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JACC White Paper

Cardiovascular Magnetic Resonance in Myocarditis: A JACC White Paper

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Cardiovascular magnetic resonance (CMR) has become the primary tool for noninvasive assessment of myocardial inflammation in patients with suspected myocarditis. The International Consensus Group on CMR Diagnosis of Myocarditis was founded in 2006 to achieve consensus among CMR experts and develop recommendations on the current state-of-the-art use of CMR for myocarditis. The recommendations include indications for CMR in patients with suspected myocarditis, CMR protocol standards, terminology for reporting CMR findings, and diagnostic CMR criteria for myocarditis (i.e., "Lake Louise Criteria").

Background: Myocarditis

Incidence and Etiology

In this paper, myocarditis is defined as inflammation of myocardial tissue. Myocarditis has been reported in up to 12% of young adults presenting with sudden death (1–4) and is an important underlying etiology of other myocardial diseases such as dilated (5) and arrhythmogenic right ventricular (6) cardiomyopathy. The incidence of nonfatal myocarditis is likely greater than actually diagnosed, mostly as a result of the challenges of establishing the diagnosis in standard clinical settings.

Infectious disease accounts for most cases in previously healthy patients typically either because of a direct viral infection or post-viral immune-mediated reaction. Myocardial inflammation, however, also may be triggered by reversible and/or irreversible toxic, ischemic, or mechanical injury, drug-related inflammation, transplant rejection, or other immune reactions.

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Pathogenesis and Pathology

The pathogenetic features of myocarditis are reviewed in detail elsewhere (7). After the initial injury, local and systemic immune responses activate cytokines and B cells with subsequent edema, additional myocyte injury, and autoantibody production. Although the molecular and cellular pathophysiology may differ between different etiologies, cellular infiltration, edema, necrosis, and (in later stages) fibrotic scars are common features.

Diagnostic Approaches to Myocarditis and Their Limitations

Currently, no single clinical or imaging finding confirms the diagnosis of myocarditis with absolute certainty. Rather, an integrated synopsis, including history, clinical assessment, and noninvasive test results, should be used to diagnose the disease and guide treatment.

History and physical exam. Although of limited specificity, a careful history and thorough clinical assessment have to precede further diagnostic tests. Patients may appear almost normal, may have nonspecific symptoms, but also may present with features of acute myocardial infarction or heart failure with hemodynamic compromise. Physical exams of patients with myocarditis are often unremarkable.

Ventricular functional analysis. Although many patients with myocarditis have regional or global wall motion abnormalities (8–10), dysfunction is not specific to inflammation, and its sensitivity is limited (9,11–13). Biventricular dysfunction in myocarditis, however, was found to be the main predictor of death and transplantation (14).

Electrocardiogram (ECG). The ECG findings associated with myocarditis may include ST-segment and T-wave changes, Q waves, atrioventricular block, and bundle-branch block. Arrhythmias such as ventricular tachycardia and ventricular fibrillation occur. The diagnostic value of the ECG in myocarditis, however, is limited. Aside from a low specificity, either ST-segment elevation or T-wave inversion is present as the most sensitive ECG criterion in <50% of patients, even during the first weeks of the disease (15).

Biomarkers. Depending on the severity and time of testing during the course of disease, serum biomarkers of myocardial injury such as creatine kinase, creatine kinase-myocardial band, and troponin may be increased. When present, the magnitude of increase as well as the time to clearance is similar to that of a small- to medium-sized myocardial infarction and indicates more severe disease. The prevalence of an increased troponin T in biopsy-proven myocarditis, however, is only 35% to 45% (16).

Biopsy. Endomyocardial biopsy (EMB) is a widely accepted method for diagnosing myocarditis, based upon histopathology, immunohistology, and molecular techniques to identify viral genomes. A Joint Scientific Statement of several professional societies on its use in various clinical scenarios has been published (17).

Some limitations of EMB have to be considered. First, the sensitivity of EMB is limited as the result of so-called sampling error (18–21). Second, severe complications (perforation, tamponade) occur in 0.1% to 0.5%, and the overall complication rate is 6% (17). Third, substantial debate exists regarding diagnostic criteria for analyzing myocardial tissue specimens (22). The utility of the Dallas criteria (23), with inflammatory infiltration and associated myocyte necrosis uncharacteristic for an ischemic event as disease markers, is limited by poor interobserver agreement (24,25).

Immunohistochemistry has a greater sensitivity than standard histopathology for the diagnosis of myocarditis (26,27), and immunohistology protocols and evaluation criteria have been proposed (10,28). Cost, availability, and limited standardization, however, have limited the widespread use of immunohistology and viral genome analysis. Finally, in adults, the recommended indications for endomyocardial biopsy are confined to patients with heart failure (17) and, therefore, EMB is not recommended in many patients with myocarditis.

In summary, history, clinical exam, ECG, and serology have an unsatisfactory diagnostic accuracy in myocarditis. Biopsy, including immunohistochemistry, remains the widely accepted standard, but may not be appropriate for many patients, especially those with less severe disease.

Imaging Modalities Other Than CMR

A detailed review of noninvasive imaging in myocarditis can be found elsewhere (29). Ultrasound studies of the heart in myocarditis typically are performed to visualize associated functional abnormalities, wall thickness, and pericardial effusion (8,30). The diagnostic value of echocardiography is limited by the fact that many patients with less severe myocarditis have a normal echocardiogram and the highly variable echocardiographic findings lack specificity (8).

