Functional and Morphological Parameters with Tissue Characterization of Cardiovascular Magnetic Imaging in Clinically Verified "Infarct-like Myocarditis"

Funktionelle und morphologische Parameter einschließlich Gewebecharakterisierung mittels kardiovaskulärer Magnetresonanztomografie bei Patienten mit klinisch gesicherter „infarct-like myocarditis"

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Zusammenfassung

Ziel: Die kardiovaskuläre Magnetresonanztomografie (CMR) hat sich in den letzten Jahren zunehmend als wertvolles diagnostisches Verfahren herausgestellt. Ziel der vorliegenden Arbeit war es, den diagnostischen Wert funktioneller und morphologischer Parameter einschließlich der Gewebecharkaterisierung bei Patienten mit „infarct-like myocarditis" zu erfassen.

Material und Methoden: In einer retrospektiven Fall-Kontroll-Studie wurden 43 Patienten mit klinisch gesicherter „infarct-like myocarditis" (medianer Zeitraum von Klinikaufnahme mit akuten Symptomen bis zur MRT-Untersuchung 3 Tage) und 35 nach Alter und Geschlecht gematchte Kontrollpersonen eingeschlossen. Die Untersuchungen wurden an einem 1,5 T-Gerät unter Anwendung der steady-state-free-precession-Sequenzen, T2 gewichteter bzw. T1 gewichteter Bildgebung vor und nach Kontrastmittelapplikation und Late-Gadolinium-Enhancement-Sequenzen durchgeführt. Gemäß der Consensusvereinbarungen (Lake-Louise-Kriterien) lag eine Myokarditis vor, wenn 2 von 3 CMR-Techniken positiv ausfielen.

Ergebnisse: Es fanden sich bei 30 % der Patienten mit „infarct-like myocarditis" eine reduzierte LVEF, ein erhöhter LVEDVI bei 11 %, sowie eine Zunahme des LVMI bei 35 %. Die Sensitivität von Wandbewegungsstörungen betrug 63 %. Regionale Wandbewegungsstörungen traten bei 49 % auf, wobei diese in 47 % in den lateralen linksventrikulären Segmenten vorlagen. Perikardergüsse wurden in 65 % beobachtet, mit zirkulärer Manifestation in 21 % und fokaler in 44 %. Die Sensitivität, Spezifität, und diagnostische Genauigkeit der CMR bei den Patienten mit „infarct-like myocarditis" betrug 67 %, 100 % und 82 %. Bei der LGE-Sequenz als alleinigem Testparameter fanden sich die höchsten Werte mit 86 %, 100 % und 92 %.

Schlussfolgerung: Die Ergebnisse der vorliegenden Studie beziehen sich auf eine Subgruppe mit

Abstract

Purpose: Cardiac magnetic resonance (CMR) has increasingly proved to be a valuable diagnostic tool for evaluating patients with suspected myocarditis. The objective of this study was to evaluate the diagnostic value of functional and morphological parameters including tissue characterization in patients with "infarct-like myocarditis".

Materials and Methods: 43 patients with clinically verified cases of "infarct-like myocarditis" (median time to MRI scanning after admission for acute symptoms 3 days) and 35 control patients matched by age and sex were included in this retrospective case control study. In this study we used a 1.5 T MRI scanner conducting steady-state-free-precession sequences, T2-weighted imaging, T1-weighted imaging before and after contrast administration and late gadolinium enhancement sequences. According to the recommendations for CMR diagnosis of myocarditis (Lake Louise consensus criteria), a scan was positive for acute myocarditis if 2 of 3 CMR criteria were present.

Results: 30 % of the patients with "infarct-like myocarditis" had a reduced left ventricular ejection fraction, 11 % had an increased LV end-diastolic volume index and 35 % had an increased LV mass index. The sensitivity of wall motion abnormalities was 63 % with a regional distribution in 49 %. In 47 % of cases regional wall motion abnormalities were present in the lateral left ventricular segments. Pericardial effusions were discovered in 65 % of cases with a circular appearance in 21 % and focal manifestation in 44 %. The diagnostic sensitivity, specificity, and accuracy of CMR in patients with "infarct-like myocarditis" were 67 %, 100 % and 82 %, respectively. The LGE alone was the most sensitive test parameter with 86 %, providing a specificity of 100 % and accuracy of 92 %.

Conclusion: Our study results can be applied to the subgroup of patients with "infarct-like myocarditis", where we found that LGE alone was the

Patienten mit „infarct-like myocarditis“, in der sich das LGE alleine als der sensitivste Testparameter herausstellte. Die Analyse der funktionellen und morphologischen Parameter stellt neben der Gewebecharakterisierung eine sinnvolle Ergänzung der Diagnostik bei der akuten Myokarditis dar.

Kernaussagen:

- Die „infarct-like myocarditis“ kann mittels CMR valide diagnostiziert werden.
- Bester Testparameter ist das LGE alleine mit einer Sensitivität von 86 %
- Funktionelle und morphologische CMR-Parameter stützen die Diagnose einer akuten Myokarditis in Ergänzung zur Gewebecharakterisierung.

most sensitive test parameter. In addition to tissue characterization, the functional and morphological analysis of patients with acute myocarditis provides a useful further diagnostic tool.

Key Points:

- Infarct-like myocarditis can be diagnosed by CMR with high validity and reliability.
- LGE allone performed best with a sensitivity of 86 %.
- Functional and morphological CMR parameters in addition to tissue characterization are useful tool in the diagnosis of acute myocarditis.

