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Myocardial Deformation in Acute Myocarditis With Normal Left Ventricular Wall Motion

– A Cardiac Magnetic Resonance and 2-Dimensional Strain Echocardiographic Study –

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Background: The aim of our study was to assess longitudinal (L), circumferential (C) and radial (R) strain (S) of the left ventricle (LV) in patients with acute myocarditis and preserved LV wall motion.

Methods and Results: Of the 26 male patients that were enrolled, 13 patients (26±8 years) suffered from acute myocarditis and 13 (25±2 years) were healthy participants (controls). Both patients and controls underwent cardiac magnetic resonance (CMR) and 2-dimensional S imaging (2D-S) echocardiography on the same day. Myocardial strains (RS, LS and CS) were quantified by 2D-S. In patients with myocarditis, a delayed enhancement (DE) CMR study was performed to identify damaged myocardial segments. In the myocarditis group there was a significant LS reduction compared with controls (–25±7 vs –20±7, P<0.0001), whereas no difference was found between the 2 groups concerning CS and RS. Subepicardial DE areas were found in 12 of 13 patients. Segments with DE showed a significantly lower LS in comparison with segments without DE (–19±4 vs –23±6, P<0.0001). In contrast, no difference in CS and RS was found when comparing segments with DE vs segments without DE.

Conclusions: In patients with acute myocarditis, evidence of subepicardial damage and no wall motion abnormalities, longitudinal deformation is diffusely impaired, whereas circumferential impairment is regionally sited in the areas of subepicardial damage. (*Circ J* 2010; **74:** 1205–1213)

Key Words: Magnetic resonance imaging; Myocarditis; Tissue Doppler imaging

Ventricular contractile function depends on a complex longitudinal, circumferential and radial deformation that is deeply dependent on myocardial fiber architecture.[1–3] Regional myocardial deformation can be assessed by many techniques such as sonomicrometry, tagging cardiac magnetic resonance (CMR) and tissue Doppler imaging (TDI) echocardiography. One of the most recent techniques aimed at quantifying myocardial deformation is 2-dimensional strain imaging (2D-S), a new non-invasive and accurate method.[4–9]

A transmural heterogeneity of left ventricular (LV) wall deformation has been documented in healthy patients: longitudinal and circumferential strain is higher in subendocardial than subepicardial layers, and a base to apex strain gradient exists, with longitudinal, circumferential and radial strain higher at the apex than at the base.[10,11] In myocardial infarction, the distribution of strain impairment reveals the extent of necrosis: a transmural infarction is characterized by reduced longitudinal, circumferential and radial strain, while in subendocardial necrosis only the longitudinal and radial strain are reduced, and the circumferential strain is preserved.[8,9,12]

Acute myocarditis is characterized by inflammatory myocardial damage that can result in severe LV dysfunction.[13] In acute focal myocarditis, however, the myocardial damage is mainly circumscribed to the subepicardial layers, whether or not it is associated with any wall motion abnormality.[14–15] Focal myocarditis thus may be a suitable model for assessing the abnormalities of myocardial deformation induced by selective damage of the subepicardial layer.

CMR associated with the delayed enhancement (DE) technique reveals the location, size and transmural extent of myocardial damage. This technique shows the compromised

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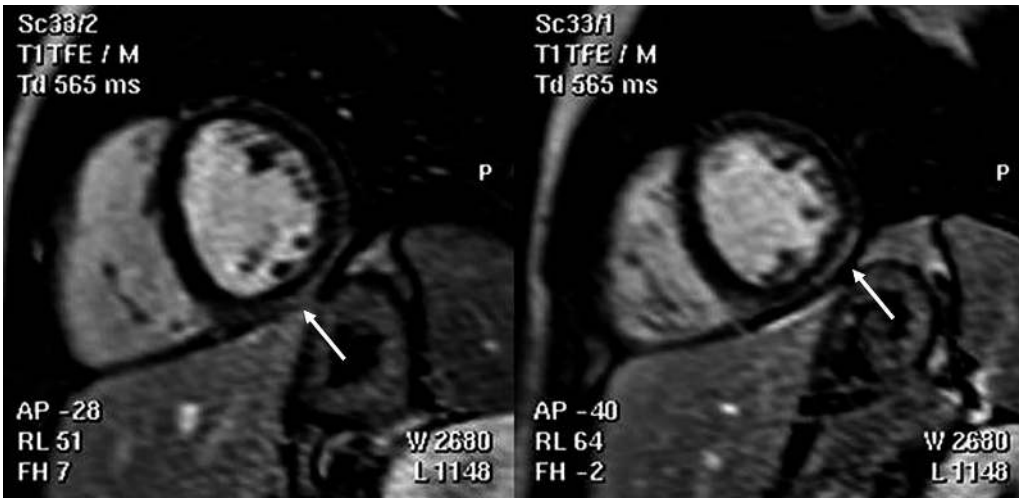

