Strain Values of Left Ventricular Segments Reduce Non-homogeneously in Dilated Cardiomyopathy with Moderately and Severely Deteriorated Heart Function Assessed by MRI Tissue Tracking Imaging

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Summary
Changes of global and segmental ventricular strain at different deterioration levels of cardiac function in patients with dilated cardiomyopathy (DCM) using cardiac magnetic resonance (CMR) have not yet been explored. In total, 101 patients diagnosed with DCM consecutively underwent CMR. They were categorized according to the reduction in left ventricular ejection fraction (LVEF) into the following groups: moderately reduced (n = 43) and severely reduced group (n = 58). LV global longitudinal strain (GLS), global radial strain (GRS), global circumferential strain (GCS), and segmental strain values were assessed using tissue tracking technique. LV segmental circumferential strain (CS) and radial strain (RS) in healthy volunteers increased from base to apex stepwisely. The LV base-to-apex increasing pattern disappeared in the moderate DCM group (RS: 26.61% ± 20.63% versus 21.97% ± 4.85% versus 29.05% ± 9.90%, P > 0.05; CS: -13.16% ± 6.40% versus -12.96% ± 2.45% versus -15.32% ± 3.89%, P > 0.05). While in the severe group, CS and RS of base segment had the highest values, there was no significant difference between mid and apex segments. GLS_LV, GRS_LV, and GCS_LV were significantly reduced in moderate and severe groups in steps, similar to the three parameters of RV. During a 17-month median follow-up, 25 patients had an index composite outcome event. GLS_LV > -11.62%, GCS_LV > -9.35%, and GRS_LV > 12.42% were significantly associated with the occurrence of cardiac events in DCM patients. LV segmental values reduce non-homogeneously in DCM patients with moderately and severely deteriorated heart function.

Key words: Strain analysis, Cardiac magnetic resonance, Cardiac event

Diopathic dilated cardiomyopathy (DCM), characterized by left ventricular (LV) or biventricular dilatation with impaired systolic function, is associated with a high morbidity rate and a 10-year mortality rate of more than 40% caused by heart failure (HF). Accurate evaluation of cardiac function may help better assess the heart function and guide effective treatment. Conventional parameters, such as LV ejection fraction (LVEF) and stroke volume (LVSV), and LV end-diastolic volume (LVEDV), can only reveal the cardiac function deterioration, which are not sensitive to myocardial wall motion abnormalities due to extensive impairment of myocardial contractility in DCM. Until recently, ultrasonographic strain analysis has been the mainstay for assessing regional and global myocardial performance. Matsumoto, et al demonstrated that 3D global circumferential strain (GCS) below 2.71% with dobutamine stress assessed by echocardiography could predict cardiovascular events with 83% sensitivity and 80% specificity. Cardiac magnetic resonance (CMR) imaging based on steady-state free precession (SSFP) cine sequence has been successfully used to evaluate wall motion and strain changes. The strain results from CMR are more accurate and reproducible than those from echocardiography. Previous studies have mainly focused on assessing global LV mechanics in patients with DCM. Global longitudinal strain (GLS) and GCS have shown to be closely correlated with EF and to be essential for the clinical assessment of LV function. However, the segmental performance of LV has not yet been explored at different deterioration levels of cardiac function in DCM. The aim of this study was to investigate global and segmental ventricular strain changes at different deterioration levels of cardiac function in DCM.
Figure 1. Analysis of left ventricle global and segmental radial, circumferential, and longitudinal strain; example of tissue-tracking imaging in a patient with DCM. A: Four-chamber long-axis view of a patient with DCM. B: Polar maps of different strain analysis for AHA segments. C: Two-chamber short-axis view. D: Multiple long-axis views (2-, 3-, 4-chamber views). E: Strain curves per segment.

Methods

Study population: In total, 103 consecutive patients initially diagnosed as having DCM according to the 1995 World Health Organization/International Society and Federation of Cardiology criteria were enrolled between April 2012 and November 2016 in this study. Inclusion criteria were as follows: 1) patients who met Framingham heart failure diagnostic criteria from 1971 (NYHA functional class ≤ III); and 2) patients with impaired systolic function (LVEF ≤ 45%) assessed with CMR. Exclusion criteria were as follows: 1) patients with valvular disease; 2) patients with congenital heart diseases; 3) patients with significant coronary artery disease (luminal stenosis > 70%) by coronary angiography; 4) patients with atrial fibrillation; 5) patients with an estimated glomerular filtration rate of < 30 mL/minute/1.73 m². Patients with DCM had damaged EF. In line with the recommendations for cardiac-resynchronization therapy (CRT), LVEF < 30% was defined as severe deterioration of the systolic function of the heart. Enrolled patients with DCM were categorized into 2 groups: moderate group (30% ≤ LVEF < 45%) and severe group (LVEF < 30%). CMR scans from 30 healthy volunteers served as the control group. Before CMR scanning, each participant provided a written informed consent in accordance with the ethical committee approval.

