European Heart Journal – Cardiovascular Imaging (2015) **16**, 307–315
doi:10.1093/ehjci/jeu181

Assessment of myocardial deformation with cardiac magnetic resonance strain imaging improves risk stratification in patients with dilated cardiomyopathy

Sebastian J. Buss[1], Kristin Breuninger[1], Stephanie Lehrke[2], Andreas Voss[3], Christian Galuschky[4], Dirk Lossnitzer[1], Florian Andre[1], Philipp Ehlermann[1], Jennifer Franke[1], Tobias Taeger[1], Lutz Frankenstein[1], Henning Steen[1], Benjamin Meder[1], Evangelos Giannitsis[1], Hugo A. Katus[1], and Grigorios Korosoglou[1]*

[1]Department of Cardiology, Angiology and Pneumology, University of Heidelberg, INF 410, Heidelberg 69120, Germany; [2]Department of Radiology, Ev.-Luth. Diakonissenanstalt, Knuthstraße 1, Flensburg 24939, Germany; [3]Department of Psychology, University of Heidelberg, Hauptstrasse 47-51, Heidelberg 69117, Germany; and [4]TomTec Imaging Systems GmbH, Munich, Germany

Received 24 April 2014; accepted after revision 18 August 2014; online publish-ahead-of-print 6 November 2014

Aims To investigate the prognostic impact of left-ventricular (LV) cardiac magnetic resonance (CMR) deformation imaging in patients with non-ischaemic dilated cardiomyopathy (DCM) compared with late-gadolinium enhancement (LGE) quantification and LV ejection fraction (EF).

Methods and results A total of 210 subjects with DCM were examined prospectively with standard CMR including measurement of LGE for quantification of myocardial fibrosis and feature tracking strain imaging for assessment of LV deformation. The predefined primary endpoint, a combination of cardiac death, heart transplantation, and aborted sudden cardiac death, occurred in 26 subjects during the median follow-up period of 5.3 years. LV radial, circumferential, and longitudinal strains were significantly associated with outcome. Using separate multivariate analysis models, global longitudinal strain (average of peak negative strain values) and mean longitudinal strain (negative peak of the mean curve of all segments) were independent prognostic parameters surpassing the value of global and mean LV radial and circumferential strain, as well as NT-proBNP, EF, and LGE mass. A global longitudinal strain greater than −12.5% predicted outcome even in patients with EF < 35% ($P < 0.01$) and in those with presence of LGE ($P < 0.001$). Mean longitudinal strain was further investigated using a clinical model with predefined cut-offs (EF < 35%, presence of LGE, NYHA class, mean longitudinal strain greater than −10%). Mean longitudinal strain exhibited an independent prognostic value surpassing that provided by NYHA, EF, and LGE (HR = 5.4, $P < 0.01$).

Conclusion LV longitudinal strain assessed with CMR is an independent predictor of survival in DCM and offers incremental information for risk stratification beyond clinical parameters, biomarker, and standard CMR.

Keywords Dilated cardiomyopathy • Cardiac magnetic resonance • Prognosis • Biomarker • Left ventricular function • Two-dimensional strain imaging

Introduction

Non-ischaemic dilated cardiomyopathy (DCM) is a heart muscle disease which significantly contributes to cardiovascular morbidity and mortality in developed countries with a reported 10-year mortality of over 40%.[1,2] Clinical courses vary and are often strongly heterogeneous, ranging from asymptomatic patients to those suffering from intractable heart failure or sudden cardiac death due to arrhythmias. Classical risk factors associated with an adverse outcome include age and male gender, NYHA class, impaired left-ventricular ejection fraction (EF), and cardiac biomarkers.[2–4]

* Corresponding author. Tel: +49 6221/56 8611; fax: +49 6221/56 5515, Email: gkorosoglou@hotmail.com

Cardiac magnetic resonance imaging (CMR) has emerged as an accurate method for the evaluation of left-ventricular (LV) function[5] due to its excellent intrinsic blood-to-tissue contrast and high reproducibility. Furthermore, assessment of late-gadolinium enhancement (LGE) allows diagnostic classification, prediction of therapy response, and risk stratification in patients with DCM.[6–10] Myocardial deformation assessment was shown to provide additional incremental prognostic value in heart failure patients.[11–13] In this regard, feature tracking imaging (FTI) originally developed for the detailed echocardiographic evaluation of myocardial deformation has recently been proved as a reliable method for determining LV strain with CMR.[14,15] Hereby, FTI can be applied to standard CMR cine sequences and therefore obviates the need for dedicated, technically complex pulse sequences and associated post-processing software tools for the quantification of myocardial strain.[15–17] Furthermore, FTI and can be applied to cine images from different CMR vendors and field strengths.

The purpose of our study was to investigate whether LV deformation imaging using FTI can provide incremental prognostic information to standard CMR parameters including LGE, serological biomarkers, and clinical parameters in a large cohort of patients with stable DCM over a long follow-up time period.

Methods

Study population

Our study population consisted of 210 consecutive patients with DCM who were prospectively included in our study and myocardial deformation was analysed retrospectively after referral to the 'Cardiomyopathy Center' at the University Hospital Heidelberg between May 2005 and November 2009. Some patients were part of a previous report.[7] CMR was performed as part of our standard institutional protocol for the evaluation of cardiomyopathies, unless one of the following contraindications to CMR was present: cardiac pacemaker or implantable cardioverter defibrillator (ICD), other not CMR compatible metallic implants, severe claustrophobia, obesity preventing patient entrance into the scanner bore, pregnancy, and lactation. Chronic renal failure with an estimated GFR < 30 mL/min/1.73 m^2 was added as an exclusion criterion for administration of intravenous CMR contrast agents after July 2007.