Figure 1. Delayed enhancement-cardiac magnetic resonance images of 2 contiguous mid short-axis views of the left ventricle in a patient with acute myocarditis. White arrows indicate the myocardial damage (hyperenhancement areas) involving the subepicardial layers of the inferior and inferolateral walls.

myocardium as a hyperenhanced area that always involves the endocardial layer in myocardial infarction, whereas in focal myocarditis subepicardial layers are predominantly affected.[14–17] The hypothesis of the present study was that LV strain abnormalities can be a subliminal sign of subepicardial damage in patients with acute myocarditis, as documented by DE-CMR, in absence of wall motion abnormalities. The aim of this study was to analyze global and regional 2D myocardial strain in patients with acute focal myocarditis in the presence of epicardial damage but without wall motion abnormalities.

Methods

Patients

From February 2007 to October 2008, 27 male patients were enrolled. Fourteen consecutive patients (mean age: 27±9 years) had a diagnosis of suspected acute myocarditis based on the following criteria: (A) history of flu-like symptoms within 8 weeks before admission (14/14); (B) 1 of the following symptoms: fatigue/malaise (4/14), chest pain (14/14), dyspnea (2/14), palpitation (4/14); (C) 1 of the following ECG patterns: ST-segment elevation (14/14), T wave abnormalities (5/14); and (D) increase of inflammation markers (14/14) and cardiac enzymes (14/14).

Thirteen healthy male participants (mean age: 25±2 years) without a history of heart disease and with normal ECG and transthoracic echocardiogram were enrolled as the control group. Both patients and controls were free from any other concomitant disorder (hypertension, dyslipidemia, diabetes, obesity). Both patients and controls underwent a standard transthoracic echocardiogram study, 2D-S evaluation and CMR on the same day and in random order. Coronary angiography was performed to rule out coronary artery disease on the basis of the DE pattern.

The study was approved by the local ethics review committee and the investigation conformed to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

CMR Data Acquisition and Analysis

CMR was performed using a 1.5-T system (Gyroscan NT; Philips Medical Systems, Best, The Netherlands) with a cardiac phased-array coil and vectorcardiogram synchronization. A breath-hold balanced fast field echo sequence was used to evaluate wall motion and global LV function. Sequence parameters were: TR 3.8 ms, TE 1.92 ms, flip angle 60°, slice thickness 8 mm, matrix 192×512, field of view 500 mm, FOV 50% and number of phases 30. In each patient, depending on LV volume, a total of 9–14 short-axis views and 2 long-axis views (4-chamber view and 2-chamber view, respectively) were acquired.

DE images by a gradient echo inversion recovery sequence were obtained within 10–20 min after bolus injection of 0.2 mmol/kg of gadobutrol (Gadovist®, Schering, Germany); a 2D-T1-weighted turbo-field-echo technique was used in the same short and long axis views. Sequence parameters were: TR 4.3 ms, TE 1.54 ms, flip angle 15°, slice thickness 10 mm, matrix 208×512 and field of view 350 mm, FOV 80%). Inversion time (200–320 ms) was optimized to a null signal from normal myocardium. DE images were obtained only in patients with suspected myocarditis. LV volumes, mass and ejection fraction (EF) were measured using a previously validated software (EasyVision, version 4.0; Philips Medical Systems, Best, The Netherlands).

As reported in a previous study,[18] the areas of DE were assessed by visual approach with a scheme based on the transmural extent of DE within each quartile (0–25%, 26–50%, 51–75% or >75%). According to the literature, patients were labeled as suffering from myocarditis if myocardial damage was evident on the LV wall but involvement of the endocardial layer was absent (**Figure 1**).[14–17]

The 2-Dimensional Echocardiography Data Acquisition and Analysis

Echocardiographic images were obtained using a commercial ultrasound machine (My Lab 50, Esaote, Florence, Italy) equipped with a 2.5-MHz phased array transducer. Parasternal short axis views at the basal, mid and apical levels and 3

