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ORIGINAL PAPER

Speckle tracking echocardiography in acute myocarditis

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Abstract To evaluate 2-dimensional speckle tracking echocardiography as a diagnostic and prognostic tool in patients with acute myocarditis. In this retrospective cohort study, 45 patients (age, 39 ± 15 years; 32 male) with suspected acute myocarditis and 83 healthy controls (age, 39 ± 13 years; 27 male) underwent 2-dimensional speckle tracking echocardiography. Main outcome measures were circumferential and longitudinal strain and strain rate as prognostic and diagnostic markers. Patients with myocarditis had lower circumferential strain (−13.3 ± 5.6 % vs. −22.3 ± 4 %), circumferential strain rate (−0.9 ± 0.3 vs. −1.4 ± 0.3 s^{-1}), longitudinal strain (−11.7 ± 4 % vs. −17.7 ± 1.9 %), and longitudinal strain rate (−0.7 ± 0.2 vs. −1.0 ± 0.1 s^{-1}) (all $P < .001$). For diagnostic purposes, longitudinal strain had the greatest area under the curve, 0.93 (optimal cutoff value, −15.1 %; sensitivity, 78 %; specificity, 93 %). Future events were defined as cardiac death, heart transplant, placement of left ventricular assist device or implantable cardioverter-defibrillator, pulmonary edema–related respiratory failure, cardiogenic shock, and rehospitalization due to cardiac events. For every 1 % decline in longitudinal or circumferential strain, the hazard ratios (95 % CIs) were 1.26 (1.10–1.47) and 1.34 (1.14–1.63), respectively; for every 0.1 s^{-1} decline in longitudinal or circumferential strain rate, the hazard ratios (95 % CIs) were 1.43 (1.09–1.89) and 1.52 (1.19–2.01), respectively ($P < .01$). Kaplan–Meier curve and log-rank test showed event-free survival significantly related to these 4 measurements. In acute myocarditis, left ventricular strain and strain rate may be promising diagnostic and prognostic tools, even in patients with preserved left ventricular ejection fraction. Most importantly, this imaging technique had a role in predicting deterioration and overall event-free survival.

Keywords Acute myocarditis · Strain and strain rate · Diagnosis and prognosis · 2-D speckle tracking echocardiography · Mechanical function · Myocarditis

Abbreviations

CMR	Cardiovascular magnetic resonance
FOV	Field of view
HR	Hazard ratio
LGE	Late gadolinium enhancement
OR	Odds ratio
SSFP	Steady-state free precession
TE	Echo time
TI	Inversion time
TR	Repetition time

Introduction

Acute myocarditis has been reported to account for up to 12 % of sudden deaths in young adults [1]. The presenting symptoms of acute myocarditis are highly variable and its diagnosis is challenging [2–4]. Currently, no single clinical or imaging technique can confirm the diagnosis or provide

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prognostic value. The diagnostic accuracy of clinical history, physical examination, electrocardiography, and serology are not satisfactory [1–4]. The findings of acute myocarditis on conventional echocardiography are nonspecific [3, 5]. Endomyocardial biopsy is a widely accepted standard method. It is highly specific but invasive and not appropriate for every patient [1–5]. Most recently, cardiovascular magnetic resonance (CMR) has become the primary noninvasive tool for diagnosing acute myocarditis. However, prior studies in this area have been limited by small sample sizes, variable patient inclusion criteria, and single-center data collection [3–5].

Two-dimensional speckle tracking echocardiography can quantitatively measure myocardial mechanics (strain and strain rate) in longitudinal, radial, and circumferential directions. In many clinical settings such as cardiomyopathy or coronary artery disease, a decrease in longitudinal strain by 2-dimensional speckle tracking echocardiography has been shown to detect left ventricular dysfunction before the occurrence of changes in left ventricular ejection fraction [6–8]. However, the diagnostic and prognostic importance of 2-dimensional speckle tracking echocardiography in patients with acute myocarditis has not been assessed.

The aim of our study was to calculate left ventricular mechanics by 2-dimensional speckle tracking echocardiography for these patients and to evaluate it as a diagnostic and prognostic tool. Only longitudinal and circumferential strain and strain rate were evaluated in our study because of the better inter- and intra-observer reproducibility shown by several previous studies [9–13].

