortgaande pogingen zijn om echocardiografische technieken te optimaliseren, is recent 'myocardial work' ontwikkeld en geïntroduceerd als nieuwe parameter voor het evalueren van LV myocardiale prestatie, waarbij niet alleen rekening wordt gehouden met GLS maar ook met de LV afterload. De eerste resultaten van het gebruik van myocardiale work bij HCM patiënten is veelbelovend, maar er is meer onderzoek en ervaring nodig om te bepalen wat de rol zou kunnen zijn bij de behandeling van HCM patiënten.

Bij primaire MI is de pathofysiologie welke leidt tot de mitralisklep afwijkingen nog niet volledig begrepen. Er is een genetische component beschreven, wat ook ondersteund wordt door de resultaten van dit proefschrift, waarbij aangetoond werd dat de prevalentie van familiaire MI bij patiënten met primaire MI als gevolg van mitralisklep prolaps relatief hoog is en een genetische component overwogen moet worden. Daarnaast ondersteunen de resultaten van dit proefschrift de hypothese dat mitralisklep annulus afwijkingen cruciaal zijn bij deze pathologie, waarschijnlijk reeds aanwezig in een vroeg stadium van de aandoening en verantwoordelijk voor de progressieve veranderingen van de mitralisklepbladen, welke uiteindelijk leiden tot significante MI. Deze hypothese benadrukt het belang van het identificeren van annulus afwijkingen, met name wanneer familieleden van patiënten met primaire MI wordt onderzocht, omdat familiaire screening belangrijk is voor een vroege diagnose zodat patiënten die een verhoogd risico hebben op plotse hartdood geïdentificeerd

worden en de timing van chirurgie verbeterd wordt. Er zijn prospectieve studies nodig met systemische en complete familiaire screening om de exacte prevalentie van familiaire MI te bepalen, de betrokken genen te ontdekken en meer inzicht te geven in het ontwikkelen van mitralisklep afwijkingen in het verloop van de tijd. Tenslotte, wanneer er sprake is van progressie van MI, kan LV GLS helpen in het identificeren van patiënten met een verhoogd risico op negatieve uitkomsten en daarom ook een nieuwe parameter zijn voor het optimaliseren van timing van chirurgie. Prospectieve studies moeten verder inzicht geven hoe LV GLS de behandeling en chirurgie op maat kan maken, waarbij ook rekening wordt gehouden met de verschillende etiologieën.

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Curriculum Vitae

Yasmine Lisanne Hiemstra werd op 1 september 1987 geboren in Arnhem en groeide op in Bemmel. In 2005 haalde zij haar gymnasiumdiploma aan het Stedelijk Gymnasium Nijmegen. Na een seizoen als skilerares te hebben gewerkt in Oostenrijk, begon zij in 2006 met de studie Bewegingswetenschappen alvorens zij aan haar studie Geneeskunde begon in 2007 aan de Rijksuniversiteit in Groningen. Na het behalen van het artsexamen in 2014, heeft zij gewerkt als arts assistent niet in opleiding (ANIOS) cardiologie in het toenmalige Medisch Centrum Haaglanden (nu Haaglanden Medisch Centrum). In 2015 begon zij aan haar promotieonderzoek op de afdeling cardiologie van het Leids Universitair Medisch Centrum (LUMC) onder leiding van prof. dr. J.J. Bax en dr. N. Ajmone Marsan, waarvan de resultaten in dit proefschrift staan beschreven en gepresenteerd zijn op meerdere internationale congressen. Tevens was zij tijdens deze periode actief binnen de werkgroep Cardiologie & Sport van de Nederlandse Vereniging Voor Cardiologie. Per 1 januari 2019 is zij begonnen met de opleiding Sportgeneeskunde in het Onze Lieve Vrouwe Gasthuis locatie West te Amsterdam (opleider drs. S. Goedegebuure).