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## Cardiovascular Magnetic Resonance in Myocarditis: A JACC White Paper

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### Abstract

Cardiovascular magnetic resonance (CMR) has become the primary tool for non-invasive assessment of myocardial inflammation in patients with suspected myocarditis. The *International Consensus*

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*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 (“Lake Louise Criteria”).

## Keywords

Cardiovascular Magnetic Resonance; Myocarditis; Consensus

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## 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) (2) (3) (4) and is an important underlying etiology of other myocardial diseases such as dilated (5) and arrhythmogenic right ventricular (6) cardiomyopathy. The incidence of non-fatal myocarditis is likely higher than actually diagnosed, mostly due to the challenges of establishing the diagnosis in standard clinical settings.

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

### Pathogenesis and pathology

Pathogenetic features of myocarditis are reviewed in detail elsewhere (7). Following 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 non-specific symptoms, but may also present with features of acute myocardial infarction, or heart failure with hemodynamic compromise. Physical exams of patients with myocarditis are often normal.

**Ventricular functional analysis**—Although many patients with myocarditis have regional or global wall motion abnormalities (8) (9) (10), dysfunction is not specific to inflammation, and its sensitivity is limited (9) (11) (12) (13). Biventricular dysfunction in myocarditis, however, was found to be the main predictor of death and transplantation (14).

**ECG**—ECG findings associated with myocarditis may include ST segment and T wave changes, Q waves, AV 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, the presence of either ST elevation or T inversion as the most sensitive ECG criterion is present in less than 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, CK-MB and troponin may be elevated. When present, the magnitude of rise 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 35–45% (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:

- The sensitivity of EMB is limited due to so-called sampling error (18) (19) (20) (21).
- Severe complications (perforation, tamponade) occur in 0.1 to 0.5%, the overall complication rate is 6% (17).
- There is substantial debate about 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 inter-observer agreement (24) (25).

Immunohistochemistry has a higher sensitivity than standard histopathology for the diagnosis of myocarditis (26) (27) and immunohistology protocols and evaluation criteria have been proposed (28) (10). Cost, availability, and limited standardization, however, have limited the widespread use of immunohistology and viral genome analysis.

- 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, which may however not be appropriate for many patients, especially those with less severe disease.

### Imaging Modalities Other than CMR

A detailed review of non-invasive 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). <sup>111</sup>Indium antimyosin antibody and <sup>67</sup>gallium nuclear imaging have been used to diagnose myocarditis (31). The specificity of these approaches, however, is very limited (32). Nuclear medicine techniques are also hampered by limited availability of tracers mentioned above, poor

spatial resolution and radiation issues. In current clinical practice, nuclear medicine is only rarely used to diagnose myocarditis.

## Cardiovascular Magnetic Resonance (CMR) in Myocarditis

### Published Data

CMR imaging offers a unique combination of safety, clarity of anatomical visualization, inter-observer consistency, and quantitative accuracy. Furthermore, it allows for the comprehensive use of a wide spectrum of diagnostic targets, especially using the modifiable inherent tissue contrast. CMR has become a standard tool in many medical centers and currently is considered by many 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 studies have investigated the diagnostic utility of non-contrast (11) (13) (34) and contrast-enhanced (35) (11) (36) (12) (13) (37) (38) (39) (40) (41) (42) (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 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, had a small sample size, variable inclusion criteria, and non-uniform patient populations. Furthermore, CMR studies were performed at variable time points after disease onset, used different imaging diagnostic criteria, and mostly did not include biopsy for confirmation.

Furthermore, the specificity was mostly compared to normal controls or 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 (multi-center) 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**—CMR assessment of right and left ventricular (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, reemphasized 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) (46) (47). Although not specific for myocarditis, its presence is supportive evidence for active inflammation.

Regional distribution, extent and hemodynamic significance of pericardial effusion can be assessed in 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 (figure 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, i.e. 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, 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 non-fluid components (fibrinous deposits, thrombus) is pathologic.

