Value of Speckle Tracking-Based Deformation Analysis in Screening Relatives of Patients With Asymptomatic Dilated Cardiomyopathy

JACC: CARDIOVASCULAR IMAGING VOL. 13, NO. 2, 2020

PUBLISHED BY ELSEVIER

SPECIAL ISSUE: FOCUS ON LV STRAIN FOR PREDICTING HARD OUTCOMES

ORIGINAL RESEARCH

Value of Speckle Tracking–Based Deformation Analysis in Screening Relatives of Patients With Asymptomatic Dilated Cardiomyopathy

Job A.J. Verdonschot, MD, MS,[a,b,*] Jort J. Merken, MD,[a,*] Hans-Peter Brunner-La Rocca, MD,[a] Mark R. Hazebroek, MD, PhD,[a] Casper G.M.J. Eurlings, MD,[a] Eline Thijssen, BSc,[a] Ping Wang, PhD,[b] Jerremy Weerts, BSc,[a] Vanessa van Empel, MD, PhD,[a] Georg Schummers, MSc,[c] Marcus Schreckenberg, MSc,[c] Arthur van den Wijngaard, PhD,[b] Joost Lumens, PhD,[d] Han G. Brunner, MD, PhD,[b,e] Stephane R.B. Heymans, MD, PhD,[a,f,g] Ingrid P.C. Krapels, MD, PhD,[b,†] Christian Knackstedt, MD, PhD[a,†]

ABSTRACT

OBJECTIVES This study sought to investigate the prevalence of systolic dysfunction using global longitudinal strain (GLS) and its prognostic value in relatives of dilated cardiomyopathy (DCM) patients that had normal left ventricular ejection fraction (LVEF).

BACKGROUND DCM relatives are advised to undergo cardiac assessment including echocardiography, irrespective of the genetic status of the index patient. Even though LVEF is normal, the question remains whether this indicates absence of disease or simply normal cardiac volumes. GLS may provide additional information regarding (sub)clinical cardiac abnormalities and thus allow earlier disease detection.

METHODS A total of 251 DCM relatives and 251 control subjects with a normal LVEF (≥55%) were screened. Automated software measured the GLS on echocardiographic 2-, 3-, and 4-chamber views. The cutoff value for abnormal strain was >−21.5. Median follow-up was 40 months (interquartile range: 5 to 80 months). Primary outcome was the combination of death and cardiac hospitalization.

RESULTS A total of 120 relatives and 83 control subjects showed abnormal GLS (48% vs. 33%, respectively; $p < 0.001$). Abnormal GLS was independently associated with DCM relatives and cardiovascular risk factors, rather than genetic mutations. Subjects with abnormal GLS had more frequent cardiac hospitalizations and a higher mortality as compared with subjects with normal GLS (hazard ratio: 3.29; 95% confidence interval: 1.58 to 6.87; $p = 0.001$). Additionally, follow-up LVEF was measured in a subset of relatives, and it decreased significantly in those with abnormal as compared with normal GLS ($p = 0.006$).

CONCLUSIONS Relatives of DCM patients had a significantly higher prevalence of systolic dysfunction detected by GLS despite normal LVEF compared with control subjects, independent of age, sex, comorbidities, and genotype. Abnormal GLS was associated with LVEF deterioration, cardiac hospitalization, and death. (J Am Coll Cardiol Img 2020;13:549–58)

From the [a]Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, Maastricht, the Netherlands; [b]Department of Clinical Genetics, Maastricht University Medical Center, Maastricht, the Netherlands; [c]TOMTEC Imaging Systems GmbH, Unterschleissheim, Germany; [d]Department of Biomedical Engineering, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, the Netherlands; [e]Department of Human Genetics, and Donders Center for Neuroscience, Radboudumc Nijmegen, Nijmegen, the Netherlands; [f]Department of Cardiovascular Research, University of Leuven, Leuven, Belgium; and the [g]Netherlands Heart Institute (ICIN), Utrecht, the Netherlands. *Drs. Verdonschot and Merken contributed equally to this work and are joint first authors. †Drs. Krapels

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2019.02.032

JACC: CARDIOVASCULAR IMAGING, VOL. 13, NO. 2, 2020
FEBRUARY 2020:549–58

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CI = confidence interval

DCM = dilated cardiomyopathy

GLS = global longitudinal strain

HF = heart failure

HR = hazard ratio

LVEF = left ventricular ejection fraction

"Idiopathic" dilated cardiomyopathy (DCM) is a common cause of heart failure (HF) in young adult patients and is frequently seen at the outpatient clinic (1). Adequate diagnosis is important not only for the patients but also for their family because all relatives of DCM patients are at risk of developing HF. Importantly, this risk is irrespective of the particular cause or a proven genetic mutation in the index patient as a result of familial susceptibility (2). Although often no causal genetic mutations are found in DCM families, frequent cardiac screening is advised for all first-degree relatives by the latest position papers of the American Heart Association and the European Society of Cardiology (to detect cardiac abnormalities such as left ventricular enlargement or reduced left ventricular ejection fraction (LVEF) (3–6). This constitutes a substantial proportion of patients seen by the general cardiologist, given the estimated prevalence of DCM of 1:250 to 1:500 and an average of 4 to 5 first-degree relatives in Western countries (7). Moreover, relatives are of different age categories, and cardiovascular risk factors accumulate with increasing age, thus potentially influencing cardiac function irrespective of family history.

SEE PAGE 559

Of course, ready identification and treatment of disease are warranted in this group of individuals to prevent disease progression and occurrence of adverse cardiac events (e.g., sudden cardiac death). However, subtle functional or structural changes of the myocardium are likely to be missed when using classic echocardiographic parameters such as LVEF because ventricular volumes may be preserved or subtle changes of LVEF may remain concealed as a result of measurement noise in early stages of cardiac disease (8). Global longitudinal strain (GLS) seems to be able to detect subtle changes preceding deterioration of LVEF in different HF cohorts (8). Therefore, this study evaluated the role of GLS in asymptomatic DCM relatives with normal LVEF to identify subtle cardiac abnormalities and associate those findings with distinctive clinical parameters, genotype, and prognosis. The findings are compared with those in control subjects with normal LVEF and similar age, sex, and comorbidity distribution, to be able to investigate the true family effect in DCM relatives.

