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Registry of Patients with Suspected Myocarditis: Diagnosing Edema using STIR+ *via* 3-D-Cardiovascular Magnetic Resonance Imaging-Real World Experience

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Abstract

Aim: The occurrence and frequency of edema in ambulant patients with clinically possible myocarditis is unknown. In a real-world context, we evaluated the occurrence of myocardial edema *via* a three-dimensional STIR sequence in a registry of patients presenting suspected early myocarditis after respiratory infection or palpitations and newly-diagnosed ventricular premature beats.

Material and Methods: We examined 340 outpatients with suspected myocarditis and 69 controls matched for gender and age. An Echocardiography (ECG)-triggered three-dimensional STIR sequence (STIR+) was used. We calculated the global or local signal intensity ratio (signal intensity of the whole heart muscle in relation to skeletal muscle) (global or local STIR+ ratio). Following the MR Lake-Louise criteria, we applied a global or local STIR+ ratio of 2.0 or more to confirm edema. Late gadolinium enhancement data were obtained, as were left ventricular (LV) function and dimensions in patients and controls.

Result: Two hundred and thirty (67.6%) of these patients revealed evidence of edema. Their mean global STIR+ ratio was 2.21 ± 0.31, *vs.* 1.81 ± 0.29 in controls ($p<0.0001$). The local ratios of the septal, anterior, lateral, and inferior wall were also significantly different. Patients had a significantly lower Left Ventricular Ejection Fraction (LV-EF) of 61.9 ± 8.2% than controls (LV-EF 65.6 ± 7.6%, $p=.001$). Positive late gadolinium enhancement was also more frequent in patients than controls (61.7% and 5.8%, $p<0.0001$).

Conclusion: In this real-world registry, we observed highly robust discrimination between patients with suspected myocarditis compared to controls using the three-dimensional STIR+ ratio. The global or local STIR+ ratio therefore facilitates the diagnosis of myocarditis in daily practice.

Keywords: STIR+; Modified three-dimensional T2-weighted fast-spin-echo triple inversion recovery sequence; Real-world experience; Cardiovascular magnetic resonance imaging; Myocarditis; Left ventricular function; Late gadolinium enhancement

Abbreviations: CMRI: Cardiovascular Magnetic Resonance Imaging; ECG: Electrocardiogram; LV-EF: Left Ventricular Ejection Fraction; EDV: End-Diastolic Volume; LVEDD: Left Ventricular End-Diastolic Diameter; LGE: Late Gadolinium Enhancement; LV: Left Ventricular, Left Ventricle; STIR+: Spin Echo Triple Inversion Recovery (s); STIR+ ratio: STIR+ of heart muscle in relation to skeletal muscle

Introduction

Myocarditis is a key cause of cardiac morbidity and mortality, accounting for up to 20% of sudden unexpected deaths in adults younger than 40 yrs [1]. Myocarditis can trigger arrhythmias in the acute phase, and it is a frequent precursor of Dilated Cardiomyopathy (DCM) [2,3]. However, diagnosing it remains difficult due to its variable clinical presentation, especially in outpatients. Cardiac Magnetic Resonance Imaging (CMRI) is a non-invasive and well-established modality that has become a valuable clinical tool [4]. Patients presenting the clinical manifestation of myocarditis are increasingly undergoing CMRI [3-5]. T2-weighted images help us to identify areas of edema and inflammation. Tissue edema is a key factor in the myocardium's acute inflammatory process in patients with myocarditis [6]. T2-weighted imaging using a triple inversion breath hold sequence with Spin Echo Triple Inversion Recovery (STIR+) has improved image quality. These sequences were tested in previous studies [7-9], but some authors reported considerable technical problems associated with the (STIR+) sequence, potentially limiting its clinical utility [10-12]. In an earlier study, we evaluated how a three-dimensional (3D) T2-weighted fast-Spin-echo Triple Inversion Recovery sequence (STIR+) covering the entire left ventricle with a constant slice thickness of 10 mm and no interslice gap assesses myocardial edema in patients with suspected myocarditis in the acute phase and during follow-up in a small patient cohort [13]. Premature ventricular beats in patients without structural heart disease such as hypertrophy, cardiomyopathy, valve disease, or coronary artery disease can be due to acute or previous myocarditis [14,15]. In this study we report retrospectively on real-world data from our registry of consecutive outpatients with suspected myocarditis after respiratory

infection and patients with palpitations and newly-diagnosed ventricular premature beats examined by this CMRI sequence in a larger patient population.

