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# Subclinical left ventricular dysfunction and correlation with regional strain analysis in myocarditis with normal ejection fraction. A new diagnostic criterion

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ABSTRACT

*Background:* The diagnosis of myocarditis is challenging, especially in case of normal left ventricular systolic function. The aim of this study is to test the hypothesis that 2D speckle tracking echocardiography (2DSTE) can detect subclinical left ventricular (LV) dysfunction in patients with myocarditis and preserved LV function without regional wall motion abnormalities and that regional strain analysis can correlate with cardiac magnetic resonance (CMR) findings.

*Methods:* Study population consisted of 25 consecutive patients with myocarditis and 19 controls. All patients underwent a full echocardiographic study at the first day of their admission and in addition to conventional echocardiographic measurements, global longitudinal and circumferential strain of the left ventricle (LVGLS, LVCS accordingly), as well as regional strains of the lateral wall, were estimated. Moreover, all patients underwent a CMR scan during the first week from their admission.

*Results:* Although there was no statistical difference between the two groups of patients in systolic function, myocarditis patients demonstrated significantly impaired LVGLS ($-16.5 \pm 2.2$ vs $-20.5 \pm 1.3\%$, $p < 0.0001$) and LVCS ($-16.4 \pm 3.7$ vs $-20.9 \pm 2\%$, $p = 0.002$), as well as segmental longitudinal strains of the lateral wall. CMR in all myocarditis patients revealed late gadolinium enhancement in the lateral left ventricle free wall.

*Conclusions:* In patients with acute myocarditis with preserved ejection fraction, 2DSTE evaluation appears to be a promising, useful noninvasive and inexpensive tool in addition to existing methods used for the diagnosis of acute myocarditis, since it seems to be able to identify myocardial fibrosis early in the setting of the disease.



## 1. Introduction

Establishing the diagnosis of acute myocarditis is sometimes too complicated because of the wide range of symptoms, varying from chest pain and new arrhythmia appearance to acute heart failure and sudden cardiac death [1]. The reported frequency of myocarditis as the cause of heart failure ranges from 0.5 to 4% [2]. This variation is probably due to under diagnosis of myocarditis in both community and hospital environment. Currently the diagnosis of myocarditis is based on clinical history, physical examination findings, rest electrocardiogram (ECG), troponin levels, echocardiography, cardiovascular magnetic resonance (CMR) and coronary angiography, mainly by excluding other medical conditions, since there are no specific findings of the disease.

As mentioned above, the findings of acute myocarditis by conventional echocardiography are non-specific and thus it is necessary to combine the echo data with other, especially non-invasive, imaging techniques [3,4]. Endomyocardial biopsy is widely accepted as the "gold standard" method with high specificity but it is an invasive method with serious technical problems [5–7]. Nowadays CMR has become the primary noninvasive tool for acute myocarditis diagnosis, offering 79% accuracy rate [8], by assessing the presence and extension of myocardial fibrosis using late gadolinium enhancement (LGE). However, CMR itself – without electrocardiogram findings or elevation of troponin levels or suspicion raised from echo – cannot establish the diagnosis of acute myocarditis and has not sufficient prognostic value [9,10]. Furthermore, the access to CMR is often restricted for many patients and the waiting list is usually long.

Two-dimensional speckle tracking echocardiography (2DSTE) can estimate and quantitatively measure myocardial mechanics

*Abbreviations:* AST, aspartate aminotransferase; AUC, Area Under the Curve; CMR, cardiovascular magnetic resonance; CRP, C-reactive protein; ECG, electrocardiogram; ICC, intra-class correlation coefficient; LDH, lactate dehydrogenase; LGE, late gadolinium enhancement; LV, left ventricle; LVCS, left ventricular circumferential strain; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; ROC, Receiver Operating Characteristic; RS, radial strain; WBC, leucocytes; 2DSTE, two-dimensional speckle tracking echocardiography.