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Introduction

Manifestations of acute myocarditis vary from subclinical to fulminant and fatal disease, including an infarct-like presentation with acute chest pain, arrhythmias or severe heart failure [1]. In this challenging clinical setting, magnetic resonance imaging (MRI) has proven to be an extremely valuable diagnostic tool, providing information about functional and morphological parameters as well as tissue characterization [2, 3]. Endomyocardial biopsy (EMB) and especially immunohistological analysis are still regarded as the gold standard for diagnosis [4]. According to the EuroCMR registry and the MRCT Registry of the European Society of Cardiac Radiology (ESCR), myocarditis is one of the most common indications for cardiac MRI [5]. MRI diagnosis of acute myocarditis is based on 3 techniques: 1) T2–weighted images (T2w) for determination of myocardial edema; 2) T1-weighted images (early gadolinium enhancement = EGE) for determination of myocardial hyperemia; 3) late gadolinium enhancement (LGE) for determination of necrosis or myocardial fibrosis. Using the recommendations for CMR diagnosis of myocarditis, also known as Lake Louise consensus criteria, a scan is positive for myocarditis if 2 out of the 3 criteria are met [3].

The aim of this case-control study was to evaluate functional and morphological parameters in patients with clinical diagnosis of “infarct-like myocarditis” (subgroup of acute myocarditis = AMC). Additionally we wanted to evaluate the sensitivity, specificity and diagnostic accuracy for disease-related tissue changes using the Lake Louise criteria compared to a control group matched with respect to age and sex.

Materials and methods

Patients

43 consecutive patients (38 men, age 34.7 ± 15.2 years) with clinical diagnosis of infarct-like myocarditis were included retrospectively in the study. Clinical diagnosis of infarct-like myocarditis required the presence of at least one criterion in each of the 3 categories of clinical findings (1.Symptoms; 2.ECG; 3. Elevated troponin T) (**Table 1**). Pathological ECG changes included ST segment elevation or depression, T-wave inversion, atrioventricular block or bundle branch block. These ECG findings are used together with serum markers for myocyte necrosis such as troponin in the diagnosis of acute coronary syndromes (STEMI and NSTEMI). Therefore, we selected a positive troponin test (elevated high sensitive serum troponin T) as a mandatory inclusion criterion for patients with infarct-like myocarditis. The median time to MRI scanning after admission for acute symptoms was 3 days (min. duration 1 day, max. duration 17 days). The patients of the control group had gone for cardiac MRI scanning for noninvasive exclusion of relevant cardiac disease in the absence of acute symptoms, ECG changes and troponin elevation. Patients were excluded from the study if there was evidence of significant coronary artery disease or valvular abnormalities. Significant coronary artery disease was ruled out invasively by coronary angiography in 16 patients, by cardiac multi-slice CT in 1 patient and by noninvasive stress testing (exercise electrocardiographic stress testing or stress echocardiography) in 26 patients. Patients with previously diagnosed cardiomyopathy or a contraindication to MRI were also excluded. A control group of 35 patients, who were matched according to age and sex (31 men, 35.4 ± 13.8 years), who did not fulfill any of the clinical criteria in any category and furthermore had a normal echocardiography study with LV-EF > 55 %, was generated for comparison.

Magnetic resonance imaging

All patients were scanned in a whole-body MRI unit with a field strength of 1.5 Tesla (Gyroscan Intera CV, Philips Medical Systems, Best, the Netherlands). The MRI protocols all followed the recommendations of previously published papers [3]. Visual analysis of MRI scans was performed in consensus with both a specialized radiologist and cardiologist, each with more than ten years of cardiac imaging experience. Our hospital is a CMR training center approved by the German Society of Cardiology.

Table 1 Clinical criteria of infarct-like myocarditis.

Tab. 1 Klinische Kriterien einer „infarct-like myocarditis“.

category	criteria
1. Symptoms	– chest pain – dyspnea – palpitations
2. ECG	– ST segment elevation; ST segment depression; T-wave inversion. – atrioventricular block (I-III, intermittent or persistent); bundle branch block (RBBB, LBBB, LAFB or LPFB).
3. Labor	– elevated troponin T

ECG = electrocardiogram; RBBB = right bundle branch block; LBBB = left bundle branch block; LAFB = left anterior fascicular block; LPFB = left posterior fascicular block.

Early gadolinium enhancement (= EGE) was acquired with a T1-weighted fast spin echo sequence before and 3 min after intravenous administration of a gadolinium-based contrast agent (Gadopentetat-Dimeglumin, Magnesvist© Schering, Gemany, 0.2 mmol per kg body weight). For determination of myocardial edema, we used a fat-saturated T2-weighted sequence [3, 6 – 9]. For all quantitative analyses CMR software was used (ViewForum R6.3, Philips Medical Systems, Best, The Netherlands). Standard methods of left ventricular functional analysis were performed by manual tracing of the endocardial and epicardial contours by steady-state-free-precession (SSFP) sequences [6, 13]. **Table 3** shows our MRI sequences in detail, following the recommendations of the German Roentgen Society [5]. No quantitative analyses of T1-weighted images or T2–weighted images were performed. Therefore, no early gadolinium enhancement ratio or edema ratio was available. Late gadolinium enhancement (= LGE) imaging was done with a 2 D or 3 D T1-weighted inversion recovery turbo gradient echo sequence. Images were acquired 5, 10 and 20 min after contrast medium administration [3 – 5, 10 – 12]. Positive areas of late enhancement were tracked visually by the presence of increased signal intensity (hyperintensity) and not by quantitative analysis. MRI diagnosis of acute myocarditis was established according to the Lake Louise criteria if 2 out of the 3 sequences were showing pathology [3].

Table 2 Characteristics of case and control group.