^{111}Indium antimyosin antibody and ^{67}gallium nuclear imaging have been used to diagnose myocarditis (31). The specificity of these approaches, however, is very limited (32). Nuclear medicine techniques also are hampered by the limited availability of tracers mentioned previously, poor spatial resolution, and radiation issues. In current clinical practice, nuclear medicine is used only rarely to diagnose myocarditis.

Table 1

Published Controlled Studies on Cardiovascular Magnetic Resonance in Myocarditis

	Validation	No. of Patients	No. of Control Patients
Friedrich et al., *Circulation* 1998 (9)	Clinical	19	18
Laissy et al., *Chest* 2002 (11)	Clinical	20	7
Rieker et al., *Rofo* 2002 (36)	Clinical	11	10
Laissy et al., *Radiology* 2005 (37)*	Clinical	24	31
Abdel-Aty et al., *J Am Coll Cardiol* 2005 (13)	Clinical	25	22
Mahrholdt et al., *Circulation* 2006 (40)	Histology	87	26
Gutberlet et al., *Radiology* 2008 (34)†	Histology	48	35
Yilmaz et al., *Heart* 2008 (43)†	Histology	55	30
Total		289	179

*Compared with patients with acute myocardial infarction. †Compared with patients with clinical evidence but lack of immunohistologic evidence for chronic myocarditis.

CMR in Myocarditis

Published Data

The use of CMR imaging offers a unique combination of safety, clarity of anatomical visualization, interobserver consistency, and quantitative accuracy. Furthermore, it allows for the comprehensive use of a wide spectrum of diagnostic targets, especially the modifiable inherent tissue contrast. This modality has become a standard tool in many medical centers and currently is considered by many to be the most versatile and powerful cardiovascular imaging modality.

Since the first description of T2-weighted CMR findings in children with myocarditis by Gagliardi et al. in 1991 (33) and the first controlled clinical study using contrast-enhanced CMR in 1998 (9), numerous investigators have studied the diagnostic utility of noncontrast (11,13,34) and contrast-enhanced (11–13,34–43) CMR in patients with myocarditis. Results have consistently shown the clinical feasibility and high diagnostic accuracy with different single-technique or combined CMR protocols. Tables 1 to 4 show a list of published controlled trials on CMR in myocarditis (Table 1), and data on the diagnostic accuracy of left ventricular (LV) dysfunction (Table 2) and of CMR criteria for myocarditis (Table 3: individual criteria; Table 4: combined criteria).

Although published data on diagnostic accuracy provide solid evidence for the use of CMR in clinical settings, it is important to emphasize that most of these studies were single-center reports and had a small sample size, variable inclusion criteria, and nonuniform patient populations. Furthermore, CMR studies were performed at variable time

Table 2

Diagnostic Accuracy of LV Dysfunction as Assessed in Controlled Trials

LV Dysfunction (EF <55%)	Validation	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
Friedrich et al., *Circulation* 1998 (9)	Clinical	100	100	100	100	100
Laissy et al., *Chest* 2002 (11)	Clinical	62	100	75	100	58
Laissy et al., *Radiology* 2005 (37)*	Clinical	46	62	57	37	70
Abdel-Aty et al., *J Am Coll Cardiol* 2005 (13)	Clinical	38	100	61	100	49
Gutberlet et al., *Radiology* 2008 (34)	Histology	50	63	55	65	48
Pooled data (n = 276)		54%	76%	64%	71%	60%

*Compared with patients with acute myocardial infarction.
EF = ejection fraction; LV = left ventricular; NPV = negative predictive value; PPV = positive predictive value.

Table 3

Overview of the Diagnostic Accuracy of Individual Tissue Criteria as Assessed in Controlled Trials

	Validation	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
Early myocardial gadolinium enhancement						
Friedrich et al., *Circulation* 1998 (9)	Clinical	84	89	86	89	84
Laissy et al., *Chest* 2002 (11)	Clinical	85	100	89	100	70
Abdel-Aty et al., *J Am Coll Cardiol* 2005 (13)	Clinical	80	68	74	74	75
Gutberlet et al., *Radiology* 2008 (34)	Histology	63	86	72	86	63
Pooled data (n = 194)		74	83	78	86	70
T2						
Rieker et al., *Rofo* 2002 (36)	Clinical	100	50	76	69	100
Laissy et al., *Chest* 2002 (11)	Clinical	45	100	59	100	39
Abdel-Aty et al., *J Am Coll Cardiol* 2005 (13)	Clinical	84	74	79	78	81
Gutberlet et al., *Radiology* 2008 (34)	Histology	67	69	67	74	60
Pooled data (n = 178)		70	71	70	77	63
Late enhancement						
Rieker et al., *Rofo* 2002 (36)	Clinical	45	60	52	56	50
Abdel-Aty et al., *J Am Coll Cardiol* 2005 (18)	Clinical	44	100	71	78	62
Mahrholdt et al., *Circulation* 2006 (40)	Histology	95	96	96	99	81
Gutberlet et al., *Radiology* 2008 (34)	Histology	27	80	49	65	44
Yilmaz et al., *Heart* 2008 (43)	Histology	35	83	51	81	38
Pooled data (n = 336)		59	86	68	89	53

Abbreviations as in Table 2.

points after disease onset, used different imaging diagnostic criteria, and mostly did not include biopsy for confirmation.

