The International Journal of Cardiovascular Imaging (2019) 35:1101–1109
https://doi.org/10.1007/s10554-019-01588-8

ORIGINAL PAPER

Two-dimensional and three-dimensional cardiac magnetic resonance feature-tracking myocardial strain analysis in acute myocarditis patients with preserved ejection fraction

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Received: 4 January 2019 / Accepted: 23 March 2019 / Published online: 30 March 2019

Abstract
To explore the potential role of two- (2D) and three-dimensional (3D) cardiac magnetic resonance (CMR) feature tracking (FT) myocardial strain analysis in identifying sub-clinical myocardial systolic and diastolic dysfunction in acute myocarditis patients with preserved ejection fraction (EF). Prospective two centre study-control study. Thirty patients (9 female, 37.2 ± 11.8 years.) with a CMR diagnosis of acute myocarditis according to the Lake Louise Criteria and preserved EF ($\geq 55\%$) were included in the analysis. CMR data from 24 healthy volunteers (11 female, 36.2 ± 12.5 years.) served as control. 2D and 3D LV tissue tracking analysis were performed in a random fashion by two double-blinded operators. Variables were checked for normality and analysed with parametric test. The baseline characteristics of myocarditis patients with preserved EF and the healthy volunteers were perfectly comparable, except for the LV mass index and T1 and T2 mapping values ($p < 0.001$). The results of the interobserver variability in the 2D and 3D LV CMR FT myocardial strain analysis were $p > 0.42$, ICC > 0.80 and $\eta^2 > 0.98$. There was no statistical difference in 2D and 3D global radial, circumferential and longitudinal strain peak (%) and both systolic and diastolic strain rate (1/s) between acute myocarditis with preserved EF and healthy volunteers (all $p =$ ns). There were no difference in 2D and 3D global radial, circumferential and longitudinal strain peak and both systolic and diastolic strain rate of the LV between acute myocarditis patients with preserved ejection fraction and healthy volunteers.

Keywords Cardiovascular magnetic resonance · Acute myocarditis · Feature tracking · Myocardial strain analysis · Diastolic dysfunction

Introduction

In the last decade, cardiovascular magnetic resonance (CMR) has become the best non-invasive imaging modality for evaluating the inflammation of the myocardial tissue in patients with acute myocarditis [1].

The clinical presentation of acute myocarditis is variable, ranging from a subclinical disease to a recent onset of heart failure, an arrhythmic event or an infarct-like syndrome [2]. Also its clinical evolution is variable, ranging from complete remission [3] to various and severe complications [4]. Recent studies reported several prognostic parameters: clinical symptoms, type of viruses, left ventricle (LV) size and function and late gadolinium enhancement [4–8]. In particular, some authors [4, 6, 8] showed that baseline reduced LV function is the strongest predictor of worse prognosis regardless of the clinical pattern at the onset of the disease.

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Overall, segmental wall motion abnormalities are rare and systolic function is preserved in a large number of cases of acute myocarditis patients, especially in the infarct-like subjects, who also have a good prognosis [3]. However, also patients with acute myocarditis and preserved systolic function, may incur into an incidence of about 8% of major adverse events in a 5 years follow-up [9] and the occurrence of heart failure seems to be related to the presence of a diastolic dysfunction [10].

Recently, many authors showed that CMR feature-tracking (FT) myocardial strain analysis has the potential to identify even subclinical myocardial dysfunctions and may work as an independent prognostic factor across many cardiovascular diseases [11].

The main indication for CMR in acute myocarditis is for hemodynamically stable patients with preserved ejection fraction (EF). Only few studies analysed the outcome of CMR FT myocardial strain analysis in myocarditis patients with preserved EF in comparison to control subjects; the results were however contradictory, from absence of significant differences [12, 13] to presence of many alterations in LV and/or atrial and/or right ventricular (RV) strain parameters [14–17].

We considered the issue worth of further exploration and planned a study to explore the potential role of 2D and 3D CMR FT myocardial strain analysis in identifying sub-clinical myocardial dysfunction in acute myocarditis patients with preserved EF.

