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Diagnostic Performance of CMR Imaging Compared With EMB in Patients With Suspected Myocarditis

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OBJECTIVES The goal of this study was to assess the diagnostic performance of cardiac magnetic resonance (CMR) compared with endomyocardial biopsy in patients with suspected acute myocarditis (AMC) and chronic myocarditis (CMC).

BACKGROUND Several studies have reported an encouraging diagnostic performance of CMR in myocarditis. However, the comparison of CMR with clinical data only and the use of preselected patient populations are important limitations of the majority of these reports.

METHODS One hundred thirty-two consecutive patients with suspected AMC (defined by symptoms ≤14 days; n = 70) and CMC (defined by symptoms >14 days; n = 62) were included. Patients underwent cardiac catheterization with left ventricular endomyocardial biopsy and CMR, including T_2-weighted imaging for assessment of edema, T_1-weighted imaging before and after contrast administration for evaluation of hyperemia, and assessment of late gadolinium enhancement. CMR results were considered to be consistent with the diagnosis of myocarditis if 2 of 3 CMR techniques were positive.

RESULTS Within the total population, myocarditis was the most common diagnosis on endomyocardial biopsy analysis (62.9%). Viral genomes were detected in 30.3% (40 of 132) of patients within the total patient population and significantly more often in patients with AMC than CMC (40.0% vs. 19.4%; p = 0.013). For the overall cohort of patients with either suspected AMC or CMC, the diagnostic sensitivity, specificity, and accuracy of CMR were 76%, 54%, and 68%, respectively. The best diagnostic performance was observed in patients with suspected AMC (sensitivity, 81%; specificity, 71%; and accuracy, 79%). In contrast, diagnostic performance of CMR in suspected CMC was found to be unsatisfactory (sensitivity, 63%; specificity, 40%; and accuracy, 52%).

CONCLUSIONS The results of this study underline the usefulness of CMR in patients with suspected AMC. In contrast, the diagnostic performance of CMR in patients with suspected CMC might not be sufficient to guide clinical management. (J Am Coll Cardiol Img 2012;5:513–24) © 2012 by the American College of Cardiology Foundation

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The diagnosis of myocarditis and myocardial inflammation represents an enormous clinical challenge. Several clinical signs and symptoms have been described to be associated with myocarditis, such as flu-like or angina-like symptoms, signs of heart failure, or subclinical presentation (1,2). However, there are no unambiguously defined clinical criteria for the diagnosis of myocarditis and myocardial inflammation.

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Endomyocardial biopsy (EMB) is widely considered to be the gold standard for diagnosis of myocarditis, especially due to standardized immunohistological criteria (3). Recently, several studies have suggested cardiac magnetic resonance (CMR) as a promising noninvasive diagnostic alternative in patients with suspected myocarditis (4–13). Three CMR techniques have been applied in myocarditis: 1) late gadolinium enhancement (LGE) sequences for detection of myocardial necrosis and/or fibrosis; 2) T_2-weighted images for assessment of myocardial edema; and 3) T_1-weighted sequences before and after contrast injection for detection of myocardial hyperemia.

ABBREVIATIONS AND ACRONYMS

AMC = acute myocarditis
CMC = chronic myocarditis
CMR = cardiac magnetic resonance
EMB = endomyocardial biopsy
ER = edema ratio
gRE = global relative enhancement
LGE = late gadolinium enhancement
NPV = negative predictive value
PPV = positive predictive value

A pooled analysis of studies on CMR in myocarditis (4–12) resulted in a consensus paper and recommendations on the use of CMR for myocarditis (14). Within this consensus report, the "Lake Louise criteria" for CMR diagnosis of myocarditis were proposed, stating that CMR findings are consistent with the diagnosis of myocarditis if 2 of 3 of the above-mentioned sequences were found to be positive/pathological.

However, the retrospective nature, the small sample size (5,8,10–12), the comparison of CMR results with clinical data only (5,8,10–12), preselected patient populations, and the use of only 1 or 2 of 3 proposed imaging techniques (4,8–10,12) are important limitations of most of the reports on which the consensus paper is based on. Moreover, the diagnostic performance of CMR as suggested by the consensus paper in a real-world clinical setting is still unknown.

In this study, we applied currently proposed CMR techniques for image acquisition, analysis, and interpretation (14) prospectively in an unselected patient cohort with both suspected acute myocarditis (AMC) and chronic myocarditis (CMC). The goal of this study was to evaluate the diagnostic performance of comprehensive CMR for myocarditis in a real-world clinical setting compared with EMB.

METHODS

Patients and study protocol. In this prospective study, patients with clinical suspicion of myocarditis were included. Myocarditis was suspected in patients who fulfilled all of the following criteria: 1) new onset or persisting symptoms suggestive of myocarditis (shortness of breath, effort intolerance, fatigue, palpitations, or chest pain); 2) evidence of recent or ongoing myocardial damage (left ventricular dysfunction, electrocardiogram abnormalities, or elevated troponin levels); 3) history of systemic viral disease; and 4) exclusion of relevant coronary artery disease on selective angiography. These inclusion criteria were adjusted from the currently proposed criteria for CMR in myocarditis (14). Inclusion criteria were established by detailed assessment of patients' medical history, physical examination, echocardiography for assessment of left ventricular dysfunction, and blood samples to determine troponin levels. Assessment protocols for CMR and catheterization are outlined in the following discussion.

Patients with contraindication to cardiac catheterization, EMB, or CMR were excluded. In addition, patients with nondiagnostic EMB or CMR were not included in the final analysis.

Patients were divided into 2 groups according to duration of symptoms from onset to hospital admission to separate patients with suspected AMC (symptoms ≤14 days [group 1]) from those with suspected CMC (symptoms >14 days [group 2]). Within group 1, a subgroup of patients with suspected "infarct-like myocarditis" was further defined according to the following criteria: 1) elevated troponin levels; 2) chest pain; and 3) ST-segment elevation.

The study was approved by the local ethics committee, and all patients provided written informed consent.