Furthermore, the specificity was mostly compared with normal control patients or those with myocardial infarction and not to other heart diseases with similar clinical presentation, such as acute coronary syndrome or other secondary cardiomyopathies. Current data do not allow for a clear definition of the diagnostic accuracy of CMR in various clinical, histological, and immunohistochemical subgroups, and data from larger (multicenter) trials with standardized protocols comparing comprehensive CMR studies to biopsy-derived criteria are lacking.

The prognostic value of CMR criteria for myocarditis remains to be defined. In a small study, increased myocardial early gadolinium enhancement ratio at 4 weeks after clinical onset of the disease was associated with an impaired prognosis regarding functional recovery and symptoms after a 3-year follow-up (44). Confirmative studies on the prognostic value of the various parameters are required.

Diagnostic Targets of CMR in Myocarditis

Different from other diagnostic modalities, targets for CMR not only include functional and morphological abnormalities but also tissue pathology as diagnostic features of myocardial inflammation.

Functional abnormalities. The CMR assessment of right ventricular and LV function is very reproducible and thus allows for identifying, quantifying, and following even mild functional abnormalities, if present. In patients with more severe myocarditis, global LV dysfunction is frequent. It is, however, re-emphasized that regional or less severe LV wall motion abnormalities have a low specificity for the underlying pathophysiology.

Pericardial effusion. Pericardial effusion has been reported in 32% to 57% of patients with myocarditis (45–47). Although not specific for myocarditis, its presence is supportive evidence for active inflammation.

Regional distribution and extent and hemodynamic significance of pericardial effusion can be assessed by the use of standard short- and long-axis steady-state free precession (SSFP) images acquired for morphology and function. This sequence type has an inherent T2 sensitivity, rendering pericardial fluid bright signal intensity (Fig. 1A). The differentiation from epicardial fat (which also appears bright) is straightforward: the latter is found around coronary vessels (which are embedded in the epicardial fat layer) or in the AV groove and, in SSFP images, typically separated from effusion by a (single-pixel) thin chemical shift artifact layer, that is, a fine line without signal. Furthermore, fat mostly appears with a slightly lower signal intensity, and effusion may have a more "deformable" appearance through the cardiac cycle. In T1-weighted images (e.g., spin-echo images) fluid has low signal intensity. In phase-sensitive inversion-recovery sequences, however, it may be black or white, depending on the inversion time settings.

Small, physiological accumulations of pericardial fluid are not circumferential and may not be considered pathologic. A fluid layer that contains nonfluid components (fibrinous deposits, thrombus) is pathologic.

Table 4

Overview of the Diagnostic Accuracy of Several Combinations of Tissue Criteria

	Validation	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
T2 + LGE						
Abdel-Aty et al., *J Am Coll Cardiol* 2005 (13)	Clinical	40	100	69	100	61
Gutberlet et al., *Radiology* 2008 (34)	Histology	17	91	48	73	44
Pooled data (n = 130)		25	95	56	86	50
T2 and/or LGE						
Abdel-Aty et al., *J Am Coll Cardiol* 2005 (13)	Clinical	88	74	81	100	85
Gutberlet et al., *Radiology* 2008 (34)	Histology	50	57	52	80	25
Pooled data (n = 130)		60	66	62	79	43
Any 1 of 3						
Abdel-Aty et al., *J Am Coll Cardiol* 2005 (13)	Clinical	100	48	75	68	100
Gutberlet et al., *Radiology* 2008 (42)	Histology	81	49	67	68	65
Pooled data (n = 130)		88	48	70	68	76
Any 2 of 3						
Abdel-Aty et al., *J Am Coll Cardiol* 2005 (13)	Clinical	76	96	85	95	79
Gutberlet et al., *Radiology* 2008 (34)	Histology	63	89	73	88	63
Pooled data (n = 130)		67	91	78	91	69

LGE = late gadolinium enhancement; other abbreviations as in Table 2.

Morphological abnormalities. A transient increase of wall thickness during myocarditis was first described in echocardiography studies (48) and may serve as a supportive finding during follow-up. A decrease of LV mass during the course of uncomplicated myocarditis was found to be associated with edema as assessed by T2-weighted CMR (49). A transient increase of LV volumes has been observed in the course of myocarditis (9) and may also may serve as retrospective, supportive evidence for recent myocarditis.

Tissue Characterization With CMR

Given the unique potential of CMR to visualize tissue changes, this area is of special interest. As outlined previously, expected tissue pathology in active myocarditis includes intracellular and interstitial edema, capillary leakage, hyperemia, and, in more severe cases, cellular necrosis and subsequent fibrosis (50).

Edema. An important hallmark of inflammatory cell injury is the increased permeability of cellular membranes. Whereas initial membrane defects are of a functional nature, leading to Na^+ influx and subsequent intracellular edema, a more severe injury allows for a net efflux of water and transmembranous leakage of larger molecules such as troponin, eventually leading to loss of cellular functions.