Materials and methods

Study design and population

The study was piloted in agreement with the 1964 Helsinki declaration and its later amendments, was approved by the institutional review board and all subjects provided written informed consent.

This was a prospective two centre study-control study. Inclusion criteria were: (i) age from 18 to 80 years; (ii) clinical suspicion of acute myocarditis [18] (iii) exclusion of obstructive coronary artery disease with coronary artery angiography or coronary CT angiography and (iv) CMR examination with a diagnosis of acute myocarditis according to the Lake Louise Criteria [1]. Exclusion criteria were: (i) reduced EF (< 55%); (ii) history of cardiomyopathies; (iii) ICD or pacemaker; (iv) inability to hold breath or to lay down for 45 min; (v) claustrophobia; (vi) recent history of alimentary/alcoholic/respiratory intoxication; (vii) risk for nephrogenic systemic fibrosis (estimated glomerular filtration rate < 30 mL/min/1.73 m^2); (viii) history of allergic reaction to MR contrast media and (ix) pregnancy or breast-feeding.

Sixty-four patients met the inclusion criteria. Thirty-one patients had depressed EF and three had a concurrent cardiomyopathy and thus were excluded from the study. A total of 30 patients were included in the analysis. Endomyocardial biopsies were performed in 16/30 patients, with confirmation of acute myocarditis.

CMR data from 24 healthy volunteers served as control. This population was selected with these inclusion criteria: a negative comprehensive health history and physical examination and normal cardiac dimensions, function and "normal" T1 and T2 mapping value on CMR.

CMR protocol

CMR imaging was performed with a 1.5-Tesla scanner (Achieva and Achieva dStream, Philips Medical Systems, Eindhoven, The Netherlands) using a body and phased array coil (32-channel).

For functional analysis cine steady-state free precession (cine-SSFP) CMR images were acquired in four-, two- and three-chamber and short-axis (repetition time [TR] = 3.4 ms; echo time [TE] = 1.7 ms; flip angle = 80°; slice thickness = 8 mm without interslice gap and 30 cardiac phases per heartbeat). Oedema sensitive black-blood T2-weighted short tau inversion recovery (T2w-STIR) images were acquired on long- and on short-axis chamber covering the entire LV (TR = 2 × RR interval; TE = 60 ms; flip angle = 90°; inversion time [TI] = 180 ms; slice thickness = 8 mm without interslice gap). Functional parameters of the left ventricle and myocardial hyperaemia were evaluated, as previously reported [19], using the SSFP cine images acquired from mitral valve plane to the apex after intravenous administration of 0.15 mmol/kg of gadobutrol (Gadovist, Bayer Healthcare, Berlin, Germany). The late gadolinium enhancement (LGE) images were acquired 10 min after contrast administration using segmented inversion recovery gradient echo sequences (IR-GRE) on long- and on short-axis chamber covering the entire LV (TR = 6.1 ms; TE = 3 ms; flip angle = 25°; TI determined by using a Look Locker based TI scout; slice thickness = 10 mm without interslice gap).

In 8 patients were also acquired T1 and T2 mapping. For myocardial T1 mapping a shortened modified Look-Locker inversion recovery (ShMOLLI) technique and for T2 mapping an optimized 6-echo gradient spin echo (GraSE) sequence were used as previously described [20].

In healthy volunteers, no contrast medium was administered and were performed sequences for functional analysis (i.e. cine-SSFP) and for T1 and T2 mapping [21].

Imaging analysis

All CMR studies were analysed in consensus by two experienced observers [A.E. and R.F. (with more than 10 years of

experience in CMR)] using the MR Extended Work Space software and IntelliSpace Portal (Philips Healthcare, Best, Netherlands) according to the Lake Louise Criteria [1].

Functional parameter (i.e. ventricular volumes, EF and mass) were calculated by tracing endocardial and epicardial contours on short-axis stacks in end-diastole and end-systole by multiplying each traced area by the section thickness and summing the volumes of the separate section [22]. For each patient was also calculated as previously described [1, 3, 23] the T2 ratio (i.e. > 1.9 suggests active inflammation), hyperaemia (i.e. myocardium having signal intensity higher than the mean signal intensity plus 2 SD of normal myocardium; positive for inflammation when > 12.1 gr) [19] and the % of LGE (i.e. areas with signal intensity at least 3 standard deviations greater than for normal myocardium) [23]. Myocardial T1 and T2 relaxation times and extracellular volume (ECV) were analysed as previously described [20].