METHODS

STUDY SUBJECTS. DCM relatives. This retrospective study was carried out in a group of relatives of genotyped DCM patients who were seen for genetic analysis at the Maastricht University Medical Centre in Maastricht, the Netherlands between 2009 and 2017. Initially, pedigree analysis and sequencing of a 47 cardiomyopathy-associated gene panel was performed in all index patients to determine genetic status (Supplemental Table 1). Genetic counseling, testing, and analysis were performed previously as described (9). Genetic DCM was defined as a confirmed class 4 or 5 pathogenic mutation; a list of all pathogenic mutations can be found in Supplemental Table 2.

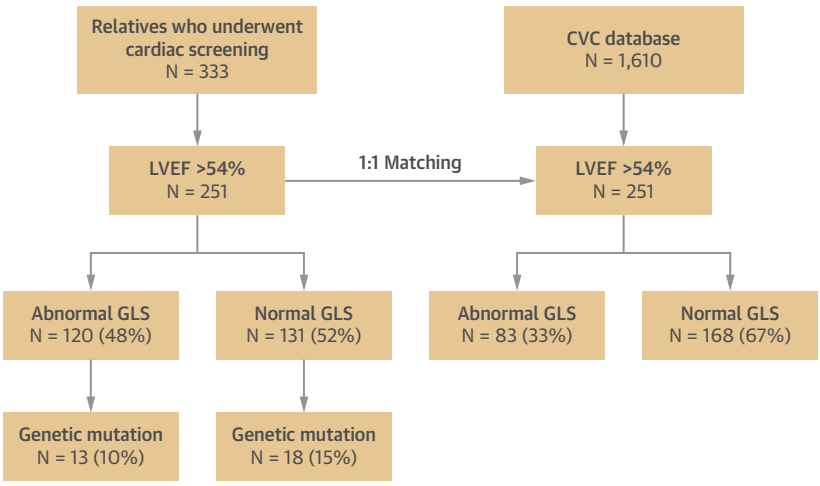
All index patients were counseled to inform their first-degree relatives about their cardiac disease and the necessity for cardiac screening regardless of genetic status. Pedigrees of 607 unrelated DCM index patients were retrospectively analyzed. In total, 333 relatives from 158 different families were seen in our hospital for cardiac screening, which consisted of medical history, physical examination, electrocardiography, and echocardiography. Only first-degree relatives with a completely normal LVEF (≥55%) were included for analysis (10) (**Figure 1**). The study was performed according to the Declaration of Helsinki and was approved by the Medical Ethics Committee of Maastricht University Medical Centre (METC 16-4-222).

Control subjects. Control subjects were selected from the Outpatient Cardiology Clinic Registry (CVC database) from the Maastricht University Medical Centre including patients referred for chest pain, dyspnea, or palpitations between April 2006 and February 2008. Cardiac screening included physical examination, electrocardiography, and echocardiography. A total of 1,610 of 2,110 patients demonstrated normal LVEF (≥55%) on echocardiography. Control patients were randomly selected from these 1,610 patients. A cohort of 251 control subjects was selected from the outpatient database with similar age, sex, and comorbidity

and Knackstedt contributed equally to this work and are joint senior authors. Dr. Eurlings has received grant support from INTERREG NWE702. Drs. Schummers and Schreckenberg are both employees at TOMTEC Imaging Systems, GmbH. Dr. Lumens has received funding from the Netherlands Organization for Scientific Research (NWO-ZonMw, VIDI grant 016.176.340). Dr. Knackstedt has received research support (software, hardware) from TOMTEC Imaging Systems. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received December 14, 2018; revised manuscript received February 23, 2019, accepted February 28, 2019.

FIGURE 1 Flowchart of Patient Selection



Echocardiograms of 333 relatives were available at our center. Eventually, 251 patients had a normal left ventricular ejection fraction (LVEF) (≥55%) and an echocardiogram, which was suitable for analysis of global longitudinal strain (GLS). These 251 relatives had no significant differences in baseline characteristics compared with a control cohort of 251 control subjects. CVC = Outpatient Cardiology Clinic Registry.

distribution (hypertension, diabetes, atrial fibrillation, coronary artery disease [CAD]).

ECHOCARDIOGRAPHIC PROTOCOL. All echocardiographic images were made during clinical routine using a Philips IE33 ultrasound system (Philips, Eindhoven, the Netherlands) obtaining standard parasternal, apical, and subcostal views according to current recommendations (10). Standard measurements were retrieved from the clinical echocardiographic database including cardiac dimensions, LVEF using Simpson's method, and presence of any relevant valve disease (11). Still, a minority of patients had only evaluation of LVEF by the Teichholz method (n = 67; 13.3%).

In addition to the existing measurements, analysis of left ventricular function with speckle tracking-based GLS was performed, applying a dedicated software package (AutoSTRAIN, TOMTEC-ARENA* 1.2, TOMTEC Imaging Systems GmbH, Unterschleissheim, Germany) with a recently published algorithm (12). Briefly, apical 2-, 3- and 4-chamber views of all patients were uploaded onto a computer. Three experienced physicians reviewed all echocardiograms for image quality and completeness (C.K., J.M., J.V.). Incomplete echocardiograms or studies of insufficient quality were not taken into consideration for analysis. The user was requested to indicate the correct loops to the software. Regional and global longitudinal peak systolic strain was calculated applying a contour detection algorithm. Furthermore, the contours suggested by the automated software were revised and corrected if deemed necessary by 4 independent investigators (C.K., J.M., J.V., J.W.). For this analysis, we used a vendor-specific cutoff value of −21.5 to define abnormal GLS, as previously described (13).

FOLLOW-UP. Minimum follow-up duration after the first outpatient visit was 1 month, and follow-up ranged up to 8 years. Total median follow-up of the whole cohort was 40 months (interquartile range: 5 to 80 months). Follow-up data on death and cardiac hospitalization were collected using medical records. The primary outcome endpoint was the combination of death and cardiac hospitalization.

In addition to baseline measurement, 69 DCM relatives (27.5%) with a normal LVEF at baseline underwent echocardiography during follow-up. LVEF deterioration was defined as an LVEF <55% with a minimal decrease of 5% at follow-up.