Tab. 2 Charakterisierung der Fall- und Kontrollgruppe.

	infarct-like myocarditis (n = 43)	control group (n = 35)	p-value
demographic data			
age, yrs	34.7 ± 15.2	35.4 ± 13.8	0.850
female	5 (11.6)	4 (11.4)	1.000
BMI, kg/m^2	25.9 ± 3.2	25.4 ± 4.2	0.581
symptoms			
dyspnea	9 (20.9)	0 (0)	< 0.003
chest pain	41 (95.3)	0 (0)	< 0.001
palpitations	1 (2.3)	0 (0)	1.000
peripheral edema	2 (4.7)	0 (0)	0.499
elevated temperature	12 (27.9)	0 (0)	< 0.001
infect (during the last 8 weeks)	26 (60.5)	–	–
pathological laboratory findings			
elevated troponin T	43 (100.0)	0 (0)	< 0.001
elevated creatine kinase	32 (76.2)[1]	0 (0)[2]	< 0.001
elevated creatine kinase –MB	28 (93.3)[3]	0 (0)[4]	< 0.001
elevated C-reactive protein	39 (95.1)[5]	0 (0)[3]	< 0.001
pathological ECG findings			
ST segment depression	3 (7.0)	0 (0)	0.246
ST segment elevation	33 (76.7)	0 (0)	< 0.001
T-wave inversion	17 (39.5)	0 (0)	< 0.001
atrioventricular block	5 (11.6)	0 (0)	0.061
bundle branch block	6 (27.9)	0 (0)	0.030

Values are median ± standard deviation or total number (percentage of group). BMI = body mass index; MB = myocardial band; ECG = electrocardiogram.
[1] n = 42. [2] n = 25. [3] n = 30. [4] n = 22. [5] n = 41.

Statistics

All data were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed data are expressed as mean ± SD, whereas non-normally distributed data are given as median and interquartile range. Normally distributed data were analyzed with the t-test and non-normally distributed data with the Mann-Whitney-U test. Proportions in 2 groups were compared by the Chi-squared test or the Fisher exact test according to sample size. To compare the distributions of several dependent variables, the Cochran's Q test was used. All statistical data were based on a 2-sided alpha = 0.05 significance level. Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were determined for all functional and morphological parameters and for the use of the single MRI sequences and the 2-of-3 approach. The 95 % confidence intervals were calculated according to Clopper and Pearson [14]. Statistical analysis took place using Microsoft® Office Excel (2003, Microsoft Corporation, Redmond) in combination with Plug-in-WinSTAT® (2009 Fitsch Software, Bad Krotzingen).

Table 3 MRI protocol.

Tab. 3 MRI Protokoll.

	cine imaging	myocardial edema	early gadolinium enhancement	late gadolinium enhancement
MRI technique	SSFP (steady-state-free-precession)	SPIR (spectral inversion recovery)	TFE (turbo-fast spin echo)	IRGE (inversion recovery gradient echo)
sequence type	T1 / T2-weighted gradient echo	saturated T2-weighted triple inversion recovery	T1-weighted spin echo	T1-weighted inversion recovery gradient echo
coil	cardiac	cardiac	cardiac	cardiac
breathing	breath-hold	breath-hold	breath-hold	breath-hold
triggering	retrospective ECG triggering	retrospective ECG triggering	retrospective ECG triggering	retrospective ECG triggering
TE [ms]	1.3	80	1.3	1.9
TR [ms]	2.7	depending on RR	depending on RR	3.7
IT [ms]				200 – 250
matrix	256 × 160	512 × 256	512 × 256	256 × 256
slice thickness [mm]	8	6	8	5.5
FOV [mm]	380	350	420	350

Table 4 Comprehension of cardiac function and morphology.

Tab. 4 Erfassung funktioneller und morphologischer Parameter.

	infarct-like myocarditis (n = 43)				control group (n = 35)				
	minimum	median	maximum	IQR	minimum	median	maximum	IQR	p-value[1]
LVEF (%)	20.0	60.0	77.0	12.0	58.0	69.0	81.0	23.0	< 0.001
LVEDVI (ml/m²)[2]	51.9	82.0	221.1	16.2	53.1	75.9	125.8	11.2	0.005
LVESVI (ml/m²)[2]	14.3	31.9	174.4	17.6	12.4	24.7	38.8	6.7	< 0.001
COI (l/min/m²)[2]	2.0	3.6	5.3	1.2	2.4	3.5	5.8	0.7	0.757
LVMI (g/m²)[3]	48.7	76.6	159.9	21	46.3	70.2	111.7	16.8	0.034

Norm values: LVEF ≥ 55 %; LVEDVI ≤ 99 ml/m² (female), ≤ 112 ml/m² (male); LVESVI ≤ 40 ml/m² (female), ≤ 45 ml/m² (male); COI ≥ 2.5 l/min/m²; LVMI ≤ 67 g/m² (female), ≤ 83 g/m² (male).
[1] Mann-Whitney-U test. [2] n = 38 in infarct-like myocarditis group. [3] n = 37 in infarct-like myocarditis group.

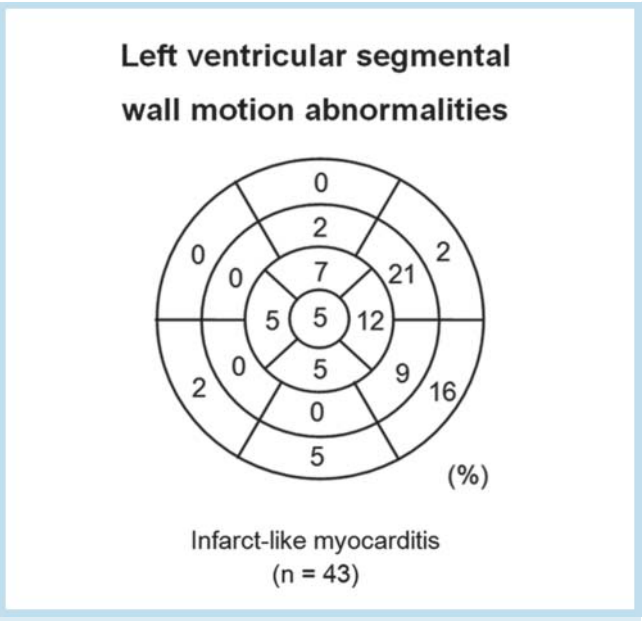

Fig. 1 Circumferential polar plot of the 17 myocardial segments. Distribution of left ventricular segmental wall motion abnormalities in infarct-like myocarditis.