The two- (2D) and three-dimensional (3D) LV tissue tracking analysis were performed in a random fashion by two double-blinded operators who were not involved in the clinical MRI evaluation (F.B. and M.G. with years 2 and 6 of experience respectively). Before starting the analysis, the two observers made an initial check of the procedure and during the analysis the observer neither knowledge of the measurement by the other, nor was able to visualize her/his own measurements during the review of the images, in order to be sure that the measure was perfectly reproducible and not biased. The cine images datasets were transferred to an off-line workstation and processed using commercially available software (CVI^{42}, Circle Cardiovascular Imaging, Calgary, Canada, v.5.6.4). Short axis and two-, three and four chamber series were loaded into the software. The observers selected the end-diastole (reference phase) by determining the phase in which the LV intracavity blood pool was at its biggest by visual assessment at the mid-ventricular level and then traced endo- and epicardial contours with rounded contours both in short and in long axis and draw the long axis extent contour in the LV. The algorithm performs an automatic strain analysis (i.e. strain will be automatically computed in all slices, that contain endo- and epicardial contours). In particular, the 2D algorithm fits a 2D incompressible deformable model of the myocardium to individual image slices (e.g. long or short axis acquisitions) over the cardiac cycle. The deformation of the model is assumed to be completely determined by a set of control points placed on the middle curve of the myocardial wall. First, these points are constructed only at the diastolic phase where endo and epi boundaries are defined by the user. Then, the shape of the model (i.e. the positions of the control points) in all the others phases is detected based on the feature tracked boundaries and the incompressibility constraint of the model. The 3D algorithm fits a 3D deformable model of the myocardium in between the endo and epi surfaces generated by interpolating the tracked boundaries from the 2D algorithm. The surface interpolation is performed using both long and short axis image information, which makes it suitable for the inference of the radial, circumferential and longitudinal motions of the myocardium. As in the case of the 2D model, the deformation of the 3D model is assumed to be completely determined by a set of control points placed within the myocardial wall. These points are first constructed in the diastole phase (phase index is found by the 2D algorithm) and the algorithm finds their correspondent positions in all the others phases by surface registration technique. Finally, were used the overlays to check the performance of myocardial tracking and, if necessary, were manually corrected. 2D and 3D global radial (GRS), circumferential (GCS) and longitudinal (GLS) peak strain (%), peak systolic strain rate (PSSR) based on maximum and peak diastolic strain rate (PDSR) based on maximum were recorded.

Statistical analysis

Continuous variables satisfied the normality test of Shapiro–Wilks and were thus expressed as average ± standard deviation. Independent variable was compared with unpaired t-test.

Categorical variables, reported as counts and percentages, were arranged in cross-correlation tables and studied with the χ^2 test (with Yates' correction for 2 × 2) or Fisher's exact test.

The interoperator variability was studied with Wilcoxon test, and the η^2 coefficient (0–1), also known as Cronbach coefficient, and the intraclass correlation coefficient were both derived from the analysis of variance.

Statistical significance was set at two-tails $p < 0.05$. The analysis was performed with StatPlus:Mac v.6 (AnalysisSoft. Walnut. CA. USA).

Results

The baseline characteristics of myocarditis patients with preserved EF (study group) and of the healthy volunteers (control group) are listed and compared in Table 1. The two groups are homogeneous, except for the LV mass index (60 ± 13 g/m^2 vs. 45 ± 11 g/m^2; $p < 0.001$) and for the T1 (1101.4 ± 32.7 ms vs. 1021.9 ± 14.0 ms; $p < 0.001$) and T2 myocardial mapping (55.7 ± 4.2 ms vs. 46.8 ± 1.6 ms; $p < 0.001$) values which were higher in the study population.