STATISTICAL ANALYSIS. Data are presented as frequencies, mean ± SD, or median (interquartile range). Comparisons between groups were performed using chi-square tests for categorical data and Student's *t*-test or Mann-Whitney *U* test for continuous data, as appropriate. The Kruskal-Wallis test was used to analyze and to compare continuous data among 3 groups.

Univariable and multivariable regression analysis with a generalized estimating equations (GEE) approach in a binomial model was performed to test the association between clinical parameters and

TABLE 1 Baseline Characteristics of the DCM Relatives and Control Subjects

	DCM Relatives (n = 251)	Control Subjects (n = 251)	p Value
Male	113 (45)	129 (51)	0.15
Age (yrs)	46 ± 17	46 ± 13	0.65
Body mass index (kg/m^2)	26 ± 4	26 ± 5	0.7
NYHA functional class III–IV	8 (3)	16 (6)	0.09
cLBBB	6 (2)	15 (6)	0.07
Chemotherapy	7 (3)	16 (6)	0.13
Genetic status			
Familial DCM	126 (50)	0 (0)	<0.001
Relative of index with mutation	61 (24)	0 (0)	<0.001
Familial gene mutation present	31 (12)	0 (0)	<0.001
Cardiovascular history			
Coronary artery disease	14 (6)	7 (3)	0.11
Stroke	6 (2)	2 (1)	0.17
CABG	3 (1)	0 (0)	0.12
PCI	6 (2)	5 (2)	0.74
Valvular disease	42 (17)	49 (20)	0.42
Comorbidities			
Atrial fibrillation	2 (1)	4 (2)	4 (2)
Hypertension	65 (26)	57 (23)	57 (23)
COPD	10 (4)	13 (5)	13 (5)
Hypercholesterolemia	30 (12)	44 (18)	44 (18)
Diabetes mellitus	21 (8)	15 (6)	15 (6)
Medication			
Beta-blocker	29 (12)	45 (18)	0.33
ACE inhibitor	17 (7)	19 (8)	0.73
ARB	18 (7)	24 (10)	0.84
MRA	2 (1)	1 (0)	0.59
Diuretics	17 (7)	13 (5)	13 (5)
Calcium antagonists	11 (4)	22 (9)	22 (9)
Statins	37 (15)	44 (18)	44 (18)

Values are n (%) or mean ± SD.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CABG = coronary artery bypass grafting; cLBBB = complete left bundle branch block; COPD = chronic obstructive pulmonary disease; DCM = dilated cardiomyopathy; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

abnormal GLS in the total cohort (n = 502). A GEE approach was performed with an exchangeable correlation structure to adjust for correlated observations within families because there are large families with multiple first-degree relatives included in the DCM relatives cohort. For multivariable analysis, we first included all parameters with a cutoff for entry of $p < 0.10$ in the univariable analysis. The final multivariable model was created by backward elimination with a cutoff of $p > 0.05$.

To assess which clinical variables influenced the progression of LVEF in a longitudinal fashion, univariate analysis was performed using GEE in a subset of study cohort with multiple echoes (n = 69). Univariable Cox proportional hazards regression analysis was performed to assess clinical and demographic covariates associated event-free survival. The level of significance was $p < 0.05$, and tests were 2-sided. Calculations were done using SPSS software version 23.0 (IBM Corp., Armonk, New York), and R environment version 3.5 (R Foundation, Vienna, Austria).

RESULTS

Baseline characteristics of the study and control group did not show significant differences (**Tables 1 and 2**). A total of 120 DCM relatives (48%) compared with 83 healthy control subjects (33%) had an abnormal GLS despite having a normal LVEF and volumetric parameters ($p < 0.001$) (**Figure 1**, Supplemental Table 3).

GENETIC STATUS OF DCM RELATIVES. A total of 41 (26%) of the 158 index DCM patients, used for the selection of DCM relatives, had a genetic mutation, with predominantly *TTN* and *LMNA* mutations (Supplemental Table 2). In total, 92 (28%) of the 333 relatives who underwent cardiac screening were related to these 41 DCM index patients with a genetic mutation (Supplemental Figure 1). Thus, the majority of the DCM relatives who underwent cardiac screening were related to DCM index patients without a proven genetic mutation, reflecting typical daily practice. DCM relatives with an LVEF <55% at baseline were excluded, showing no significant difference in patient selection between DCM relatives related to mutation-positive as compared with mutation-negative DCM index patients (30% vs. 21%; $p = 0.07$) (Supplemental Figure 1). In total, 44 DCM relatives of mutation-positive DCM index patients underwent genetic testing: 32 carriers and 12 without the familial mutation (Supplemental Table 2).

GLS DIFFERENCE BETWEEN DCM RELATIVES AND CONTROL SUBJECTS. The absolute GLS value in DCM relatives was worse compared with the control group (−21.6 [interquartile range (IQR): 19 to 24] vs. −23.1 [IQR: 21 to 26], respectively; $p < 0.001$) (**Figure 2A, Table 2**). Importantly, DCM relatives with a genetic mutation had a significant worse absolute GLS value as compared with relatives without a genetic mutation and control subjects (−20.1 [IQR: 18 to 23] vs. −21.7 [IQR: 20 to 24] vs. −23.1 [IQR: 21 to 26], respectively; Kruskal-Wallis $p < 0.001$) (**Figure 2B**).

CLINICAL PARAMETERS INFLUENCING GLS. All clinical factors associated with abnormal GLS in univariable analysis are depicted in **Table 3**. Importantly, in the multivariable regression analysis with GEE approach, male sex, increased age, chemotherapy, CAD, chronic obstructive pulmonary disease, and status as a DCM relative remained independent factors associated with abnormal GLS (**Table 3**). Interestingly, a DCM relative had a 2-fold increased risk of

an abnormal GLS compared with the nonrelated control subjects after correcting for sex, age, and comorbidities (odds ratio: 2.25; 95% confidence interval: 1.51 to 3.35; p < 0.001) (**Central Illustration**).

ABNORMAL GLS IS ASSOCIATED WITH LVEF DETERIORATION IN DCM RELATIVES. Follow-up echocardiograms were available in 69 DCM relatives (26 normal GLS; 43 abnormal GLS) (Supplemental Table 4). Relatives with a follow-up echo were more often related to an index patient with a genetic mutation or were carrier of a genetic mutation themselves. Moreover, CAD and valvular disease were more prevalent in these relatives with a follow-up echo (Supplemental Tables 5 and 6).