Abb. 1 Verteilung der linksventrikulären Wandbewegungsstörungen bei „infarct-like myocarditis" im 17-Segment Modell.

Results

Patient characteristics

Infarct-like myocarditis was suspected in 43 patients according to the given clinical criteria (**Table 1**). All patients in our AMC group met the criteria for infarct-like myocarditis. 41 patients (95.3 %) presented with acute chest pain, only 9 patients (20.9 %) with dyspnea, 1 patient (2.3 %) with palpitations and 2 patients (4.7 %) with peripheral edema. Elevated troponin as a serum marker of myocardial damage was a mandatory inclusion criterion for the AMC group. The creatine kinase myocardial band was increased in 93.3 % of the AMC group and C-reactive protein in 95.1 %. Fever (temperature > 38 °C) was found in only 27.9 % of patients in the AMC group. However, detailed history taking revealed a recent infection in the preceding 8 weeks before inclusion into the study in 60.5 % of our patients. ST segment elevations resembling the changes in ST segment elevation myocardial infarction (STEMI) were detected in 76.7 % of our infarct-like myocarditis group, whereas ST segment depression and T-wave inversion mimicking the abnormalities commonly seen in non-ST segment elevation myocardial infarction (NSTEMI) were detected in 46.5 %. All patient characteristics of the AMC group and the matched control group are shown in **Table 2**. The 35 patients in the control group did not show any of the above-mentioned ECG changes or any elevations of cardiac serum markers (troponin T or CK).

Results of cine MRI imaging

Minimum, median and maximum values, interquartile ranges of the left ventricular ejection fraction (LVEF), the left ventricular end-diastolic volume index (LVEDVI), the left ventricular end-systolic volume index (LVESVI) and the left ventricular mass index (LVMI) of the AMC group and control group are shown in **Table 4**. The LVEF ($p < 0.001$) was found to be significantly reduced and the LVEDVI ($p = 0.005$), LVESVI ($p < 0.001$), LVMI (0.034) were found to be significantly elevated in the AMC group compared to the control group (**Table 4**).

30 patients with infarct-like myocarditis (70 %) had a normal LVEF ≥ 55 %, 8 patients (18.6 %) had an LVEF between 55 % and 45 % and 5 patients (11.6 %) had a significantly reduced LVEF of less than 45 %. The LVEF values were in the range of 20 % to 77 %. All patients (100 %) of the control group had a normal LVEF ≥ 55 %. Compared to the control group, 13 patients with infarct-like myocarditis (30 %) had a reduced LVEF ($p < 0.001$). 4 patients of the AMC group (11 %) had an elevated LVEDVI compared to 1 patient of the control group (3 %) and 3 patients of the AMC group (8 %) were found to have an increased LVESVI compared to no patient of the control group. In the AMC group 13 patients (35 %) showed an increased LVMI compared to 6 patients in the control group (17 %).

Wall motion abnormalities were seen in 27 patients (63 %) of the AMC group with regional wall motion abnormalities in 21 patients (49 %) and global hypocontractility in 7 patients (16 %). There were no pathological findings in the control group. Compared to the control group, a significant difference was shown in wall motion abnormalities ($p < 0.001$), regional wall motion abnormalities ($p < 0.001$) and global hypocontractility ($p = 0.015$). Global wall motion abnormalities were found in the left ventricle alone in 14 % and were biventricular or right ventricular in 2 %. The segmental distribution of wall motion abnormalities was assessed using the 17-segment model [15]. 20 patients (47 %) had

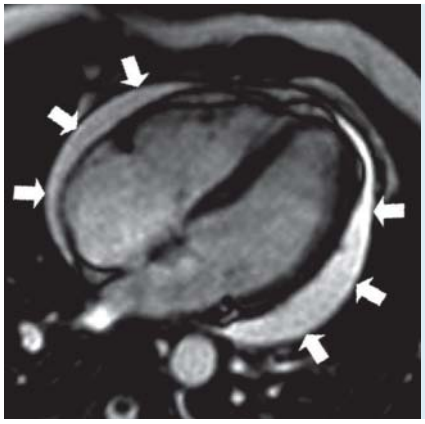

Fig. 2 Steady-state-free-precession imaging. Circumferential large pericardial effusion (white arrows) in an end-diastolic 4-chamber view.

Abb. 2 Steady-state-free-precession Bildgebung. Zirkulärer Perikarderguss (weiße Pfeile) während der Enddiastole im 4-Kammerblick.

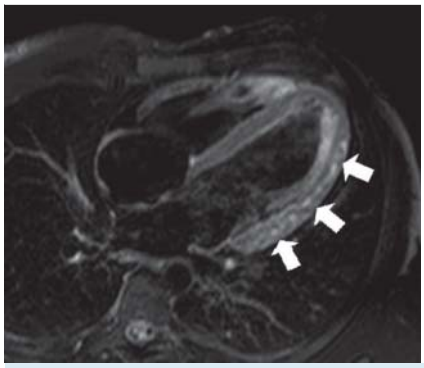

Fig. 4 T2-weighted magnetic resonance imaging. Focal areas (white arrows) of high signal intensity within the lateral wall of the left ventricle (4-chamber view), indicating regional myocardial edema.

Abb. 4 T2-gewichtete MR-Bildgebung. Fokale Areale (weiße Pfeile) mit erhöhter Signalintensität in der lateralen linksventrikulären Wand (4-Kammerblick) als Ausdruck einer regionalen myokardialen Ödembildung.