The diagnosis of DCM was based on the 1995 World Health Organization/International Society and Federation of Cardiology criteria.[18] Inclusion criteria were: patients with impaired systolic function (LV-EF $\leq 50\%$) on a non-CMR study, and absence of (i) significant coronary artery disease (defined as $\geq 50\%$ luminal stenosis) by coronary angiography, previous coronary revascularization or myocardial infarction, (ii) valvular disease, (iii) hypertensive heart disease, and (iv) congenital abnormalities. All patients had congestive heart failure and were examined in a clinically stable condition (NYHA functional class $\leq$ III). All patients gave their informed consent and our study was approved by the institutional Ethics Committee. NT-proBNP was analysed using a commercially available assay (ELECSYS, Roche Diagnostics, Mannheim, Germany) and log transformed for statistical analysis (lnBNP), values from subjects with GFR < 30 mL/min/1.73 m^2 were excluded.

Follow-up data and definition of study endpoints

Personnel unaware of the CMR results contacted each subject or an immediate family member. Cardiac death, heart transplantation, and sudden cardiac death aborted by appropriate ICD discharge due to ventricular tachycardia or fibrillation were defined as hard cardiac events building the *primary endpoint* of our study. Cardiac events together with the occurrence of hospitalization due to congestive heart failure were used as a *secondary endpoint*. In case of patients undergoing heart transplantation, the follow-up data were censored at the time of transplantation. In case of several simultaneous cardiac events per patient, the worst event was selected (cardiac death $>$ transplantation $>$ aborted SCD due to appropriate ICD shock $>$ hospitalization due to heart failure). Otherwise, only the first event for each patient was included in the analysis for composite end-points.

CMR acquisition and analysis

Standard CMR was performed on a 1.5T clinical scanner (Achieva®, Philips Healthcare, Best, The Netherlands) equipped with a cardiac phased array receiver coil. For details see our Supplementary data online. Cine images were obtained using a breath-hold segmented-k-space balanced fast-field echo sequence (SSFP) employing retrospective ECG gating in long axis planes (2, 4, and 3 chamber views) as well as in contiguous short axis slices covering the whole ventricles from the annulus of the AV valves to the apex, with 35 phases per cardiac cycle. All analyses were performed on a commercially available workstation (Viewforum®, Philips Healthcare). Results for ventricular volumes, ejection fraction, and LV myocardial mass were derived from short-axis slices. The presence and extent of late enhancement were evaluated by two independent experienced observers who were blinded to clinical data and outcome.

Feature-tracking imaging

For strain analysis, short- and long-axis views of the ventricle were divided according to the standard 17-segment model. The apical cap (segment 17) was not considered for analysis. Retrospective image analyses were conducted employing the 2D CPA CMR Feature tracking software (TomTec Imaging Systems, Munich, Germany). This tool comprises a software-based feature-tracking algorithm, which has been validated previously in experimental and clinical studies.[15,19,20] Feature tracking measures radial, circumferential, and longitudinal strain and strain rate as well as myocardial velocities along a user-defined endocardial border throughout the cardiac cycle on standard CMR SSFP sequences (*Figure 1*). In our study, global strain values were measured by a blinded observer and calculated according to the following approach: (i) on a patient level, the peak segmental values of radial, circumferential, and longitudinal strain (red arrows in *Figure 1*) were measured three times and then averaged for each strain direction, resulting in global radial, circumferential, and longitudinal strain; (ii) in order to investigate a more practical and faster approach for clinical routine, we additionally measured the average peak of the mean curve of all segments. This curve represents the average of all segments over the whole cardiac cycle (black arrow in *Figure 1*). This value was measured three times and then averaged for the long- and short-axis views, resulting in mean radial, circumferential, and longitudinal strain.

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation for parametric or as median with interquartile range (IQR) for non-parametric variables. For continuous variables, differences between two groups were compared using Students' *t*-test or Mann–Whitney *U* test. Categorical variables were expressed as counts and percentages and compared by χ^2 test or Fisher exact test, respectively. Survival curves were estimated by the Kaplan–Meier method and compared by log-rank tests. Receiver operating characteristics analysis was used in order to define the optimal cut-off values. Univariate and multivariate Cox proportional hazards regression analysis was performed to calculate

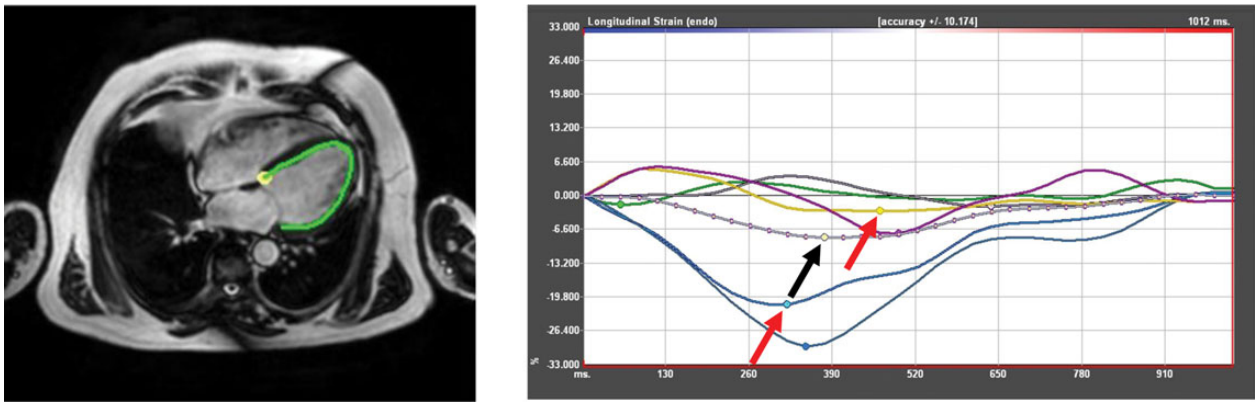

Figure 1 Feature-tracking imaging. A four chamber view of a patient with reduced longitudinal strain but ejection fraction >35% is shown. The black arrow indicates the negative peak of the mean strain curve representing mean longitudinal strain. The red arrows indicate the segmental peak negative strain.