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Table 1. CMR Imaging Sequences and Parameters

	Cine Imaging	Edema Imaging	Hyperemia Imaging	LGE Imaging
Sequence	Steady-state free precession	T2-weighted triple inversion recovery	T1-weighted fast spin echo saturation bands across atria	3D inversion recovery, turbo gradient echo
Triggering	Gated	Gated	Nongated	Gated
Free breathing/breath-hold	Breath-hold	Breath-hold	Free breathing	Breath-hold
Coil setup	5-element phased array	Body coil	Body coil	5-element phased array
Slices acquired	Vertical long axis, 4-chamber view, SAX covering LV and RV	SAX covering LV and RV	5 identical TS covering entire myocardium, pre-contrast and post-contrast (15 s) injection	Vertical long axis, 4-chamber view, SAX covering LV and RV
Repetition time, ms	3.6	2 × R-R interval	1× R-R interval	4.8
Echo time, ms	1.8	100	15	2.3
Inversion time, ms	–	150	–	Constantly adjusted
Echo train length, ms	–	33	3	–
Flip angle, °	60	90	90	15
Slice thickness	8	10	8	10
Field of view, cm	280–380	350–400	350–400	350–400
Partial field of view	1	0.75	1	1
Matrix, pixels	240 × 236	256 × 256	512 × 512	256 × 256

3D = 3-dimensional; CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement; LV = left ventricle; RV = right ventricle; SAX = short-axis sections; TS = transverse sections.

CMR imaging and analyses. CMR was performed using a 1.5-T magnetic resonance scanner (Gyroscan Intera CV, Philips Medical Systems, Best, the Netherlands). CMR assessment of myocardial inflammation/myocarditis included determination of: myocardial edema or rather edema ratio (ER); myocardial hyperemia or rather global relative enhancement (gRE); and myocardial fibrosis/necrosis or rather myocardial LGE. All CMR protocols for image acquisition, sequence and setup adjustments, and analyses were adapted from the previously published consensus paper (14) and are summarized in Table 1.

Image analysis was performed by experienced, blinded operators. For all quantitative analyses, certified CMR image evaluation software was used (cmr42, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). Standard methods of left ventricular functional analysis were performed by manual tracing of the endocardial and epicardial contours. Assessment of ER (Figs. 1 and 2) (5,7,14,15), gRE (Fig. 3) (7,8,14), and LGE (Fig. 4) (15) has been described previously. A detailed description of image acquisition and analyses protocols applied in this study is contained in the Online Appendix.

According to the Lake Louise criteria (14), CMR findings were considered to be consistent with myocardial inflammation/myocarditis if at least 2 of 3 of the above-mentioned imaging criteria (ER, gRE, and LGE) were found to be pathological (i.e., the 2 of 3 approach).

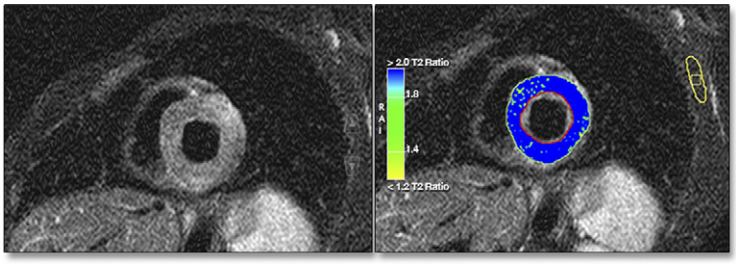

Figure 1. T_2-Weighted MR Imaging and Assessment of Global Myocardial Edema

(Left) T_2-weighted magnetic resonance (MR) images demonstrating global myocardial edema in a patient with acute myocarditis (short-axis slice). **(Right)** Computer-aided signal intensity (SI) analysis of the T_2-weighted images with color-coded display of relative SI normalized to skeletal muscle **(blue** indicates an SI ratio of myocardium/skeletal muscle >1.9, indicating edema; **green/yellow** indicates normal ≤1.9). The **yellow** contour marks the region of interest for SI assessment of the skeletal muscle.

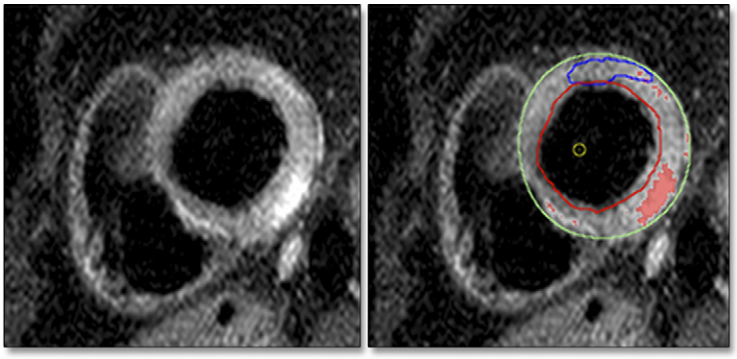

Figure 2. T_2-Weighted Imaging and Assessment of Focal Myocardial Edema

T_2-weighted magnetic resonance (MR) imaging in a patient with focal areas of visually apparent high signal intensity (SI) (short-axis slice, **[left]**). Semi-quantitative assessment detects a focal subepicardial high SI (SI >2 SDs above the SI of normal myocardium, **blue contour**) **(red overlay)**, indicating regional myocardial edema in this patient **(right)**.

Coronary angiography and EMBs. Selective coronary angiograms of the left and the right coronary artery were acquired. Significant coronary artery disease was defined by coronary artery stenosis >50% in at least 1 coronary artery segment. For EMB sampling, a myocardial biopsy forceps (Teleflex Medical Tuttlingen GmbH, Tuttlingen, Germany) was used. Five to 6 EMB specimens were taken from the left ventricle under fluoroscopic guidance. EMB specimens were taken from different locations within the left ventricle.

EMB analysis. All histological, immunohistological, and molecular pathological analyses diagnosing myocardial inflammation and viral infections were performed at the Department of Molecular Pathology, University Hospital Tuebingen (Tuebingen, Germany) as previously described (4,6,16,17). In brief, myocardial inflammation was defined as the detection of ≥14 infiltrating leukocytes/mm^2 (CD3+ T-lymphocytes and/or CD68+ macrophages) in addition to enhanced human leukocyte antigen class II expression in professional antigen-presenting immune cells.