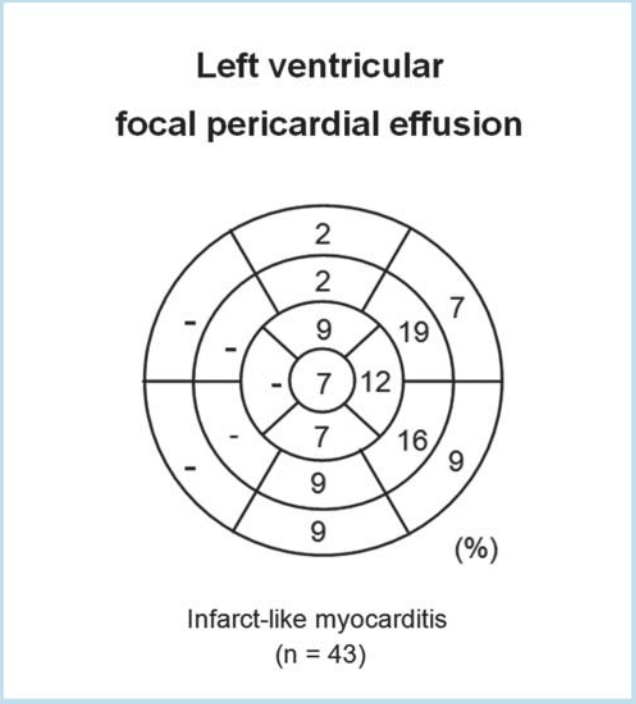

Fig. 3 Circumferential polar plot of the 17 myocardial segments. Distribution of left ventricular focal pericardial effusion in infarct-like myocarditis.

Abb. 3 Verteilung des linksventrikulär lokalisierten Perikardergusses bei „infarct-like myocarditis" im 17-Segment Modell.

focal wall motion abnormalities in the lateral left ventricular wall (segments: 5, 6, 11, 12, 17) (**Fig. 1**).

Pericardial effusions (PE) were discovered in 28 patients (65 %) of the AMC group compared to none in the control group ($p < 0.001$). Circumferential PE (**Fig. 2**) could be detected in 9 patients (21 %) with a significant difference with respect to the control group ($p = 0.003$) and focal PE in 19 patients (44 %) also with a significant difference with respect to the control group ($p < 0.001$). Focal pericardial effusions were located around the left ventricle in 17 patients (40 %) and at the right ventricle in 6 patients (14 %). **Fig. 3** shows the distribution of focal PE in the 17-segment model again with a predominance for the lateral left ventricular segments.

The diagnostic performance, including sensitivity, specificity, PPV, NPV and accuracy for the functional and morphological parameters are summarized in **Table 5, 6**.

Results of tissue characterization

Hyperintensities as a sign of focal myocardial edema (T2w) were detected in 24 patients (56 %) of the AMC group vs. no patients (0 %) in the control group ($p < 0.001$), myocardial hyperemia (EGE) in 22 patients (51 %) vs. 2 patients (6 %) ($p < 0.001$) and a significant

parameter	sensitivity	specificity	PPV	NPV	accuracy
LV ejection fraction	30 (17 – 47)	100 (90 – 100)	100 (75 – 100)	54 (41 – 66)	62 (50 – 72)
LV end-diastolic volume index	11 (3 – 25)	97 (85 – 100)	82 (28 – 99)	47 (38 – 62)	52 (40 – 64)
LV end-systolic volume index	8 (2 – 21)	100 (90 – 100)	100 (29 – 100)	47 (38 – 62)	52 (40 – 64)
cardiac output index	13 (4 – 28)	97 (85 – 100)	85 (36 – 100)	48 (38 – 63)	53 (41 – 65)

Values are percentage (95 % confidence interval). PPV = positive predictive value; NPV = negative predictive value; LV = left ventricle.

Table 5 Diagnostic performance of functional parameters.

Tab. 5 Diagnostische Wertigkeit der funktionellen Parameter.

parameter	sensitivity	specificity	PPV	NPV	accuracy
LV mass index	35 (20 – 53)	83 (66 – 93)	71 (43 – 87)	51 (40 – 68)	58 (46 – 70)
wall motion dyskinesia	63 (47 – 77)	100 (90 – 100)	100 (87 – 100)	69 (54 – 81)	79 (69 – 88)
pericardial effusion	65 (49 – 79)	100 (90 – 100)	100 (88 – 100)	70 (55 – 82)	89 (78 – 79)

Values are percentage (95 % confidence interval). PPV = positive predictive value; NPV = negative predictive value; LV = left ventricle.

Table 6 Diagnostic performance of morphological parameters.

Tab. 6 Diagnostische Wertigkeit der morphologischen Parameter.

sequence	total	subepicardial	intramural	subendocardial	transmural	p-value[1]
T2w	24 (56)	21 (49)	6 (14)	1 (2)	1 (2)	< 0.001
EGE	22 (51)	18 (42)	7 (16)	1 (2)	0 (0)	< 0.001
LGE	37 (86)	30 (70)	12 (28)	1 (2)	2 (5)	< 0.001

n = 43. Values are total number (percentage of group). T2w = T2-weighted sequence. EGE = early gadolinium enhancement; LGE = late gadolinium enhancement.
[1] Cochran's Q test.

Table 7 Extent of T2w, EGE and LGE in the infarct-like myocarditis group.

Tab. 7 Verteilungsmuster des linksventrikulären Ödems (T2w), EGE und LGE in der „infarct-like myocarditis" Gruppe.

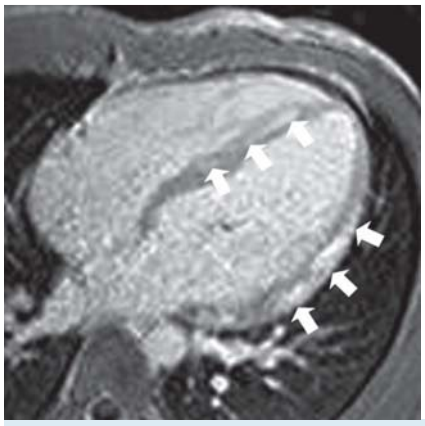

Fig. 5 T1-weighted magnetic resonance imaging. Focal early gadolinium enhancement (white arrows) within the septal and lateral wall of the left ventricle (4-chamber view), indicating regional myocardial hyperemia/inflammation.