hazard ratios (HR) and 95% confidence intervals (CI). In addition, integrated discrimination improvement and net reclassification calculations were performed. For all analyses, a *P*-value of <0.05 was regarded statistically significant. Inter- and intraobserver variabilities for mean strain values were assessed by repeated analysis of 30 randomly selected patients. Readings were separated by 8 weeks to minimize recall bias. The SPSS 15.0 (SPSS, Chicago, IL, USA) and MedCalc 12.3 (MedCalc software, Mariakerke, Belgium) computer programs were used throughout. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

Clinical characteristics and outcomes

Data were prospectively collected in 210 patients during a median follow-up of 5.3 years. During the follow-up period, 45 cardiac events occurred in 39 patients. Cardiac death or heart transplantation occurred in 10 and 5 patients, respectively, whereas 11 further patients experienced an aborted sudden cardiac death (SCD) due to appropriate ICD shock ($n = 26$ patients with primary endpoint/hard cardiac events). Thirteen additional patients experienced severe heart failure symptoms requiring hospitalization, thus $n = 39$ patients who reached the composite secondary endpoint.

Baseline characteristics and haemodynamic data in patients with ($n = 39$) and without cardiac events ($n = 171$) are illustrated in *Table 1*. Patients with cardiac events were older and exhibited more advanced heart failure symptoms. Significant differences were observed for patients with cardiac events in terms of several baseline CMR-parameters, cardiac medications, and laboratory markers like NT-proBNP. Of all patients with LGE ($n = 79$), mid-wall patterns were observed in 28, patchy in 19, epicardial in 24, and diffuse in 8 patients. Regarding myocardial deformation imaging all systolic strain parameters were significantly impaired in subjects with cardiac endpoints (*Table 2*).

Survival analysis

For longitudinal, circumferential, and radial strain ROC optimized cut-offs were selected for the survival analysis (see Supplementary data online, *Figure S1*). Kaplan–Meier curves for the primary endpoint event-free survival are demonstrated in (*Figure 2 A–C*). Patients with global longitudinal strain ($> -12.5\%$), global circumferential strain ($> -13.1\%$), and global radial strain ($\leq 15.7\%$) experienced a significantly higher rate of hard cardiac events. Comparable results were obtained for the prediction of the secondary endpoint (see Supplementary data online, *Figure S2*).

A reduced global longitudinal strain ($\geq -12.5\%$) was even predictive for worse outcomes irrespective of the presence or absence of severely reduced LV ejection fraction and the presence late-gadolinium enhancement, as shown in *Figure 3*.

Uni- and multivariate analysis

Several clinical parameters including age and NYHA class, CMR parameters like LV ejection fraction, normalized LV end-diastolic volumes, LV mass and LGE, longitudinal, circumferential, and radial systolic strain parameters were univariate predictors of the primary and the secondary endpoint (*Table 3*). At first, we tested in multivariate Cox regression models the predictive value of the different strains in separate models for the global and mean strains. In these two models, global longitudinal strain (HR 1.26, $P < 0.01$) and mean longitudinal strain (HR 1.24, $P < 0.05$) remained as independent predictors for cardiac outcomes.

Subsequently, a multivariate Cox regression model was built including log transformed NT-proBNP (lnBNP), ejection fraction, quantitative LGE mass, and global longitudinal strain. Hereby, global longitudinal strain still exhibited independent prognostic value for the assessment of the primary and secondary endpoint surpassing that provided by LV ejection fraction and lnBNP (*Table 4*).

In addition, the mean longitudinal strain was tested in a model including a priori defined, clinically established predictor variables (NYHA class, EF < 35%, presence of LGE and mean longitudinal strain $> -10\%$). Here again an LV mean longitudinal strain $> -10\%$ remained as an independent predictor for the primary and secondary endpoint (*Table 4*).

Table 1 Demographic data of patients with and without cardiac events

Parameters	All patients ($n = 210$)	Patients without endpoint ($n = 171$)	Patients with endpoint ($n = 39$)	*P*-value
Clinical data				
Age	52 ± 15	50 ± 15	58 ± 14	<0.01
Male gender, *n* (%)	159 (76)	128 (75)	31 (79)	NS
Arterial hypertension, *n* (%)	81 (39)	62 (36)	19 (49)	NS
Hyperlipidaemia, *n* (%)	43 (20)	35 (20)	8 (21)	NS
Smoking, *n* (%)	85 (40)	73 (43)	12 (31)	NS
Diabetes mellitus, *n* (%)	22 (10)	17 (10)	5 (13)	NS
Familiar cardiomyopathy, *n* (%)	27 (13)	25 (15)	2 (5)	NS
Body mass index (kg/m^2)	25.6 ± 3.9	25.6 ± 4.0	25.8 ± 3.8	NS
NYHA class	2.1 ± 0.7	2.0 ± 0.7	2.3 ± 0.7	0.02
Laboratory data				
Serum creatinine (mg/dL)	1.05 ± 0.85	1.05 ± 0.93	1.04 ± 0.34	NS
ln NT proBNP (pg/mL)	6.3 ± 1.9	5.9 ± 1.8	7.6 ± 1.4	<0.001
Cardiac medications				
β-blockers, *n* (%)	184 (88)	146 (85)	38 (97)	0.04
ACE-inhibitors/AT II blockers, *n* (%)	196 (93)	157 (92)	39 (100)	0.07
Spironolactone, *n* (%)	84 (40)	64 (37)	20 (51)	NS
Diuretics, *n* (%)	104 (50)	76 (44)	28 (72)	<0.01
Digoxin, *n* (%)	39 (19)	22 (13)	17 (44)	<0.001
Coumadin, *n* (%)	72 (34)	50 (29)	22 (56)	<0.01

Data are presented as mean ± SD or as proportions. NS, not significant.