AMC requiring myocyte injury/necrosis was differentiated from CMC, which was defined by the following criteria: absence of myocyte necrosis but detection of interstitial fibrosis, ≥14 infiltrating leukocytes/mm^2 (CD3+ T-lymphocytes and/or CD68+ macrophages), and degeneration of neighboring myocytes, being morphologically consistent with the formerly defined "borderline" myocarditis.

Nested (RT-) polymerase chain reaction for the detection of viral genomes was performed as previously described (4,6). Masson trichrome staining allowed the visualization of fibrosis. For the diagnosis of hypertrophic cardiomyopathy (18,19) and

Figure 3. T_1-Weighted MR Imaging and Assessment of Myocardial Hyperemia

Pre-contrast **(left)** and post-contrast **(right)** axial T_1-weighted spin echo images of the same slice used to calculate global relative enhancement from the mean signal intensities within the manually outlined borders around the left myocardium **(purple contour)** and right erector spinae muscle **(yellow contour)**. An additional saturation section is positioned across the atria to reduce signal from slow-flowing blood. In this patient, image analysis revealed a global relative enhancement ratio >4, indicating myocardial hyperemia/inflammation. Abbreviation as in Figure 1.

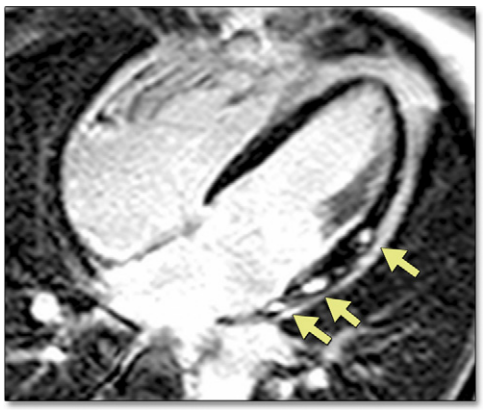

Figure 4. Assessment of Myocardial Fibrosis/Necrosis/Scarring by Visualization of Late Enhancement on MR

Late gadolinium enhancement imaging of a patient with active myocarditis on endomyocardial biopsy shows focal late gadolinium enhancement **(arrows)** within the lateral wall of the left ventricle (long-axis view). Abbreviation as in Figure 1.

amyloidosis (20), additional electron microscopy and Congo red staining, respectively, were performed. The diagnosis of dilated cardiomyopathy was primarily made in association with additional angiographic and CMR data, especially when histopathological data were ambiguous for dilated cardiomyopathy.

Figure 5 illustrates typical examples of histological and immunohistological stainings. Whereas in uninflamed myocardium, inflammatory cells are absent (Figs. 5A to 5C), high numbers of T-lymphocytes and macrophages are found in cases with AMC (Figs. 5D and 5F), and lower amounts of infiltrating cells in CMC (Figs. 5G to 5I).

Statistical analysis. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed data are expressed as mean ± SD; non-normally distributed data are given as median (interquartile range). Proportions are expressed as number of patients and percentages. Unpaired samples between patient groups were analyzed with the 2-tailed unpaired Student *t* test or Mann-Whitney *U* test. Categorical variables were compared using the Fisher exact test. All statistical testing was based on a 2-sided alpha = 0.05 significance level.

Sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of the individual CMR sequences and the 2 of 3 approach were determined; the immunohistological EMB results were used as the reference standard. As previously described (21), 95% confidence intervals for sensitivity, specificity, and accuracy were calculated. The different sensitivities,

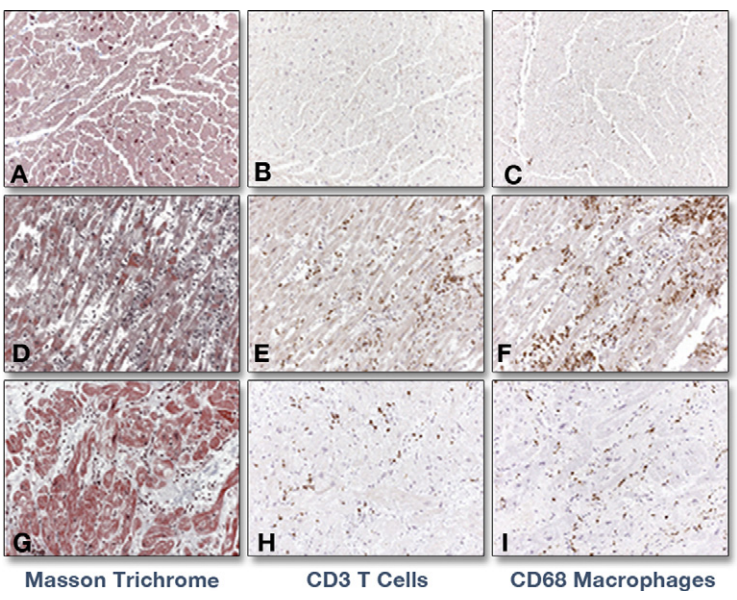

Figure 5. Histopathology and Immunohistology in Normal Hearts, Acute Myocarditis, and Chronic (Borderline) Myocarditis

Histopathology and immunohistology in normal hearts (without inflammation) **(A to C)**, acute myocarditis **(D and F)**, and chronic (borderline) myocarditis **(G to I)**. Masson trichrome staining **(A, D, G)** reveals severe myocyte necrosis in acute myocarditis **(D)**, whereas interstitial fibrosis **(blue areas)** is obvious only in patients with chronic myocarditis **(G)**. Whereas in normal hearts, T lymphocytes **(B)** and macrophages **(C)** are almost absent, T lymphocytes **(E and H)** and macrophages **(F and I)** are detected in high amounts in acute myocarditis and in lower numbers in chronic myocarditis.

specificities, and accuracies were compared between groups (patients with suspected AMC vs. CMC) as independent proportions using the chi-square test with continuity correction.

Statistical testing and data analysis were performed with SPSS version 16 (SPSS, Inc., Chicago, Illinois), R version 2.10 (R Development Core Team 2009, Vienna, Austria), and GraphPad Prism version 5.0b (GraphPad Software, San Diego, California).