T2-weighted imaging sensitively detects tissue edema with the long T2 of water-bound protons as the contrast-generating mechanism, resulting in a high signal intensity of edematous tissue (Fig. 1C). Triple inversion recovery turbo spin echo sequences with inversion pulses for fat and blood suppression (51) provide excellent contrast between regional edema and normal myocardium because of the dual suppression of the fat and flowing blood signal. Double inversion recovery sequences may provide a greater signal-to-noise ratio and be used alternatively. Importantly, edema in patients with myocarditis may have a global myocardial distribution and, thus, a quantitative signal intensity analysis of the entire myocardium may be necessary. A high diagnostic accuracy has been shown for this approach in acute inflammatory or ischemic injury (13,34,52).

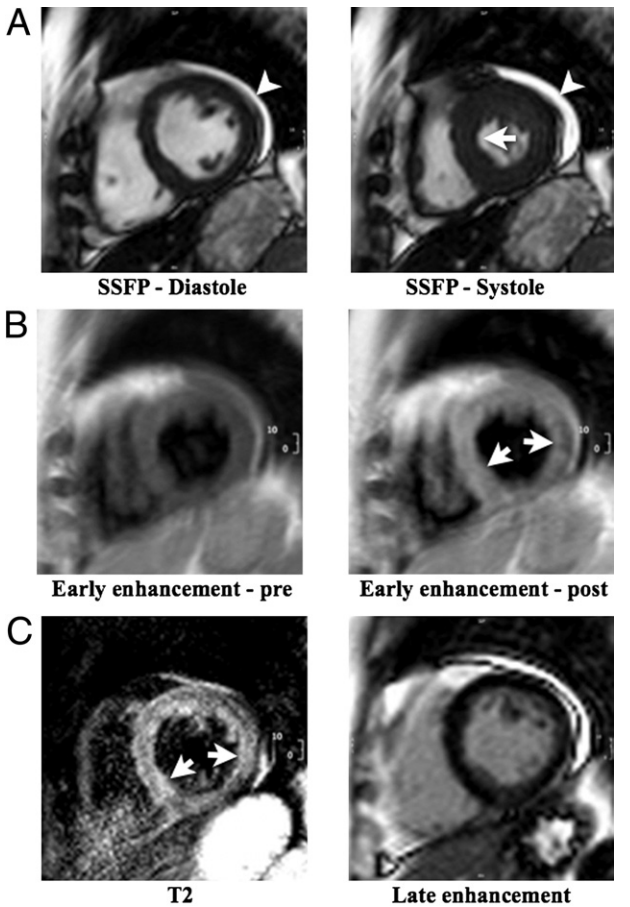
Regional edema visible on T2-weighted CMR images was not observed in "borderline myocarditis" but could be found in 36% of patients with histologically "active myocarditis" as defined by the Dallas criteria (39). Thus, regional edema may have a limited sensitivity in less severe inflammation. Short-axis views typically provide a more robust image quality than long axis images, although apical slices may have to be discarded because of artifacts related to intraventricular blood signal.

The signal-to-noise ratio of T2-weighted images strongly depends on sequence parameters. Particularly in patients with arrhythmia and other motion artifacts, image quality may not allow for reliable visualization or quantification of edema. Newly developed sequences may yield a more consistent image quality and better diagnostic accuracy than currently used fast spin-echo triple inversion recovery prepared protocols (53,54).

Hyperemia and capillary leak (myocardial early gadolinium enhancement). Regional vasodilatation is an integral feature of tissue inflammation. The increased blood volume in the inflamed area leads to an increased uptake of contrast agents during the early vascular phase. Because gadolinium-based contrast agents distribute quickly into the interstitial

Figure 1

Short-Axis CMR Views in a Patient With Clinically Acute Myocarditis



(A) Still frames from a cine series at end-diastole **(left)** and end-systole **(right)** showing only very mild septal hypokinesis **(arrow)** with preserved ejection fraction. Small pericardial effusion is present along the lateral segments **(arrowheads)**. These findings represent 2 supportive criteria for myocarditis. **(B)** T1-weighted spin-echo images before **(left)** and shortly after **(right)** gadolinium administration with early gadolinium accumulation in the septum **(arrows)**. Quantitative evaluation of the signal enhancement (skeletal-muscle normalized myocardial enhancement ratio of ≥4.0 or an absolute enhancement of ≥45%) is required to use information from this pulse sequence as a positive criterion. **(C) (Left)** T2-weighted spin-echo image with high signal intensity of the septum and lateral wall **(arrows)**. Evidence for regional edema, or a signal intensity ratio of ≥2.0 (signal intensity normalized to skeletal muscle in the same slice), renders T2 findings positive. **(Right)** Late enhancement image without evidence for significant delay of gadolinium washout. The thin subepicardial layer of high signal intensity in the inferolateral region represents fat.

space after administration, this phase lasts for the first minutes after the contrast bolus. Contrast-enhanced fast spin-echo T1-weighted MR during this time can be used to assess experimentally induced myocardial hyperemia (55) and to detect muscular inflammation (56). Accordingly, the purpose of myocardial early gadolinium enhancement ratio (EGEr) is to detect an overall increased volume of gadolinium distribution into the intravascular and interstitial space during the early washout period.