Materials and Method

Patients: We examined 340 outpatients with possible myocarditis after a viral infection of the respiratory tract and patients with palpitations and newly-diagnosed ventricular premature beats, as well as 69 controls matched for gender and age. Relying on the modified Lake-Louise MR criteria [6], we considered a global or local STIR+ ratio of 2.0 or more as positive to confirm edema. Patients and controls underwent 12-lead ECG (Echocardiography) and transthoracic echocardiography. Our controls were examined for atypical thoracic pain or during their check-ups. No control presented any signs, symptoms, or history of cardiovascular disease. No control revealed wall motion abnormalities on transthoracic Echocardiography, or any signs of ischemia on 12 lead ECG. All controls underwent a non-invasive stress test (bicycle exercise and/or dynamic stress echocardiography or adenosine CMRI) or CT scan (Computed Tomography) of the coronary arteries to rule out coronary artery disease.

Our patient cohort included those with palpitations and newly-diagnosed ventricular premature beats and patients with symptoms of fatigue, and/or dyspnea, and/or weakness and/or palpitations after respiratory tract infection. These patients had been referred by their general practitioners for outpatient cardiologic evaluation including CMRI for clinically suspected myocarditis. Patients and controls were excluded if they had a history or findings suggestive of coronary artery disease, dilated cardiomyopathy, congenital heart disease, right heart failure, signs of pulmonary hypertension on Continuous Wave Doppler, significant LV hypertrophy (diameter of the septum and/or inferior wall ≥ 12 mm), significant valvular regurgitation (>degree 1 on echocardiography and/or CMRI) or valvular stenosis, renal failure (creatinine ≥ 1.8 mg/dl) or a known history of claustrophobia.

Our study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the local institution´s human research committee [16]. All procedures in this registry involving human participants were carried out in accordance with the ethical standards of the institutional research committee. All patients provided written informed consent for participation.

Cardiovascular Magnetic Resonance Imaging (CMRI)

Cardiovascular magnetic resonance studies were conducted on a 1.5 T magnetic resonance system (Intera CV 1.5 T, Phillips Medical Systems, Best, The Netherlands) using specifically designed software (Release 11). A five-element cardiac phased-array coil was used combined with a homogeneity correction algorithm (Constant Level Appearance; CLEAR). This algorithm generates sensitivity maps for each synergy coil element (relative to the body coil sensitivity) to calculate uniformity correction [17]. Data acquisition was ECG-triggered. Functional and morphological data were evaluated using the software package "*View Forum 6.5*" (Phillips Medical Systems, Best, and The Netherlands). Regions of interest were drawn manually. Two, 3 and 4-chamber long-axis views in conventional biplane technique and short-axis volume data were acquired by steady-state free precession imaging as described previously [18]. Phase-contrast velocity images in the ascending aorta were obtained to measure stroke volume and rule out significant aortic insufficiency in conventional biplane technique. ECG-triggered, 3D T2-weighted fast-Spin-echo Triple Inversion Recovery sequences covering the entire left ventricle (STIR+) were acquired in all patients and controls as described before, [13] data are provided per patient. The relative global myocardial signal intensity was calculated by the ratio of global mean myocardial signal intensity and mean skeletal muscular signal intensity (global STIR+ ratio). The relative local myocardial signal intensity was calculated by the ratio of mean septal or anterior, or lateral, or inferior myocardial signal intensity and mean skeletal muscular signal intensity (regional STIR+ ratios). A local or global ratio of 2.0 or more according to the new MR Lake-Louise criteria indicated myocardial edema.