RESULTS

Patient characteristics. Initially, 138 patients were included in the study. EMB was found to be nondiagnostic in 1 patient. Due to arrhythmia, inability to perform breath-holds, or severe motion artifacts due to patients' noncompliance, initial steady-state free precession cine imaging failed to provide reliable information on biventricular volumes and function in 5 patients, and CMR was therefore abandoned in these patients. The final analyses were performed in 132 patients.

According to the above-mentioned criteria, AMC was suspected in 70 patients (group 1) and CMC in 62 patients (group 2). Within group 1, a total of 37 patients (53%) met criteria for infarct-like myocarditis. The patient characteristics are shown in Table 2. The mean age within the total population was 47 ± 16 years. Patients with suspected CMC were significantly older compared with patients with suspected AMC (52 ± 13 years vs. 44 ± 17 years; p = 0.004). There were more women in group 2 (19 vs. 9; p = 0.02). The majority of patients complained of fatigue, irrespective of duration of symptoms (82.6% and 88.3% within groups 1 and 2, respectively). Dyspnea was more often seen in group 2 (85.5% vs. 56.6% in group 1; p = 0.001), whereas chest pain was more frequent in group 1 (68.1% vs. 51.7%; p = 0.047). Patients presenting with acute symptoms had a higher frequency of elevated troponin, creatine kinase-myocardial band, and C-reactive protein. The cardiovascular risk factor profile was similar between the 2 groups, apart from a higher frequency of smokers in group 1 (34.8% vs. 18.3%; p = 0.047).

Table 2. Patient Characteristics

	All Patients (N = 132)	Group 1 (Symptoms ≤14 Days; n = 70)	Group 2 (Symptoms >14 Days; n = 62)	Group 1 vs. 2, p Value
Age, yrs	47 ± 16	44 ± 17	52 ± 13	0.004
Female	28 (21.2)	9 (13.0)	19 (30.6)	0.02
Duration of symptoms in days	14 (3–40)	3 (1–7)	42 (28–90)	<0.001
Symptoms				
Dyspnea	90 (68.2)	39 (56.6)	51 (85.5)	0.001
Fatigue	110 (83.3)	57 (82.6)	53 (88.3)	0.64
Peripheral edema	20 (15.2)	6 (8.6)	14 (23.3)	0.03
Palpitations	39 (29.5)	21 (30.4)	18 (30.0)	0.99
Chest pain	78 (59.1)	47 (68.1)	31 (51.7)	0.047
LV ejection fraction	45 (27–59)	52 (31–62)	39 (25–55)	0.01
Pathological ECG findings				
Block	23 (17.7)	9 (13.2)	14 (23.7)	0.17
ST-segment elevation	45 (34.1)	39 (57.4)	6 (10.2)	<0.001
ST-segment depression	74 (56.1)	42 (61.8)	32 (54.2)	0.38
Elevated troponin	37 (38.5)	31 (51.7)	6 (17.1)	<0.001
Elevated creatine kinase-MB	42 (42.4)	35 (58.3)	7 (17.9)	<0.001
Elevated C-reactive protein	58 (68.2)	43 (86.0)	15 (44.1)	<0.001
Cardiovascular risk factors				
Hypertension	59 (44.7)	27 (39.1)	32 (53.3)	0.16
Smoker	35 (26.5)	24 (34.8)	11 (18.3)	0.047
Ex-smoker	12 (9.1)	3 (4.3)	9 (15.0)	0.07
Diabetes	19 (14.4)	9 (13.0)	10 (16.7)	0.63
Hyperlipoproteinemia	20 (15.2)	8 (11.6)	12 (20.0)	0.23
Obesity	21 (15.9)	9 (13.0)	12 (20.0)	0.35

Values are mean ± SD, n (%), or median (interquartile range).
ECG = electrocardiogram; LV = left ventricle; MB = myocardial band.

Table 3. Results of EMB

	All Patients	Group 1 (Symptoms ≤14 Days)	Group 2 (Symptoms >14 Days)	Group 1 vs. 2, p Value
Myocardial inflammation consistent with myocarditis	83 (62.9)	53 (75.7)	30 (48.4)	<0.001
Acute myocarditis (myocardial injury/necrosis)	7 (5.3)	6 (8.6)	1 (1.6)	0.07
Chronic myocarditis (fibrosis/degeneration)	75 (56.8)	47 (67.1)	28 (45.2)	0.01
Loeffler's endomyocarditis	1 (0.8)	–	1 (0.8)	0.29
Presence of virus genome	40 (30.3)	28 (40.0)	12 (19.4)	0.013
Latent virus genome presence in absence of inflammation	4 (3.0)	1 (1.4)	3 (4.8)	0.34
Healed myocarditis with no significant myocardial inflammation	8 (6.0)	4 (5.7)	4 (6.5)	0.99
Hypertrophic cardiomyopathy	4 (3.0)	1 (1.4)	3 (4.8)	0.06
Dilated cardiomyopathy	20 (15.2)	6 (8.6)	14 (22.6)	0.029
Toxic cardiomyopathy	1 (0.8)	–	1 (1.6)	0.47
Amyloidosis	2 (1.5)	–	2 (3.2)	0.22
No pathological diagnosis	10 (7.6)	5 (7.1)	5 (8.1)	0.99

Values are n (%).
EMB = endomyocardial biopsy.

EMB analysis. No procedural complications related to EMB occurred. Details of EMB analysis are summarized in Table 3. Within the total population, myocarditis was the most common diagnosis on EMB analysis (62.9%). Signs of significant myocardial inflammation with evidence of myocardial injury/necrosis (i.e., AMC) were observed in 5.3% and without myocardial damage but with fibrosis (i.e., CMC) in 56.8% (Fig. 5); 1 patient (0.8%) had Loeffler's endomyocarditis. Within group 1, there was a significantly higher incidence of myocarditis (75.7% vs. 48.4%; $p < 0.001$). Viral genomes were detected in 30.3% (40 of 132) of patients within the total patient population and significantly more often in group 1 compared with group 2 (40.0% vs. 19.4%; $p = 0.013$). Distributions of cardiotropic viruses are illustrated in Figure 6.