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(strain and strain rate) of premature (subclinical) left ventricular (LV) deformation abnormalities in longitudinal, circumferential and radial directions, even when conventional echocardiography does not reveal impairment of LV ejection fraction (LVEF) [11,12]. In many clinical settings such as cardiomyopathy or coronary artery disease, a decrease in longitudinal strain by 2DSTE has been shown to detect early LV dysfunction before the occurrence of changes in LVEF [11,13]. Recently, in a few studies subclinical LV dysfunction in patients with myocarditis and preserved LVEF has been reported [14,15]. On the other hand, assessment and analysis of myocardial fibrosis by CMR in patients with a variety of cardiac diseases including myocarditis, have been established, although not correlated to impaired strain [16,17].

The aim of our study was to verify the hypothesis that in patients with acute myocarditis and preserved LVEF without regional wall motion abnormalities by conventional echocardiography at rest, 2DSTE can reveal not only subclinical LV dysfunction but also an association of a possible predictive diagnostic value between impaired strain and a specific LV segment. Finally, we investigated the association of myocarditis with segmental LV strain impairment by LGE-CMR in the acute setting of myocarditis.

## 2. Materials and methods

### 2.1. Patients

Study population was consisted of 44 patients who were divided in two groups. Group A included 25 consecutive patients with acute myocarditis (21 men and 4 women aged 26.8 ± 11.5 years) and group B consisted of 19 age-matched controls (15 men and 4 women aged 23.3 ± 10 years). All Group A patients underwent echocardiography at their admission day to the hospital and additionally to conventional measurements we obtained LV global longitudinal (LVGLS) and circumferential strain (LVCS) and the segmental strains of all LV walls. Furthermore, all patients with myocarditis underwent coronary angiography for the exclusion of coronary artery disease and CMR with late gadolinium enhancement during the first week of their hospitalization.

### 2.2. Blood biochemistry

As far as it concerns diagnostic work out for myocarditis by blood analysis, the diagnosis was confirmed by the findings of transient elevation of C-reactive protein (CRP), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), leucocytes (WBC) and mainly cardiac troponin T in blood, in serial daily measurements for at least one week. High sensitivity troponin T has been measured quickly and easily in whole blood by enzyme-linked immunosorbent assay (ELISA) and it was especially useful for immediate diagnosis.

### 2.3. Echocardiographic protocol

All subjects underwent transthoracic echocardiographic examination according to recommendations of European Association of Cardiovascular Imaging. LVEF has been calculated using biplane Simpson's method of discs, auto-EF calculation based on speckle tracking method (GE software) and 3D echo (auto-LVQ GE software and TOMTEC software) in patients with high quality images. Myocardial global longitudinal, radial and circumferential strain (GLS, RS and CS) values were measured by the Vivid 7 GE full pack updated machine. Two-dimensional multiframe gray-scale images were obtained in the apical four, two-chamber and long-axis views for GLS, and parasternal short-axis view at the level of papillary muscles for RS and CS. Speckle-tracking analysis was performed offline using GE EchoPAC workstation version 110 software, with Q analysis and AFI protocol for Bull's eye projection. In brief, the endocardial border of the ventricle was manually traced (8–10 points) over 1 frame, and endocardial borders were automatically tracked throughout the cardiac cycle. The adequacy of tracking was verified manually, and the region of interest was adjusted to achieve optimal tracking.

Sector size, depth and focus point were adjusted to achieve optimal visualization of all LV myocardial segments at the highest possible frame rate for further analysis (70–80 fps) and to avoid "out of point" motion. Three consecutive cardiac cycles of each view were acquired and systolic timing was clarified by the timing of aortic valve closure, assessed from the aortic valve motion in the apical long-axis view. According to our software, the strain analysis for all subjects was limited for endocardial values.

### 2.4. Reproducibility

Reproducibility for strain analysis was performed in 7 (28%) patients. The intraobserver intra-class correlation coefficient (ICC) for LVGLS was 0.899 (95% CI: 0.7–0.98), for the basal lateral wall was 0.88 (95% CI: 0.7–0.98), for the mid lateral wall was 0.97 (95% CI: 0.85–0.99) and for the apical lateral wall was 0.7 (95% CI: 0.66–0.95). The interobserver ICC for LVGLS was 0.88 (95% CI: 0.6–0.98), for the basal lateral wall was 0.86 (95% CI: 0.6–0.97), for the mid lateral wall was 0.93 (95% CI: 0.77–0.99) and for the apical lateral wall was 0.77 (95% CI: 0.76–0.95).