Finally, Late Gadolinium Enhancement (LGE) images were acquired in all patients and controls ten minutes after the IV administration of 0.2 mmol/kg intravenous gadolinium-diethylenetriamine-pentaacetate (Magnevist, Schering, Germany). 3D inversion recovery turbo gradient echo sequences with a contiguous stack of slices obtained covering the entire LV with no gap during two breath holds were obtained as previously reported [15,18]. A 4-chamber long axis view was also obtained. LGE was assessed visually and a qualitative analysis of LGE images conducted to identify regional increases in myocardial signal intensity. Our protocol consisted of: SSFP (Steady State Free Precession) 2, 3 and 4-chamber long-axis views, short-axis volume data acquisition. STIR+ 3D volume data acquisition, phase-contrast velocity images in the ascending aorta and LGE in contiguous stack of slices covering the entire ventricle and a 4-chamber long axis view. The regions of interest were drawn manually. Locally-thickened pericardium was defined as ≥ 4 mm. To exclude partial volume effects, pericardial thickening and enhancement were obtained in short and long axis views. To minimize sampling bias, all measurements in controls and patients were taken by just two experienced investigators (Jeserich and Kimmel) unaware of clinical findings.

Statistical Analysis

Data are presented as means and Standard Deviation (SD) as indicated for quantitative variables and as absolute and relative frequencies for categorical variables. After assessing normality, we compared the quantitative variables between patients and controls using unpaired t-tests. All tests were two-sided and used significance level of 0.05 to indicate statistical significance.

Results

Patient characteristics and functional parameters

Two hundred and thirty (67.6%) patients revealed evidence of edema. Baseline characteristics of these patients and of our controls are shown in Table 1. Controls did not differ from patients in age or sex, blood pressure, or heart rate. At the visit, 29% of patients complained of dyspnea, 29% of thoracic pain, 61% of fatigue, and 55% of palpitations. Sixty-seven percent had documented ventricular premature beats at resting ECG. Troponin levels were 0.02 ± 0.02 ng/ml, reference levels 0.00-0.40 ng/ml, BNP 55.4 ± 172 ng/ml.

Functional parameters are listed in Table 2. We detected no significant difference between patients and controls in LV dimensions or stroke volume. Patients had a significant lower Left Ventricular

Ejection Fraction (LV-EF) than controls, as well as lower cardiac output (Table 2). Twenty-six patients had an LV-EF below 55%; the lowest was 37%. Four patients required hospital admission; the others could be monitored as outpatients. Fifty-nine percent of patients presented disturbed septal or anterior relaxation compared to 20% of controls (p<0.0001).

Variable	Patients	Controls	P-Value
Mean age (years)	53.9 ± 13.5	54.1 ± 15.8	0.85
Male (%)	62.2	63.8	0.86
Height (cm)	174.3 ± 9.2	174.0 ± 9	0.84
Weight (kg)	78.0 ± 13.1	79.6 ± 11.8	0.51
Systolic blood pressure (mmHg)	135.5 ± 16.2	136.1 ± 17.7	0.81
Diastolic blood pressure (mmHg)	80.9 ± 10.0	79.3 ± 8.7	0.81
Heart rate (beats per min)	74.1 ± 15.4	73.2 ± 15.8	0.73

Table 1: Clinical characteristics of patients with edema and controls. Values are expressed as means ± SD.

Assessment of myocardial edema

Two hundred and thirty (67.6%) patients revealed evidence of edema. Their mean global STIR+ ratio was significantly higher than the controls' (Table 2), as were their regional STIR+ ratios. In our registry, we observed focal edema in 23.5% and global edema in 76.5%. We obtained a global STIR+ ratio in all patients and controls. The regional anterior and septal STIR ratios were un-assessable in one control. We were unable to obtain reliable regional inferior-wall STIR+ values in 9% of the patients' examinations and in 6% of the controls. Figure 1 provides an example of one patient's STIR+ measurement and Figure 2 an example of a control.

