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Research article

Incremental value of cardiovascular magnetic resonance feature tracking derived atrial and ventricular strain parameters in a comprehensive approach for the diagnosis of acute myocarditis

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ABSTRACT

Purpose/introduction: This study aims to evaluate the incremental diagnostic value of cardiac magnetic resonance (CMR) feature tracking (FT) derived atrial and ventricular strain-analysis in patients with acute myocarditis (myocarditis) as an additional tool to established Lake-Louise criteria (LLC).

Material and methods: A total of 86 patients with clinically proven myocarditis and 30 healthy controls underwent a comprehensive CMR protocol. In addition to established LLC, FT derived strain parameters from the left (LA) and right atrium (RA) as well as the left (LV) and right ventricle (RV) were assessed. Receiver operating characteristics analysis was performed to compare diagnostic performance.

Results: Patients with myocarditis showed significantly reduced LA passive strain (LA ε_e: 26.3 ± 14.5 vs. 33.5 ± 10.1%, p = .007), LA peak early negative strain rate (LA SRe: −1.94 ± 0.59 1/s vs. −1.46 ± 0.62 1/s, p < .001), LV global longitudinal strain (LV GLS: −17.2 ± 4.9% vs. −13.3 ± 6.2%, p < .001), LV mid-ventricular circumferential strain (LV mid CS: −25.9 ± 4.7% vs. −22.0 ± 6.5%, p < .001), and an increased RV basal circumferential SR (RV basal CSR: −0.70 ± 028 vs. −0.58 ± 0.34 1/s, p = .096) compared to healthy controls. In a subgroup analysis of patients with myocarditis and preserved LV function, RV basal CSR was also significantly increased compared to healthy controls (−0.74 ± 0.27 vs. −0.57 ± 0.26 1/s; p = .035) whereas LA SRe (−1.49 ± 0.59 vs. −1.32 ± 0.74%; p = .005) was significantly reduced. In multinominal logistic regression analysis, LA SRe and RV basal CSR proved to be the best independent predictors of myocarditis with preserved LV function. Combined with LLC, strain parameters enhanced the diagnostic performance in such patients (Areas under the curve (AUC): LLC: 0.78, LLC + LV GLS + LA SRe: 0.86), whereas LA SRe was the best performing single parameter (AUC: 0.72).

Conclusion: Combining quantitative CMR derived atrial and ventricular strain parameters with established LLC parameters can improve the diagnostic performance in patients with suspected myocarditis, including those with preserved LV function. Further investigations should focus on LA function, which appears to be more sensitive to early functional changes than LV function.

1. Introduction

In patients with acute chest pain and elevated troponin levels but non-obstructed coronary arteries, acute myocarditis is an important differential diagnosis [1]. Myocarditis has been reported to account for up to 20% of deaths in adults younger than 40 years and therefore represents an important cause of cardiac morbidity and mortality [2]. Furthermore, dilated cardiomyopathy as a sequela from chronic inflammatory activation is seen in patients with inadequate immune response [3].

Cardiac magnetic resonance (CMR) is an outstanding diagnostic tool because of its ability to characterize inflammatory myocardial tissue changes in vivo. In this respect, CMR is increasingly used in patients with clinically suspected myocarditis [4]. To date, the CMR diagnosis of myocarditis is made if two out of three “Lake-Louise criteria” (LLC) are met, which rely either on direct depiction of inflammatory myocardial involvement or on relative changes compared with a reference tissue [5–8]. However, several studies have shown controversial results regarding the diagnostic potential of LLC [4,9]. Recent studies have shown that quantitative techniques such as T1 and T2 mapping as wells

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as myocardial strain analysis have the potential to improve the diagnostic accuracy of CMR in the setting of acute myocarditis [4,10–13].

Several echocardiographic studies demonstrated the connection between left ventricular (LV) dysfunction and myocarditis even in patients with preserved LV ejection fraction (EF) [14–16]. Moreover, LV diastolic dysfunction assessed by echocardiography has been reported in patients with myocarditis [14,16], which has been shown to directly correlate to left atrial (LA) function. Since ventricular and atrial function is characterized by an interactive and dynamic relationship, LA deformation analysis is suggested to play an important role in determining prognosis and risk stratification in different states of disease – especially in those that are associated with ventricular diastolic dysfunction.

Recently, first studies reported the feasibility to perform atrial strain analysis derived from conventional cine steady-state free-precision imaging using a dedicated feature tracking (FT) post-processing algorithm [17,18]. However, these investigations were performed in relatively small cohorts and should be further validated in larger studies. Moreover, ventricular and atrial strain have not been investigated together in a single study so far.

Therefore, the aim of this study was to investigate the role of CMR FT derived strain analysis, especially focusing on atrial function, in a comprehensive multiparametric imaging approach including LLC for the diagnosis of acute myocarditis.

2. Material and methods

This study had institutional review board and local ethics committee approval. Cardiac MR imaging studies in myocarditis patients were clinically indicated. Written informed consent requirement in the patient cohort was waived because of the retrospective nature of the study. For each volunteer, written informed consent was obtained prior to CMR.