Abb. 5 T1-gewichtete MR-Bildgebung. Fokale early gadolinium enhancement Areale (weiße Pfeile) im Septum und in der lateralen linksventrikulären Wand (4-Kammerblick) als Ausdruck einer regionalen myokardialen Hyperämie/Inflammation.

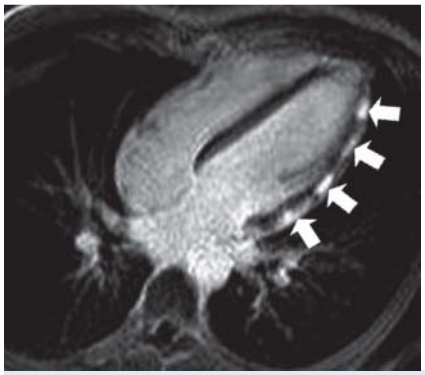

Fig. 6 Focal subepicardial late gadolinium enhancement (white arrows) within the lateral wall of the left ventricle (4-chamber view), indicating regional myocardial necrosis/fibrosis.

Abb. 6 Fokales subepikardiales late gadolinium enhancement (weiße Pfeile) in der lateralen linksventrikulären Wand (4-Kammerblick) als Ausdruck einer regionalen myokardialen Nekrose/Fibrose.

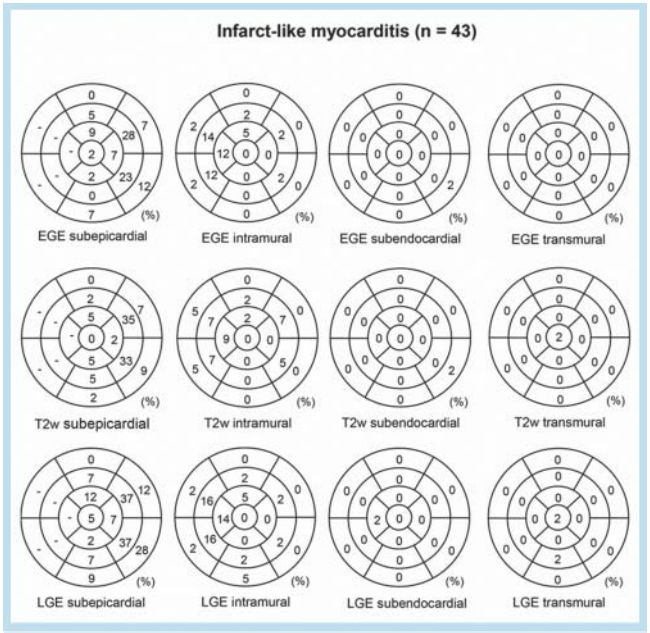

Fig. 7 Circumferential polar plot of the 17 myocardial segments. Distribution of left ventricular EGE, T2w and LGE in infarct-like myocarditis.

Abb. 7 Verteilungsmuster des linksventrikulären EGE, Ödems (T2w) und LGE bei „infarct-like myocarditis" im 17-Segment Modell.

necrosis or myocardial fibrosis (LGE) in 37 patients (86 %) vs. 0 patients (0 %) ($p < 0.001$). The extent of T2w signals (**Fig. 4**), EGE (**Fig. 5**), and LGE (**Fig. 6**) in the AMC group and the predominance for a subepicardial location in all sequences are listed in **Table 7**. In addition, the location of signal intensities in T2w, EGE and LGE images of the septal, lateral, anterior and inferior wall differed significantly ($p < 0.001$). We observed significant differences in signal intensity with a lateral location in 49 % versus a septal location in 9 %, an inferior location in 7 % and an anterior location in 2 % in the T2w sequence, a lateral location in 42 % versus a septal location in 14 %, an inferior location in 7 % and an anterior location in 7 % in EGE and a lateral location in 68 % versus a septal location in 26 %, an inferior location in 16 % and an anterior location in 9 % in LGE (**Table 8**). The 17-segment model shows the location of signal intensities in T2w, EGE and LGE images (**Fig. 7**).

The diagnostic performance, including sensitivity, specificity, PPV, NPV and accuracy for tissue characterization is summarized in **Table 9**.

Discussion

Infarct-like myocarditis

We deliberately chose a patient collective with infarct-like myocarditis (AMC group). This is mirrored in the inclusion criteria that were met: 95 % of patients had chest pain, 100 % had elevated troponin T (TRT), 93 % had elevated CK and 77 % had ST elevation. This differs from the study of Lurz et al., who found in their group 1 (= acute myocarditis with symptoms ≤ 14 days) chest pain in 68 %, TRT elevation in 57 %, CK-MB elevation in 58 % and ST elevation in 58 % [16]. Whereas Francone et al. showed a 100 % incidence of chest pain as well as TRT and ST elevation in their 21 pa-

sequence	total	septal	lateral	anterior	inferior	p-value[1]
T2w	24 (56)	4 (9)	21 (49)	1 (2)	3 (7)	< 0.001
EGE	22 (51)	6 (14)	18 (42)	3 (7)	3 (7)	< 0.001
LGE	37 (86)	11 (26)	29 (68)	4 (9)	7 (16)	< 0.001

n = 43. Values are total number (percentage of group). MRI = magnet resonance imaging; T2w = T2-weighted sequence; EGE = early gadolinium enhancement; LGE = late gadolinium enhancement; lateral = segment: 2, 3, 8, 9, 14; septal = segment: 5, 6, 11, 12, 16; anterior = segment: 1, 7, 13; inferior = segment: 4, 10, 15.
[1] Cochran's Q test.

Table 8 Location of abnormal signal intensity of MRI in the infarct-like myocarditis group.

Tab. 8 Lokalisation der pathologischen Signalveränderungen in der MR Bildgebung in der „infarct-like myocarditis" Gruppe.

Table 9 Diagnostic performance of tissue characterization of MRI for the diagnosis of infarct-like myocarditis.