### 2.5. CMR

The 'International Consensus Group on CMR Diagnosis of Myocarditis' has published detailed recommendations on the indication, implementation and analysis of appropriate CMR techniques for diagnosis of myocarditis (Lake Louise criteria) [3], based on preclinical and clinical studies. Especially T1-weighted early signal enhancement and gadolinium-delayed imaging of the heart can establish positive diagnosis of myocarditis, as they can assess the presence and extension of fibrosis. Also, T2-weighted images reveal the regions of the heart affected by inflammation (myocardial edema). CMR imaging can differentiate acute myocarditis from acute myocardial infarction as acute myocarditis exhibits erosive or spotty areas in the epicardium, while lesions of acute myocardial infarction spread from the endocardium like a wave front.

### 2.6. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 20) software. Results were expressed as mean values ± SD. Normal distribution of the echocardiographic indices was checked with Kolmogorov–Smirnov and Shapiro–Wilk tests. The normality of the distributions was confirmed and the overall differences between subgroups were performed using one-way ANOVA multivariable test. A p value < 0.05 was considered statistically significant. Average value of lateral wall GLS was tested for its ability to discriminate patients with myocarditis using Receiver Operating Characteristic (ROC) curves. The overall performance of the ROC analysis was quantified by computing Area Under the Curve (AUC). An area of 1 indicated perfect performance, while 0.5 indicated a performance that was not different than chance. Using ROC analysis we determined the optimal sensitivity and specificity of various cut-off values for the discrimination of patients with myocarditis.

## 3. Results

A total of twenty-five consecutive subjects met the study criteria for the diagnosis of myocarditis with subsequent maintenance of good systolic LV function and they have been compared to nineteen age-matched healthy subjects. All patients with myocarditis were referred due to chest pain and elevated troponin concentration with a wide range of peak levels in at least 3 measurements. Ntpro-BNP levels were normal in all myocarditis patients. The inflammatory parameters, i.e. CRP and/or LDH, AST, WBC were elevated in 21 of 25 patients. Classic diffuse ST-segment elevation on ECG was observed in only one patient. None of the patients reported any other concomitant disorder, such as diabetes, dyslipidemia and prior ischaemic heart disease, except for two patients who reported arterial hypertension under treatment.

Baseline characteristics and echocardiographic parameters of both groups are shown in Table 1A. There was no statistical difference between patients and controls as far as it concerns age, male sex, LV end-diastolic diameter and S wave by Tissue Doppler Imaging (Table 1A). In all subjects overall LV systolic function by echocardiography expressed by LVEF was within normal limits with no regional wall motion abnormalities at rest (normal Wall Motion Score Index) (Table 1A). Nevertheless, there was a significant difference in LVEF between the two groups (Table 1A) due to the fact that although myocarditis group demonstrated normal LVEF values, they were significantly lower than those of controls group.

Overall LVGLS was significantly reduced (−16.5 ± 2.2%) in patients with myocarditis (Table 1) compared to age-controlled normal subjects ($p < 0.001$) (Table 1B). Additionally, in group A regional LS was notably reduced in all lateral segments; basal, medial, and apical in comparison to healthy subjects ($p < 0.001$, $p < 0.001$, $p < 0.005$, respectively) (Fig. 2). Average LVCS at the level of papillary muscles was also significantly lower in group A ($p < 0.001$). Regional CS was noted to be reduced only in the lateral segments at the level of papillary muscles. There was no significant difference in radial strain between the two groups (Table 1B). We have not noticed a correlation of troponin and the number of segments with reduced strain.

ROC curve analysis showed that the optimal cut-off value of the lateral wall GLS for the discrimination of patients with myocarditis was −17% with sensitivity and specificity equal to 95%. The AUC was