**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 serve as retrospective, supportive evidence for recent myocarditis.

### CMR Tissue Characterization

Given the unique potential of CMR to visualize tissue changes, this area is of special interest. As outlined above, 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 functional nature, leading to Na<sup>+</sup> 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 using the long T2 of water-bound protons as the contrast-generating mechanism resulting in a high signal intensity of edematous tissue (figure 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 due to the dual suppression of the fat and flowing blood signal. Double inversion recovery sequences may provide a higher SNR 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 (52) (13) (34).

Regional edema visible on T2-weighted CMR images was not observed in “borderline myocarditis”, but could be seen 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.

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 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) (35) (13) (34).

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”)—**Myocardial late gadolinium enhancement (LGE) specifically reflects irreversible myocardial injury, i.e. necrosis and fibrosis. LGE 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 (figure 2). After inflammatory clearance of necrotic regions, a mesh of fibrocytes 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 can also be observed by LGE.

Both, microscopic (57), animal (58) and clinical (59) studies have confirmed the role of LGE imaging as a 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 non-ischemic injury (60), but also may indicate the underlying etiology of the non-ischemic 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) (40) (39) (34) (43). Using the

Dallas criteria, De Cobelli et al. found LGE to be less sensitive in “borderline” myocarditis (44%) than in “active” myocarditis (84%) (39).

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 non-focal irreversible injury. More studies are needed to address this issue.

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

## CMR Indications, Procedure and Protocol

### 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.

### CMR procedure

The patient should be monitored throughout the session including ECG, blood pressure, breathing, and O<sub>2</sub> saturation. Furthermore, communication to the patient should be ensured using 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 using gadolinium gadopentetate dimeglumine (gadolinium-DTPA) and thus recommendations are only valid for this substance or compounds with an equivalent pharmacokinetic profile.

### CMR protocol

Recommended imaging parameters and detailed protocol recommendations are provided in the supplemental material of this article.

CMR sequences generally will be ECG-gated and performed using 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 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 (figure 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 (see 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 naked 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 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). This 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 cavitory 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. Viewing the T2 images side by side with



co-localized 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)**

EGEr is defined as an increased normalized gadolinium-DTPA accumulation in the myocardium during the early washout period. Although sometimes visually appreciated (see 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 co-existing 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-gadolinium and post-gadolinium images of more than 45% should be 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 non-diagnostic.

### **Necrosis and fibrosis (late gadolinium enhancement/LGE)**

Several patterns of LGE may be seen in patients with active myocarditis (fig. 2). Focal signal increases are typically localized to the sub-epicardial regions of the left ventricle and extend to a variable extent through the ventricular wall. LGE may be localized in inferolateral and less frequently anteroseptal segments (Figure 1B). However, LGE may be multi-focal or diffuse in distribution (Figure 1C,D). As a rule, the sub-endocardium typically is not involved in an isolated fashion, clearly distinguishing this injury pattern from ischemia-mediated injury. In the basal septum, the left ventricular outflow tract and the membranous 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 which 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”)**

Due of the lack of large-scale multi-center data, current recommendations can only reflect the experts’ best achievable consensus based on currently available literature. It is important to reemphasize 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 to endomyocardial biopsy for the pulse sequences recommended in this paper 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 three tissue markers. If all sequences can be performed and two or more of the three 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 which require a higher sensitivity, even if this comes with a reduced specificity, or vice versa. One example may 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 autoimmune 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 myocarditis, this will usually include the inflammatory activity, left ventricular 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 etc. 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**

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

### **Summary**

This paper provides recommendations on the use of cardiovascular magnetic resonance as part of a comprehensive diagnostic approach in patients with suspected myocardial inflammation.

CMR appears suitable to identify patients with significant ongoing inflammation. This may be especially important for patients with recurrent or persisting symptoms, and in patients with new onset heart failure.