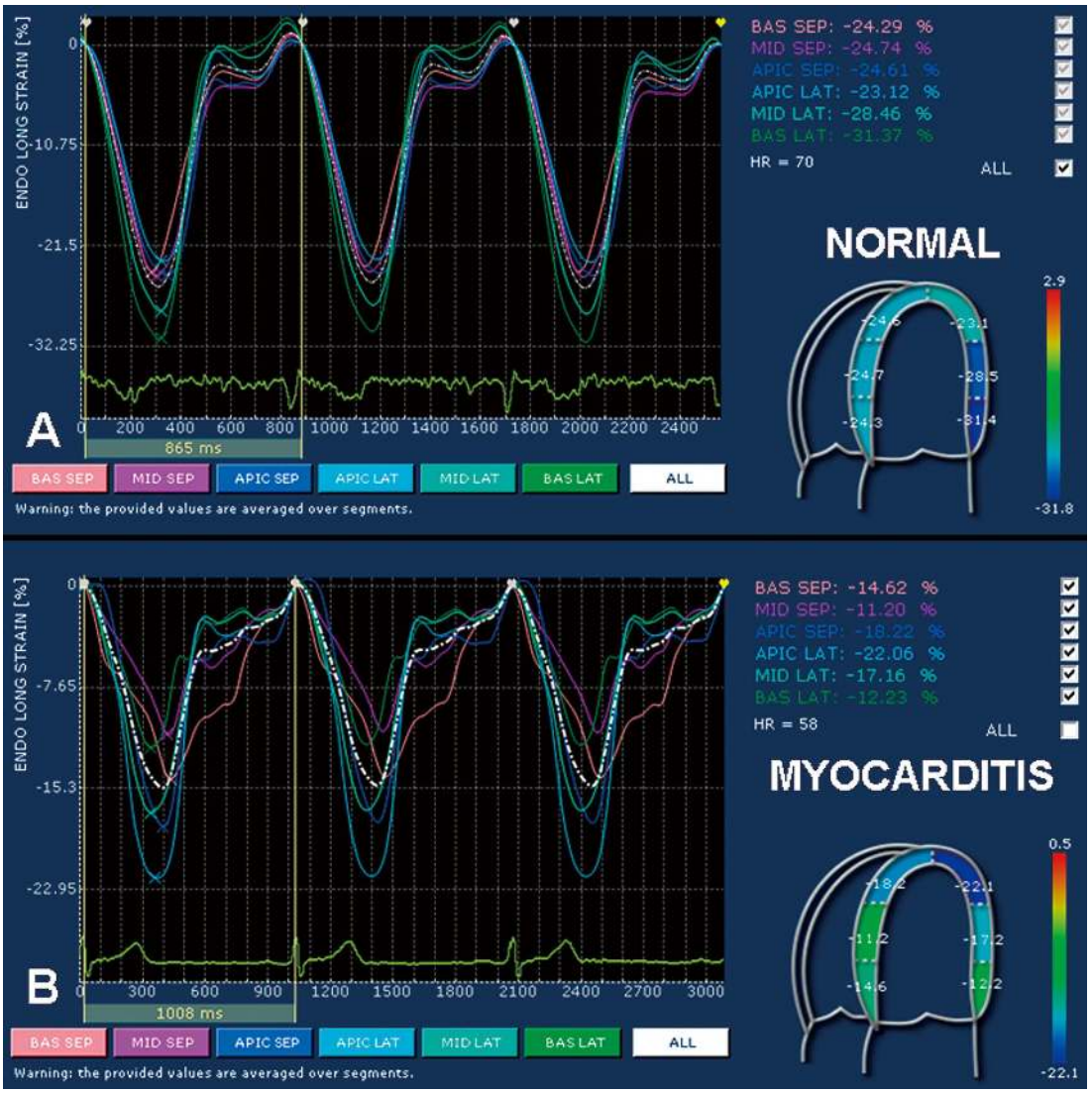

Figure 2. Longitudinal strain curves of left ventricle in a (**A**) normal subject and (**B**) patient suffering from myocarditis.

standard apical views (4-chamber, 2-chamber and long-axis) were acquired. LVEF was calculated by biplane Simpson's method; LV diastolic function was quantified by the ratio between the E wave velocity of the pulsed wave Doppler mitral flow image and the early diastolic velocity of the septum at the mitral annulus level (E' wave) on TDI.[19] A 16-segment model was used to divide the LV.[20]