Table 2 Baseline standard CMR-data and myocardial deformation parameters of patients with and without cardiac events

Parameters	All Patients ($n = 210$)	Patients without endpoint ($n = 171$)	Patients with endpoint ($n = 39$)	*P*-value
Baseline CMR-data				
LV ejection fraction (%)	36.1 ± 13.8	38.4 ± 12.7	25.8 ± 14.2	<0.001
LVEDV (mL)	261 ± 99	248 ± 85	320 ± 131	<0.001
LVEDV/BSA (mL/m^2)	132 ± 48	125 ± 39	164 ± 69	<0.001
LVESV (mL)	176 ± 107	159 ± 86	253 ± 138	<0.001
LVESV/BSA (mL/m^2)	89 ± 52	81 ± 42	130 ± 73	<0.001
Cardiac output (L/min)	5.8 ± 1.7	6.0 ± 1.7	5.2 ± 1.7	<0.01
Cardiac index (L/min*m^2)	3.0 ± 0.8	3.0 ± 0.8	2.6 ± 0.8	<0.01
LV mass (g)	156 ± 116	142 ± 46	212 ± 238	<0.001
LV mass/BSA (g/m^2)	78 ± 52	72 ± 21	105 ± 107	<0.001
LGE present, *n* (%)	79 (38)	59 (34)	20 (51)	0.07
Quantitative LGE mass (g)	1.6 ± 3.3	1.4 ± 3.0	2.4 ± 4.0	0.1
CMR myocardial deformation				
Global longitudinal strain (%)	−15.2 ± 4.7	−16.2 ± 4.3	−11.1 ± 3.7	<0.001
Global circumferential strain (%)	−14.0 ± 6.5	−16.5 ± 5.6	−11.4 ± 5.1	<0.001
Global radial strain (%)	20.7 ± 7.7	21.7 ± 7.5	16.3 ± 6.3	<0.001
Mean longitudinal strain (%)	−13.1 ± 5.1	−14.1 ± 4.8	−8.8 ± 4.3	<0.001
Mean circumferential strain (%)	−15.6 ± 5.8	−15.1 ± 6.1	−9.3 ± 5.9	<0.001
Mean radial strain (%)	17.8 ± 7.0	18.9 ± 6.8	12.9 ± 5.5	<0.001

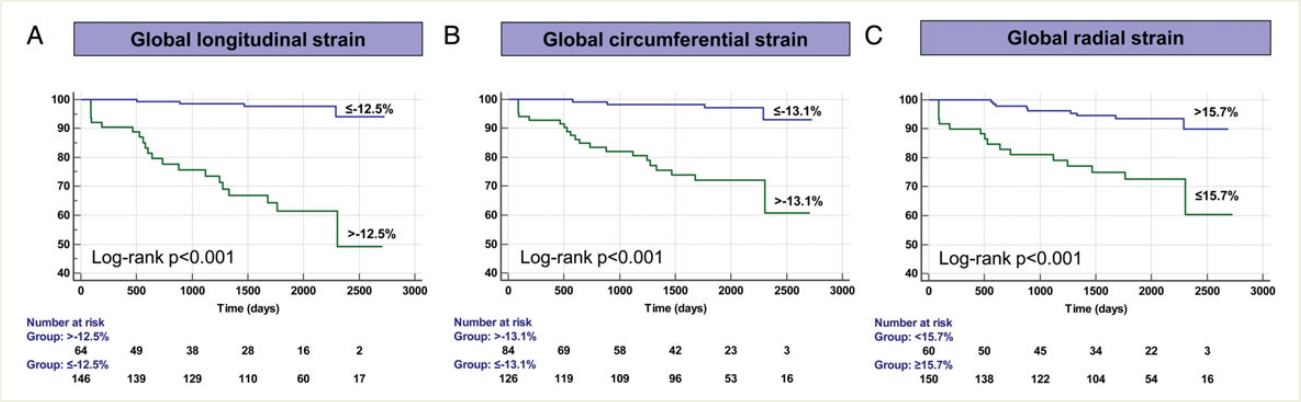

Figure 2 Kaplan–Meier estimates of the time to events by myocardial deformation. Patients with global longitudinal strain (> −12.5%), global circumferential strain (> −13.1%), and global radial strain (<15.7%) experienced a significantly higher rate of cardiac events compared with those with lower global longitudinal, circumferential, and radial strains.

Series of Cox proportional-hazards models and integrated discrimination improvement

In the first series of sequential cox regression models an incremental benefit for the prediction of outcome could be observed regarding the different strain directions (*Figure 4 A*). Next quantitative CMR parameters were analysed. Relative end-diastolic volume (LVEDV/BSA), LV ejection fraction, and LGE mass exhibited incremental value for the prediction of the primary endpoint (*Figure 4 B*). Furthermore, global longitudinal strain significantly increased the power of the model, surpassing that of standard CMR parameters (*Figure 4 B*). These results were verified by an increase in integrated discrimination improvement analysis. LV global longitudinal strain yielded higher integrated discrimination improvement (IDI) values compared with clinical variables, serological biomarkers, and CMR parameters (Supplementary data online, *Table S1*).

Observer variability

Intra- and interobserver variability was 6.6 and 7.5%, respectively, for mean radial, 3.1 and 3.5%, respectively, for mean circumferential, and 2.9 and 3.5%, respectively, for mean longitudinal strain. Interobserver variability was 8.5% for LGE quantification.