Methods

Patients and controls

Patients admitted to Mayo Clinic in Rochester, Minnesota, between January 2004 and August 2009 with a clinical diagnosis of suspected acute myocarditis were enrolled. Based on previous descriptions of myocarditis [1–3, 14, 15], the inclusion criteria were (1) clinical symptoms compatible with a diagnosis of acute myocarditis, such as fever, viral prodrome, chest pain, palpitations, dyspnea, effort intolerance, or presyncope or syncope within 6 weeks of admission; (2) evidence of structural or functional abnormalities by echocardiography or evidence of myocardial damage as indicated by an elevated biomarker (troponin T level >0.1 ng/mL [reference value, ≤0.03 ng/mL] or creatine kinase MB fraction >6.2 ng/mL [reference value, ≤6.2 ng/mL]); and (3) absence of evidence of coronary artery disease by coronary angiography in patients older than age 35 years. Exclusion criteria were previous heart surgery, myocardial infarction, severe valvular disease, cardiac rhythms other than sinus, and poor echocardiographic window. Normal controls were individuals with no history of cardiovascular disease who had normal echocardiograms, unremarkable abnormal findings on physical examination, and low pretest probability of heart disease. This study was approved by the Mayo Clinic Institutional Review Board. Written informed consent was obtained from all enrolled patients.

Conventional 2-dimensional echocardiography

Comprehensive 2-dimensional transthoracic echocardiography was performed by a registered diagnostic cardiac sonographer using commercial echocardiographic systems (Sequoia [Siemens AG, Munich, Germany]; Vivid 7 [GE Healthcare, General Electric Company, Fairfield, Connecticut]; and iE33 [Philips Electronics, Amsterdam, the Netherlands) following a standardized protocol in the Mayo Clinic echocardiography laboratory in Rochester, Minnesota, at the time of presentation.

Two-dimensional echocardiography was used to measure left ventricular end-diastolic diameter, left ventricular end-systolic diameter, end-diastolic septal thickness, and ejection fraction according to the American Society of Echocardiography recommendations [16, 17]. Left ventricular mass was calculated from the left ventricular linear dimension, stroke volume was determined by Doppler echocardiography, and cardiac output was the result of multiplying the stroke volume by the patient's heart rate. Then these measurements were indexed by body surface area to derive left ventricular mass index, stroke volume index, and cardiac output index [16, 17]. Regional wall motion of the 16 segments was scored individually on the basis of the motion and systolic thickening. Segment scores were as follows: 1 = normal, 2 = hypokinesis, 3 = akinesis, 4 = dyskinesis, and 5 = aneurysmal changes. The wall motion score index was the sum of all the segment scores divided by the number of segments assessed [16].

2-dimensional speckle tracking echocardiography and analysis

Three-beat cine-loop clips, stored in DICOM digital format, were selected from the parasternal short-axis views at the papillary muscle level and from 3 apical views (4-, 3-, and 2-chamber views). The images were downloaded from the central archive to the computer workstation with an average frame rate of 43 Hz and analyzed offline using velocity vector imaging (Syngo Vector Imaging, version 2.0 [Siemens Healthcare, Malvern, Pennsylvania]).

Images were manually traced at the myocardium close to the endocardial surface, with avoidance of papillary muscles and trabeculations. Eight to 12 points were placed,

starting and ending at the 12-o'clock position for the short-axis view or at the mitral annulus for the apical view. The tracing was performed at end-systole or mid-systole, whichever had better endocardial definition, and was then assessed visually and adjusted repeatedly until optimal tracking was obtained. The global peak longitudinal strain or peak systolic longitudinal strain rate was averaged from all 3 apical views, and mean peak circumferential strain or systolic circumferential strain rate was averaged from the short-axis view.

Cardiovascular magnetic resonance

All studies were performed on a 1.5T system (Excite Twinspeed; GE Healthcare, Waukesha, Wisconsin). After initial scout images, multiple long-axis and short-axis cine steady-state free precession (SSFP) images were obtained from the atrioventricular ring to the apex. The sequence parameters for the SSFP images were as follows: echo time (TE) 1.6 ms, repetition time (TR) 3.7 ms, flip angle 45°, matrix 256 × 160, field of view (FOV) 320–440 mm with phase FOV 0.75–1.0, and 8-mm slice thickness with 1-mm interslice gap. Late gadolinium enhancement (LGE) images covering the left ventricle in multiple short-axis and long-axis views were obtained 7–12 min after an intravenous bolus of 0.2 mmol/kg gadodiamide (Omniscan; GE Healthcare, Princeton, New Jersey) with segmented inversion recovery fast gradient echo sequences (TE 1.6 ms, TR 3.7 ms, flip angle 20°, matrix 256 × 160, FOV 320–440 mm). Selection of the optimal TI for LGE images was accomplished with a multi-TI cine fast gradient echo sequence, which generates 40 images in a single slice location with increasing TIs.

In selected cases, T2-weighted imaging was performed with triple inversion recovery sequences to assess for myocardial edema. Assessment for early gadolinium enhancement was performed in selected cases with T1-weighted imaging sequences obtained both before gadolinium administration and again 2 min after gadolinium administration. All images were reviewed by 1 reader who was blinded to clinical parameters, results of echocardiography, and left ventricular mechanics. Presence of LGE in each segment was assessed according to the standardized myocardial segmentation, with segment 16 evaluated in the short-axis and long-axis views. Myocardial edema and early gadolinium enhancement were detected by comparing a region of interest to skeletal muscle with use of the ratios described by Friedrich et al. [3].