Tab. 9 Diagnostische Wertigkeit der Gewebecharakterisierung in der MR-Bildgebung in der Diagnosestellung einer „infarct-like myocarditis".

sequence	sensitivity	specificity	PPV	NPV	accuracy
T2w	56 (40 – 71)	100 (90 – 100)	100 (51 – 100)	65 (51 – 77)	76 (65 – 85)
EGE	51 (36 – 67)	94 (81 – 99)	92 (73 – 99)	61 (47 – 74)	71 (59 – 80)
LGE	86 (72 – 95)	100 (90 – 100)	100 (76 – 100)	85 (71 – 94)	92 (84 – 97)
2of-3 approach	67 (51 – 81)	100 (90 – 100)	100 (88 – 100)	72 (57 – 83)	82 (72 – 90)

Values are percentage (95 % confidence interval). Infarct-like myocarditis group (n = 43); control group (n = 35); MRI = magnet resonance imaging; T2w = T2-weighted sequence; EGE = early gadolinium enhancement; LGE = late gadolinium enhancement; PPV = positive predictive value; NPV = negative predictive value.

Table 10 Overview of the diagnostic accuracy of LV dysfunction in previous studies (modified from Friedrich et al. 2009 [3]).

Tab. 10 Übersicht über die diagnostische Genauigkeit der LV-Dysfunktion in bisherigen Studien (modifiziert nach Friedrich et al. 2009).

	studies	field strength (T)	validation	sensitivity [%]	specificity [%]	accuracy [%]	PPV [%]	NPV [%]
LV dysfunction	our study results	1.5	Clinical	30	100	62	100	54
	Friedrich et al. 1998 [9]	1.0	Clinical	100	100	100	100	100
	Laissy et al. 2002 [18]	1.0	Clinical	62	100	75	100	58
	Laissy et al. 2005 [19]	1.5	Clinical	46	62	57	37	70
	Abdel-Aty et al. 2005 [7]	1.5	Clinical	38	100	61	100	49
	Gutberlet et al. 2008 [8]	1.5	Histology	50	63	55	65	48

tients with infarct-like myocarditis [17]. In contrast to the data of our study and the one of Francone et al., only 37 patients of 70 in group 1 (acute myocarditis) were differentiated as infarct-like myocarditis by Lurz et al. This accounts for the low percentage of chest pain, TRT and ST elevation observed by Lurz et al.

Functional analysis

Our analysis of functional parameters revealed a significant incidence of reduced LV-EF in patients with infarct-like myocarditis. In comparison to Francone et al., the sensitivity of reduced LV-EF in patients with infarct-like myocarditis was considerably lower in our study with 30 % vs. 100 % [17]. The specificity was 100 % for both collectives. The accuracy, however, was 100 % vs. 62 % in our patients. Abdel-Aty et al. [7] reached a sensitivity of 38 %, a specificity of 100 % and an accuracy of 61 %, which comes very close to our results. The study design of Abdel-Aty et al. is comparable to ours and also included a clinical evaluation without EMB. **Table 10** shows the diagnostic accuracy of LV dysfunction in our study compared to the previous studies in the literature [3, 8, 9, 18, 19]. The elevated LVMI in the AMC group (p = 0.034) results from acute inflammation with successive edema. Edema within the myocardium may result in capillary compression and reduced diastolic and systolic cardiac function [20, 21]. We were able to identify wall motion abnormalities in 63 % of the AMC group, which can be broken down into regional distribution in 47 % and global distribution in 16 %. 47 % of regional wall abnormalities were apparent in the left lateral segments (seg. 5, 6, 11, 12, 16). In contrast to this, Hombach et al. found only random distribution of wall motion abnormalities with a likelihood of 26 – 37 % for each of the 17 segments [22]. Pericardial effusions can be discovered in 32 – 57 % of patients with acute myocarditis [3]. We found a sensitivity of 65 %, specificity of 100 % and accuracy of 89 %. PE was detected in patients with a shorter duration of symptoms, more ECG abnormalities, and elevated TRT values [23].

Tissue characterization

Using the 2-of-3 approach in accordance with the consensus paper, we found a sensitivity of 67 %, specificity of 100 %, accuracy of 82 %, PPV of 100 % and NPV of 72 % in our study population. Francone et al. [17] demonstrated a sensitivity of 81 % in patients with infarct-like myocarditis using control groups with cardiomyopathies and arrhythmogenic cardiac disorders by using the same approach. **Table 11** shows an overview of the diagnostic accuracy of tissue characterization in controlled trials for single MRI sequences and the 2-of-3 approach according to the Lake Louise consensus criteria in myocarditis [3, 7, 8, 18, 23 – 27]. If only LGE is used for analysis, a sensitivity of 83 % is calculated in the infarct-like group of Lurz at al. and 71 % in the infarct–like group of Francone [16, 17], versus 86 % in our infarct-like group. The reason for this is that LGE generally represents cellular necrosis (= cardiomyocyte death), which is obviously present in infarct-like myocarditis [24]. The LGE can be verified early at the time of initial clinical presentation and multiple small lesions are found most frequently subepicardial in the lateral and posterolateral wall [24, 28, 29]. Depending on the

Table 11 Overview of the diagnostic accuracy of tissue criteria in previous studies (modified from Friedrich et al. 2009 [3]).