Discussion

We report on the so far largest group of patients with DCM, systematic assessment of LV deformation, and its association with clinical outcome. The main findings of our study encompass the incremental value of longitudinal, radial, and circumferential strain for the prediction of cardiac events, independent of clinical and laboratory markers, LV ejection fraction, and LGE. Particularly, longitudinal strain proved to be the most robust predictor of outcome and provided improved risk stratification even in subgroups of patients with ≥35 or <35% LV ejection fraction and in patients with and without LGE.

Previous studies for non-invasive risk stratification in DCM

An early diagnosis and accurate risk stratification in patients with suspected heart failure and the reliable detection of the remodelling processes is crucial for timely therapeutic intervention and reduction of mortality.[21] Non-invasive cardiovascular imaging methods, such as CMR, may be well suited for the precise and cost-effective diagnostic classification of patients with heart failure symptoms.[5,22,23] Ventricular function as assessed by ejection fraction (EF) measurements determines prognosis of patients with DCM and serves as an indicator for the need of defibrillator implantation, resynchronization therapy and treatment of congestive heart failure. However, due to the intricate myocardial architecture, global left-ventricular function is determined not only by radial, but also by longitudinal, circumferential, and torsional components,[24] which are not detected by mere EF assessment. In particular, the quantification of longitudinal function may be a better measure of contractile myocardial function than the geometric change of the entire left ventricle.[11,25] In addition, we and others previously demonstrated the incremental value of longitudinal and circumferential compared with radial strain for the detection of ischaemic myocardium and for the risk stratification of patients with ischaemic heart disease and cardiomyopathies.[11,12,26]

Longitudinal strain for the estimation of outcomes and technical aspects

In our study, we demonstrated that longitudinal strain assessed with FTI seems to be the most robust predictor of cardiac outcome in patients with DCM, surpassing the value of clinical and laboratory markers as well as LGE and EF. In this regard, the prognostic significance of a reduced strain is not completely dependent on the degree of the underlying radial left-ventricular dysfunction, as mainly reflected by the EF. Thus, subgroup analysis revealed that longitudinal strain provided further risk stratification even in DCM patients with LV ejection fraction <35% and in those with LGE. Patients with preserved longitudinal strain exhibited excellent long-term outcome despite the presence of severely impaired LV function

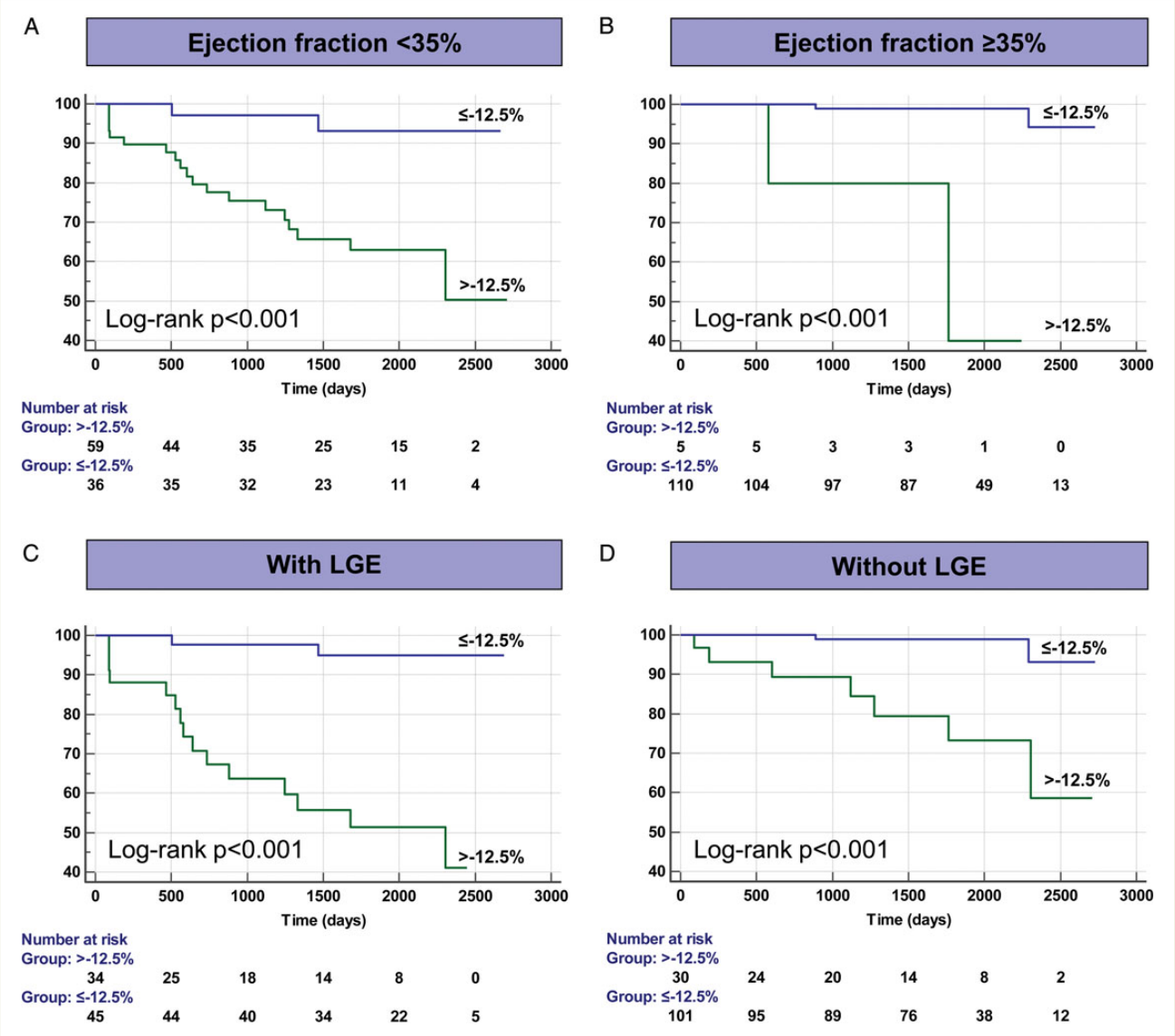

Figure 3 Kaplan–Meier estimates of subgroups with or without severely impaired ejection fraction and LGE. A global longitudinal strain $> -12.5\%$ was predictive for the primary endpoint irrespective of the presence or absence of a severely reduced LV ejection fraction (EF$<$35%) or late gadolinium enhancement.