In the absence of inflammation/myocarditis, dilated cardiomyopathy was the most common histopathological diagnosis (15.2% in the total population; 22.6% in group 2 vs. 8.6% in group 1 [$p = 0.029$]).

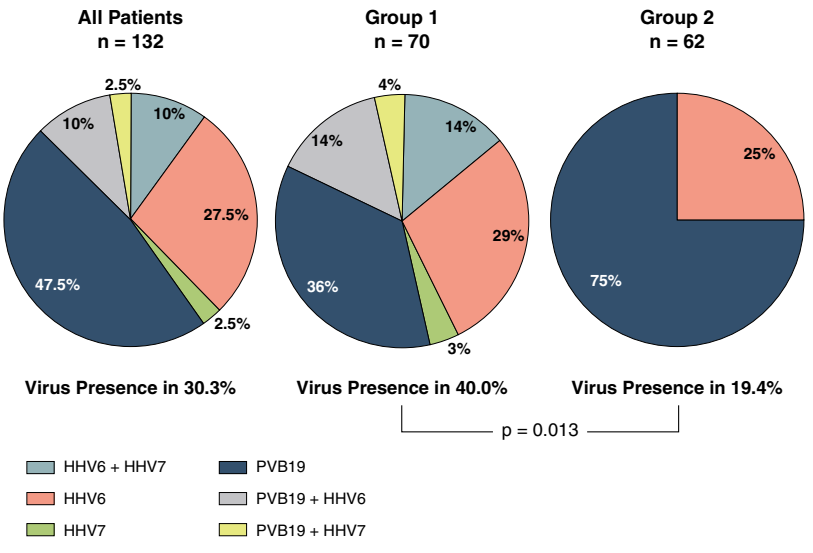

Figure 6. Distribution of Cardiotropic Viruses Detected by Polymerase Chain Reaction in EMB Specimens

Pie charts illustrate the distribution of cardiotropic viruses detected using polymerase chain reaction in endomyocardial biopsy (EMB) specimens. Viral genomes were detected in 30.3% (40 of 132) of patients within the total patient population and significantly more often in group 1 compared with group 2 (40% vs. 19.4%; $p = 0.013$). HHV = human herpes virus; PVB19 = parvovirus B19.

Results of CMR imaging. Within the total population, left ventricular functional impairment (ejection fraction <50%) was observed in 79 patients (59.8%). Median ejection fraction was 45% (interquartile range 27% to 59%), whereas it was significantly lower in group 2 (39% vs. 52%; p = 0.01).

A significant localized myocardial increase in T_2 signal intensity (defined as focal myocardial edema) was detected in 6 (4.5%) of 132 patients (6 of 6 within group 1). An ER ≥1.9 indicating global myocardial edema was found in 61 of 132 patients (37 of 70 in group 1 and 24 of 62 in group 2) (p = 0.12).

An increased gRE ratio ≥4 indicating myocardial hyperemia was found in 81 of 132 patients (41 of 70 in group 1 and 40 of 62 in group 2) (p = 0.59).

Significant LGE was evident in 84 (63.6%) patients (64.3% in group 1 and 62.9% in group 2) (Table 4). LGE localization was predominantly subepicardial in 50% of patients, intramyocardial in 33.3%, predominantly subendocardial in 7.1%, and predominantly transmural in 9.5%; there were no significant differences between groups 1 and 2. With regard to regional distribution, LGE was found to be located anteriorly in 23.5%, septally in 30.3%, laterally in 45.5%, and inferiorly in 46.2% of patients. Overlap did occur.

Performance of CMR imaging for diagnosis of myocarditis. The diagnostic performance, including sensitivity, specificity, and accuracy for the individual imaging techniques, is summarized in Table 5. For the overall cohort, edema imaging yielded sensitivity, specificity, and diagnostic accuracy values of 56%, 65%, and 59%, respectively. Assessment of gRE for diagnosis of hyperemia and capillary leakage had a higher sensitivity (74%) but lower specificity, whereas accuracy was similar to ER (60%). Equally, LGE imaging resulted in sensitivity, specificity, and diagnostic accuracy values of 69%, 46%, and 61%, respectively.

The use of any 2 of the 3 parameters—gRE, ER, or LGE—for CMR detection of myocarditis yielded the highest diagnostic accuracy (68%) and sensitivity (76%) but low specificity (54%). For all parameters (ER, gRE, LGE, and the 2 of 3 approach), values for PPV were found to be higher than for NPV.

Subgroup analyses. Using the 2 of 3 approach, values for sensitivity, specificity, PPV, NPV, and diagnostic accuracy within group 1 were 81%, 71%, 90%, 55%, and 79%, respectively. Apart from NPV, which was found to be low in groups 1 and 2, measures of diagnostic performance were higher in group 1 compared with group 2 (p = 0.02 for accuracy, p = 0.1 for sensitivity, and p = 0.087 for specificity). Within group 2, CMR for myocarditis yielded markedly lower values for sensitivity (63%), specificity (40%), PPV (53%), NPV (50%), and diagnostic accuracy (52%). Highest values for diagnostic performance of CMR were seen within the subgroup of patients with infarct-like myocarditis (sensitivity, specificity, PPV, NPV, and diagnostic accuracy 86%, 75%, 93%, 60%, and 84%, respectively).

Assessing only those patients with viral positive myocardial inflammation on EMB, sensitivity of ER, gRE, LGE, and the 2 of 3 approach were 86%, 54%, 75%, and 82%, respectively.

Table 4. Extent and Localization of LGE on CMR Images

	All Patients	Group 1 (Symptoms ≤14 Days)	Group 2 (Symptoms >14 Days)	Group 1 vs. 2, p Value
Presence of LGE	84 (63.6)	45 (64.3)	39 (62.9)	0.99
Extent				
Epicardial	42 (50.0)	25 (55.6)	17 (43.6)	0.35
Intramyocardial	28 (33.3)	13 (28.9)	15 (38.5)	0.52
Endocardial	6 (7.1)	1 (2.2)	5 (12.8)	0.1
Transmural	8 (9.5)	6 (13.3)	2 (5.1)	0.28
Localization				
Anterior	31 (23.5)	20 (28.6)	11 (17.7)	0.16
Septal	40 (30.3)	17 (24.3)	23 (37.1)	0.13
Lateral	60 (45.5)	38 (54.3)	22 (35.5)	0.04
Inferior	61 (46.2)	34 (48.6)	27 (43.5)	0.6

Values are n (%).
CMR = cardiac magnetic resonance; LGE = late gadolinium enhancement.