The results of the inter-operators' variability in the LV CMR FT myocardial strain analysis established the reliability of the system: Wilcoxon's $p > 0.42$ (range 0.42–0.98), ICC > 0.80 (range 0.80–0.98) and $\eta^2 > 0.98$ (range 0.88–0.99).

Table 1 Baseline characteristic of the study population

Characteristics	Acute myocarditis with preserved ejection fraction patients	Healthy volunteers	p-value
Number of patients (n)	30	24	
Female [n (%)]	9 (30%)	11 (46%)	0.26
Age (years)	37.2 ± 11.8	36.2 ± 12.5	0.84
BSA (m^2)	1.9 ± 0.14	1.8 ± .02	0.09
CK-MB (µg/L) peak value	49.49 ± 319	na	na
Troponin I (µg/L) peak value	10.1 ± 8.7	na	na
Time interval between onset of symptoms and CMR (days)	6.87 ± 4.34 days	na	na
LVEDVi (ml/m^2)	83 ± 18	78 ± 13	0.13
LVEF (%)	60 ± 3	61 ± 3	0.28
Mass index (g/m^2)	60 ± 13	45 ± 11	< 0.001
No of T2 segment involved	6.24 ± 3.1	na	na
T2 ratio	3.84 ± 1.45	na	na
Hyperaemia (g)	14.3 ± 5.7	na	na
No of LGE segment involved	5.48 ± 3.15	na	na
% LGE	24.06 ± 15.10	na	na
T1 mapping (ms)	1101.4 ± 32.7 (8 patients)	1021.9 ± 14.0	< 0.001
T2 mapping (ms)	55.7 ± 4.2 (8 patients)	46.8 ± 1.6	< 0.001
ECV (%)	32.0 ± 3.3 (8 patients)	na	na

BSA body surface area, *CK-MB* creatin kinase-myocardial band, *CMR* cardiovascular magnetic resonance, *LVEDVi* left ventricular end diastolic volume index, *LVEF* left ventricular ejection fraction, *EGE* early gadolinium enhancement, *LGE* late gadolinium enhancement

Table 2 CMR FT myocardial strain analysis: comparison in acute myocarditis with preserved ejection fraction vs. healthy volunteers

Strain parameter	Acute myocarditis with preserved ejection fraction patients	Healthy volunteers	p-value
GRS 2D (%)	41.82 ± 7.79	41.74 ± 6.70	0.656
GCS 2D (%)	− 21.96 ± 2.14	− 21.97 ± 2.37	0.648
GLS 2D (%)	− 20.28 ± 2.57	− 20.41 ± 2.15	0.914
GRS 3D (%)	39.84 ± 9.95	38.67 ± 8.30	0.316
GCS 3D (%)	− 16.63 ± 2.54	− 16.51 ± 2.78	0.486
GLS 3D (%)	− 14.48 ± 3.34	− 15.55 ± 1.84	0.432
PSSRR 2D (1/s)	2.48 ± 0.69	2.43 ± 0.63	0.796
PSSRC 2D (1/s)	− 1.34 ± 0.39	− 1.40 ± 0.35	0.606
PSSRL 2D (1/s)	− 1.10 ± 0.25	− 1.10 ± 0.22	0.912
PSSRR 3D (1/s)	2.71 ± 0.94	2.60 ± 0.82	0.653
PSSRC 3D (1/s)	− 0.97 ± 0.24	− 1.02 ± 0.28	0.527
PSSRL 3D (1/s)	− 0.84 ± 0.22	− 0.89 ± 0.21	0.397
PDSRR 2D (1/s)	− 2.71 ± 0.78	− 2.69 ± 0.96	0.485
PDSRC 2D (1/s)	1.36 ± 0.26	1.45 ± 0.35	0.306
PDSRL 2D (1/s)	1.11 ± 0.25	1.18 ± 0.25	0.343
PDSRR 3D (1/s)	− 2.78 ± 0.90	− 2.66 ± 0.80	0.640
PDSRC 3D (1/s)	1.05 ± 0.23	1.07 ± 0.23	0.772
PDSRL 3D (1/s)	0.86 ± 0.26	0.96 ± 0.20	0.165