A dedicated software package (XStrain™, Esaote, Florence, Italy) was used for an off-line quantification of circumferential, radial and longitudinal strain. This software provides angle-independent 2D strain based on speckle tracking.[21–23] For the quantification of radial and circumferential strain, the software was applied on parasternal short-axis views, while for the quantification of longitudinal strain, the same software was applied on apical views. More specifically, XStrain[24] relies on a "feature tracking" algorithm and, in order to improve the border tracking results, it combines speckle tracking based with other information such as tissue-to-blood border detection, the periodicity of the cardiac cycle and the fact that the cardiac borders maintain their own "overall spatial coherence" over time. All data were elaborated with the aid of Fourier techniques that ensure a higher accuracy using the periodicity of the heart motion. The software asks the user to identify the initial border position by identifying a sequence of points on an arbitrary single frame of the acquired loop. Then the border is automatically followed frame by frame, by searching for each single point and the maximum likelihood in the greyscale pattern over its neighbourhood in the following frames. Strain is obtained by comparing displacements of the speckles in relation to each other along the endocardial contour/border for quantify circumferential and longitudinal strain or between endocardial and epicardial contours/borders for radial strain. Frame by frame displacement of these points was automatically evaluated by generating strain curves (**Figure 2**).

Only images with good quality and adequate frame rates (50–70 frames/s) were used. The tracking quality was verified for each segment and subsequent manual adjustments were

Table 1. Demographic and Echocardiographic Characteristics

	Controls (n=13)	Myocarditis (n=13)	P value
Age (years)	25±2	26±8	NS
Male gender (%)	100	100	NS
LV mass (g)	161±28	164±38	NS
LVEDD (mm)	50±3	50±4	NS
LVESD (mm)	32±3	32±3	NS
LVEDV (ml)	77±15	80±8	NS
LVESV (ml)	27±6	30±4	NS
LVEF (%)	65±4	62±2	0.04
LA area (cm^2)	14±2	14±2	NS
RA area (cm^2)	16±2	16±2	NS
E/E'	4±2	4±1	NS

LV, left ventricular; EDD, end-diastolic diameter; ESD, end-systolic diameter; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; LA, left atrium; RA, right atrium.

performed when required.

All images used for quantification of longitudinal and circumferential strain were independently analyzed off-line by 2 cardiologists (G.D.B. and C.Z.) who were unaware of the clinical condition. Inter-observer variability was assessed.

Follow-up

The follow-up was performed by history, clinical evaluation and a 2D-S echocardiographic study. The events evaluated were: a new occurrence of acute myocarditis or a new hospitalization for any cardiac reason, heart failure and sudden death.

Statistical Analysis

Continuous variables were expressed as mean±1 SD and categorical variables were expressed as percentages. An unpaired t-test was used to assess the differences between the myocarditis and control groups.

One-way analysis of variance (ANOVA) and Bonferroni post hoc tests, when appropriate, were used to compare data between the three groups (No-DE vs DE 1–25% vs DE >25%).

Receiver-operating characteristic (ROC) curves were constructed, and areas under the curves were measured to determine cut-off values of strain for optimal sensitivity and specificity. The ROC analyses were set to identify the segments of the myocarditis group compared with the controls.

Interobserver and intraobserver variability were assessed using the Bland-Altman method. For any statistical comparison, a P-value <0.05 was considered significant. Statistical analyses were performed using SPSS version 12 (SPSS Inc, Chicago, IL, USA).

Results

All participants underwent transthoracic echocardiogram, 2D-S and CMR within 48 h from admission. Of the 14 patients suffering of acute myocarditis, only 1 patient (7%) showed an akinesia of apical LV segments with a LV dysfunction (EF was 37%). This patient had a non-ischemic localization of DE (epicardial layer of inferior and anterior wall and mid-wall of septum) and an impairment of longitudinal (–14±5), circumferential (–13.6±4.4) and radial (15±4.4) strain. Thus the 13 remaining patients with acute myocarditis and preserved wall motion and EF were labeled as the myocarditis group. Table 1 shows that no significant difference is present