or LGE. This is in line with earlier observations, in which longitudinal strain was the most robust strain parameter for the risk stratification of patients with non-ischaemic heart failure.[11]

Feature-tracking imaging was originally designed for echocardiographic image analysis and provides two-dimensional deformation information about the myocardium. It has previously been validated and recently been applied to SSFP sequences, with good correlation in comparison to CMR tagging for circumferential but not longitudinal strain despite high observer variabilites on segmental level.[14,15,17,19] Tag fading, which results in low SNR during the cardiac diastole with tagging sequences, can be circumvented with FTI. Of note, FTI myocardial deformation can be assessed with CMR images, without the need for dedicated pulse sequences and may be performed independent of CMR vendors and field strength.[16] Apart from the excellent morphological image quality of CMR, FTI offers the opportunity to perform all measurements using a single imaging modality and to receive multi-dimensional information about the LV contraction pattern. For clinical routine, fast and reproducible approaches are required. Therefore, we investigated the role of the mean strain curves for the prediction of outcome (*Table 4*; Supplementarydata online *Table S1* and *Figure S4*). With this simplified analysis and predefined cut-offs, we still found that the mean longitudinal strain served as an independent predictor of survival. In concordance, just recently an EACVI-industry initiative for the standardized assessment of myocardial deformation was formed.[27]

Assessment of fibrosis by LGE and mapping techniques

Cardiac remodelling also propagates to myocardial fibrosis, and significant fibrosis can be detected in at least one-third of patients

Table 3 Univariate analysis

Variable	Primary endpoint			Secondary endpoint		
	HR	95% CI	*P*-value (unadjusted)	HR	95% CI	*P*-value (unadjusted)
Age (years)	1.03	1.00–1.06	<0.05	1.04	1.01–1.06	<0.01
NYHA class	1.84	1.04–3.25	<0.05	1.85	1.16–2.94	<0.01
β-blocker usage	4.70	0.64–34.1	NS	7.3	1.00–51.3	0.05
EF (%)	0.91	0.88–0.94	<0.0001	0.93	0.91–0.96	<0.0001
LVEDV/BSA (mL/m^2)	1.02	1.01–1.03	<0.0001	1.01	1.00–1.02	<0.0001
lnBNP (pg/mL)	1.75	1.41–2.20	<0.0001	1.66	1.40–1.97	<0.0001
LGE present	3.36	1.50–7.50	<0.01	1.87	0.99–3.47	0.05
LGE mass (g)	1.11	1.04–1.18	<0.01	1.07	0.99–1.14	0.06
Global longitudinal strain (%)	1.33	1.21–1.47	<0.0001	1.26	1.15–1.33	<0.0001
Global circumferential strain (%)	1.23	1.13–1.34	<0.0001	1.16	1.09–1.24	<0.0001
Global radial strain (%)	0.89	0.84–0.95	<0.0001	0.92	0.87–0.96	<0.001
Mean longitudinal strain (%)	1.35	1.2–1.49	<0.0001	1.23	1.15–1.32	<0.0001
Mean circumferential strain (%)	1.26	1.15–1.37	<0.0001	1.17	1.1–1.24	<0.0001
Mean radial strain (%)	0.85	0.80–0.91	<0.0001	0.88	0.84–0.93	<0.0001

Table 4 Multivariate proportional-hazard models with global and mean longitudinal strains ($n = 210$)

	Primary endpoint			Secondary endpoint		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Global longitudinal strain						
lnBNP (pg/mL)	1.21	0.86–1.68	NS	1.31	1.02–1.69	<0.05
EF (%)	0.99	0.93–1.06	NS	1.01	0.96–1.06	NS
LGE mass (g)	1.20	1.08–1.33	<0.001	1.12	1.02–1.23	<0.05
Global longitudinal strain (%)	1.27	1.06–1.52	<0.02	1.20	1.05–1.38	<0.01
Mean longitudinal strain						
NYHA	0.93	0.51–1.66	NS	1.16	0.71–1.89	NS
EF (<35%)	2.41	0.65–8.84	NS	1.92	0.77–4.84	NS
LGE present	2.54	1.13–5.7	<0.05	1.44	0.77–2.72	NS
Mean longitudinal strain (> −10%)	5.44	1.64–18.1	<0.01	2.78	1.17–6.61	<0.05

Missing values: 14 NT-proBNP values.

of patients with DCM.[28] Distinct patterns of fibrosis are observed and all are more or less associated with a poor prognosis.[29] Especially, the presence of mid-wall enhancement has recently been shown to predict sudden cardiac death in DCM.[6,9,30] In our study, LGE was an independent predictor for both hard cardiac events and of the composite endpoint by multivariate analysis and added incremental value to LV-EF and clinical as well as laboratory parameters for the estimation of outcomes. Nowadays, with the development of T1-mapping techniques, diffuse myocardial fibrosis can be quantified by measuring the extracellular volume fraction. This significantly expands the ability of CMR for tissue characterization and for the recognition of diffuse fibrosis, which may be an early marker of early or even subclinical DCM. Unfortunately, however, such techniques currently lack standardization and comparability with other sites, as suggested by the recently published standardized post-processing report.[31] Furthermore, both T1-mapping techniques and LGE require the administration of gadolinium-based contrast agents, which is not recommended in patients with severe renal failure, due to the risk of nephrogenic systemic fibrosis. In such patients, strain imaging may become an important cornerstone for the quantification of LV function and for risk assessment.