GRS global radial strain, *GCS* global circumferential strain, *GLS* global longitudinal strain, *PSSRR* peak systolic strain rate radial, *PSSRC* peak systolic strain rate circumferential, *PSSRL* peak systolic strain rate longitudinal, *PDSRR* peak diastolic strain rate radial, *PDSRC* peak diastolic strain rate circumferential, *PDSRL* peak diastolic strain rate longitudinal

The overall results of CMR FT myocardial strain analysis in the study and control group are shown in Table 2 and Figs. 1, 2. No significant difference between the two groups was observed for the 2D and 3D global radial, circumferential and longitudinal strain peak (%) or the systolic and diastolic strain rate.

A representative case is shown in Fig. 3.

Discussion

Our study investigated the role of CMR FT myocardial strain analysis in identifying sub-clinical myocardial dysfunctions, comparing a study group of 30 acute myocarditis patients with preserved EF with a control group of 24 healthy volunteers. The two groups were homogenous, except for the LV mass index which was higher in the study population (60 ± 13 g/m^2 vs. 45 ± 11 g/m^2; $p < 0.001$) and for the increased T1 (1101.4 ± 32.7 ms vs. 1021.9 ± 14.0 ms; $p < 0.001$) and T2 myocardial mapping (55.7 ± 4.2 ms vs. 46.8 ± 1.6 ms; $p < 0.001$) values. The difference in LV mass index and the T1 and T2 myocardial mapping values could be related, as previously hypothesized [3, 20], to the presence of oedema, moreover the increased value of T1 mapping is partly related to the increased extracellular space and myocyte necrosis. All these findings are a consequence acute inflammation in acute myocarditis patients, and thus constitute part of the definition of the study group characteristics.

Our analysis was zoomed on the strain of the left ventricle, for which we did not evidence any significant difference among the endpoints of the two groups: the 2D and 3D global radial, circumferential and longitudinal strain peak (%) and both systolic and diastolic strain rate of the LV were similar for two groups.

Table 3 compares our results with those of the other authors who performed analyses on the same variables. The three top rows of Table 3 concern the myocardial peak strain (%) analysis. Five studies [14–17, 24] found significant differences in CMR FT LV myocardial peak strain (%) analysis (first three rows in Table 3) between patients with acute myocarditis with preserved EF and healthy volunteers. However, it should be noted that in two of the three largest studies the cut-off value for "normal" EF was 50% and this might be a bias. The normal value of the EF in a population

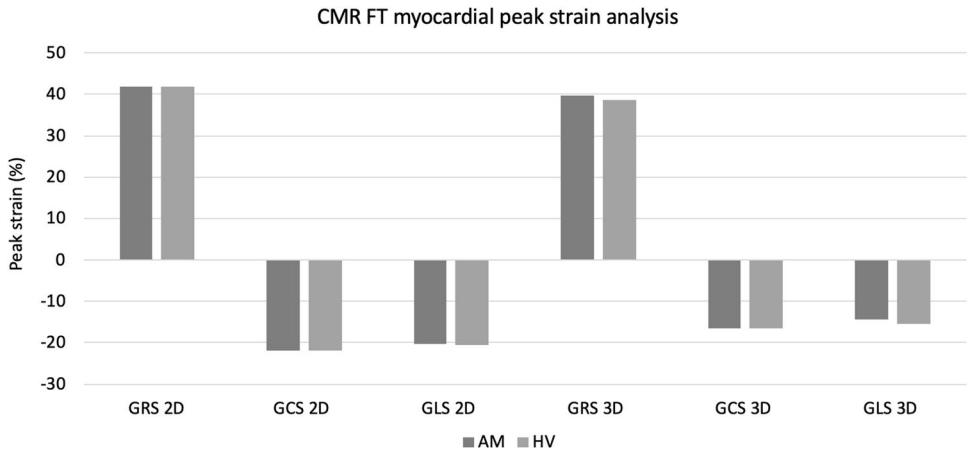

Fig. 1 Box plot of 2D and 3D radial (GRS), circumferential (GCS) and longitudinal (GLS) global peak strain (%) in acute myocarditis (AM) and healthy volunteers (HV)