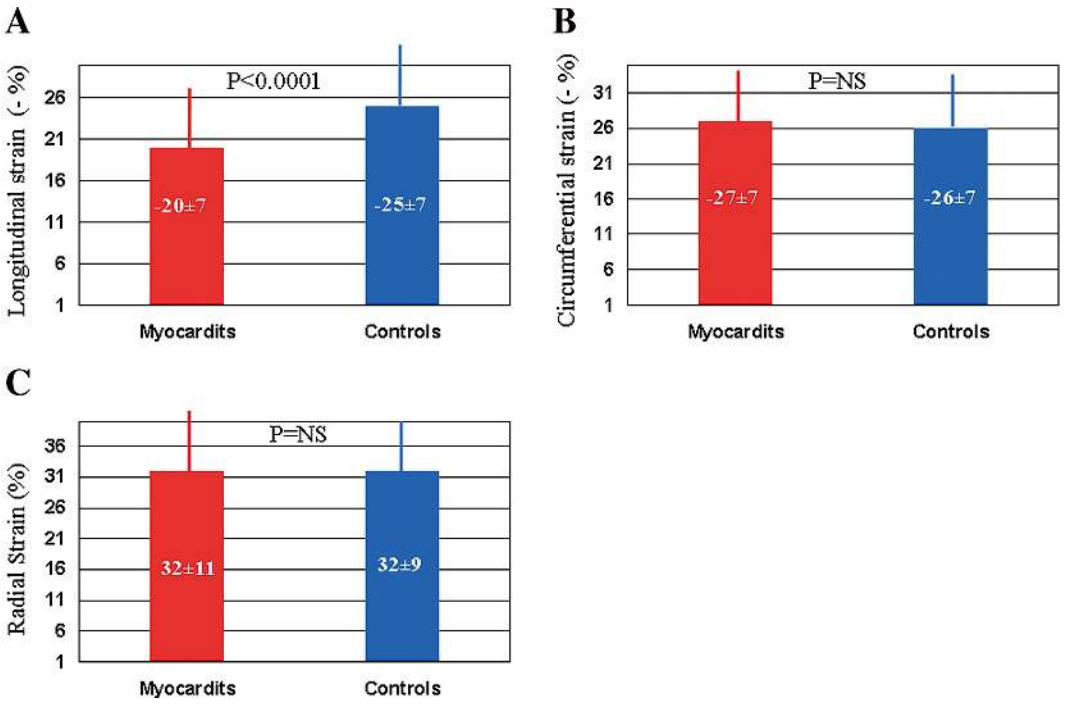

Figure 3. (A) Longitudinal, (B) circumferential and (C) radial strain in patients with myocarditis and in controls.

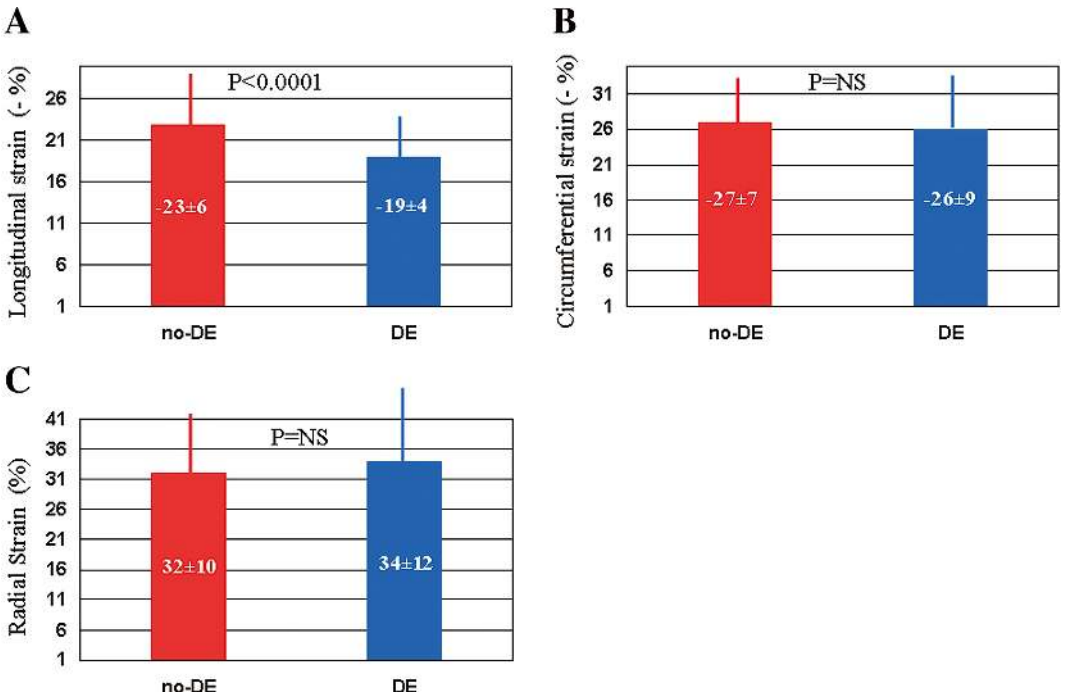

Figure 4. (**A**) Longitudinal, (**B**) circumferential and (**C**) radial strain in myocardial segments without (no-DE) and with (DE) delayed enhancement (data relative to the whole population, including both patients and controls).