2.1. Study population

We included 86 patients (60 males, mean age 38 ± 14 years; 30 patients had been reported in a previous proof-of-concept study [17]) who were referred to CMR after clinical diagnosis of acute myocarditis. The clinical diagnosis was made based on the established recommendations given by the position statement of the European Society of Cardiology Working Group on myocardial and pericardial diseases [19]. CMR diagnosis of myocarditis was based upon the presence of ≥ 2 out of 3 LLC [7]. In contrast to the initial patient cohort consisting solely of patients with CMR-positive myocarditis, the validation cohort was composed of patients with CMR-positive myocarditis (n = 20) as well as patients with clinically diagnosed myocarditis and either 1 (n = 26) or none (n = 10) of the LLC fulfilled. Patients with CMR findings characteristic for other diseases than myocarditis were excluded from further analyses. Furthermore, patients were divided according to their LV function, where an LV-EF of 55% or lower was classified as impaired and 55% or above were classified as preserved.

30 healthy volunteers (14 males, mean age 37 ± 13 years) were included as controls. The status "healthy" was based on: (i) uneventful medical history, (ii) absence of any symptoms indicating cardiovascular dysfunction (iii) normal cardiac dimensions and function proven by cine CMR, and (iv) no history of inflammatory disease including common cold virus in the last four weeks before the examination. Demographics and LV volumetric data of patients and controls are summarized in Table 1.

2.2. Cardiac MR imaging data acquisition

All studies were performed on a 1.5 T whole body scanner (Philips Achieva, Philips Healthcare, Best, the Netherlands). A balanced steady-state free precession (b-SSFP) cine sequence in breath-hold technique and with retrospective ECG-triggering was acquired for functional analysis and subsequent FT analysis. Imaging parameters were chosen as follows: repetition time (TR) 28 ms, echo time (TE) 1.4 ms, flip angle (FA) 60°, field of view (FOV) 343 × 380 mm^2, matrix 256 × 256, slice thickness 8 mm, 50 cardiac phases. In all patients, standard longs axes (4-chamber (HLA), 2-chamber (VLA), and 3-chamber (LVOT)) as well as a short axis (SAX) stack covering the entire LV were obtained to assess LV and right ventricular (RV) function. Functional analysis was performed off-line using dedicated post-processing software (IntelliSpace Portal, Version 6, Philips Healthcare, Best, the Netherlands) and in concordance with previously published recommendations [20].

For oedema imaging, an oedema sensitive black blood T2-weighted sequence with fat saturation was used in SAX orientation. In order to detect inflammation induced myocardial hyperaemia, myocardial early gadolinium enhancement was assessed using fast spin- echo T1-weighted images during the first minutes after 0.1 mmol/kg Gd-DOTA (Dotarem, Guerbet, Villepinte, France) contrast administration in free-breathing as previously described [8]. For the detection of myocardial necrosis and scarring, LGE imaging was performed 15 min after a cumulative double dose of Gd-DOTA (Dotarem, Guerbet, Villepinte, France; cumulative dose 0.2 mmol/kg Gd-DOTA) contrast administration using an inversion-recovery gradient-echo sequence in the long axes and in the SAX as previously described [21].

2.3. Analysis of Lake-Louise criteria

In patients suspected of having myocarditis, the presence of focal myocardial oedema on T2 weighted imaging and/or non-ischemic lesions on LGE images was visually assessed. T2-ratio for the presence of global myocardial oedema and EGEr for the presence of inflammation-induced hyperaemia were calculated as recommended for the assessment of LLC [6–8]. Due to ethical concerns, the control group did not receive intravenous contrast media administration.

2.4. Feature tracking derived strain analysis

FT derived strain analysis was obtained from bSSFP cine images using a dedicated software (Image-Arena VA Version 3.0 and 2D Cardiac Performance Analysis MR Version 1.1.0; TOMTEC Imaging Systems, Unterschleißheim, Germany) as previously described [22]. Briefly, endocardial contours were drawn manually in end-diastolic images with subsequent software-driven automatic tracking of the endocardial contour throughout the entire cardiac cycle. Automatic tracking was checked for accuracy and contours were manually adjusted and tracking repeated in case of insufficient tracking.

HLA view was used to derive global RV and LV longitudinal strain (GLS) and their according strain rate (SR) values, respectively. Regional and global circumferential (CS and GCS) as well as radial strain (RS and GRS) and SR parameters of both RV and LV were determined in short axis view at a basal, mid-ventricular (mid) and apical level of the ventricle. To ensure a standardized analysis for each subject, planes were defined as previously described [22]. Global radial and circumferential strain and SR values were obtained by averaging values over all three SAX slices.

The HLA and VLA views were used to derive LA longitudinal strain and SR values. RA longitudinal strain and SR analysis was based on the four-chamber view only. Tracking of the LA was performed once on the four- and two-chamber view, respectively, whereas tracking of the RA was performed twice on the four-chamber view. Afterwards, the two measurements were averaged for further analyses. LA and RA strain were analysed in concordance to previous definitions [23]: Briefly, three aspects of atrial strain were analysed: (i) passive strain (ε_e, corresponding to atrial conduit function), (ii) active strain (ε_a, corresponding to atrial contractile booster pump function) and (iii) total strain, which is the sum of passive and active strain (ε_s, corresponding to atrial reservoir function). Accordingly, three SR parameters were

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