CMR protocol: CMR studies were performed on 3.0T Philips medical system (Philips Healthcare, Best, The Netherlands). The scanning protocol included routine localizer images, cine images, first-pass perfusion images, and late gadolinium enhancement (LGE) images. Cine images were obtained using a breath-hold balanced SSFP sequence employing retrospective ECG-triggering in the long-axis planes (2-, 3-, and 4-chamber views), as well as in the stack of standard short axis covering the whole ventricles from the base to the apex, with 30 phases per cardiac cycle. This was done using typical imaging parameters, which were set as follows: TR = 3.2; TE = 1.5; flip angle = 45°; in-plane resolution = 1.9 × 1.9 mm²; acquisition matrix = 232 × 219; slice thickness = 8 mm with no slice gap. LGE acquisition was obtained 10 minutes after injecting 0.2 mmol/kg of the contrast (gadobutrol/Gadovist; Berlin-Wedding, Schering, Germany).

Magnetic resonance imaging analysis: All analyses were performed using dedicated post-processing software (cvi 42, Circle Cardiovascular Imaging, Inc., Calgary, Canada). LV global radial, circumferential, and longitudinal strains (GRS, GCS, and GLS) were acquired by short-axis 2-chamber images and long-axis 2-, 3-, and 4-chamber images (Figure 1). Right ventricular global radial, circumferential, and longitudinal strains (GRS, GCS, and GLS) were derived on the stack of short-axis 2-chamber and right ventricular 2- and 3-chamber views in the long axis. Additionally, segmental analysis of radial and circumferential strain from LV base to apex was performed, as previously described.12)
In tissue tracking (TT) analysis, ventricle endocardial and epicardial borders were manually contoured in end-diastolic images. A deformable model was created from the reference phase, while several control points were identified within the myocardium. The algorithm with a proprietary cost function determined the estimated borders of the myocardium from phase to phase and found the best fit, using forward and backward approaches. Subsequently, voxel-wise parameters were automatically calculated by the software. In addition to strain analysis, LV and RV end-diastolic volume, stroke volume (SV), EF, and LV mass were calculated. LVEDV, LVSV, and LV mass were indexed to body surface area as LVEDVI, LVSI, and LVMII, respectively.

**Clinical follow-up data and definition of study endpoints:** Patients were followed up at 6-month intervals after CMR examination via clinic visits or phone calls. The primary outcome was defined as the combination of endpoints of cardiac death, heart transplantation, and hospitalization for deterioration of HF. In case of simultaneous cardiac events per patient, the worst event was selected (cardiac death > heart transplantation > hospitalization for HF). Otherwise, the first event per patient was included in the analysis.

**Statistical analysis:** Statistical analysis was performed using IBM SPSS Statistics (version 17.0; SPSS, Chicago, Illinois) and MedCalc software (MedCalc, Mariakerke, Belgium). Continuous data were expressed as mean ± SD. Multiple groups were compared using analysis of variance (ANOVA) with Holm-Sidak post-hoc test. Categorical data, presented as counts and percentages, were compared using chi-square test. Twenty patients and twenty healthy volunteers were randomly selected for the assessment of intra- and interobserver variability, which were tested by the Bland-Altman method and expressed as the mean of the absolute differences between the two measurements divided by the mean value (%). Additionally, receiver-operating characteristic (ROC) method was used to determine the optimal cut-off values for the prediction of the combination of endpoints. Combined endpoint event-free survival curves were estimated by the Kaplan-Meier method. A P value of <0.05 was considered statistically significant.

**Results**

**Basic demographic and conventional data:** Out of 103 patients, 2 were excluded from the study due to poor image quality. In total, 101 patients and 30 healthy volunteers completed the study protocol. Basic clinical and demographic characteristics in the moderately reduced EF group (n = 43) and severely reduced EF group (n = 58) are summarized in Table I. Except for NYHA functional class, there was no significant difference found in the baseline characteristics between the groups, including age, BSA, sex, medication use, history of hypertension, and diabetes mellitus.