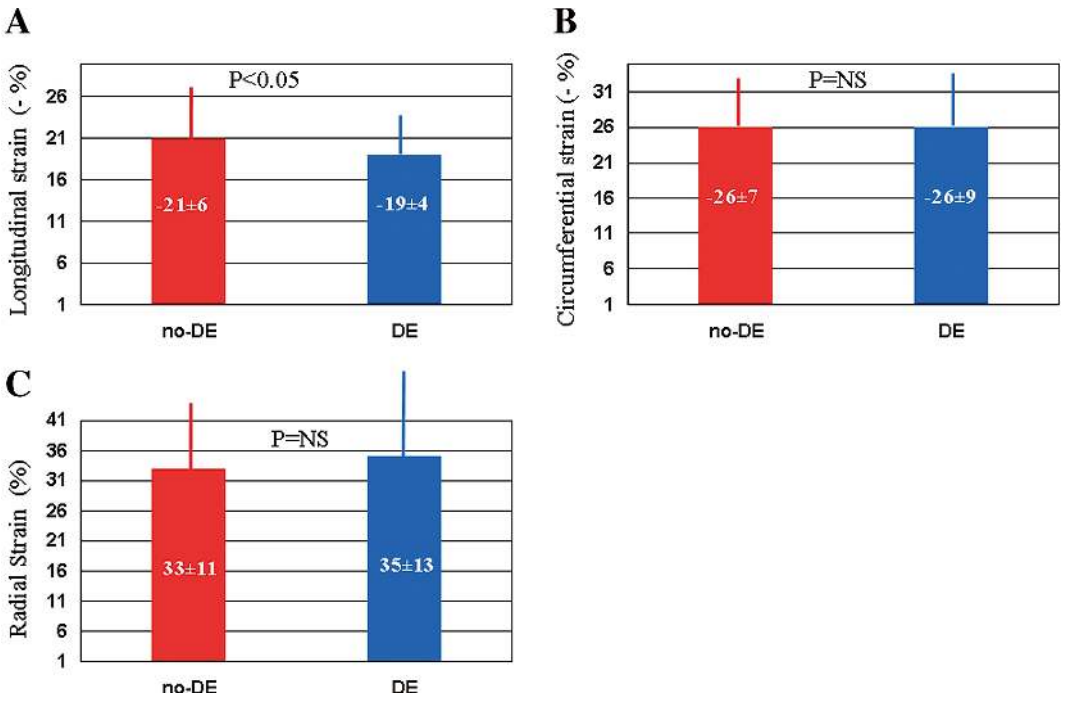

Figure 5. (**A**) Longitudinal, (**B**) circumferential and (**C**) radial strain in myocardial segments without (no-DE) and with (DE) delayed enhancement (data relative to patients with myocarditis).

Table 2. Longitudinal, Circumferential and Radial Strain of Left Ventricle Walls

	Longitudinal strain			Circumferential strain			Radial strain		
	Controls (n=13)	Myocarditis (n=13)	P value	Controls (n=13)	Myocarditis (n=13)	P value	Controls (n=13)	Myocarditis (n=13)	P value
Anterior wall (%)	–26±5	–20±5	<0.0001	–27±6	–26±7	NS	32±7	36±14	NS
Lateral wall (%)	–24±6	–20±6	0.001	–28±7	–25±7	0.02	31±10	33±11	NS
Inferior wall (%)	–29±8	–22±5	<0.0001	–27±6	–25±8	NS	34±12	30±9	NS
Septal wall (%)	–23±6	–20±5	<0.0001	–27±6	–26±9	NS	32±8	31±12	NS

Lateral wall includes all anterolateral and inferolateral segments of the left ventricle. Septal wall includes all anteroseptal and inferoseptal segments of the left ventricle.

Table 3. Longitudinal, Circumferential and Radial Strain in Segments Without DE (No DE), With DE Transmural Extent of 1–25% (DE 1–25%) and With DE Transmural Extent >25% (DE>25%)

	No DE	DE 1–25%	DE>25%	P value	P value*	P value**
Longitudinal strain (%)	–23±6	–20±4	–19±4	0.04	0.001	NS
Circumferential strain (%)	–27±7	–28±3	–24±6	NS	NS	NS
Radial strain (%)	32±10	39±12	34±14	NS	NS	NS

P value, No DE vs DE 1–25%; P value*, No DE vs DE>25%; P value**, DE 1–25% vs DE>25%.
DE, delayed enhancement.

between the myocarditis and control groups concerning LV size, volume and mass, atrial areas and diastolic LV function. In the myocarditis group, LVEF was within the normal range but significantly lower than in normal participants (P=0.04).

CMR: Functional Parameters

The 2 groups (myocarditis and control) did not show any significant difference concerning diastolic and systolic LV volume (156±21 ml vs 170±33 ml, P=NS; 68±12 ml vs 71±15 ml, P=NS); LV mass was almost identical in both groups (105±27 g vs 103±45 g, P=NS). LVEF, although in the normal range, was lower in the myocarditis than in the control group (55±3 vs 59±1, P=0.02).