Table 5. Diagnostic Performance of CMR Compared With EMB

Study Group	Sensitivity	Specificity	PPV	NPV	Accuracy
Total population (N = 132)					
ER	56 (45–66)	65 (51–79)	75	44	59 (51–67)
gRE	74 (65–84)	33 (19–46)	67	41	60 (51–68)
LGE	69 (59–78)	46 (31–60)	70	44	61 (52–69)
2 of 3 approach	76 (67–85)	54 (40–69)	76	54	68 (60–76)
Group 1 (n = 70)					
ER	64 (51–77)	65 (42–87)	85	37	63 (53–76)
gRE	76 (64–87)	53 (29–77)	83	41	70 (59–81)
LGE	74 (62–85)	65 (42–87)	87	44	71 (61–82)
2 of 3 approach	81 (71–92)	71 (49–92)	90	55	79 (69–88)
Infarct-like myocarditis (n = 37)					
ER	69 (52–86)	63 (29–96)	87	36	68 (52–83)
gRE	79 (65–94)	63 (29–96)	89	46	76 (62–90)
LGE	83 (69–97)	63 (29–96)	76	50	78 (65–92)
2 of 3 approach	86 (74–99)	75 (45–100)	93	60	84 (72–96)
Group 2 (n = 62)					
ER	42 (26–59)	66 (48–100)	58	50	55 (41–66)
gRE	73 (58–88)	21 (6–100)	51	40	48 (36–61)
LGE	61 (44–77)	35 (17–100)	51	44	48 (36–61)
2 of 3 approach	63 (46–79)	40 (22–100)	53	50	52 (39–64)

Values are % (95% confidence interval) or %.
ER = edema ratio; gRE = global relative enhancement; NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Tables 3 and 4.

DISCUSSION

To the best of our knowledge, this is the largest prospective study on CMR in patients with clinically suspected AMC and CMC in which a comprehensive CMR protocol including assessment of edema, hyperemia, and fibrosis was applied. The study was conducted according to proposed standards of image acquisition, analyses, and interpretation (14).

In this study, we demonstrated a satisfactory diagnostic performance of CMR in suspected AMC. The best values of diagnostic performance were found in patients with suspected infarct-like AMC. In contrast, the diagnostic performance of CMR in patients with suspected CMC was found to be insufficient.

Patients with suspected AMC. Rigorous data of CMR evaluated against the currently considered gold standard of EMB for the diagnosis of myocarditis in consecutive, unselected patients are limited. Due to the lack of data, current recommendations reflect the best achievable expert consensus based on currently available literature. As suggested by the CMR consensus paper (14), the 2 of 3 approach yields the best diagnostic accuracy compared with the individual imaging techniques. So far, there is only 1 report on CMR in patients with acute symptoms of myocarditis using the 2 of 3 approach with a reported sensitivity, accuracy, and PPV of 76%, 85%, and 95%, respectively (5). These findings are comparable to our results (81%, 79%, and 90%). In contrast, values for specificity and NPV in our study were lower compared with the study by Abdel-Aty et al. (5) (specificity 71% vs. 96%; NPV 55% vs. 79%). These differences are mainly attributed to a lower specificity and NPV of LGE and gRE assessment. Especially for LGE, a wide variety of diagnostic accuracies in myocarditis has been reported, ranging from 50% to 96% (4,5,7,9,12,13,17). Some general considerations of LGE imaging have to be taken into account when diagnostic performance of LGE in myocarditis is discussed. Pathophysiologically, the finding of LGE in myocarditis is considered to specifically reflect irreversible injury (i.e., myocardial necrosis and/or fibrosis). However, myocarditis may not always lead to large enough necrotic regions to be visually detectable. Accordingly, LGE may be insensitive for detection of symptomatic myocarditis with limited or very subtle myocyte necrosis and inflammation as well as in patients with nonfocal irreversible injury. In our study, the majority of patients with myocardial inflammation were classified as having CMC in the presence of chronic inflammation and fibrosis but

absence of acute myocyte necrosis, which at least partially explains the low NPV of LGE imaging.

Furthermore, LGE cannot be considered to be specific to myocarditis, as it has been described in various pathologies including myocardial infarction, in patients with dilated or hypertrophic cardiomyopathy, or amyloidosis (22). Therefore, false-positive results are to be expected and will reduce the specificity of this imaging technique. This finding is reflected in a pooled analysis of studies using LGE sequences for diagnosis of myocarditis, reporting a mediocre accuracy of 68% (14), which is in keeping with the 71% accuracy found in our patient population.

Values of diagnostic performance of gRE in patients with suspected AMC were slightly lower than reported in previous studies, particularly the case for specificity and NPV. Previous studies (5,7,8,10) clearly differ in terms of validation of CMR findings (clinical vs. EMB), patient characteristics, and duration of patients' symptoms, which complicates a fair comparison to our study. However, general limitations of this imaging technique are its susceptibility for artifacts, especially in patients with arrhythmia and irregular breathing patterns (14). Other drawbacks of gRE include the following: 1) increased gRE is not specific to myocarditis (23–25); 2) the coincidence of skeletal muscle myositis (26) and thereby increases in skeletal muscle signal intensity can cause pseudonormalization of the gRE ratio, resulting in falsely negative results; and 3) the development of focal hyperemia (27) can be missed and can result in falsely negative gRE values. Thus, the low NPV of gRE assessment in our study might therefore not be surprising.