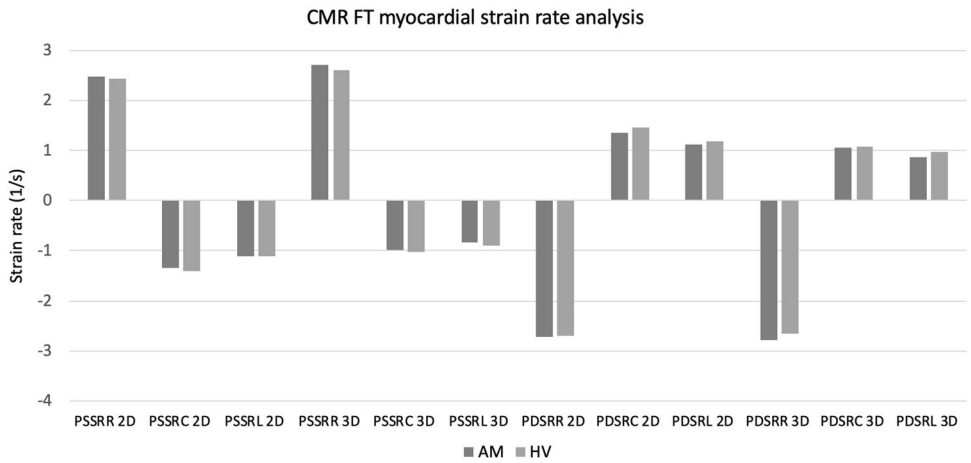

Fig. 2 Box plot of 2D and 3D radial (GRS), circumferential (GCS) and longitudinal (GLS) global Peak Systolic Strain Rate (PSSR) and Peak Diastolic Strain Rate (PDSR)