CMR: DE

Areas of DE were found in 12 of the 13 patients in the myocarditis group. One patient without DE underwent coronary angiography, which did not show any coronary artery disease. A total of 54 (26%) out of 208 LV segments had DE with subepicardial distribution. The location of DE was: the inferior wall (2 patients; 17%), the infero-lateral wall (4 patients; 33%), the antero-lateral wall (3 patients; 25%) and both antero-lateral and infero-lateral walls (3 patients; 25%). Therefore, the 83% of segments with DE were located in the anterolateral and inferolateral wall.

The transmural extent of DE did not exceed 75% of the LV wall thickness in any segment. The subepicardial DE extent was 1–25% in 26 segments (48.2%), 26–50% in 24 segments (44.4%) and only 51–75% in 4 segments (7.4%).

Segments with a subepicardial transmural DE extent >26% (28 segments) were mainly located in the antero-lateral and infero-lateral walls (22 segments, 79%).

Longitudinal, Circumferential and Radial Strain

Longitudinal strain was measured in 379 segments (91%), circumferential strain in 337 segments (81%) and radial strain in 261 segments (63%). The remaining segments were excluded because of poor echocardiographic image quality. The myocarditis patients had a significant global longitudinal LV strain decrease in comparison with normal participants (–20±7% vs –25±7%, P<0.0001), while global circumferential strain and radial strain did not show any difference between the 2 groups (P=NS) (Figure 3).

Considering all participants together (both the myocarditis and control groups), analysis of segments with DE (49 segments) showed that these had a significantly lower global longitudinal strain (P<0.0001) than segments without DE (330 segments). In contrast, no significant difference in global circumferential strain and radial strain was found between segments with and without DE (Figure 4). Considering the myocarditis group only, longitudinal strain was significantly lower (P=0.04) in segments with DE (49 segments; –19±4%) than in those without DE (162 segments, –21±6%), while no difference in circumferential strain and radial strain was observed in segments with DE, when compared to those without DE (Figure 5).

Analysis of myocardial deformation, performed separately for each LV wall, revealed that patients had: (1) a significant longitudinal strain decrease in each wall; (2) a significant decrease in circumferential strain only in the lateral wall; (3) no difference in radial strain (Table 2); (4) longitudinal strain impairment in all segments with DE, independent of DE transmurality (Table 3); and (5) circumferential strain lower in segments with >25% transmural DE extent, with respect to segments with or without DE transmural extent <25% (Table 3).

Longitudinal strain showed a moderate predictive value (area under the ROC curve was 0.73, 95%CI: 0.66–0.79) that distinguished the 2 groups. A longitudinal strain cut-off point of ≤–21% yielded the best result in terms of combined sensitivity (69%) and specificity (65%). However, using a longitudinal strain value ≤–21% in 2 or more contiguous segments, as a marker of longitudinal LV dysfunction, sensitivity was 100%, specificity was 62%, diagnostic accuracy was 81%, positive predictive was 72% and negative predictive value was 100% for the diagnosis of acute myocarditis.

Follow-up Data

Ten of the 13 patients (77%) in the myocarditis group were included in the follow-up evaluation. The average duration of follow up was approximately 23±11 months. Mainly, our follow-up data showed that: (1) no patients had any clinical

event recurrence; and (2) the evaluation of myocardial deformation by 2D-S showed no significant recovery of segmental longitudinal deformation between acute phase myocarditis (–20±7%) than follow-up myocarditis (–19±5). Furthermore, circumferential and radial deformations were similar between the acute phase and follow-up (–27±7 vs –26±5 and 32±11 vs 32±14, respectively).

Reproducibility

There was good inter-observer agreement concerning longitudinal (mean –2.1%, SD 11.7), circumferential (mean –0.4%, SD 4.6) and radial strain (mean 4.6 %, SD 20). Intra-observer agreement of longitudinal (mean –4.4%, SD 14), circumferential (mean –1%, SD 6) and radial strain (mean 4.7 %, SD 28) was also good.

Discussion

The main results of this study showed that both longitudinal and circumferential myocardial strain were impaired in patients with acute myocarditis with preserved wall motion and evidence of subepicardial damage. Particularly, longitudinal strain was reduced in all myocardial walls independently from the presence or absence of subepicardial damage, although segments with subepicardial DE had a greater impairment of longitudinal strain than those without DE. This suggests that subepicardium contributes together with subendocardium to longitudinal strain.