The diagnostic performance of T_2-weighted edema imaging was similar to previous reports. As stated earlier for LGE and gRE imaging, assessment of myocardial edema on T_2-weighted images is not specific to myocarditis but can occur in other pathologies associated with myocardial infiltration and/or injury (28,29). The low signal-to-noise ratio might hamper diagnostic performance (14). These limitations are likely to prohibit a better performance of this imaging sequence in myocarditis. Newer sequences, especially T_2 mapping, may overcome these limitations with subsequent better diagnostic accuracy (29).

In previous studies (5,7), the combined use of all 3 tissue-based CMR parameters and application of the 2 of 3 approach (13) resulted in the best overall diagnostic accuracy. The results of our study in patients with AMC strongly support such a combined and comprehensive CMR approach in these patients. The highest values of diagnostic performance were found in the subgroup of patients with infarct-like myocarditis. This finding might be explained by a higher degree of acuteness and manifestation of the disease. This is reflected in troponin release and marked electrocardiogram changes in this patient cohort. It seems reasonable to expect a higher degree of myocardial edema, hyperemia, and myocardial injury in these patients, which may result in an improved diagnostic performance of CMR compared with patients with borderline or chronic disease.

Patients with suspected CMC. Reports on CMR in suspected CMC are scarce. In a previous retrospective study, a fair diagnostic performance of CMR has been reported (7). These results could not be confirmed in this larger prospective study, in which diagnostic performance of CMR was found to be insufficient. Within the chronic group, the findings of a long duration of symptoms before referral, very subtle changes in C-reactive protein, troponin, and creatine kinase-myocardial band, and in particular the very low incidence of immunohistologically AMC ($n = 1$) are suggestive of mild inflammation only in this cohort. Consequently, the extent of myocardial edema and hyperemia as signs of acute myocardial injury are likely to be subtle, which might explain the high percentage of falsely negative CMR results in this cohort. In addition, these minor myocardial changes cannot be differentiated from fibrosis in the myocardium, which develops as a consequence of myocarditis. Furthermore, EMB results demonstrate a marked heterogeneity of pathologies in this group. As stated before, CMR sequences can be falsely positive in noninflammatory cardiomyopathies with fibrotic areas, which might explain the reduced specificity and accuracy of CMR in this study. Results of CMR in patients with CMC are presumed to depend on patient selection, incidence of myocarditis, and severity of disease. Clearly, further studies are needed to define the capacity of CMR in the diagnosis of CMC. However, when currently proposed methodological standards are applied in a real-world scenario, CMR does not seem to reliably confirm or omit the diagnosis of myocarditis in patients with chronic symptoms.

Justification of the Lake Louise criteria. In 2008, a task force of the Society for Cardiovascular Magnetic Resonance summarized imaging protocol recommendations in the setting of suspected myocar-

ditis (30). Within these recommendations, the presence or absence of LGE forms the integral diagnostic criterion, whereas edema imaging is optional and gRE more controversial. As pointed out earlier, LGE but also ER and gRE sequences are not specific to myocarditis. Therefore, studies have suggested using a 2 of 3 approach, which is also referred to as the Lake Louise criteria. We have now demonstrated that diagnostic accuracy using the 2 of 3 approach is higher compared with using LGE imaging only. Although there are significant limitations of CMR in myocarditis at present, regardless of which sequences and criteria are applied, the superior accuracy of the 2 of 3 approach supports the use of these criteria rather than LGE and optional T2 imaging only, as suggested by the earlier recommendations (30).

Clinical implications. The results of this study suggest that CMR adds significantly to the diagnostic work-up in patients with suspected AMC. On the basis of the high PPV, a pathological CMR scan in the setting of suspected AMC can be considered to be diagnostic in 9 of 10 patients. Due to the low NPV of CMR in suspected AMC, negative CMR results do not entirely exclude the diagnosis of myocarditis, and further diagnostic testing might be advisable.

In patients with suspicion of CMC, the diagnostic performance of CMR has to be considered as not sufficient to guide clinical management. Therefore, at present, CMR in these patients cannot be recommended for diagnosis confirmation or exclusion.

Study limitations. A general limitation of all diagnostic studies in patients with suspected myocarditis is the lack of consensus for the diagnosis of myocarditis. In the last few years, it turned out that the Dallas criteria are not sufficient to differentiate various forms of AMC and CMC (31). Although the introduction of quantitative immunohistochemistry has improved the assessment of inflammatory heart diseases, there is still controversy about the relevance of viral genomes. Although it is well known that myocarditis is mostly induced by viruses, viral genomes in our study were present in less than one-half of patients with myocardial inflammation (48%), which is consistent with previous reports (7,17). Whereas absence of viral genomes in myocarditis might be explained by relevant sampling error of EMB, it also has to be considered that in a certain percentage of patients, an efficient early immune response can restrict cardiac viral replication, and very low numbers of viral copies are not detectable using current methods.

The use of left ventricular EMBs only in our study represents a possible limitation. In a recent report, the combination of left and right ventricular EMBs was suggested to be superior to left ventricular EMB only (17). Furthermore, acquiring right ventricular EMB represents the predominant approach at some centers. Therefore, diagnostic performance of CMR might differ when compared with right ventricular or biventricular EMB.

Across equal setups and parameters of CMR sequences, algorithms used on different scanners and vendors can differ, which could result in some variation of signal intensity and results of image analyses. Therefore, we cannot exclude the possibility that diagnostic performance of CMR acquired in a comparable patient population but on a different scanner might differ.

CMR image acquisition, analysis, and interpretation were made according to the JACC Consensus White Paper and recommendations on the use of CMR for myocarditis (14). Findings of this study might not be applicable when using other recommendations on CMR (30) in this patient population.

Finally, our findings reflect the performance of CMR when only diagnostic scans are considered, whereas nondiagnostic scans were not included in the analyses.

CONCLUSIONS

The results of this study underline the usefulness of CMR for assessment of myocardial inflammation/myocarditis in patients with suspected AMC. In contrast, with the current criteria, techniques, and sequences, the diagnostic performance of CMR in patients with suspected CMC is not sufficient to guide clinical management.