Limitations

As the study started already in 2005 and plasma NT-proBNP is affected by renal function, only 93% of NT-proBNP values were available in our patients. Similarly, methods for quantification of diffuse fibrosis with T1 mapping were not available at this time point, so that extracellular volume could not be analysed. Echocardiography is considered as the recommended technique for the assessment of LV strain, but a 'universal' reference standard technique is currently not available for human studies. Finally, we observed an overall low cardiac event rate during the follow-up period, which is a limitation.

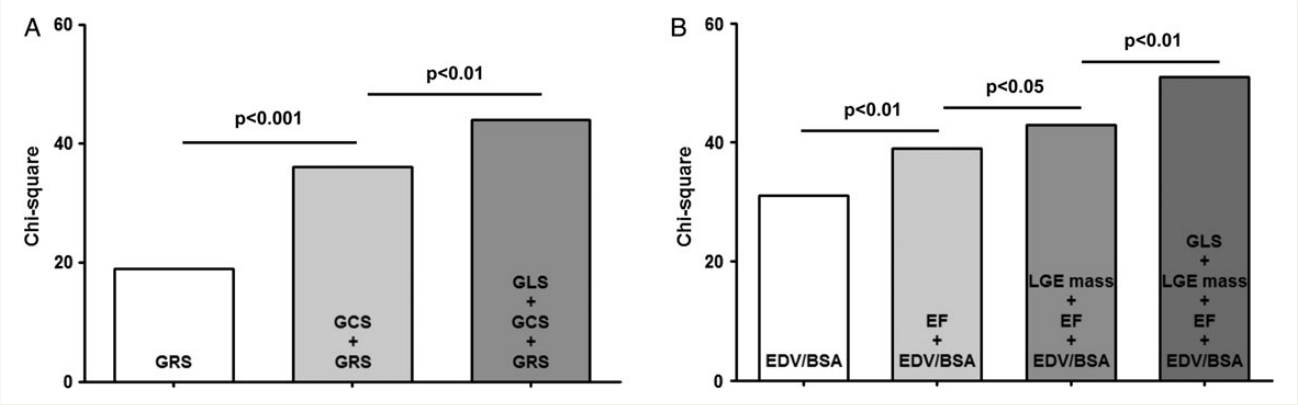

Figure 4 Incremental predictive value of global longitudinal strain in hierarchical models. In the first multivariate model, the three strain directions global radial strain (GRS), global circumferential strain (GCS), and global longitudinal strain (GLS) were entered sequentially for the prediction of the primary endpoint (*A*). In the second model (*B*) standard CMR parameters (LVEDV/BSA, EF, LGE mass) were entered sequentially followed by the addition of GLS. In both models, global longitudinal strain offered a significant incremental value.

Conclusions

Pathological myocardial deformation as represented by a reduction of LV longitudinal strain identified patients with DCM at high risk for future cardiac events, surpassing the prognostic value of standard CMR imaging techniques, such as EF and LGE and that of established cardiac serological biomarkers. Therefore, the thorough evaluation of LV contraction with two-dimensional deformation imaging might become an additional diagnostic method to detect functional impairment and may serve as a novel CMR imaging biomarker in patients with DCM and cardiomyopathies in the future. Larger, multi-centre trials using a standardized global longitudinal strain approach are now warranted to confirm our findings and to determine whether the assessment of myocardial strain may aid structured patient treatment.

Supplementary data

Supplementary data are available at *European Journal of Echocardiography* online.

Acknowledgements

We thank Birgit Hörig, Daniel Helm, and Angela Stöcker-Wochele for their excellent technical assistance with the acquisitions of all CMR scans.

Conflict of interest: C.G. is employee of TomTec Imaging Systems. The other authors declare that they have no competing interests regarding this manuscript.

References

1. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D *et al.* Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* 2006;**113**:1807–16.
2. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL *et al.* Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000;**342**:1077–84.
3. Michels VV, Driscoll DJ, Miller FA, Olson TM, Atkinson EJ, Olswold CL *et al.* Progression of familial and non-familial dilated cardiomyopathy: long term follow up. *Heart* 2003;**89**:757–61.
4. Miller WL, Hartman KA, Burritt MF, Burnett JC Jr, Jaffe AS. Troponin, B-type natriuretic peptides and outcomes in severe heart failure: differences between ischemic and dilated cardiomyopathies. *Clin Cardiol* 2007;**30**:245–50.
5. Karamitsos TD, Francis JM, Myerson S, Selvanayagam JB, Neubauer S. The role of cardiovascular magnetic resonance imaging in heart failure. *J Am Coll Cardiol* 2009;**54**:1407–24.
6. Assomull RG, Prasad SK, Lyne J, Smith G, Burman ED, Khan M *et al.* Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. *J Am Coll Cardiol* 2006;**48**:1977–85.
7. Lehrke S, Lossnitzer D, Schob M, Steen H, Merten C, Kemmling H *et al.* Use of cardiovascular magnetic resonance for risk stratification in chronic heart failure: prognostic value of late gadolinium enhancement in patients with non-ischaemic dilated cardiomyopathy. *Heart* 2011;**97**:727–32.
8. Wu KC, Weiss RG, Thiemann DR, Kitagawa K, Schmidt A, Dalal D *et al.* Late gadolinium enhancement by cardiovascular magnetic resonance heralds an adverse prognosis in nonischemic cardiomyopathy. *J Am Coll Cardiol* 2008;**51**:2414–21.
9. Gulati A, Jabbour A, Ismail TF, Guha K, Khwaja J, Raza S *et al.* Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. *JAMA* 2013;**309**:896–908.
10. Leong DP, Chakrabarty A, Shipp N, Molaee P, Madsen PL, Joerg L *et al.* Effects of myocardial fibrosis and ventricular dyssynchrony on response to therapy in new-presentation idiopathic dilated cardiomyopathy: insights from cardiovascular magnetic resonance and echocardiography. *Eur Heart J* 2012;**33**:640–8.
11. Motoki H, Borowski AG, Shrestha K, Troughton RW, Tang WH, Thomas JD *et al.* Incremental prognostic value of assessing left ventricular myocardial mechanics in patients with chronic systolic heart failure. *J Am Coll Cardiol* 2012;**60**:2074–81.
12. Buss SJ, Emami M, Mereles D, Korosoglou G, Kristen AV, Voss A *et al.* Longitudinal left ventricular function for prediction of survival in systemic light-chain amyloidosis: incremental value compared with clinical and biochemical markers. *J Am Coll Cardiol* 2012;**60**:1067–76.
13. Choi EY, Rosen BD, Fernandes VR, Yan RT, Yoneyama K, Donekal S *et al.* Prognostic value of myocardial circumferential strain for incident heart failure and cardiovascular events in asymptomatic individuals: the Multi-Ethnic Study of Atherosclerosis. *Eur Heart J* 2013;**34**:2354–61.
14. Schuster A, Kutty S, Padiyath A, Parish V, Gribben P, Danford DA *et al.* Cardiovascular magnetic resonance myocardial feature tracking detects quantitative wall motion during dobutamine stress. *J Cardiovasc Magn Reson* 2011;**13**:58.
15. Hor KN, Gottliebson WM, Carson C, Wash E, Cnota J, Fleck R *et al.* Comparison of magnetic resonance feature tracking for strain calculation with harmonic phase imaging analysis. *JACC Cardiovasc Imaging* 2010;**3**:144–51.
16. Schuster A, Morton G, Hussain ST, Jogiya R, Kutty S, Asrress KN *et al.* The intra-observer reproducibility of cardiovascular magnetic resonance myocardial