Variable	Patients	Controls	P-Value
LV ejection fraction (%)	61.9 ± 8.2	65.6 ± 7.6	0.001
LV end-diastolic diameter (mm)	52.0 ± 8.0	50.9 ± 7.1	0.31
Cardiac output (L/min)	6.5 ± 1.4	6.8 ± 1.5	0.16
Scar (%)	61.7	5.8	<0.0001
STIR+ myocardium/ske. muscle	2.21 ± 0.31	1.81 ± 0.29	<0.0001
STIR+ septal myoc./ske. muscle	2.23 ± 0.35	1.86 ± 0.30	<0.0001
STIR+ anter. myoc./ske. muscle	2.10 ± 0.38	1.76 ± 0.33	<0.0001
STIR+ later. myoc./ske. muscle	2.22 ± 0.37	1.86 ± 0.34	<0.0001
STIR+ infer. myoc./ske. muscle	2.30 ± 0.32	1.92 ± 0.39	<0.0001

Table 2: Magnetic resonance functional measurements in patients with edema and controls; LV indicates left ventricular. Values are expressed as means ± SD. STIR+: modified three-dimensional T2-weighted fast-spin-echo triple inversion recovery sequence (s); Myoc: myocardium; Ske: skeletal.

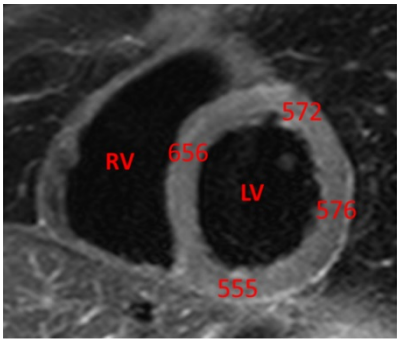

Figure 1: STIR+ image of a 41-year-old male patient with fatigue, exertional dyspnea and newly documented very frequent premature ventricular beats with couplets and triplets after respiratory tract infection. Global STIR+ ratio was 2.61. STIR+ values of the septal, anterior, lateral wall and of the skeletal muscle are visible. The ratios were 2.81 septal 2.45 anterior, 2.40 lateral and 2.38 inferior. Of note, elevated global STIR+ indicating edema, in addition very high septal STIR+ values comparable with dominant edema in the septum; Two-chamber view; LV: Left Ventricle. RV: Right Ventricle.

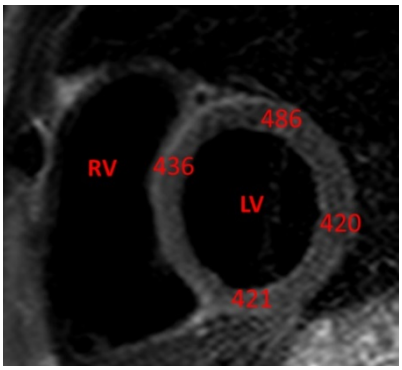

Figure 2: STIR+ image of a 32-year-old male control. Global STIR+ ratio was 1.81 STIR+ values of the septal, anterior, lateral wall and of the skeletal muscle are visible. The ratios were 1.80 septal 1.95 anterior, 1.73 lateral and 1.74 inferior. Two-chamber view; LV: Left Ventricle. RV: Right Ventricle.