There was a median time span of 36 months (interquartile range: 24 to 63 months) between baseline and follow-up echocardiograms that did not differ between the 2 groups (DCM relatives with normal GLS vs. abnormal GLS) (p = 0.99). Patients with an abnormal GLS showed a significant decrease in LVEF over time (60 ± 0.6% to 56 ± 1.1%; p = 0.006) in contrast to patients with a normal GLS at baseline (61 ± 0.7% to 60 ± 0.9%; p = 0.22) (**Figure 3A**). Moreover, relatives with an abnormal GLS more frequently had an abnormal LVEF (<55%) at follow-up compared with relatives with a normal GLS (17 [40%] vs. 3 [12%]; p = 0.013, respectively) (**Figure 3B**). An abnormal GLS at baseline was associated with an LVEF decrease over time using GEE analysis (−2.71%; 95% confidence interval [CI]: −4.4 to −1.03; p = 0.002) (**Table 4**).

DETRIMENTAL LONG-TERM PROGNOSIS IN DCM RELATIVES WITH AN ABNORMAL GLS AT BASELINE. An abnormal GLS at baseline resulted in a worse event-free survival as compared with subjects with a normal GLS in DCM relatives (hazard ratio [HR]: 3.37; 95% CI: 1.11 to 10.2; p = 0.03) (**Table 5**). In addition to an abnormal GLS, age, hypercholesterolemia, CAD, hypertension, New York Heart Association functional class III or IV, and chemotherapy in the previous history were all associated with a worse event-free survival in DCM relatives.

Abnormal GLS was also associated with worse outcome in the whole study group (n = 502) including DCM relatives and control subjects (HR: 3.29; 95% CI: 1.58 to 6.87; log rank p = 0.001) (**Table 5, Figure 4**), even after correcting for age (HR: 2.51; 95% CI: 1.18 to 5.33; p = 0.017). In total, 17 (8%) subjects with an abnormal baseline GLS were hospitalized for cardiac reasons, significantly more frequently compared with 8 (3%) cardiac hospitalizations among subjects with a normal GLS at baseline (HR: 2.84; 95% CI: 1.2 to 6.6; p = 0.015) (Supplemental Table 7). During follow-up, a total of 11 cardiovascular deaths occurred, 9 in the subjects with an abnormal GLS (HR: 5.6; 95% CI: 1.2 to 26.2; p = 0.027). There were no significant differences in events between the control subjects and DCM relatives (Supplemental Table 8).

TABLE 2 Echocardiographic Baseline Parameters of the DCM Relatives and Control Subjects

	DCM Relatives (n = 251)	Control Subjects (n = 251)	p Value
Systolic function			
LVEF (%)	61 ± 3.8	61 ± 3.9	0.23
LVEDD (mm)	49 ± 4.9	49 ± 4.7	0.15
LVESD (mm)	33 ± 3.6	33 ± 3.7	0.06
IVS (mm)	8 ± 1.8	8 ± 1.2	0.36
PWT (mm)	8 ± 1.3	8 ± 1.1	0.10
LA volume index (ml/m^2)	33 ± 10.6	31 ± 8.5	0.49
GLS (%)	−21.6 (−19 to −24)	−23.1 (−21 to −26)	<0.001
Abnormal GLS	120 (48)	83 (33)	0.001
Diastolic function			
E/A ratio	1.2 ± 0.4	1.3 ± 0.4	0.07
TI velocity (cm/s)	2.2 ± 0.3	2.3 ± 0.4	0.10

Values are mean ± SD, median (interquartile range), or n (%).

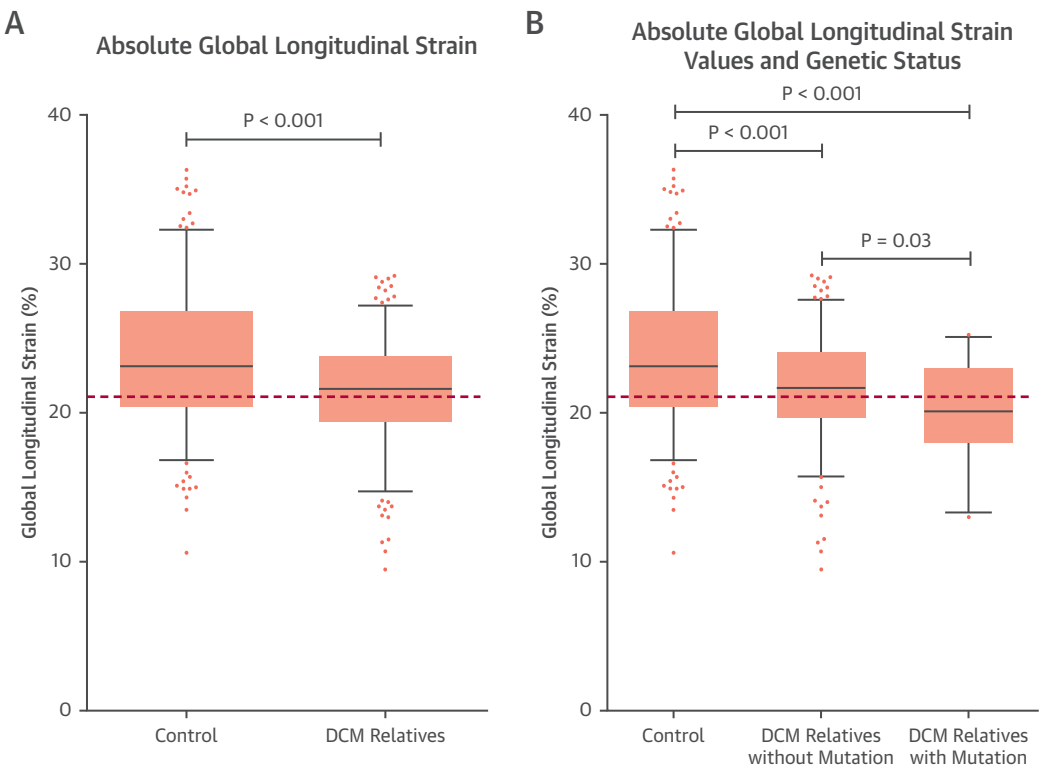
DCM = dilated cardiomyopathy; GLS = global longitudinal strain; IVS = interventricular septum; LA = left atrium; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; PWT = posterior wall; TI = time integral.