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REFERENCES

1. Feldman AM, McNamara D. Myocarditis. N Engl J Med 2000;343:1388–98.
2. Cooper LT Jr. Myocarditis. N Engl J Med 2009;360:1526–38.
3. Richardson P, McKenna W, Bristow M, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies. Circulation 1996;93:841–2.
4. Mahrholdt H, Wagner A, Deluigi CC, et al. Presentation, patterns of myocardial damage, and clinical course of viral myocarditis. Circulation 2006;114:1581–90.
5. Abdel-Aty H, Boye P, Zagrosek A, et al. Diagnostic performance of cardiovascular magnetic resonance in patients with suspected acute myocarditis: comparison of different approaches. J Am Coll Cardiol 2005;45:1815–22.
6. Baccouche H, Mahrholdt H, Meinhardt G, et al. Diagnostic synergy of non-invasive cardiovascular magnetic resonance and invasive endomyocardial biopsy in troponin-positive patients without coronary artery disease. Eur Heart J 2009;30:2869–79.
7. Gutberlet M, Spors B, Thoma T, et al. Suspected chronic myocarditis at cardiac MR: diagnostic accuracy and association with immunohistologically detected inflammation and viral persistence. Radiology 2008;246:401–9.
8. Friedrich MG, Strohm O, Schulz-Menger J, Marciniak H, Luft FC, Dietz R. Contrast media-enhanced magnetic resonance imaging visualizes myocardial changes in the course of viral myocarditis. Circulation 1998;97:1802–9.
9. Yilmaz A, Mahrholdt H, Athanasiadis A, et al. Coronary vasospasm as the underlying cause for chest pain in patients with PVB19 myocarditis. Heart 2008;94:1456–63.
10. Laissy JP, Messin B, Varenne O, et al. MRI of acute myocarditis: a comprehensive approach based on various imaging sequences. Chest 2002;122:1638–48.
11. Laissy JP, Hyafil F, Feldman LJ, et al. Differentiating acute myocardial infarction from myocarditis: diagnostic value of early- and delayed-perfusion cardiac MR imaging. Radiology 2005;237:75–82.
12. Rieker O, Mohrs O, Oberholzer K, Kreitner KF, Thelen M. Cardiac MRI in suspected myocarditis [in German]. Rofo 2002;174:1530–6.
13. Rottgen R, Christiani R, Freyhardt P, et al. Magnetic resonance imaging findings in acute myocarditis and correlation with immunohistological parameters. Eur Radiol 2011;21:1259–66.
14. Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC White Paper. J Am Coll Cardiol 2009;53:1475–87.
15. Bondarenko O, Beek AM, Hofman MB, et al. Standardizing the definition of hyperenhancement in the quantitative assessment of infarct size and myocardial viability using delayed contrast-enhanced CMR. J Cardiovasc Magn Reson 2005;7:481–5.
16. Mahrholdt H, Goedecke C, Wagner A, et al. Cardiovascular magnetic resonance assessment of human myocarditis: a comparison to histology and molecular pathology. Circulation 2004;109:1250–8.
17. Yilmaz A, Kindermann I, Kindermann M, et al. Comparative evaluation of left and right ventricular endomyocardial biopsy: differences in complication rate and diagnostic performance. Circulation 2010;122:900–9.
18. Davies MJ, McKenna WJ. Hypertrophic cardiomyopathy—pathology and pathogenesis. Histopathology 1995;26:493–500.
19. Varnava AM, Elliott PM, Baboonian C, Davison F, Davies MJ, McKenna WJ. Hypertrophic cardiomyopathy: histopathological features of sudden death in cardiac troponin T disease. Circulation 2001;104:1380–4.
20. Vogelsberg H, Mahrholdt H, Deluigi CC, et al. Cardiovascular magnetic resonance in clinically suspected cardiac amyloidosis: noninvasive imaging compared to endomyocardial biopsy. J Am Coll Cardiol 2008;51:1022–30.
21. Simel DL, Samsa GP, Matchar DB. Likelihood ratios with confidence: sample size estimation for diagnostic test studies. J Clin Epidemiol 1991;44:763–70.
22. Lin D, Kramer CM. Late gadolinium-enhanced cardiac magnetic resonance. Curr Cardiol Rep 2008;10:72–8.
23. Matsuoka H, Hamada M, Honda T, et al. Precise assessment of myocardial damage associated with secondary cardiomyopathies by use of Gd-DTPA-enhanced magnetic resonance imaging. Angiology 1993;44:945–50.
24. Nishimura T, Yamada N, Haze K, Nagata S. Experience using gadolinium-DTPA in cardiovascular MRI. Magn Reson Med 1991;22:354–7; discussion 364–5.
25. Eitel I, Lucke C, Grothoff M, et al. Inflammation in takotsubo cardiomyopathy: insights from cardiovascular magnetic resonance imaging. Eur Radiol 2010;20:422–31.
26. Greaves K, Oxford JS, Price CP, Clarke GH, Crake T. The prevalence of myocarditis and skeletal muscle injury during acute viral infection in adults: measurement of cardiac troponins I and T in 152 patients with acute influenza infection. Arch Intern Med 2003;163:165–8.
27. Herskowitz A, Wolfgram LJ, Rose NR, Beisel KW. Coxsackievirus B3 murine myocarditis: a pathologic spectrum of myocarditis in genetically defined inbred strains. J Am Coll Cardiol 1987;9:1311–9.
28. Shehab AM, Strohm O. Advanced tissue characterization in non-ischemic cardiomyopathies using contrast-enhanced cardiac magnetic resonance imaging. Saudi Med J 2010;31:115–22.
29. Eitel I, Friedrich MG. T2-weighted cardiovascular magnetic resonance in acute cardiac disease. J Cardiovasc Magn Reson 2011;13:13.
30. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance imaging (CMR) protocols, society for cardiovascular magnetic resonance: board of trustees task force on standardized protocols. J Cardiovasc Magn Reson 2008;10:35.
31. Baughman KL. Diagnosis of myocarditis: death of Dallas criteria. Circulation 2006;113:593–5.

Key Words: cardiac magnetic resonance ■ endomyocardial biopsy ■ myocardial inflammation ■ myocarditis.

▶APPENDIX

For a detailed description of the image acquisition and analyses protocols applied in this study, please see the online version of this article.