Follow-up and end points

All patients were invited for follow-up at our outpatient clinic after hospital discharge. The follow-up assessments performed were at the physicians' discretion. Major clinical events during the follow-up period were defined as cardiac death, heart transplant, placement of a left ventricular assist device or implantable cardioverter-defibrillator, respiratory failure due to pulmonary edema as confirmed by chest radiography, cardiogenic shock with need for an intra-aortic balloon pump or inotropic agent support, and rehospitalization due to cardiac events.

Statistical analysis

Continuous variables are expressed as mean ± SD and categorical variables as the numbers of subjects and percentages. For univariate analysis, a 2-sample *t* test was used for continuous values, and the χ^2 test or the Fisher exact test was used for categorical ones. Receiver operating characteristic analysis and the area under the curve were used to calculate the optimal cutoff values of the left ventricular deformation variables, and ejection fraction and stroke volume index were used as the criteria for diagnosis of myocarditis. Myocarditis patients were divided into 2 subgroups: ejection fraction of 50 % or higher and ejection fraction <50 %. Analysis of variance and the Tukey–Kramer test were used to compare the left ventricular mechanics between these 2 groups and controls. Significant variables of conventional 2-dimensional echocardiography and left ventricular mechanics were further analyzed in a multiple logistic regression model by forward stepwise selection.

The predictors of major adverse clinical events were evaluated by using the Cox univariate proportional hazards model. Risk for events was presented as hazard ratio (HR) with 95 % CI. The overall event-free survival rates were calculated using the Kaplan–Meier method and the log-rank test. The initial time point for event-free survival analysis was the date of admission. A P value <.05 was considered significant. JMP version 8 software (SAS Institute Inc [Cary, North Carolina]) was used for statistical analyses.

Reproducibility

Interobserver and intraobserver variability were assessed in 15 randomly selected subjects. Two independent observers calculated all left ventricular mechanics for interobserver variability, and the same observer repeated the measurements 1 month later for intraobserver variability. The variability was derived as the absolute difference between the 2 sets of measurements, divided by the overall mean of the 2 sets of measurements and expressed as percentages.

Results

A total of 45 patients who met the inclusion criteria (age, 39 ± 15 years; 32 [71 %] male) were enrolled, as were 83

healthy controls (age, 39 ± 13 years; 27 [33 %] male). Patients' onset of symptoms ranged from 1 to 33 days (median, 5 days) before their admission. The prominent cardiac symptoms were chest pain in 35 patients (78 %) and dyspnea in 18 patients (40 %). Other associated symptoms were fever (22 [49 %]), myalgia (9 [20 %]), and gastrointestinal or respiratory symptoms (4 [9 %] and 15 [33 %], respectively). Hypertension, diabetes mellitus, coronary artery disease, and hyperlipidemia had a similar distribution in both groups (*P* value not significant). Patients with myocarditis had a higher heart rate (86 ± 22 beats per minute) than controls (72 ± 11 beats per minute) ($P < .001$); systolic and diastolic blood pressures were similar. Twenty-eight patients (62 %) had ischemic changes on electrocardiography, including ST-segment elevation in 17 patients (38 %), T-wave abnormalities/ST-segment depression in 5 (11 %), and pathologic Q wave in 6 (13 %). Bundle branch block was noted in 3 patients (7 %). Troponin T level higher than 0.1 ng/mL was found in 38 of 43 patients (88 %) and creatine kinase MB fraction higher than 6.2 ng/mL was found in 31 of 38 patients (82 %). Either troponin T or creatine kinase MB fraction was elevated in 40 of 44 patients (91 %). A coronary angiogram was performed in 20 patients older than age 35 years to rule out an acute coronary syndrome. Right ventricular biopsy, performed in 12 patients, revealed giant cell myocarditis in 2 patients, eosinophilic myocarditis in 1, and lymphocyte predominant or mixed cell type in the other 9 patients.

Conventional 2-dimensional echocardiographic findings

Two-dimensional echocardiography was performed within 2 days after admission (median, 1 day), an average of 7 ± 7 days (range, 1–33 days) from onset of symptoms. The main findings are shown in Table 1. In patients with myocarditis, the walls were thicker, the left ventricular chamber was larger, and ejection fraction was decreased. Pericardial effusion was present in 13 patients (29 %).

Cardiovascular magnetic resonance

Twenty-two patients underwent CMR a median of 2 days after admission. LGE was found in 18 patients. Mid inferolateral and anterolateral segments were most frequently positive for LGE. Most LGE was present in the subepicardium in 71 % and in the subendocardium in 29 %. T2 sequence and T1 early gadolinium enhancement protocols were not performed routinely between 2004 and 2009 at Mayo Clinic. T2-weighted imaging was performed in 14 patients; 4 had positive T2 ratio enhancement, which represented edema. The protocol with T1 early gadolinium enhancement, which reflected inflammation, was performed in 10 patients; 2 had enhancement.