The diagnostic utility of contrast-enhanced T1-weighted imaging in patients with clinically acute and chronic myocarditis has been shown in several studies (9,13,34,35).

Currently, fast spin-echo sequences are used, which are vulnerable to inconsistent image quality in patients with varying heart rate and irregular breathing patterns. New sequences to assess the early phase of gadolinium kinetics may overcome existing limitations of image quality.

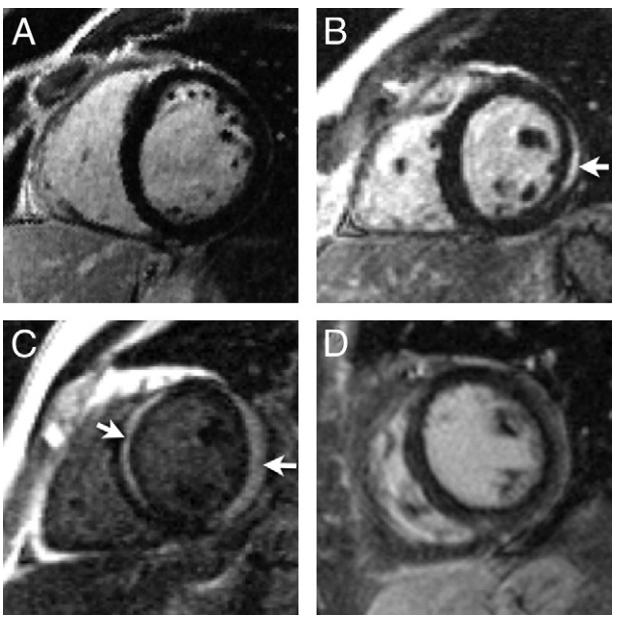
Necrosis and fibrosis (late gadolinium enhancement [LGE]).

Myocardial LGE specifically reflects irreversible myocardial injury (i.e., necrosis and fibrosis). This type of imaging uses an inversion pulse to decrease the signal response from normal myocardium, thereby highlighting areas with increased accumulation of gadolinium as bright regions.

In earlier stages of necrosis, gadolinium enters the cells through acutely injured cell membranes (7). Hence, the volume of distribution of gadolinium is increased (12) and visualizes myocarditis-related necrosis (Fig. 2). After inflammatory clearance of necrotic regions, a mesh of fibro-

Figure 2

Late Enhancement Patterns in Myocarditis



(A) Normal myocardium with no evidence of irreversible myocyte injury. **(B)** Regional subepicardial enhancement of the lateral wall **(arrow)**. **(C)** Subepicardial enhancement of lateral and midwall enhancement of the septal wall **(arrows)**. **(D)** Diffuse subepicardial enhancement.

cytes with a large interstitial component replaces formerly viable tissue, again increasing the volume of distribution for gadolinium into this extracellular space during the late washout period. Thus, the late sequelae of inflammatory tissue damage also can be observed by LGE.

Microscopic (57), animal (58), and clinical (59) studies have confirmed the role of LGE imaging as s gold standard for in vivo detection of irreversible myocardial injury associated with myocardial infarction. In patients with myocarditis, several studies have demonstrated a high specificity of LGE for the detection of such injury in myocarditis (12,13,37,38,40). The regional distribution of injury as defined by LGE not only allows differentiating ischemic (with mandatory subendocardial involvement) from nonischemic injury (60), but also may indicate the underlying etiology of the nonischemic insult (61).

As a potential limitation, LGE showed a variable sensitivity to detect active or chronic inflammation, depending on the selection of patients (12,13,34,39,40,43). Using the Dallas criteria, De Cobelli et al. (39) found LGE to be less sensitive in "borderline" myocarditis (44%) than in "active" myocarditis (84%).

One reason may be that active myocarditis may not always lead to large-enough regions of necrotic myocytes to be visually detectable, given the pixel size in CMR images. This contrasts with the situation in ischemic necrosis for which LGE has been shown to be highly sensitive. Therefore, LGE may be insensitive for the detection of symptomatic myocarditis with limited or nonfocal irreversible injury. More studies are needed to address this issue.

Combined use of tissue pathology markers. Two studies have compared all 3 tissue-based markers as well as various combinations of these. Abdel-Aty et al. (13) used combined clinical criteria for active myocarditis, whereas Gutberlet et al. (34) assessed patients with chronic myocarditis, validated against histopathological criteria of myocardial inflammation. In both studies, the approach with the best overall diagnostic accuracy was found by the combined use of all 3 tissue-based CMR parameters, with the presence of at least 2 positive criteria defining the CMR study as positive for myocarditis (Tables 3 and 4).

Indications, Procedure, and Protocol of CMR

Indications for CMR

A CMR study should only be performed if patients are symptomatic, if there is sufficient clinical evidence for myocarditis, and if the CMR result will likely affect clinical management. Thus, it is generally indicated in patients with current or persisting symptoms, evidence for significant myocardial injury, and suspected viral etiology. CMR is of potential use in patients with chest pain, elevated troponin, and normal coronary arteries, where it was shown to identify myocarditis in more than 30% of patients (62).

Additional indications may exist for subjects with possible myocarditis being exposed to strenuous physical exercise (e.g., professional athletes) or for patients with otherwise unexplained new ECG findings consistent with myocarditis, even in the absence of symptoms suggestive of myocarditis. Table 5 lists recommended criteria for requesting a CMR study in patients with suspected myocarditis.