In the normal human heart, longitudinal strain is higher in endocardium than in epicardium.[25] This is likely to depend on LV geometry and tissue incompressibility: accordingly, systole concentric shells of myocardium have proportionally greater changes in dimension with decreasing radius.[26,27] The relevant contribution of subendocardium to longitudinal strain is also confirmed by myocardial infarction, since subendocardial infarctions have a longitudinal strain reduction almost identical to that of transmural infarctions.[8,9] The contribution of both subendocardium and subepicardium to longitudinal function can be explained by the complex orientation of myocardial fibers. These are predominantly longitudinal in the subendocardial region (right-handed helix), become circumferential in the mid-wall, and resume a longitudinal orientation at the subepicardial surface (left-handed helix).[28–30] During ejection, the ventricular volume is reduced as a result of contraction of both the subendocardial and subepicardial layers.[1–3] Whenever one of these is damaged (subendocardium in myocardial infarction, subepicardium in focal acute myocarditis), longitudinal function is impaired. On the other hand, the functional recovery of viable sub-epicardial regions is an important mechanism for the improvement of longitudinal regional function in patients with myocardial infarction.[31]

Longitudinal strain was globally reduced in patients with uncomplicated diabetes, normal LV volumes, regional wall motion and EF.[32,33] This is thought to be an early, diffuse and subclinical response to myocardial accumulation of connective tissue and insoluble collagen due to diabetes.

Myocarditis shows a macroscopic damage (ie, DE on MRI) usually located in the epicardial layer of the lateral wall; however, acute myocarditis is a systemic disease as a consequence of a direct viral damage or as consequence of an immune reaction, mediated by T-lymphocytes and antibodies directed against pathogens and similar endogenous heart epitopes, involving, although without clinical sequels, all of the myocardium.[34–36] These latter findings added with the results of De Cobelli, showing a positive septal biopsy for acute myocarditis without septal DE on MRI,[15] can explain our findings that also segments without DE, but having longitudinal dysfunction.

Circumferential strain was reduced in those segments with a DE transmural extent higher than 25%. The link between the reduction of circumferential strain and the DE transmural extent is likely to depend on the localization of the circumferential fibers mainly located in the mid-myocardium.

Accordingly, circumferential strain is preserved in subendocardial infarction; on the contrary, it is impaired in transmural infarction.[9]

In contrast to longitudinal and circumferential strain, radial function was unaffected in isolated subepicardial damage because it strongly depends on the shortening of subendocardial longitudinal fibers.[1,37–41]

Study Limitations

A major limitation to this research is the relatively small number of young male patients with myocarditis and normal LV wall motion. However, the study reflects a single center experience, based on a series of selected consecutive patients with a rare disease collected over approximately 2 years. The annual incidence of myocarditis is estimated at 10–17 per 100,000 in the population, and in these patients a preserved wall motion can be found in no more than 40%.[14,15,42,43]

Endomyocardial biopsy is the gold standard for the diagnosis of myocarditis, but in patients without wall motion abnormalities and preserved EF, this approach is unnecessary or even contraindicated.[44] Therefore, CMR is the primary tool for non-invasive assessment of myocardial inflammation in patients with acute myocarditis and normal systolic function.

A further limitation of the present study is that 2D myocardial strain is a new, not well standardized tool in cardiovascular disease; chiefly this method still suffers from reproducibility issues partly from the need for manual tracings of the myocardium.

Additionally, approximately 9% longitudinal, 19% circumferential and 37% radial segments were not analyzable by 2D strain echocardiography because of poor image quality.

In the present study, we did not use tagging MRI, which is the referral non-invasive research tool to quantify segmental deformation. However, it is not widely used in clinical practice due to the complexity of the technique (reduced availability of the sequence to acquire images, and image acquisition and post-processing analysis is time consuming).

The DE technique was not performed in normal participants. However, in this group of young participants who had no history or symptoms of heart disease, and normal ECG and echocardiogram, it was very unlikely to find a scar on DE-CMR.

Conclusion

The present study demonstrates the effect of acute myocardial inflammation on LV deformation.

In acute myocarditis with evidence of subepicardial damage and without wall motion abnormalities, longitudinal deformation is diffusely impaired, whereas circumferential impairment is regionally sited in the areas of subepicardial damage and, in particular, in those segments with a higher transmural extent of DE. Impaired longitudinal and circumferential function in the absence of wall motion abnormalities may represent a useful additional diagnostic finding to

support the diagnosis of acute focal myocarditis; however, further investigations with a larger sample size are required to confirm the clinical role of 2D myocardial strain in acute myocarditis.

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Disclosure

All authors declare no conflict of interest.

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