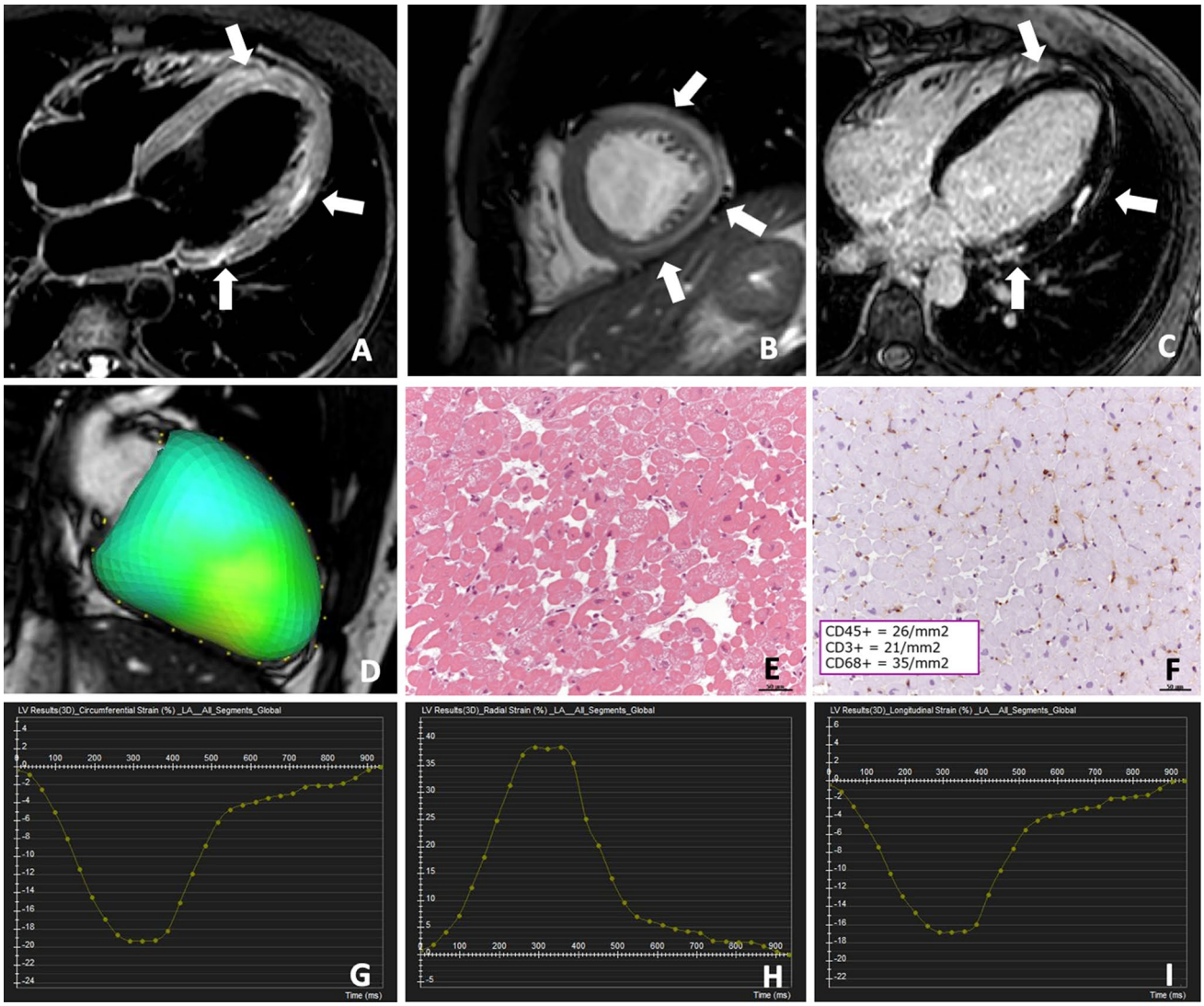

Fig. 3 A representative case in a 25-year-old man with acute myocarditis and preserved ejection fraction. Long-axis STIR (**a**) shows patchy myocardial oedema with subepicardial pattern involving basal and lateral wall (arrows in **a**), and thin intramyocardial oedema in apical septum (arrows in **a**) with corresponding late gadolinium enhancement (arrows in **c**). Short-axis cine-SSFP (**b**) documented focal hyperaemia involving inferior and lateral mid-wall. CMR diagnosis of acute myocarditis was confirmed at endomyocardial biopsy with histology (haematoxylin/eosin staining in **e**) and anti-leukocyte common antigen immunohistochemistry (**f**). CMR feature tracking myocardial strain analysis (**d**) showed normal global circumferential (**g**), radial (**h**) and longitudinal (**i**) strain peak (%) curves

Table 3 Comparison among studies on LV CMR FT myocardial strain analysis in acute myocarditis patients with preserved ejection fraction

Strain parameter	André et al. [14]	Baeßler et al. [12]	Weigand et al. [24]	Baeßler et al. [15]	Lee et al. [16]	Luetkens et al. [17]	Doerner et al. [13]	Our study (2019)
GRS 2D	Difference SS	No difference	Difference SS	No difference	Difference SS	No difference	No difference	No difference
GCS 2D	No difference	No difference	Difference SS	Difference SS	Difference SS	No difference	No difference	No difference
GLS 2D	Difference SS	No difference	No difference	Difference SS	Difference SS	Difference SS	No difference	No difference
PSSRR 2D	na	No difference	na	No difference	na	No difference	No difference	No difference
PSSRC 2D	na	No difference	na	No difference	na	No difference	No difference	No difference
PSSRL 2D	na	No difference	na	Difference SS	na	No difference	No difference	No difference

GRS global radial strain, *GCS* global circumferential strain, *GLS* global longitudinal strain, *PSSRR* peak systolic strain rate radial, *PSSRC* peak systolic strain rate circumferential, *PSSRL* peak systolic strain rate longitudinal

comparable with the typical patient with acute myocarditis, a male under 45 [2], is higher and since FT LV myocardial strain analysis is considered very sensitive, the 50% cut-off may have led to underestimate the strain value in that population. We decided to use 55% as a cut-off for normal EF in order to be comparable to most of the literature's studies.