Table 1 Conventional 2-dimensional echocardiographic findings[a]

Characteristic	Myocarditis group (N = 45)	Control group (N = 83)	*P* value
Septal thickness (mm)	10 ± 2	9 ± 1	<.001
LVEDD (mm)	51 ± 6	47 ± 4	<.001
LVESD (mm)	38 ± 8	30 ± 3	<.001
LVMI (g/m^2)	94.8 ± 21.6	74.4 ± 13.1	<.001
EF (%)	49 ± 12	64 ± 4	<.001
Stroke volume index (mL/m^2)	37.0 ± 12.2	43.8 ± 7.6	<.001
Cardiac output index ($L/min/m^2$)	3.0 ± 0.9	3.1 ± 0.6	.50
Wall motion score index	1.6 ± 0.7	1	<.001

EF ejection fraction, *LVEDD* left ventricular end-diastolic diameter, *LVESD* left ventricular end-systolic diameter, *LVMI* left ventricular mass index

[a] Values are mean ± SD

Strain and strain rate analysis

Optimal tracking quality was obtained in 258 segments (96 %) of short-axis views and in 785 segments (97 %) from the longitudinal views among the 45 patients with myocarditis. In the 83 controls, optimal tracking quality was obtained in 472 segments (95 %) of short-axis views and in 1,371 segments (92 %) of longitudinal views.

Compared with the control group, the myocarditis group had significantly lower circumferential strain (−13.3 ± 5.6 % vs. −22.3 ± 4 %), circumferential strain rate (−0.9 ± 0.3 vs. −1.4 ± 0.3 s^{-1}), longitudinal strain (−11.7 ± 4 % vs. −17.7 ± 1.9 %), and longitudinal strain rate (−0.7 ± 0.2 vs. −1.0 ± 0.1 s^{-1}) (all $P < .001$).

The results of receiver operating characteristic and area under the curve analyses are shown in Fig. 1. Longitudinal strain had the greatest area under the curve, 0.93, and optimal cutoff value of longitudinal strain at −15.1 % would have a sensitivity of 78 % and a specificity of 93 %.

Multiple logistic regression

Only significant variables in the univariate analysis (i.e, sex, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, septal thickness, ejection fraction, and stroke volume index) underwent multivariate analysis by forward stepwise selection. The final multiple logistic regression model revealed that left ventricular strain and strain rate were still independently significant after adjusting for sex, septal thickness, left ventricular ejection

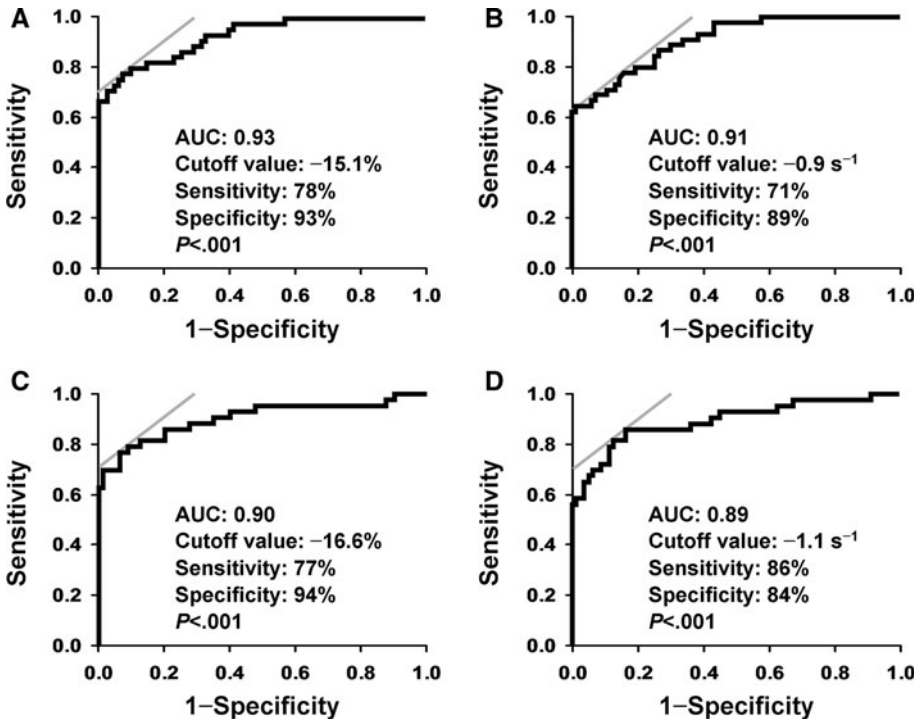

Fig. 1 Receiver operating characteristic *curves* for longitudinal and circumferential strain (**a** and **c**) and for longitudinal and circumferential strain rates (**b** and **d**). AUC indicates area under the *curve*