feature tracking strain assessment is independent of field strength. *Eur J Radiol* 2013; **82**:296–301.
17. Augustine D, Lewandowski AJ, Lazdam M, Rai A, Francis J, Myerson S *et al.* Global and regional left ventricular myocardial deformation measures by magnetic resonance feature tracking in healthy volunteers: comparison with tagging and relevance of gender. *J Cardiovasc Magn Reson* 2013;**15**:8.
18. Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J *et al.* Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies. *Circulation* 1996;**93**:841–2.
19. Pirat B, Khoury DS, Hartley CJ, Tiller L, Rao L, Schulz DG *et al.* A novel feature-tracking echocardiographic method for the quantitation of regional myocardial function: validation in an animal model of ischemia-reperfusion. *J Am Coll Cardiol* 2008;**51**: 651–9.
20. Korinek J, Wang J, Sengupta PP, Miyazaki C, Kjaergaard J, McMahon E *et al.* Two-dimensional strain--a Doppler-independent ultrasound method for quantitation of regional deformation: validation in vitro and in vivo. *J Am Soc Echocardiogr* 2005;**18**: 1247–53.
21. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG *et al.* 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol* 2009;**53**:e1–e90.
22. Assomull RG, Shakespeare C, Kalra PR, Lloyd G, Gulati A, Strange J *et al.* Role of cardiovascular magnetic resonance as a gatekeeper to invasive coronary angiography in patients presenting with heart failure of unknown etiology. *Circulation* 2010;**124**: 1351–60.
23. Moschetti K, Muzzarelli S, Pinget C, Wagner A, Pilz G, Wasserfallen JB *et al.* Cost evaluation of cardiovascular magnetic resonance versus coronary angiography for the diagnostic work-up of coronary artery disease: application of the European Cardiovascular Magnetic Resonance registry data to the German, United Kingdom, Swiss, and United States health care systems. *J Cardiovasc Magn Reson* 2012;**14**:35.
24. Wandt B. Long-axis contraction of the ventricles: a modern approach, but described already by Leonardo da Vinci. *J Am Soc Echocardiogr* 2000;**13**:699–706.
25. Dumesnil JG, Shoucri RM, Laurenceau JL, Turcot J. A mathematical model of the dynamic geometry of the intact left ventricle and its application to clinical data. *Circulation* 1979;**59**:1024–34.
26. Korosoglou G, Gitsioudis G, Voss A, Lehrke S, Riedle N, Buss SJ *et al.* Strain-encoded cardiac magnetic resonance during high-dose dobutamine stress testing for the estimation of cardiac outcomes: comparison to clinical parameters and conventional wall motion readings. *J Am Coll Cardiol* 2011;**58**:1140–9.
27. Thomas JD, Badano LP. EACVI-ASE-industry initiative to standardize deformation imaging: a brief update from the co-chairs. *Eur Heart J Cardiovasc Imaging* 2013;**14**: 1039–40.
28. Baig MK, Mahon N, McKenna WJ, Caforio AL, Bonow RO, Francis GS *et al.* The pathophysiology of advanced heart failure. *Am Heart Journal* 1998;**135**(suppl.): S216–30.
29. Klem I, Weinsaft JW, Bahnson TD, Hegland D, Kim HW, Hayes B *et al.* Assessment of myocardial scarring improves risk stratification in patients evaluated for cardiac defibrillator implantation. *J Am Coll Cardiol* 2012;**60**:408–20.
30. McCrohon JA, Moon JC, Prasad SK, McKenna WJ, Lorenz CH, Coats AJ *et al.* Differentiation of heart failure related to dilated cardiomyopathy and coronary artery disease using gadolinium-enhanced cardiovascular magnetic resonance. *Circulation* 2003;**108**:54–9.
31. Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SD, Fogel MA, Friedrich MG *et al.* Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) Board of Trustees Task Force on Standardized Post Processing. *J Cardiovasc Magn Reson* 2013;**15**:35.