The CMR Procedure

The patient should be monitored throughout the session, including ECG, blood pressure, breathing, and O_2 saturation. Furthermore, communication to the patient should be ensured by the use of intercom devices. A physician trained in cardiac resuscitation should be available. As for all cardiac diagnostic modalities, drugs and equipment for immediate interventions should be within reach.

Typically, patients are examined in a supine position. A dedicated cardiac phased-array surface coil should be used to acquire functional images. It is very important to emphasize that for all sequences used to analyze signal intensity (qualitatively or quantitatively), either a signal intensity correction algorithm or the body coil should be used. The inhomogeneous sensitivity field of surface coils may otherwise lead to false negative (inferolateral wall) or false positive (septum) results.

The coverage of the heart should allow for assessing all 17 LV segments according to published recommendations (63). Images of the apex may be of insufficient image quality and may have to be excluded.

Published data on contrast-enhanced CMR in myocarditis mostly have been obtained with the use of gadolinium gadopentetate dimeglumine and, thus, recommendations are only valid for this substance or compounds with an equivalent pharmacokinetic profile.

The CMR Protocol

Recommended imaging parameters and detailed protocol recommendations are provided in the Online Appendix of this article. CMR sequences generally will be ECG-gated and performed by the use of breath-hold protocols. These recommendations are based on the current evidence as published in peer-reviewed literature as of January 2009. Some of the currently recommended sequences have distinct

Table 5

Indications for Cardiovascular Magnetic Resonance in Patients With Suspected Myocarditis

New Onset or Persisting Symptoms Suggestive of Myocarditis	Plus	Evidence for Recent/Ongoing Myocardial Injury	Plus	Suspected Viral Etiology
Dyspnea *or* orthopnea *or* palpitations *or* effort intolerance/malaise *or* chest pain		Ventricular dysfunction *or* new or persisting ECG abnormalities *or* elevated troponin		History of recent systemic viral disease or previous myocarditis *or* absence of risk factors for coronary artery disease or age <35 yrs *or* symptoms not explained by coronary stenosis on coronary angiogram *or* recent negative ischemic stress test

ECG = electrocardiogram.

limitations. Images obtained by T1-weighted spin-echo sequences during free breathing may have limited diagnostic quality, and T2-weighted spin-echo images suffer from an inherently low signal-to-noise ratio. Although new sequences are being tested for these purposes, their value and clinical role remains to be defined.

Evaluation of CMR Images in Suspected Myocarditis

The versatility, accuracy, and reproducibility of CMR and the generally high expectations of referring physicians call for a careful, responsible evaluation of all available parameters. Table 6 summarizes CMR findings and proposed terminology in patients with suspected myocarditis.

Edema. Myocardial edema appears as an area of high signal intensity in T2-weighted images (Fig. 1C, left panel). In myocarditis, it may be regional or global. It is important to keep in mind that, in the absence of LGE, edema reflects reversible myocardial injury (52,64).

Regional edema can be identified visually (Fig. 1C), although a quantitative assessment of the signal abnormality seems appropriate. Evaluation software allows for verifying edema as regions with signal intensity more than 2 standard deviations above the mean value of normal tissue. The lower signal-to-noise of T2-weighted images should be considered, limiting the ability to correctly identify small regions of signal inhomogeneity. Thus, it is recommended to consider only areas of at least 10 adjacent pixels with high signal intensity as relevant. Areas with abnormally low signal in T2-weighted images (e.g., fibrotic scars) should not be used for normalization.

In myocarditis, edema may be global and thus not recognizable to the eye. A quantitative analysis by normalizing the signal intensity of the myocardium to that of skeletal muscle has been shown to allow for the detection of a global T2 signal abnormality. Values for the T2 ratio (for calculation, see the Online Appendix) of more than 1.9 indicate myocarditis (13).

Involvement of skeletal muscle in systemic inflammation may limit the sensitivity of a signal intensity analysis normalized to skeletal muscle (11) and should be taken into consideration in patients with evidence for ongoing myositis. Future studies will have to address the diagnostic accuracy in different scenarios.

When analyzing signal intensity, great care should be taken to exclude high signal of inadequately suppressed slowly flowing cavitary blood. This should not be a problem in visual analysis because slow flow signal would have an apparent "subendocardial" location, whereas the T2 signal hyperintensity of myocarditis is almost always subepicardial or transmural. The identification of skeletal muscle to calculate myocardium to skeletal muscle ratio in the same slice may be difficult with a fat-suppressed sequence. The viewing of T2 images side by side with colocalized SSFP or T1-weighted images is recommended to correctly identify skeletal muscle and differentiate it from subcutaneous fat.