Table 2 Multiple logistic regression model for left ventricular strain and strain rate

LV strain and strain rate	Myocarditis group[a] (N = 45)		Myocarditis with EF > 50 %[b] (n = 19)	
	OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
LS (per 1 % change)	1.98 (1.28–3.59)	.001	1.77 (1.23–2.92)	.001
LSR (per 0.1 s^{-1} change)	2.89 (1.45–7.13)	.008	2.83 (1.49–6.7)	<.001
CS (per 1 % change)	1.31 (1.06–1.68)	.02	1.27 (1.06–1.56)	.04
CSR (per 0.1 s^{-1} change)	1.41 (1.07–1.97)	.03	1.44 (1.1–2.01)	.006

CS circumferential strain, *CSR* circumferential strain rate, *EF* ejection fraction, *LS* longitudinal strain, *LSR* longitudinal strain rate, *LV* left ventricular, *OR* odds ratio

[a] In the myocarditis group, adjusting for sex, septal thickness, EF, and stroke volume index

[b] In myocarditis patients with EF > 50 %, adjusting for sex, septal thickness, left ventricular end-systolic diameter, and EF

fraction, and stroke volume index. The odds ratios (ORs) and 95 % CIs are shown in Table 2. Longitudinal strain and longitudinal strain rate had an OR of 1.98 (per 1 %) and 2.89 (per 0.1 s^{-1}), respectively.

Myocarditis with preserved left ventricular function

Nineteen patients had preserved left ventricular systolic function in the myocarditis group (ejection fraction ≥50 % by conventional 2-dimensional echocardiography). When the myocarditis patients were compared with normal controls, they were found to have septal thickness (10 ± 1 mm vs. 9 ± 1 mm; $P = .001$), left ventricular end-systolic diameter (34 ± 5 mm vs. 30 ± 3 mm; $P = .002$), and ejection fraction (59 ± 6 % vs. 64 ± 4 %; $P = .002$) significantly different from those of controls on the basis of conventional 2-dimensional echocardiography variables. Strain and strain rate of 1 patient with preserved left ventricular ejection fraction are illustrated in Fig. 2. Indices of left ventricular mechanics were better differentiators: Analysis of variance and the Tukey–Kramer test showed significant difference within these 3 groups (Fig. 3). After adjustment for sex, septal thickness, left ventricular end-systolic diameter, and ejection fraction, these variables were still significant in the multiple logistic regression model (Table 2). Results of receiver operating characteristic and area under the curve calculations with optimal cutoff values, sensitivity, and specificity are shown in Table 3 for this group.

Follow-up

All 45 patients had a follow-up of 19.8 ± 18.5 months (median, 14.7 months). A total of 24 events occurred in 13 patients—2 cardiac deaths, 2 heart transplants, 1 left

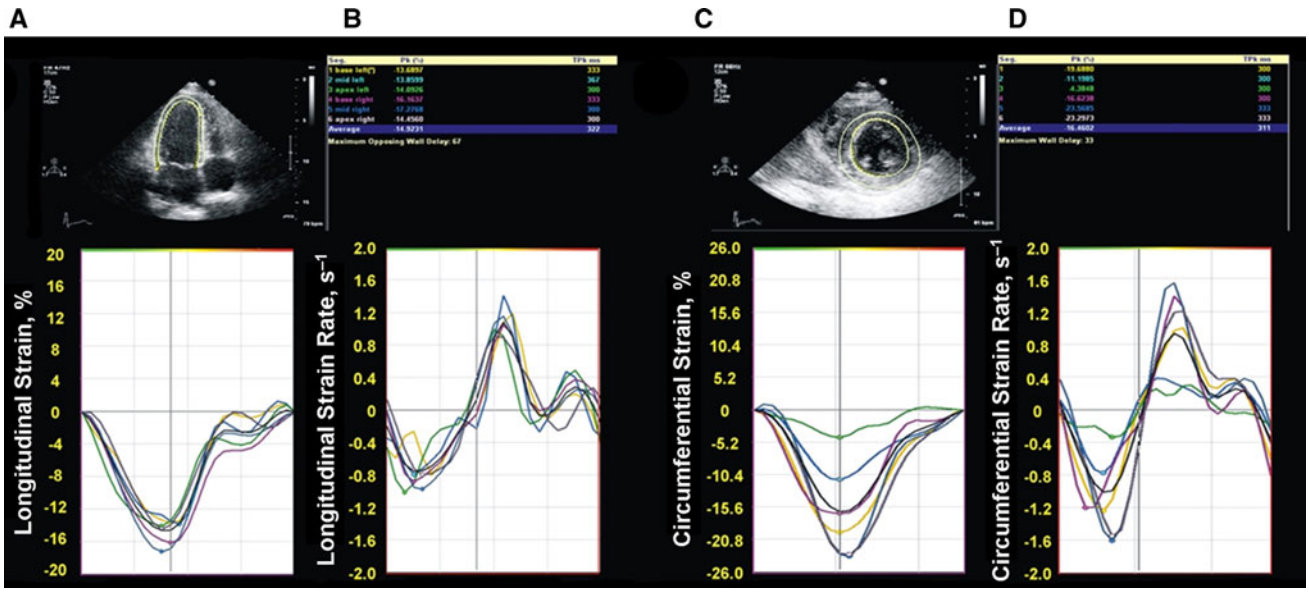

Fig. 2 Examples of longitudinal strain and strain rate (**a**, **b**) and circumferential strain and strain rate (**c**, **d**) in a myocarditis patient with preserved ejection fraction

