Advanced echocardiographic techniques in hereditary cardiac diseases

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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.

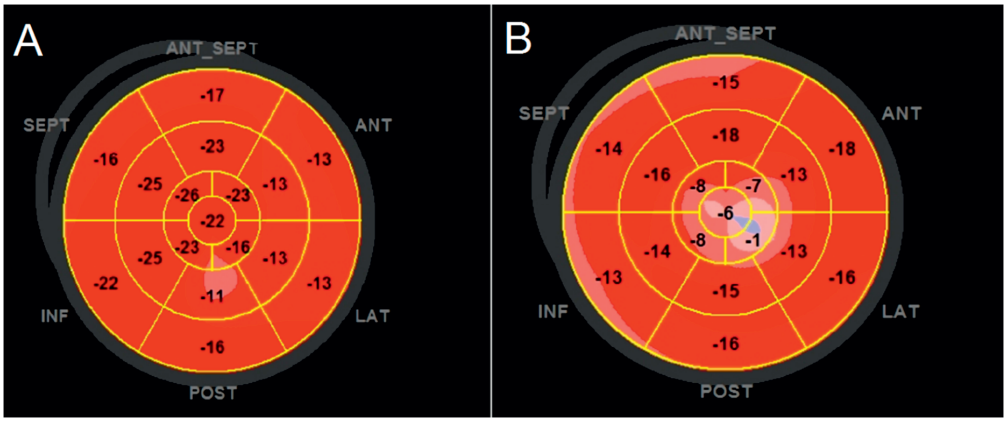

Figure 1. Example of changes in left ventricular global longitudinal strain (GLS) displayed in a bull's eye for the 17 left ventricular segments (color-coded from dark red, as preserved GLS, to pink/blue as impaired GLS). **Panel A.** Echocardiography with preserved GLS (-18.5%) in a 65-year old male 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.

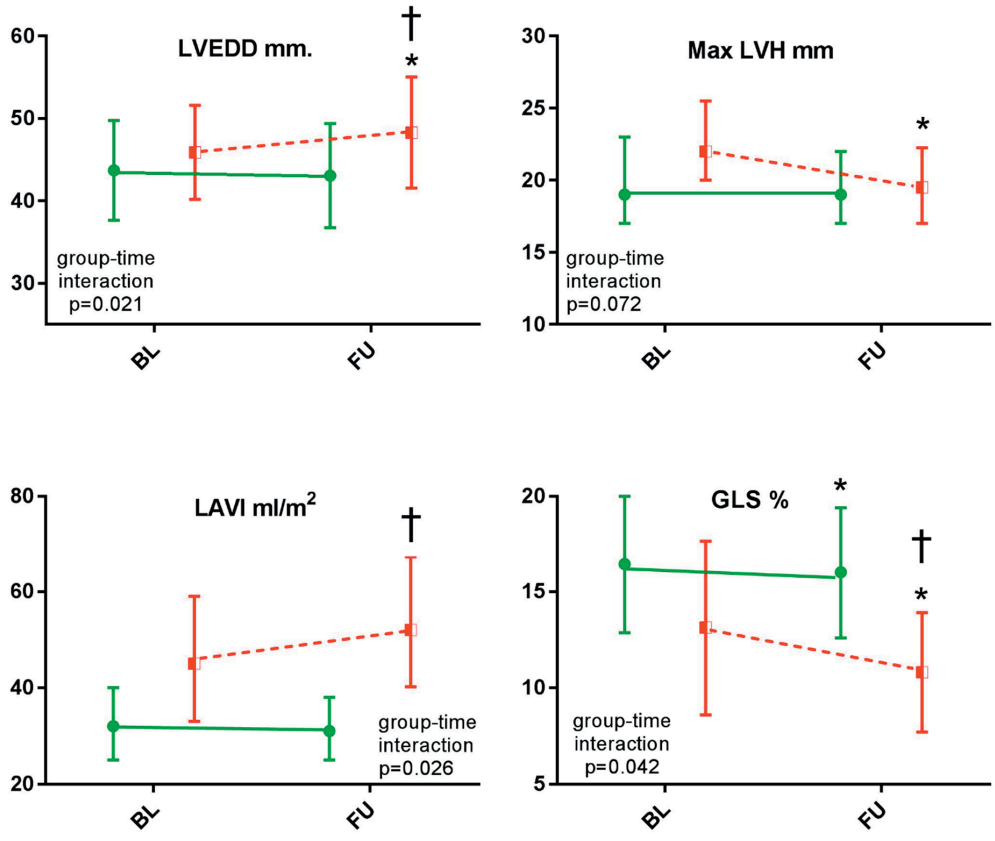

Figure 2. Linear mixed model analysis of echocardiographic changes over time, corrected for the time between the 2 echocardiographic examinations and for age and NYHA class at baseline, for patients who reached the HF endpoint (dotted line) vs. patients who did not reach the HF endpoint (solid line).
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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