DISCUSSION

This is the largest study investigating the use of GLS to detect early disease stage in relatives of DCM patients with a normal LVEF in comparison with individuals without a familial background of DCM. Our most important findings are as follows: 1) abnormal GLS is more common in DCM relatives as compared with control subjects; 2) abnormal GLS is mainly influenced by classic cardiovascular risk factors and family history of DCM instead of a proven genetic mutation; and 3) abnormal GLS is a predictor of LVEF deterioration, cardiac hospitalization, and death. Overall, abnormal GLS seems to reflect systolic dysfunction despite normal LVEF and could be of additional value for the physician in advising DCM relatives regarding cardiac screening frequency.

CLINICAL AND GENETIC FACTORS INFLUENCING GLS IN DCM RELATIVES. Common cardiovascular risk factors such as CAD influence the myocardial tissue, subsequently reflected by an abnormal GLS (14,15). This observation is in line with our data, showing an independent association of sex, age, and CAD with abnormal GLS. The Norwegian HUNT (Nord-Trøndelag Health Study) showed a similar influence of sex and age on the GLS values in a healthy group of 1,266 individuals (14). In general, abnormal GLS is

FIGURE 2 Absolute GLS Values in Control Subjects and DCM Relatives



(A) Control subjects have lower absolute global longitudinal strain (GLS) compared with dilated cardiomyopathy (DCM) relatives **(B)** with or without a genetic mutation. **Boxes** represent the median and interquartile range, **whiskers** are 5% to 95% range, and **dots** represent the outliers. The **dashed red line** is the used global longitudinal strain cutoff value of −21.5. The p values indicate results of Mann-Whitney *U* tests and the Kruskal-Wallis test for comparing global longitudinal strain among all 3 groups: $p < 0.001$.

more common in men with increasing age. A novel addition of the present study is the comparison between DCM relatives and control subjects showing the influence of being related to a DCM patient in addition to clinical factors. This indicates a certain genetic susceptibility in DCM relatives, which is likely to be more complex than the current monogenetic dogma.

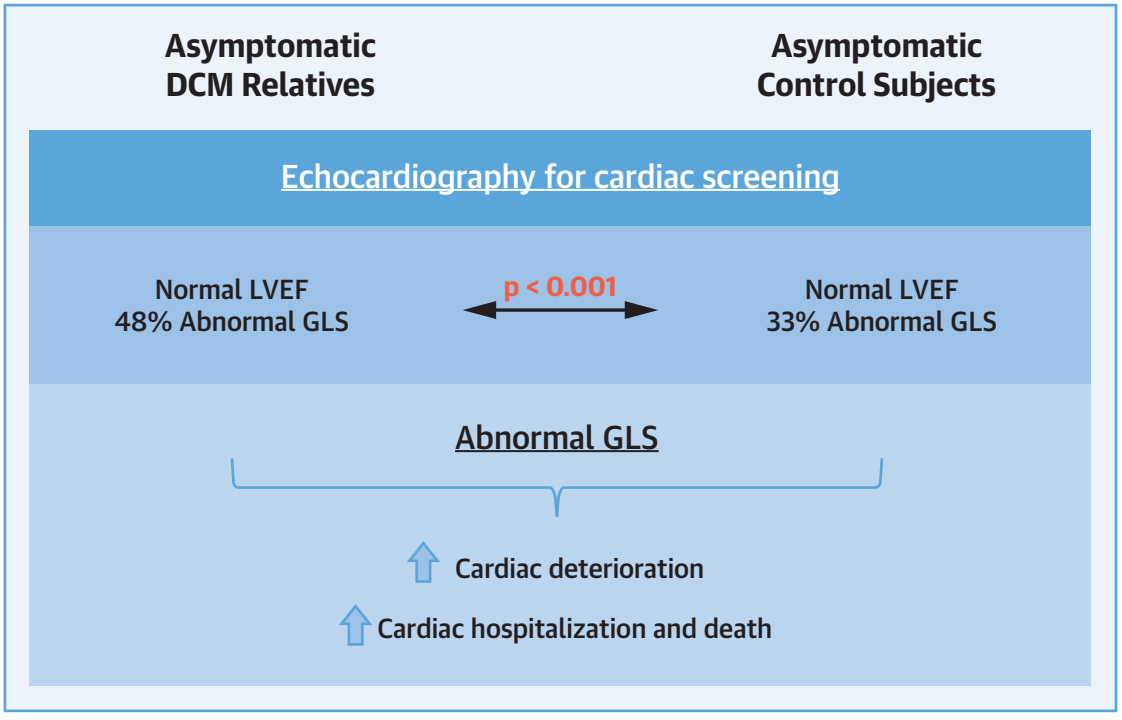
TABLE 3 Significant Abnormal GLS Associated Baseline Variables at Univariable and Multivariable Regression Analysis With GEE Approach in the Whole Cohort (n = 502)

	Univariable Analysis			Multivariable Analysis		
	OR	95% CI	p Value	OR	95% CI	p Value
DCM relative	1.86	1.31–2.67	<0.001	2.25	1.51–3.35	<0.001
Female	0.44	0.30–0.63	<0.001	0.39	0.26–0.58	<0.001
Age (yrs)	1.04	1.02–1.05	<0.001	1.03	1.02–1.05	<0.001
Body mass index (kg/m^2)	1.07	1.03–1.12	<0.001	–	–	–
Hypertension	2.89	1.91–4.37	<0.001	–	–	–
Coronary artery disease	6.72	2.40–18.78	<0.001	3.47	1.33–9.05	0.011
COPD	2.92	1.21–7.02	0.02	3.40	1.38–8.38	0.008
Hypercholesterolemia	1.95	1.20–3.17	0.007	–	–	–
Diabetes mellitus	3.66	1.81–7.37	<0.001	–	–	–
Chemotherapy	2.94	1.26–6.87	0.013	2.88	1.10–7.55	0.032

CI = confidence interval; GEE = generalized estimating equations; OR = odds ratio; other abbreviations as in Tables 1 and 2.