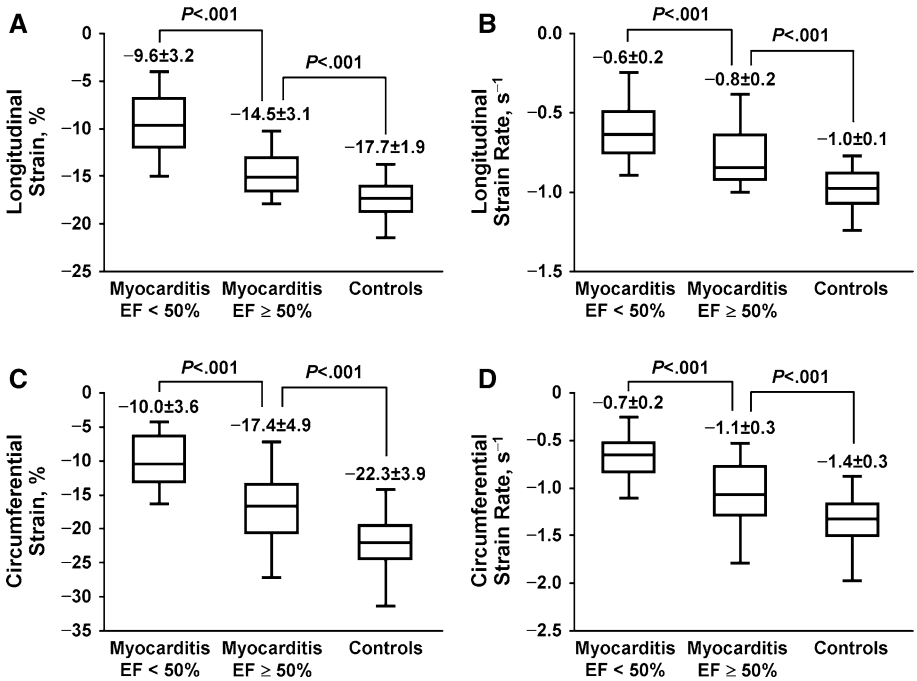

Fig. 3 The *box* and whiskers plots show the comparison between myocarditis with ejection fraction <50 % or ≥50 % and controls by analysis of variance for longitudinal strain and strain rate (**a**, **b**) and for circumferential strain and strain rate (**c**, **d**). The *horizontal line* in the *box* denotes the median of the sample, and the *bottom* and *top* of the *box* are the 25th and 75th percentiles, respectively. The whiskers show the maximum and minimum values. *EF* indicates ejection fraction

ventricular assist device implantation, 1 implantable cardioverter-defibrillator placement, 5 intra-aortic balloon pump support, 3 inotropic agent support, 4 respiratory failure due to pulmonary edema, and 6 rehospitalizations due to cardiac events.

Predictors for major clinical events

Table 4 shows the associations between clinical findings, electrocardiography findings, 2-dimensional echocardiographic variables or indices of left ventricular mechanics, and major clinical events by the Cox univariate proportional hazards model. The indices of left ventricular mechanics were more significant predictors. For every 1 % decline in longitudinal strain or circumferential strain, the HRs (95 % CIs) were 1.26 (1.10–1.47) and 1.34 (1.14–1.63), respectively; for every 0.1 s^{-1} decline in longitudinal strain rate or circumferential strain rate, the HRs (95 % CIs) were 1.43 (1.09–1.89) and 1.52 (1.19–2.01), respectively ($P < .01$). Event-free survival was significantly related to longitudinal

Table 3 Receiver operating characteristic curve and area under the curve analysis with optimal cutoff level and sensitivity and specificity in 19 myocarditis patients with ejection fraction >50 %

Characteristic	AUC	*P* value	Cutoff value	Sensitivity (%)	Specificity (%)
LS	0.83	<.001	−16.9 %	84	68
LSR	0.82	<.001	$-0.9\ s^{-1}$	74	70
CS	0.79	<.001	−19.3 %	68	80
CSR	0.78	<.001	$-1.1\ s^{-1}$	68	85

AUC area under the curve, *CS* circumferential strain, *CSR* circumferential strain rate, *LS* longitudinal strain, *LSR* longitudinal strain rate

strain, longitudinal strain rate, circumferential strain, and circumferential strain rate, as illustrated in the Kaplan–Meier curves (Fig. 4). The population was dichotomized at the median value for longitudinal strain, circumferential strain, and circumferential strain rate and at the 25th percentile for longitudinal strain rate.