Late contrast enhancement, pericardial effusion and thickening

Positive late gadolinium enhancement was observed in about 62% of our patients, whereas it was rare in controls (Table 2). Regions of contrast enhancement were distributed in a patchy pattern and originated primarily from the epicardial quartile or mid-myocardial wall, with one or several foci within the myocardium most frequently located in the patient's septum (42%) and in the lateral free wall (27%) including multiple locations (a patient`s example is provided in Figure 3). Thirty-seven percent of the patients exhibited mild-to-moderate

contrast enhancement of the pericardium, usually distributed locally in the lateral or anterolateral part of the pericardium, compared to 14% of the controls, p<0.0001. Fifty-seven patients (25%) and ten controls (14%), difference p=0.02) presented locally thickened pericardium, and 21% of the patients (but only 3 controls (4%), p=0.001) revealed small pericardial effusions. In total, 97 patients (42%) revealed pericardial abnormalities.

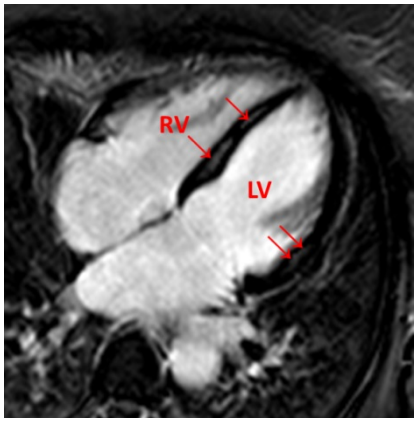

Figure 3: Late-enhancement image of a 57-year-old female patient with fatigue, exertional dyspnea and thoracic pain after a viral rhinitis and sinusitis 3 weeks before. Note the midmyocardial enhancement in the septal (↑) and posterolateral wall (↑↑). Four-chamber view; LV: left ventricle. RV: right ventricle.

Discussion

In about two-thirds of the patients with clinically suspected myocarditis we detected myocardial edema, and positive late gadolinium enhancement in 62% of them. We assessed the presence of edema by applying a 3D STIR+ sequence tested in a previous study [13]. The STIR+ ratio was significantly higher in patients than controls. It is a promising parameter that we obtained in all patients and controls. We expanded upon our previous study's results by examining more patients and more controls. To the best of our knowledge, this report covers what is the largest registry documenting outpatient with presumed myocarditis. The global STIR+ sequence was obtained in all our patients because we were able to cover the whole ventricle. This is especially important, as there are significant technical problems associated with the conventional STIR sequence that reduce its clinical utility [10-12,19] and cause it to fail in some circumstances [14]. Due to these problems, newer sequences such as T1 and T2 mapping have been developed [20-24] and compared to the conventional STIR sequences, but those results have been inconsistent. Some investigators observed better detection of myocardial involvement [21-23] by T1 or T2 mapping in myocarditis, whereas Goebel et al. [24] reported that the average native T1 value in cardiac MR imaging precludes differentiating between healthy and diffusely diseased myocardium in individual cases. Our 3D STIR+ sequence could thus be a promising, easily obtainable parameter.

In acute myocarditis, edema may be focal in approximately 30% of patients, or diffuse in the remaining 70%, and myocardial edema may be the sole disease marker [9]. In our registry we identified in about 24% focal and in 76% global edema, thus enabling good comparability.

We noted positive late gadolinium enhancement in about 60% of patients who revealed the typical sub-epicardial or midmyocardial late contrast-enhancement pattern reported in patients with myocarditis [25,26]. We observed one or several foci within the myocardium most frequently located in the patient's septum and lateral free wall, consistent with other reports [8,27]. In about 40% of our patients we detected pericardial involvement evident as pericardial thickening, enhancement, or small pericardial effusions supporting the diagnosis of acute or remote myocarditis or perimyocarditis [28,29].

Conclusion

In our real-world registry, we observed myocardial edema in about two-third of patients with clinically suspected myocarditis employing 3D STIR+ sequence. Its usefulness was confirmed to detect edema in a large ambulant patient cohort in daily practice.

Authors' Contribution Section

M.J. designed the registry with project development, made parts of the CMRI data collection and analysis and wrote the manuscript. S.K. acquired parts of the CMRI data, data collection and contributed to the management. S.A. helped to draft the manuscript, contributed to project development and revised the manuscript critically.

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