We found 31 DCM relatives with a genetic mutation but no strong correlation with GLS after multivariable correction, although DCM relatives with a genetic mutation had a significantly worse absolute GLS value. A decrease in absolute GLS was previously shown in a cohort of relatives with sarcomeric mutations (*MYH7, TPM1,* and *TNNT2*), a finding indicating early subtle abnormalities in myocardial function in gene mutation carriers (16). Similar results have been recently shown in mutation-positive DCM relatives (17). However, those previous studies mainly focused on DCM relatives with a proven genetic mutation. Given that only ~20% to 25% of DCM patients have a proven genetic mutation after extensive genetic screening, these relatives constitute only a minority of the subjects referred for cardiac screening (18). Therefore, our study mirrors

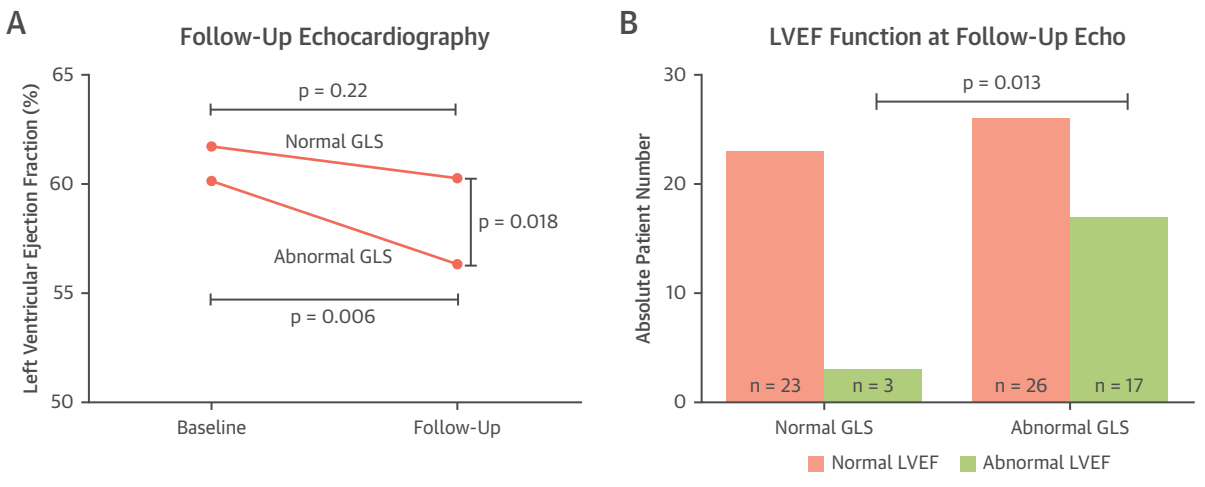
CENTRAL ILLUSTRATION **Global Longitudinal Strain Analysis in the Screening of Asymptomatic Relatives With Dilated Cardiomyopathy**



Verdonschot, J.A.J. et al. J Am Coll Cardiol Img. 2020;13(2):549-58.

First-degree relatives of patients with dilated cardiomyopathy (DCM) are frequently seen at the outpatient clinic for cardiac screening. The left ventricular ejection fraction (LVEF) is often normal; however, dilated cardiomyopathy relatives have a higher chance of abnormal global longitudinal strain (GLS). An abnormal global longitudinal strain is associated with an increased risk of left ventricular ejection fraction deterioration, cardiac hospitalization, and death.

FIGURE 3 **LVEF at Follow-Up Echocardiography in Relation to Baseline GLS in DCM Relatives (N = 69)**



(A) Relatives with an abnormal global longitudinal strain (GLS) at baseline have a significantly lower left ventricular ejection fraction (LVEF) at follow-up compared with relatives with a normal global longitudinal strain at baseline. **(B)** In addition, more patients have an abnormal left ventricular ejection fraction (<55%) at follow-up in the group with abnormal global longitudinal strain at baseline. DCM = dilated cardiomyopathy; echo = echocardiogram.

TABLE 4 Association Between Baseline Parameters and LVEF in Univariate Models for the Subset of DCM Relatives With Follow-Up Echocardiograms in GEE Models (N = 69)

	Univariable Analysis		
Baseline Variables	**β**	**95% CI**	**p Value**
Abnormal GLS	−2.71	−4.4 to −1.03	0.002
Coronary artery disease	−4.54	−7.12 to −1.95	<0.001
Diabetes mellitus	−5.17	−7.81 to −2.53	<0.001

The β reflects the change in % LVEF.
Abbreviations as in Tables 1 to 3.

clinical practice and adds significant insight into the potential clinical relevance of abnormal GLS in subjects referred for cardiac screening (i.e., DCM relatives with normal LVEF, irrespective of proven genetic mutations), and it highlights the need for cardiac screening in all first-degree DCM relatives. This is further exemplified by another small study showing reduced absolute GLS values in a cohort of first-degree DCM relatives when compared with control subjects (19).

PROGNOSTIC VALUE OF GLS. Our study indicates that abnormal GLS seems to be a predictor of LVEF deterioration, cardiac hospitalization, and death in DCM relatives. GLS as a predictor of LVEF deterioration in DCM relatives builds on knowledge of other forms of HF. An abnormal GLS is the most important marker for LVEF deterioration in patients with HF and a recovered LVEF, whereas a normal GLS predicted stable LVEF during follow-up (20). In addition, an abnormal GLS is a strong predictor of LVEF deterioration in patients receiving cardiotoxic chemotherapy (21). Our study adds another important group in which GLS may be an appropriate tool for early disease detection (22).

TABLE 5 Significant Baseline Parameters Associated With Long-Term Outcome at Follow-Up Using Univariable Cox Regression Analysis in DCM Relatives and Control Subjects

	Long-Term Outcome					
	DCM Relatives (n = 251)			Total Cohort (n = 502)		
	HR	**95% CI**	**p Value**	**HR**	**95% CI**	**p Value**
Abnormal GLS	3.37	1.11–10.2	0.03	3.29	1.58–6.87	0.001
Age (yrs)	1.07	1.03–1.11	<0.001	1.05	1.02–1.07	<0.001
Hypercholesterolemia	3.36	1.26–8.99	0.02	–	–	–
Coronary artery disease	10.54	4.06–27.3	<0.001	5.83	2.64–12.8	<0.001
Diabetes mellitus	–	–	–	2.62	1.14–6.01	0.02
Hypertension	5.08	1.91–13.5	0.001	2.62	1.35–5.09	0.004
NYHA functional class III to IV	6.05	1.68–21.79	0.006	2.95	1.14–7.61	0.03
Chemotherapy	5.75	1.59–20.8	0.008	3.48	1.43–8.46	0.006

HR = hazard ratio; other abbreviations as in Tables 1 to 3.