Reproducibility

For circumferential strain and longitudinal strain, respectively, interobserver variability was 7.7 ± 3.4 % and 4.9 ± 3.2 %, and intraobserver variability was 4.0 ± 3.9 % and 1.5 ± 0.9 %. For circumferential strain rate and longitudinal strain rate, respectively, interobserver variability was 9.8 ± 7.0 % and 5.7 ± 5.9 %, and intraobserver variability was 10.5 ± 7.7 % and 4.5 ± 2.8 %.

Discussion

To our knowledge, this is the first study to evaluate left ventricular strain and strain rate in patients with acute myocarditis and its diagnostic and prognostic value. The main findings are: (1) Longitudinal and circumferential strain and strain rate can predict major clinical events in patients with decreased or normal left ventricular ejection fraction. These variables continued to be significant after adjusting for sex, septal thickness, left ventricular end-diastolic diameter, ejection fraction, and stroke volume index; and (2) when compared with a control cohort, patients with acute myocarditis were found to have decreased longitudinal and circumferential strain and strain rate values. We investigated only longitudinal and circumferential strain and strain rate because of better reproducibility as shown by several previous studies [9–13].

Diagnostic role: left ventricular strain or strain rate versus conventional 2-dimensional echocardiography

Findings on conventional 2-dimensional echocardiography are nonspecific and are mainly used to rule out other causes of heart failure [1, 18]. Increased left ventricular volume and sphericity in acute myocarditis [19] or a transient increase in wall thickness [20] have been found. Our study also showed increases in wall thickness and left ventricular volume as well as regional wall motion abnormalities (Table 1). Segmental or global wall motion abnormalities have also been reported that could mimic myocardial infarction [21]. However, these changes are not specific to this disease entity. The echocardiographic findings are the same in a patient with clinical suspicion of myocarditis as in a patient with a normal heart.

In left ventricular strain and strain rate analysis, longitudinal strain, longitudinal strain rate, circumferential

Table 4 Cox univariate proportional hazards model risk to major clinical events

Characteristic	HR (95 % CI)	*P* value
Age (per 10 year)	1.19 (0.81–1.73)	.37
Female sex	1.36 (0.41–4.07)	.60
ECG findings		
BBB	3.18 (0.49–11.95)	.19
ST-T elevation	0.88 (0.24–2.72)	.84
Q wave	4.98 (1.49–15.17)	.01
2-D echocardiographic findings		
Septal thickness	1.02 (0.73–1.34)	.88
LVEDD	1.06 (0.97–1.14)	.17
LVESD	1.10 (1.02–1.17)	.01
LVMI	1.03 (1–1.05)	.04
Lower EF (per 1 % change)	1.14 (1.06–1.25)	<.001
Lower stroke volume index	1.11 (1.05–1.19)	<.001
Wall motion score index (per 0.1 change)	1.16 (1.07–1.29)	<.001
LV deformation		
LS (per 1 % change)	1.26 (1.1–1.47)	<.001
LSR (per 0.1 s^{-1} change)	1.43 (1.09–1.89)	.01
CS (per 1 % change)	1.34 (1.14v1.63)	<.001
CSR (per 0.1 s^{-1} change)	1.52 (1.19–2.01)	<.001

BBB bundle branch block, *CS* circumferential strain, *CSR* circumferential strain rate, *ECG* electrocardiography, *EF* ejection fraction, *HR* hazard ratio, *LS* longitudinal strain, *LSR* longitudinal strain rate, *LV* left ventricular, *LVEDD* left ventricular end-diastolic diameter, *LVESD* left ventricular end-systolic diameter, *LVMI* left ventricular mass index, *2-D* 2-dimensional