Hyperemia and capillary leakage (myocardial early gadolinium enhancement). The EGEr is defined as an increased normalized gadolinium gadopentetate dimeglumine accumulation in the myocardium during the early washout period. Although sometimes visually appreciated (Fig. 1B), quantitative evaluation of myocardial EGEr is required. Normalization of the signal intensity in T1-weighted images to that of skeletal muscle may be hampered by coexisting myositis. In patients with evidence for skeletal muscle involvement as indicated by a skeletal muscle signal intensity increase of 20% or higher or by a recent history of muscular pain, an absolute myocardial signal intensity increase between pre- and post-gadolinium images of more than 45% should be

Table 6

Proposed Terminologies for Describing CMR Findings

	Normal	CMR Findings Consistent With Myocardial Inflammation			
Edema	Lack of evidence for myocardial edema	Patchy areas or regions of high T2 signal intensity indicating focal or regional edema*	Subepicardial or septal layer of high T2 signal intensity indicating regional edema	Transmural high T2 signal intensity indicating regional edema, consistent with but not specific for myocardial inflammation	Global high T2 signal intensity indicating global edema†
Hyperemia Capillary leak	Lack of evidence for increased myocardial early gadolinium enhancement ratio	Increased myocardial early gadolinium enhancement ratio‡			
Irreversible cell injury	Lack of evidence for regional late gadolinium enhancement	Patchy areas of late gadolinium enhancement indicating focal injury	Subepicardial or septal layer of late gadolinium enhancement indicating regional injury	Transmural late gadolinium enhancement, consistent with but not specific for myocardial inflammation	
	Normal	Supportive CMR Findings			
LV dysfunction	Normal LV function	Regional systolic dysfunction	Global systolic dysfunction		
Pericardial effusion	Lack of evidence for pericardial effusion	Small pericardial effusion	Moderately large pericardial effusion	Large pericardial effusion without hemodynamic relevance	Large pericardial effusion with hemodynamic relevance

*To avoid misinterpretation of artifacts, areas with abnormal signal intensity should consist of at least 10 adjacent pixels to be regarded as relevant. †Global high T2 signal is defined by a signal intensity ratio between myocardium and skeletal muscle of ≥2.0. ‡An increased myocardial early gadolinium enhancement ratio is defined by either a signal intensity enhancement ratio between myocardium and skeletal muscle of ≥4.0 or an absolute myocardial enhancement of ≥45%.
CMR = cardiovascular magnetic resonance; LV = left ventricular.

used as a threshold consistent with myocarditis instead of the normalized myocardial early gadolinium enhancement ratio (11). In patients with irregular breathing patterns or significant arrhythmia, image quality may be reduced or even be nondiagnostic.

Necrosis and fibrosis (LGE). Several patterns of LGE may be seen in patients with active myocarditis (Fig. 2). Focal signal increases typically are localized to the subepicardial regions of the LV and extend to a variable extent through the ventricular wall. The LGE may be localized in inferolateral and, less frequently, anteroseptal segments (Fig. 1B). However, LGE may be multifocal or diffuse in distribution (Figs. 1C and 1D). As a rule, the subendocardium typically is not involved in an isolated fashion, clearly distinguishing this injury pattern from ischemia-mediated injury. In the basal septum, the LV outflow tract and the membraneous septum may mimic septal LGE in short axis images and lead to false-positive results. Also, a line of increased signal intensity may appear in the basal septum on transverse, long-axis, or short-axis images that may not represent pathologic LGE but may be related to the fusion of the right ventricular moderator band to the right ventricular portion of the interventricular septum.

Comprehensive use of CMR criteria ("Lake Louise Criteria"). Because of the lack of large-scale multicenter data, current recommendations can only reflect the experts' best-achievable consensus based on currently available literature. It is important to re-emphasize that rigorous test data of the pulse sequences evaluated against the gold standard of myocardial biopsy in clearly defined clinical subsets of patients are still scarce. The sensitivity and specificity as compared with endomyocardial biopsy for the pulse sequences recommended in this article are based on the limited number of patients in controlled trials. At the current time, this needs to be kept in mind when employing CMR for making the diagnosis of myocarditis.

The authors recommend the combined use of all 3 tissue markers. If all sequences can be performed and 2 or more of the 3 tissue-based criteria are positive, myocardial inflammation can be predicted or ruled out with a diagnostic accuracy of 78% (pooled data, Table 4); if only LGE imaging is performed, the diagnostic accuracy is 68% (pooled data, Table 3).

The authors acknowledge that there may be clinical settings that require a greater sensitivity, even if this comes with a reduced specificity, or vice versa. One example may

Table 7

Proposed Diagnostic CMR Criteria (i.e., Lake Louise Consensus Criteria) for Myocarditis

In the setting of clinically suspected myocarditis,* CMR findings are consistent with myocardial inflammation, if at least 2 of the following criteria are present: Regional or global myocardial SI increase in T2-weighted images.† Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images.‡ There is at least 1 focal lesion with nonischemic regional distribution in inversion recovery-prepared gadolinium-enhanced T1-weighted images ("late gadolinium enhancement").§
A CMR study is consistent with myocyte injury and/or scar caused by myocardial inflammation if Criterion 3 is present.
A repeat CMR study between 1 and 2 weeks after the initial CMR study is recommended if None of the criteria are present, but the onset of symptoms has been very recent and there is strong clinical evidence for myocardial inflammation. One of the criteria is present.
The presence of LV dysfunction or pericardial effusion provides additional, supportive evidence for myocarditis.