To date, studies using the prognostic value of GLS in DCM relatives are lacking. We found that abnormal GLS is associated with a higher risk for cardiac hospitalization and death at follow-up both in this group and in control subjects with normal LVEF. The latter is in line with previous findings. Thus, a Norwegian population-based study with healthy subjects without cardiovascular disease or diabetes showed an independent prognostic value of GLS on long-term risk of cardiovascular morbidity and mortality, with a median follow-up of 11 years (23). Furthermore, there is strong evidence of the prognostic value of GLS, which appears to have prognostic value superior to that of LVEF in predicting death and HF hospitalization in patients with different forms of HF (24–26). Prognostic data on GLS specifically in DCM patients are mainly available from cardiac magnetic resonance–derived feature tracking GLS, which appears to be an independent predictor of mortality (27,28). Data on echocardiographically derived GLS prognostic value in DCM are scarce, with only 1 study showing GLS to be a predictor of ventricular arrhythmias (29). Our study also shows the prognostic value of abnormal GLS in otherwise healthy relatives of DCM patients with normal LVEF.

POTENTIAL CLINICAL IMPLICATIONS. Identifying and treating DCM relatives, who are at risk of developing DCM, at an early stage could minimize the risk of cardiac deterioration, hospitalization, and death (30). Current guidelines stratify patients into having definite, probable, or possible disease according to their genetic and clinical status (18). However, the genetic status is not always known, and echocardiographic screening results are often normal using classic parameters. When genetic information is not available, the current European Society of Cardiology position statement advises systematic cardiac screening every 2 to 5 years until the age of 60 to 65 years in first-degree relatives of DCM patients (4). The American Heart Association guidelines are less stringent: the treating physician can decide to perform periodic echocardiographic screening (6). When an asymptomatic relative carries a pathogenic mutation, repeated cardiac evaluation should be performed every 1 to 3 years according to the European Society of Cardiology guidelines and every 3 to 5 years according to the American Heart Association guidelines (6). As reflected by this lack of consensus between the European and American guidelines, the level of evidence regarding echocardiographic screening of DCM relatives and determining their subsequent follow-up periods is low. On the basis of our findings, classic echocardiographic measurements could be enriched

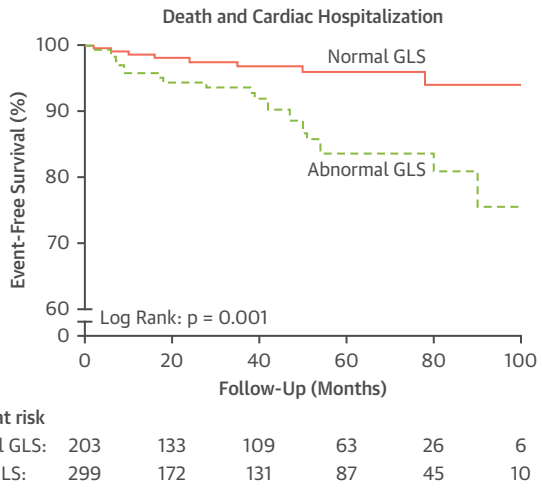
by determination of GLS in all DCM relatives. Furthermore, cardiac follow-up could be extended, with a longer interval when GLS is normal. Although there is accumulating evidence for GLS as a marker of subtle early disease, clinical decision making on the basis of GLS should be further determined in a prospective manner to evaluate its usefulness in predicting cardiac deterioration or onset of disease. When investigating the clinical value of GLS, it also needs to be considered whether starting medical treatment early (i.e., angiotensin-converting enzyme inhibitors) in these relatives with abnormal GLS may improve outcome.

STUDY LIMITATIONS. This study represents a single-center, retrospective data analysis. A prospective multicenter study will be needed to investigate whether clinical decision making on the basis of GLS is safe and more cost-effective compared with the current recommendations. We were unable to include all relatives from all families because of the voluntary character of the screening. In addition, indications for follow-up echocardiography depended on clinical background, current guidelines, and treating cardiologist; therefore, a certain selection bias cannot be excluded. This indicates that many relatives of DCM patients do not undergo cardiac screening, for many reasons. Given the relatively low event rate and available follow-up echocardiograms, the current study had insufficient power to perform multivariable modeling to test for independent predictors of LVEF deterioration and long-term outcome. Therefore, these results should be interpreted with caution. The number of asymptomatic unique mutation carriers was relatively low in our study, thus leading to a genetically heterogeneous group. Moreover, a 47-gene panel was used to screen for genetic mutation in the DCM index patients. However, we cannot exclude the contribution of other genes to the phenotype in the index patients and the carrier status in their relatives.

CONCLUSIONS

Relatives of DCM patients have a higher chance of systolic dysfunction reflected by an abnormal GLS, independent of age, sex, comorbidities, and genotype. An abnormal GLS is associated with LVEF deterioration, cardiac hospitalization, and death in asymptomatic DCM relatives with normal LVEF. GLS seems to be a promising tool for cardiac screening of relatives and could be used to identify patients at risk for adverse events who will benefit most from regular follow-up and treatment.

FIGURE 4 Baseline GLS Value and Long-Term Outcome in the Whole Cohort (N = 502)



Subjects with an abnormal global longitudinal strain (GLS) at baseline have an increased risk for cardiac hospitalization and death.

ADDRESS FOR CORRESPONDENCE: Dr. Christian Knackstedt, Department of Cardiology, Maastricht Universitair Medisch Centrum+, P.O. Box 5800, 6202 AZ Maastricht, the Netherlands. E-mail: c.knackstedt@mumc.nl.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Asymptomatic first-degree relatives of DCM patients have a higher chance of systolic dysfunction compared with nonrelated asymptomatic individuals. This is shown by an increased prevalence of abnormal GLS in DCM relatives, a subtle marker for systolic dysfunction predicting worse outcome.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Evaluation of GLS in asymptomatic patients may have prognostic implications even when cardiac volumes are normal. Therefore, GLS should be obtained in addition to echocardiographic volumes.