**Conventional parameters of heart function:** There was a progressive reduction of RVEF in patients with severe DCM, with a significant difference between healthy volunteers and patients with moderate and severe DCM (Table II). LVEDV demonstrated a stepwise increase in DCM patients in relation to LVEF decrease, whereas LVSV decreased in patients with severe DCM compared with healthy volunteers (38.47 ± 17.51 mL versus 66.44 ± 17.17 mL, P < 0.001). After being corrected by BSA, LVEDVI increased and LVSVI decreased progressively in DCM patients. LVMII in the severely reduced EF group was higher than the moderately reduced EF group (79.60 ± 25.17 g/m² versus 68.37 ± 17.46 g/m², P < 0.05).

**Change of LV segmental strain pattern:** In healthy volunteers, LV radial strain (RS) and circumferential strain (CS) values increased progressively from the base to the apex (44.35% ± 10.96% versus 53.45% ± 17.49% versus 67.11% ± 16.43%, P < 0.05, and -19.73% ± 3.02% versus -23.62% ± 4.63% versus -26.42% ± 3.91%, P < 0.05) (Figure 2), whereas the base-to-apex increasing pattern disappeared in the 2 DCM groups. RS and CS of the left ventricle showed no significant differences among base, mid, and apex in the moderately reduced EF group (RS:
26.61% ± 20.63% versus 21.97% ± 4.85% versus 20.05% ± 9.90%, P < 0.05; CS: -13.16% ± 6.40% versus -12.96% ± 3.89%, P < 0.05). However, in the severely reduced EF group, the LV segmental strain demonstrated an opposite pattern, with the highest RS and CS values at the LV base segment (RS: base 14.83% ± 8.17%, P < 0.05; CS: base 9.37% ± 4.51%, P < 0.05) showing no significant differences between the mid and apex segments (RS: 9.37% ± 4.51% versus 10.85% ± 5.40%, P > 0.05; CS: -6.41% ± 2.51% versus -7.49% ± 3.62%, P > 0.05) (Figure 2C and F; Table III).

**Global strain of RV and LV: GRSLV, GCSLV, GLSLV, and GLS were decreased progressively from healthy volunteer group to moderate group to severe group. A significant decrease of GCSLV was observed only in the severely reduced EF group compared to the moderately reduced EF group (-5.83% ± 2.93% versus -7.52% ± 3.58%, P < 0.05). GRSLV decreased significantly in the moderately reduced EF group (14.98% ± 6.39% versus 22.10% ± 10.29%, P < 0.001) compared with the control group, whereas there was no significant difference of GRSLV between moderate group and severe group (Table IV).

**Clinical outcome and ROC analysis:** During the 17-month median follow-up, 28 cardiac events occurred in 25 patients. Cardiac death occurred in 5 patients, and heart transplantation was performed in 2 of them. Another 18 patients were admitted to the hospital for deteriorating HF. 25 patients had an index composite event. ROC optimized cut-offs of GRS, GCSLV, and GLS were selected for Kaplan-Meier curves (Figure 3). Kaplan-Meier curves for the combined endpoint event-free survival demonstrated that patients with GLS > -11.62% (AUC: 0.686, 95% CI: 0.586-0.775), GCSLV > -9.35% (AUC: 0.747, 95% CI: 0.651-0.828), and GRS ≤ -12.42% (AUC: 0.738, 95% CI: 0.646-0.824) experienced a significantly higher rate of cardiac events.

**Reproducibility:** The maximum interobserver variabilities of LV global strain, LV segmental strain, and RV global strain were 7.5%, 8.3%, and 7.7%, respectively; the maximum intraobserver variabilities were 5.0%, 5.4%, and 5.5%, respectively.

**Discussion**

This study has several important findings. First, an interesting pattern of LV segmental strain change in healthy volunteers was observed, in which CS and RS of the left ventricle increased stepwise from base to apex. However, this LV segmental strain value pattern disappeared in the DCM moderate group, and then it changed into an opposite pattern in the severe group. Second, RV global strain values decreased in synchronization in the DCM groups. Third, reduced global strain values of LV have been shown to be associated with worse outcomes in patients with DCM.

In the progress of DCM, LV chamber undergoes size enlargement and damaging of systolic function accompanied with apoptosis of cardiac myocytes and proliferation of interstitial cells. A number of researches have demonstrated that CMR-based strain analysis allows precise assessment of myocardial contractility compared to conventional parameters. Convenient date acquisition has made TT far more accessible.