*The clinical suspicion for active myocarditis should be based on the criteria listed in Table 5. †Images should be obtained using a body coil or a surface coil with an effective surface coil intensity correction algorithm; global signal intensity (SI) increase has to be quantified by an SI ratio of myocardium over skeletal muscle of ≥2.0). If the edema is more subendocardial or transmural in combination with a colocalized ischemic (including the subendocardial layer) pattern of late gadolinium enhancement, acute myocardial infarction is more likely and should be reported. ‡Images should be obtained using a body coil or a surface coil with an effective surface coil intensity correction algorithm; a global SI enhancement ratio of myocardium over skeletal muscle of ≥4.0 or an absolute myocardial enhancement of ≥45% is consistent with myocarditis. §Images should be obtained at least 5 min after gadolinium injection; foci typically exclude the subendocardial layer, are often multifocal, and involve the subepicardium. If the late gadolinium enhancement pattern clearly indicates myocardial infarction and is colocalized with a transmural regional edema, acute myocardial infarction is more likely and should be reported.

Abbreviations as in Table 6.

be the use of CMR to assess patients with a high pre-test probability or children with suspected inflammation after cardiac transplantation. It is re-emphasized that both referring physicians and CMR readers should use the reported criteria as part of a comprehensive diagnostic approach, which also includes clinical, functional, and other information. Table 7 summarizes the recommended diagnostic CMR criteria for myocardial inflammation.

Follow-Up of Myocarditis by CMR

The decision regarding follow-up of patients with active myocarditis depends on the individual scenario. Anecdotal evidence suggests that CMR studies during the first days of myocarditis may be less sensitive than those obtained 7 days after clinical onset of the disease (65). This may be due to the focal nature of early stages of the disease. Thus, in a patient with strong clinical evidence for myocarditis yet negative criteria in the initial CMR study, a repeat scan may be needed to establish the diagnosis. A follow-up at least 4 weeks after the onset of disease may be useful to differentiate uncomplicated involvement of the myocardium in a systemic viral illness from a complicated course with viral persistence or autoimmunologic disease, as viral clearance usually is completed within the first days after infection and tissue inflammation should not take more than 2 to 3 weeks. Indeed, pilot data indicate a prognostic relevance of persisting CMR markers for inflammation at 4 weeks after onset (44).

Reporting of CMR Results

The report for a CMR study should address the specific questions raised by the referring physician. In suspected

Table 8

Summary of Recommended Components for the CMR Study Report

LV volume and function	LV end-diastolic volume and volume index LV end-systolic volume and volume index Ejection fraction Cardiac index LV mass and mass index
Presence or absence of markers for inflammatory activity and injury	T2 signal/edema (regional edema or global T2 ratio) Calculated global myocardial early gadolinium enhancement ratio Myocardial late gadolinium enhancement with nonischemic regional distribution
Conclusion	On the basis of the presence or absence of 2 or more criteria, considering additional evidence by the presence of LV dysfunction and/or pericardial effusion
Recommendation for follow-up	Based on clinical setting A follow-up >4 weeks after the onset of symptoms may have prognostic implications and thus is recommended.

Abbreviations as in Table 6.

Table 9

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myocarditis, this will usually include the inflammatory activity, LV function, and other information such as pericardial effusion, cardiac index, and extent of scarring.

There was consensus that for the time being the presence or absence of the 3 criteria, if acquired, should be reported. The report summary should include components as listed in Table 8. The report should relate quantitative values to published reference values. References may be cited as deemed appropriate.

It is important to be aware that CMR, like myocardial biopsy, depicts the patient's status at one point in time and cannot characterize acute, chronic, or relapsing forms. These attributes are based on the clinical course rather than imaging (or biopsy) findings. The consensus group therefore recommends against using the terms acute, chronic, and so on with respect to CMR findings, but rather to comment on the presence or absence of "active" or "ongoing" inflammation.

Future Developments of CMR for Myocarditis

The CMR methodology is evolving at a rapid pace. Among numerous interesting developments, many can be expected to be useful for application in myocarditis. As hardware and coil technology are improving, image quality and thus diagnostic yield will be more consistent. But, more importantly, novel approaches for characterizing tissue such as time-resolved assessment of gadolinium wash-out, T1 mapping, T2 mapping, parametric imaging, and the combina-

tion of imaging criteria with seromarkers will likely further increase the utility of CMR.

Conclusions

This work provides recommendations on the use of CMR as part of a comprehensive diagnostic approach in patients with suspected myocardial inflammation. The use of CMR appears suitable to identify patients with significant ongoing inflammation, which may be especially important for patients with recurrent or persisting symptoms and in patients with new onset heart failure.

On the basis of published data, we propose a comprehensive CMR protocol to determine the extent and regional distribution of reversible and irreversible myocardial injury, as well as to detect functional and other abnormalities. Furthermore, we suggest consensus criteria providing evidence for or against myocardial inflammation based on CMR findings. We are aware that these recommendations are based on limited data and that not all centers will be able to apply all components of the suggested protocol. New hardware, software, and contrast agent techniques may become available to further improve diagnostic and procedural efficiency of CMR in myocarditis.

Acknowledgments

The entire Consensus Group actively participated in the discussion that resulted in the recommendations; the members are listed in Table 9.

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Key Words: cardiovascular magnetic resonance ■ myocarditis ■ consensus.

APPENDIX

For the recommended imaging parameters and detailed protocol recommendations, please see the online version of this article.