TRANSLATIONAL OUTLOOK: The inclusion of GLS analysis in the screening of DCM relatives should be validated in larger cohorts to better illustrate the definite role and the cost-effectiveness of GLS in clinical decision making. Those approaches should be compared with the current guidelines for screening of DCM relatives.

REFERENCES

1. Japp AG, Gulati A, Cook SA, Cowie MR, Prasad SK. The diagnosis and evaluation of dilated cardiomyopathy. J Am Coll Cardiol 2016;67:2996–3010.

2. Lee DS, Pencina MJ, Benjamin EJ, et al. Association of parental heart failure with risk of heart failure in offspring. N Engl J Med 2006;355:138–47.

3. Mahon NG, Murphy RT, MacRae CA, Caforio AL, Elliott PM, McKenna WJ. Echocardiographic evaluation in asymptomatic relatives of patients with dilated cardiomyopathy reveals preclinical disease. Ann Intern Med 2005;143:108–15.

4. Charron P, Arad M, Arbustini E, et al. Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2010;31:2715–26.

5. Fatkin D, Yeoh T, Hayward CS, et al. Evaluation of left ventricular enlargement as a marker of early disease in familial dilated cardiomyopathy. Circ Cardiovasc Genet 2011;4:342–8.

6. Bozkurt B, Colvin M, Cook J, et al. Current diagnostic and treatment strategies for specific dilated cardiomyopathies: a scientific statement from the American Heart Association. Circulation 2016;134:e579–646.

7. Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. Nat Rev Cardiol 2013;10:531–47.

8. Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. J Am Coll Cardiol Img 2018;11:260–74.

9. Verdonschot JAJ, Hazebroek MR, Derks KWJ, et al. Titin cardiomyopathy leads to altered mitochondrial energetics, increased fibrosis and long-term life-threatening arrhythmias. Eur Heart J 2018;39:864–73.

10. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.e14.

11. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277–314.

12. Knackstedt C, Bekkers SC, Schummers G, et al. Fully automated versus standard tracking of left ventricular ejection fraction and longitudinal strain: the FAST-EFs multicenter study. J Am Coll Cardiol 2015;66:1456–66.

13. Merken J, Brunner-La Rocca HP, Weerts J, et al. heart failure with recovered ejection fraction. J Am Coll Cardiol 2018;72:1557–8.

14. Dalen H, Thorstensen A, Aase SA, et al. Segmental and global longitudinal strain and strain rate based on echocardiography of 1266 healthy individuals: the HUNT study in Norway. Eur J Echocardiogr 2010;11:176–83.

15. Ng AC, Delgado V, Bertini M, et al. Myocardial steatosis and biventricular strain and strain rate imaging in patients with type 2 diabetes mellitus. Circulation 2010;122:2538–44.

16. Lakdawala NK, Thune JJ, Colan SD, et al. Subtle abnormalities in contractile function are an early manifestation of sarcomere mutations in dilated cardiomyopathy. Circ Cardiovasc Genet 2012;5:503–10.

17. van der Bijl P, Bootsma M, Hiemstra YL, Ajmone Marsan N, Bax JJ, Delgado V. Left ventricular 2D speckle tracking echocardiography for detection of systolic dysfunction in genetic, dilated cardiomyopathies. Eur Heart J Cardiovasc Imaging 2019;20:694–9.

18. Pinto YM, Elliott PM, Arbustini E, et al. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: a position statement of the ESC working group on myocardial and pericardial diseases. Eur Heart J 2016;37:1850–8.

19. Sefa Okten M, Tuluce K, Yakar Tuluce S, et al. Screening first-degree relatives of patients with idiopathic dilated cardiomyopathy. Herz 2017;42:669–76.

20. Adamo L, Perry A, Novak E, Makan M, Lindman BR, Mann DL. Abnormal global longitudinal strain predicts future deterioration of left ventricular function in heart failure patients with a recovered left ventricular ejection fraction. Circ Heart Fail 2017;10:e003788.

21. Charbonnel C, Convers-Domart R, Rigaudeau S, et al. Assessment of global longitudinal strain at low-dose anthracycline-based chemotherapy, for the prediction of subsequent cardiotoxicity. Eur Heart J Cardiovasc Imaging 2017;18:392–401.

22. Smiseth OA, Torp H, Opdahl A, Haugaa KH, Urheim S. Myocardial strain imaging: how useful is it in clinical decision making? Eur Heart J 2016;37:1196–207.

23. Biering-Sorensen T, Biering-Sorensen SR, Olsen FJ, et al. Global longitudinal strain by echocardiography predicts long-term risk of cardiovascular morbidity and mortality in a low-risk general population: the Copenhagen City Heart Study. Circ Cardiovasc Imaging 2017;10.

24. Kalam K, Otahal P, Marwick TH. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. Heart 2014;100:1673–80.

25. Sengelov M, Jorgensen PG, Jensen JS, et al. Global longitudinal strain is a superior predictor of all-cause mortality in heart failure with reduced ejection fraction. J Am Coll Cardiol Img 2015;8:1351–9.

26. Mignot A, Donal E, Zaroui A, et al. Global longitudinal strain as a major predictor of cardiac events in patients with depressed left ventricular function: a multicenter study. J Am Soc Echocardiogr 2010;23:1019–24.

27. Romano S, Judd RM, Kim RJ, et al. Feature-tracking global longitudinal strain predicts death in a multicenter population of patients with ischemic and nonischemic dilated cardiomyopathy incremental to ejection fraction and late gadolinium enhancement. J Am Coll Cardiol Img 2018;11:1419–29.

28. Buss SJ, Breuninger K, Lehrke S, et al. Assessment of myocardial deformation with cardiac magnetic resonance strain imaging improves risk stratification in patients with dilated cardiomyopathy. Eur Heart J Cardiovasc Imaging 2015;16:307–15.

29. Haugaa KH, Goebel B, Dahlslett T, et al. Risk assessment of ventricular arrhythmias in patients with nonischemic dilated cardiomyopathy by strain echocardiography. J Am Soc Echocardiogr 2012;25:667–73.

30. Pankuweit S. Lamin A/C mutations in patients with dilated cardiomyopathy. Eur Heart J 2018;39:861–3.

KEY WORDS dilated cardiomyopathy, genetics, global longitudinal strain, prognosis, relatives, screening

APPENDIX For a supplemental figure and tables, please see the online version of this paper.