Tab. 11 Übersicht über die diagnostische Genauigkeit der Gewebecharaktersierung in bisherigen Studien (modifiziert nach Friedrich et al. 2009).

sequence	studies	field strength (T)	validation	sensitivity [%]	specificity [%]	accuracy [%]	PPV [%]	NPV [%]
EGE	study results	1.5	clinical	51	94	71	92	61
	Friedrich et al. 1998 [9]	1.0	clinical	84	89	86	89	84
	Laissy et al. 2002 [18]	1.0	clinical	85	100	89	100	70
	Abdel-Aty et al. 2005 [7]	1.5	clinical	80	68	74	74	75
	Gutberlet et al. 2008 [8]	1.5	histology	63	86	72	86	63
	Röttgen et al. 2011 [26]	1.5	histology	49	74	57	78	43
	Lurz et al. 2012 [16]	1.5	histology	79	63	76	89	46
T2w	study results	1.5	clinical	56	100	76	100	65
	Rieker et al. 2002 [27]	1.5	clinical	100	50	76	69	100
	Laissy et al. 2002 [18]	1.0	clinical	45	100	59	100	39
	Abdel-Aty et al. 2005 [7]	1.5	clinical	84	74	79	78	81
	Gutberlet et al. 2008 [8]	1.5	histology	67	69	67	74	60
	Röttgen et al. 2011 [26]	1.5	histology	58	57	58	73	41
	Lurz et al. 2012 [16]	1.5	histology	69	63	68	87	36
LGE	study results	1.5	clinical	86	100	92	100	85
	Rieker et al. 2002 [27]	1.5	clinical	45	60	52	56	50
	Abdel-Aty et al. 2005 [7]	1.5	clinical	44	100	71	78	62
	Mahrhold et al. 2006 [24]	1.5	histology	95	96	96	99	81
	Yilmaz et al. 2008 [25]	1.5	histology	35	83	51	81	38
	Gutberlet et al. 2008 [8]	1.5	histology	27	80	49	65	44
	Röttgen et al. 2011 [26]	1.5	histology	31	88	50	84	39
	Lurz et al. 2012 [16]	1.5	histology	83	63	78	76	50
2 of 3 approach	study results	1.5	clinical	67	100	82	100	71
	Abdel-Aty et al. 2005 [7]	1.5	clinical	76	96	85	95	79
	Lurz et al. 2012 [16]	1.5	clinical	86	75	84	93	60

actual patient collectives, a wide range of results of LGE alone (sensitivity from 27 % to 95 %) are reported for patients with myocarditis in the literature (**Table 11**). This is partially also due to different MRI techniques for patients with acute myocarditis or active and re-activated inflammation in chronic persisting myocarditis. Therefore, diagnosis of acute myocarditis should not be made based on LGE imaging alone according to the Lake Louise consensus criteria [3]. The LGE location was predominantly subepicardial in 70 % of our AMC group. In their AMC group, Lurz et al. found epicardial LGE as the most frequent location with an occurrence of 55.6 % [16]. Lateral distribution of LGE was detected in 68 % in our infarct-like group. Lateral distribution was reported to be most common with a frequency of 54.3 % by Lurz et al. [16], 25 % by Rieker et al. [27], and 60 % by Mahrholdt et al. [24], whereas Hombach et al. did not find any propensity in regional distribution pattern [22]. The cause for this predominance of lateral manifestations is not known yet.

The diagnostic performance of T2-weighted imaging alone for the detection of myocardial edema shows a sensitivity of 56 % in our infarct-like group and 69 % in the infarct-like myocarditis group reported by Lurz et al. [16]. Röttgen et al. [26] reached a sensitivity of 58 % for acute myocarditis and Gutberlet et al. [8] achieved a sensitivity of 67 % for suspected chronic myocarditis (**Table 11**). Although we analyzed the local edema only visually and not in a quantitative way, there was no relevant variance between our study and the literature. Most authors had included a quantitative measurement of local edema. The myocardial signal intensity was related to the skeletal signal intensity to calculate the T2 ratio [3]. If cut-off values > 1.9 were used for the T2 ratio in the studies, sensitivity values of 45 – 100 % and specificity values of 50 – 100 % were obtained (**Table 11**), the variations probably being attributable to the different scanner types and sequences [3, 16]. Srichai et al. [30] therefore demonstrated a high specificity but overall a low sensitivity for the diagnostic performance of T2-weighted CMR in the evaluation of acute myocardial injury (FSE-SPAIR: sensitivity 29 %, specificity 93 %, PPV 67 %, NPV 73 %; FSE-SPIR: sensitivity 38 %, specificity 91 %, PPV 67 %, NPV 75 %, with no difference in accuracy between the techniques). Surely the role of isolated T2-weighted imaging has to be recognized as limited in the diagnosis of myocarditis. Newer results of T1 and T2 mapping for the diagnosis of myocarditis sound promising for the future, because of the resulting better standardization and objectification in T1 and T2 imaging [31, 32].

Study limitations

The inclusion of our patients with infarct-like myocarditis and the control group followed clinical inclusion criteria only (**Table 1**). A referral bias in our population, resulting in the inclusion of more healthy people may be possible. A general limitation of this study is the small number of patients with infarct-like myocarditis. Additionally, we used a normal collective as a comparison and not a group of patients with myocardial infarction or dilated cardiomyopathy. Only the one patient with severely depressed LV-EF < 35 % underwent EMB. However, EMB is not commonly indicated in acute myocarditis [4].

Significant CAD was excluded by angiography only in 27 % of patients. CMR analysis was done according to the Lake Louise consensus criteria [3]. There was no quantitative assessment of T2w imaging and EGE imaging, but only a visual analysis and we did not analyze inter- or intraobserver variability in our study.

Conclusion

Our study results can only be applied to the subgroup of acute myocarditis with infarct-like myocarditis, where we found that LGE alone was the most sensitive test parameter with 86 %. In the 2-of-3 approach according to the Lake Louise criteria, we observed a slightly lower sensitivity of 67 %. In addition to tissue characterization, the functional analysis of patients with acute myocarditis provides useful additional diagnostic information, as more patients with reduced LV-EF and LV dilatation or increases in LV mass, pericardial effusions or regional wall motion abnormalities are identified.

Clinical relevance

- Infarct-like myocarditis can be diagnosed by CMR with high validity and reliability.
- LGE alone performed best with a sensitivity of 86 %.
- Functional and morphological CMR parameters in addition to tissue characterization are a useful tool in the diagnosis of infarct-like myocarditis.

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