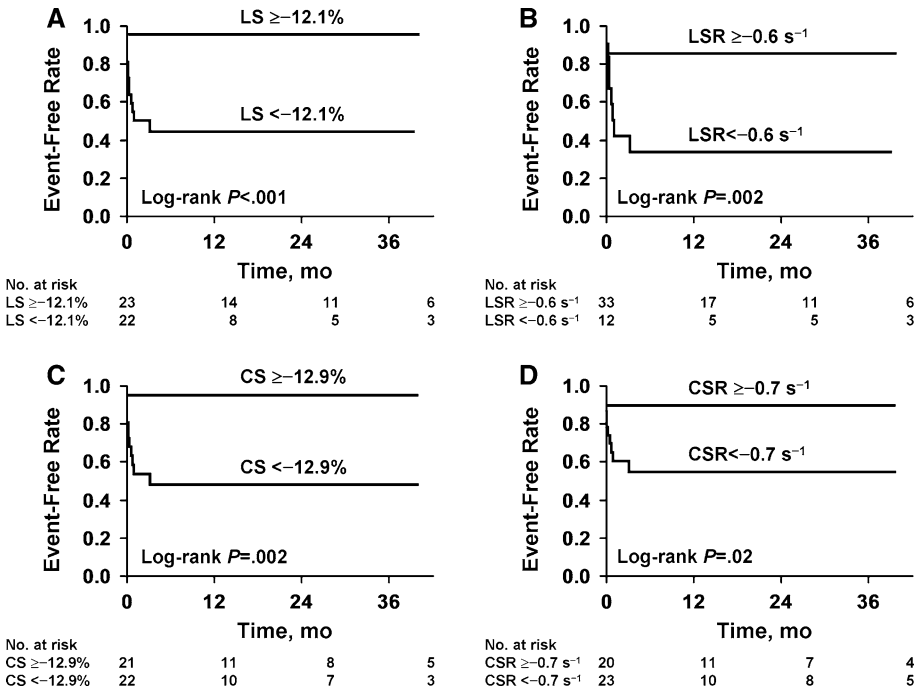

Fig. 4 Kaplan–Meier curve and log-rank test for **a** longitudinal strain (LS); **b** longitudinal strain rate (LSR); **c** circumferential strain (CS); and **d** circumferential strain rate (CSR)

strain, and circumferential strain rate were significantly decreased in the myocarditis group. For all these variables, the receiver operating characteristic calculation showed good area under the curve (from 0.89 to 0.93, Fig. 1). In the multiple logistic regression model, after adjustment for sex, septal thickness, ejection fraction, and stroke volume index, all left ventricular deformation variables were still significant, even in those patients with preserved left ventricular systolic function (Fig. 3; Tables 2, 3) in the univariate and multivariate models.

Predictors of major clinical events

According to previous studies, advanced New York Heart Association functional class or biventricular heart failure are clinical predictors of poor outcome [22, 23]. Only a few reports have focused on noninvasive studies as a predictor of outcome. In a study of 24 patients by Nakashima et al. [24], the presence of a Q wave may have indicated a more severe course in the early stages of this disease. In our study, the presence of a Q wave was also predictive, but it could not be considered applicable because the incidence was low, 13.3 %. A small-population study revealed that the presence of contrast-enhanced magnetic resonance imaging was associated with a poor clinical long-term outcome [25]. In the present study, patients who had worse left ventricular strain or strain rate had higher risk of adverse clinical outcomes. In the Cox univariate proportional hazards model, the HR was 1.34 (95 % CI, 1.14–1.63) per 1 % decline of circumferential strain, 1.26 (95 % CI, 1.1–1.47) per 1 % decline of longitudinal strain, and 1.52 (95 % CI, 1.19–2.01) per 0.1 s^{-1} decline of circumferential strain rate. The Kaplan–Meier method and the log-rank test also showed that left ventricular strain and strain rate were significant predictors of major clinical events (Fig. 4; Table 4).

Limitations

Even though our sample size was small, we believe that our findings can be applied to patients with this disease. Our study design was age-matched only. The influence of patient sex is uncertain. Few studies have investigated the influence of patient sex on myocardial strain or strain rate, and the results are controversial. Some authors have reported differences between sexes while others have not. In our study [26], normal controls were individuals with no history of cardiovascular disease and low pretest probability of heart disease. To eliminate the effect of patient sex, we corrected for this in the multivariate analysis.

Not all patients had CMR or biopsy to prove the diagnoses. CMR was performed in 22 patients (48.8 %). T2 sequence and T1 early gadolinium enhancement protocols were not performed routinely between 2004 and 2009 at Mayo Clinic. Only 12 patients (26.7 %) had a biopsy. Biopsy is specific but not sensitive, and this invasive study is not appropriate for every patient. Several well-known limitations of biopsy include sampling error, invasive studies with 0.1 to 0.5 % severe complications, and poor interobserver agreement using the Dallas criteria [3].

Our hospital is a tertiary care medical center, and our patients may represent a sicker population. More than half of our patients with acute myocarditis had left ventricular ejection fraction <50 %, and this may represent referral bias.

Patients with recently diagnosed myocarditis were included in this study; therefore, our findings should be considered only in this patient population.

Conclusions

In patients with acute myocarditis, left ventricular strain and strain rate derived by 2-dimensional speckle tracking echocardiography appear to be promising prognostic tools, even in those patients with preserved left ventricular ejection fraction. Most importantly, this imaging technique also had a role in predicting deterioration and overall event-free survival.

Left ventricular mechanics by 2-dimensional speckle tracking echocardiography should be evaluated prospectively in patients suspected of having acute myocarditis and should be explored to differentiate from other diseases, such as acute coronary syndromes, that are being considered in the differential diagnosis.

Conflict of interest None.

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