Global strains of the left ventricle have been shown to be reduced in DCM patients. LV segmental strain pattern has been explored using 3-D echocardiography speckle tracking. Duan, et al found stepwise increasing strain pattern in the healthy group, although the changes in the strain pattern of LV segments have not been further studied in DCM patients (LVEF < 50%). Niemann group have found a regional strain reduction in patients with DCM. However, no further study has been conducted to assess different deterioration degrees of cardiac function in DCM. Furthermore, they used echocardiography with relatively low spatial resolution, which could affect tracking quality. The present study is the first to use novel TT based on CMR to describe the base-to-apex strain pattern at different deterioration levels of the cardiac function in DCM. Further studies are needed to explore the clinical significance of this finding.
DCM. In addition to flat pattern with no segmental strain difference of the left ventricle in patients with DCM, which was consistent with previous reports, we found another segmental strain pattern in the severe deterioration group. RS and CS of the left ventricle from the base to apex increased stepwise in healthy volunteers, which may be due to the unique physiologic geometry of the left ventricle. A gradual thinning of the wall is observed from the base to apex, which results in a more curved wall with reduced wall stress at apex. During systolic period, the apical wall is thickened relatively larger, leading to relative displacement in circumferential and radial direction of apex to be the highest among three segments. Additionally, we found that the base-to-apex increasing pattern disappeared in moderate DCM patients, and was replaced by flat pattern. These results suggested that the LV segmental
strain values decreased at different degrees in DCM patients with moderate decrease of LVEF. For the severe DCM group, the LV segmental strain changes demonstrated an opposite pattern, with the highest CS and RS values at the base segment of LV. This change in the LV base-to-apex pattern helps us understand the deterioration progress of wall motion in DCM patients.

Fiber geometry of the left ventricle is smooth and has a right-handed helical orientation in the subendocardium, circumferential orientation in the midwall, and left-handed helical orientation in the subepicardium. Henn, et al. reported that contractile injury in non-ischemic DCM occurs asynchronously in various segments of the left ventricle accompanied with cardiac function deterioration, which suggested the heterogeneity of strain injury. In the progress of DCM, left ventricle dilates from oval to spherical, while orientation of LV fibers changes from oblique to horizontal, especially in the apex segment. These may help explain why the greatest strain change occurred in the LV apex.

A previous study has also showed that RV function was somehow impaired in the progress of DCM. RV
global longitudinal strain and peak myocardial strain in septal and lateral walls were significantly impaired in DCM patients. In our study, GRS\textsubscript{RV} and GLS\textsubscript{RV} decreased in the moderate DCM group, but GCS\textsubscript{RV} had not decreased until it was in the severe deterioration DCM group. Three global strain values of RV in the DCM groups decreased out of synchrony compared to the control group. This was due to the complex structural and physiological properties of the right ventricle. The function of the right ventricle is more characterized by volume loading than dynamic working. This asynchronous myocardial deformation in three axial directions could also be caused by LV dysfunction, or alternations of interventricular interdependence, or RV myocardial damage by DCM.

CMR-based global LV strain analysis, which is less operator-dependent than visual wall motion analysis, has been adopted to predict adverse events of DCM. After following up 210 patients with DCM for a median of 5.3 years, Buss, et al. found that GLS above -12.5% was an independent predictor of survival beyond other clinical parameters. With simplified analysis, our study initially found that not only GLS\textsubscript{LV} > -11.62% but also GRS\textsubscript{LV} parameters. With simplified analysis, our study initially found that not only GLS\textsubscript{LV} > -11.62% but also GRS\textsubscript{LV} 5 12.42% or GCS > -9.35% was associated with cardiac events in non-ischemic cardiomyopathy.

**Study limitations:** Since this was a single cohort study with a limited number of DCM patients, the follow-up duration was relatively short. Further follow-up is currently in progress. Better parameters for predicting cardiac events are expected.

**Conclusion**

LV segmental values reduce non-homogeneously in DCM patients with moderately and severely deteriorated heart function. A characteristic LV base-to-apex strain pattern can provide new insights necessary to understand the deterioration of wall motion in DCM patients. Further studies are warranted to investigate if the observed pattern is unique for DCM and its value in differential diagnosis.

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**Disclosures**

**Conflicts of interest:** The authors have no conflicts of interest to declare.

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