The three bottom rows of Table 3 concern the analysis of PSSRR 2D, PSSRC 2D e PSSRL 2D. PSSR, being an early systolic event, is more closely related to contractility than EF. There are few studies on this variable [12, 13, 15, 17]. Baeßler et al. [15] found significant differences between patients with suspected myocarditis and controls for PSSRL 2D (cut off for normal EF was 50%). The group of Cologne [12, 13] reported promising results on CMR FT RV regional myocardial strain analysis (e.g. Basal PSSRC 2D). They hypothesized that these patients have a hyperkinesia of the basal RV in relation to inflammation and that this begins to decrease as LV EF becomes more impaired. Actually, this difference was present only in the subgroup of myocarditis with preserved EF and not in the myocarditis patients with impaired EF; but the question regarding the reproducibility of segmental strain analysis, especially of the RV, is still open [25].

We also explored the PDSR rate, which is considered useful for the assessment of ventricular relaxation and estimation of filling pressures [26] and has also been shown to be an independent prognostic factor in many cardiovascular disease [27]. Two recent studies [13, 28] showed the potential role of CMR FT left atrial strain analysis for the heart diastolic evaluation, reporting significant differences between acute myocarditis patients with preserved EF and healthy volunteers, in passive strain and peak early negative strain rate, which corresponds to the atrial conduit function that is closely related to LV compliance. Moreover has been recently demonstrated that the combined evaluation of left atrial strain and left ventricular volume/time curve by CMR may allow a reliable evaluation of diastolic dysfunction [29]. However, with our approach no difference between the study and control group were found.

The 3D CMR FT strain analysis has been recently suggested as a possible breakthrough to give a more accurate evaluation of the strain [30]. 2D CMR FT strain analysis can be negatively affected by through-plane loss of features in the third dimension and this could be negatively influenced by imperfect tracking in the chosen slice which can reduce reproducibility [31]. Moreover, the calculation of strain from a limited number of short and long-axis may not properly reflect the global myocardial function. A recent algorithm implemented for 3D CMR FT strain analysis seems to be able to avoid overestimation in the strain parameters related to the twisting movement of the myocardium during contraction, that determines an out-of-plane movement of a segment; this might increase the measured degree of muscle contraction, and in fact the 2D strain values are higher than the corresponding 3D ones [30].

To the best of our knowledge, this study is the first which evaluates the role of 3D CMR FT strain analysis in this subset of population. However, even with this approach, we found no statistical difference between the two populations in 3D Peak Strain (%), PSSR based on maximum and PDSR based on maximum.

This study has some limitations. First, although prospective, it is on a limited number of patients, even if is one of the largest in literature dealing with acute myocarditis patients with preserved EF. Second, the endomyocardial biopsy was not performed in the entire population, because one institution's protocol is to perform biopsy in every patients with acute myocarditis [32], the other performs EMB only when patients present with hemodynamic instability or life-threatening [18]. Third, we focused only on CMR FT LV strain analysis and we did not evaluate neither the RV myocardial strain, nor the atrial strain. Fourth, we evaluated only the global, and neither the regional nor the segmental CMR FT myocardial strain, that could be potentially affected in acute myocarditis for its typical patchy involvement; however, segmental and regional strain analysis disregard the main aim of the study, which is focused on the evaluation of global, systolic and diastolic FT myocardial strain analysis and moreover, tracking techniques were reported to be more robust and reproducible for global rather than regional values [11]. In fact, several studies showed a good reproducibility for LV as well as for RV global strain values (coefficients of variation 7–10%) [25, 33], whereas, reproducibility of regional or segmental strain analysis was low (coefficients of variation of 24% for LV and of 36% for RV) [25, 33]. Finally, we did not correlate our results with patient outcomes; it might be interesting to see if CMR FT myocardial strain analysis can identify a subpopulation with bad prognosis in patients with preserved FE.

In conclusion, there were no difference in 2D and 3D global radial, circumferential and longitudinal strain peak and both systolic and diastolic strain rate of the LV between acute myocarditis patient with preserved ejection fraction and healthy volunteers.

Acknowledgements This research was partially supported by a grant from the Italian Ministry of Health: "Giovani Ricercatori—Ricerca Finalizzata", project number GR-2013-02356832. The funder had no role in this study.

Compliance with ethical standards

Conflict of interest All the authors are aware of the content of the manuscript and have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the insti-

tutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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