Based on published data, we propose a comprehensive CMR protocol to determine 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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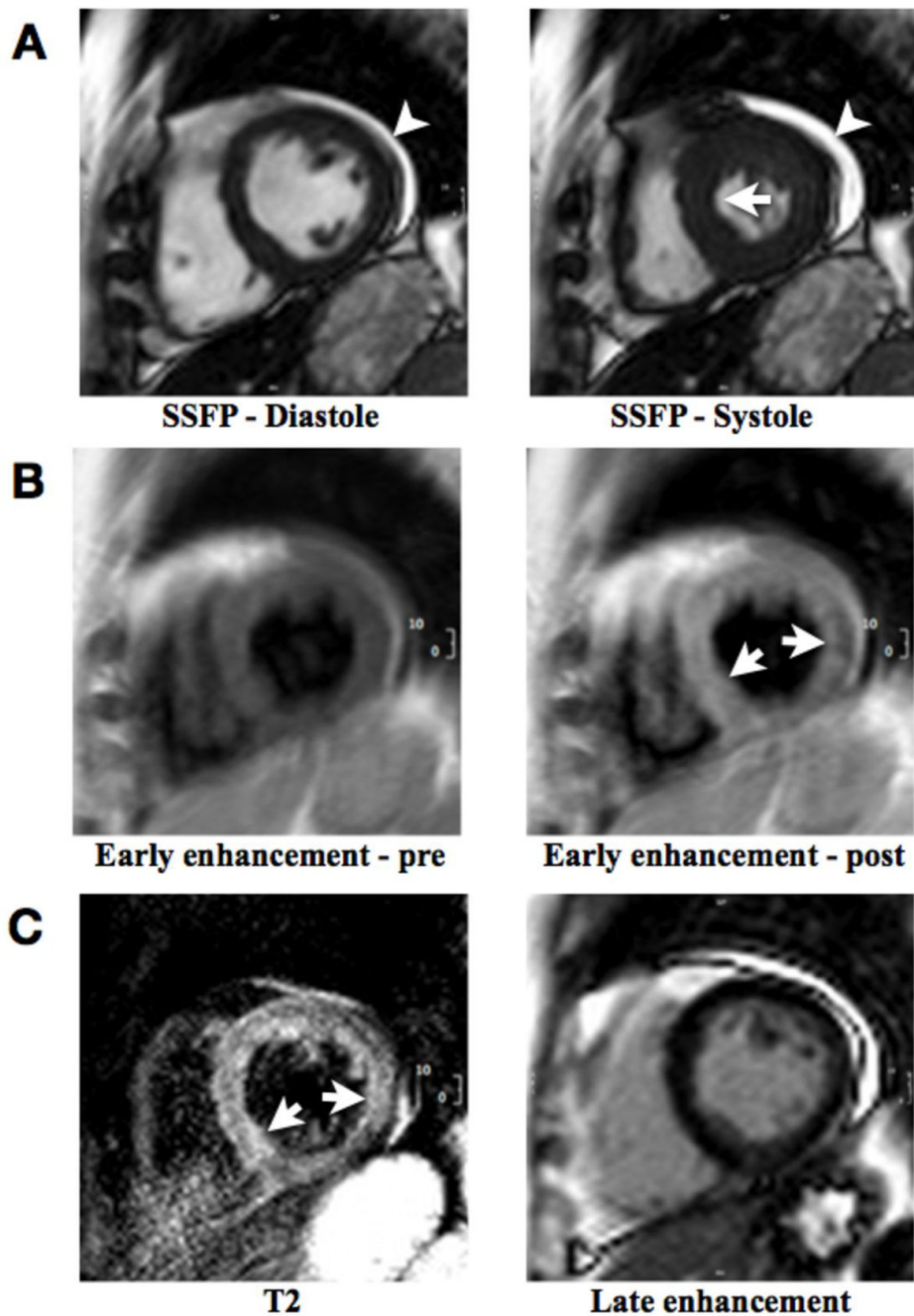
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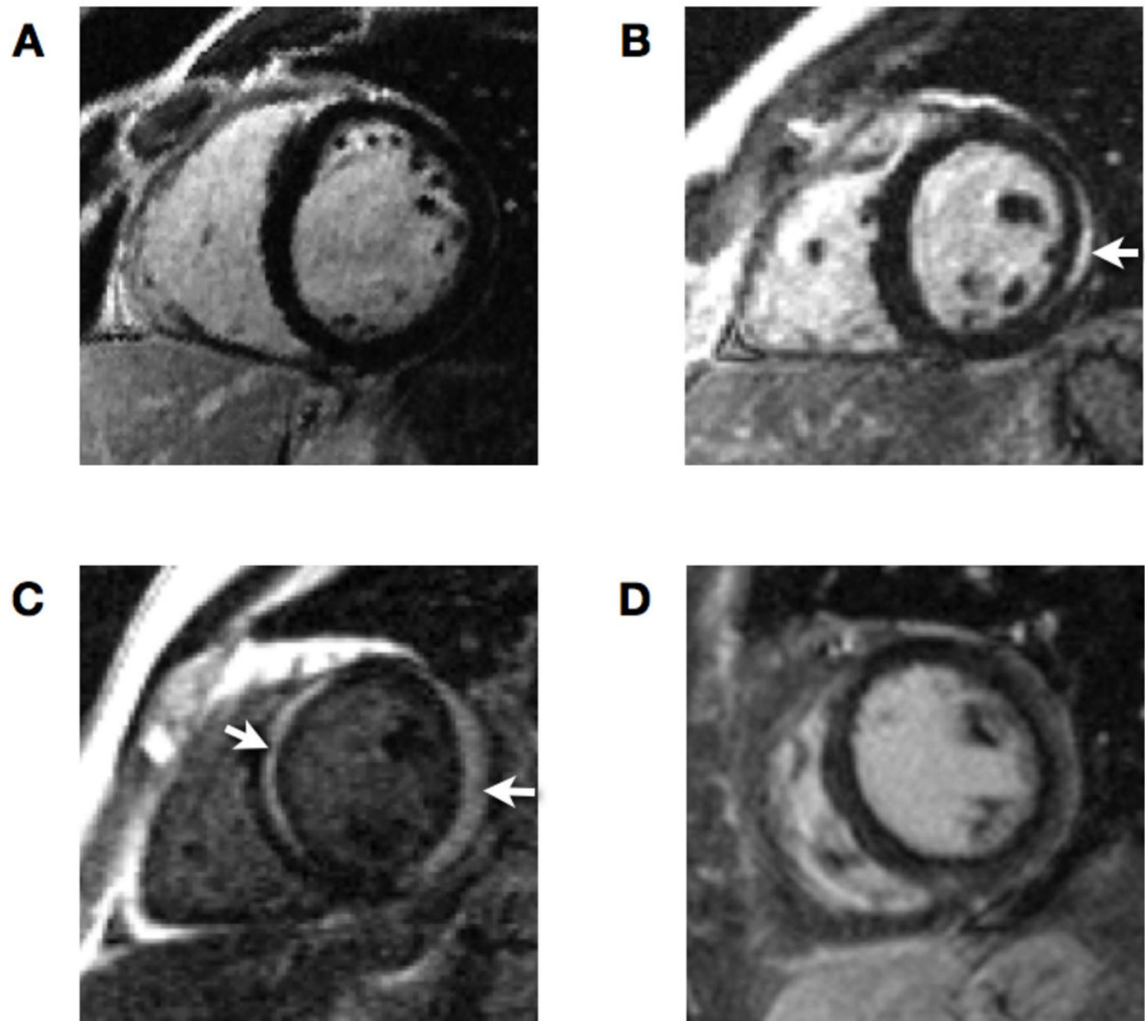
**Figure 1. Short axis CMR views in a patient with clinically acute myocarditis**

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 (arrowhead). These findings represent two 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 equal to or greater than 4.0 or an absolute enhancement of equal to or greater than 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 equal to or greater than 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.



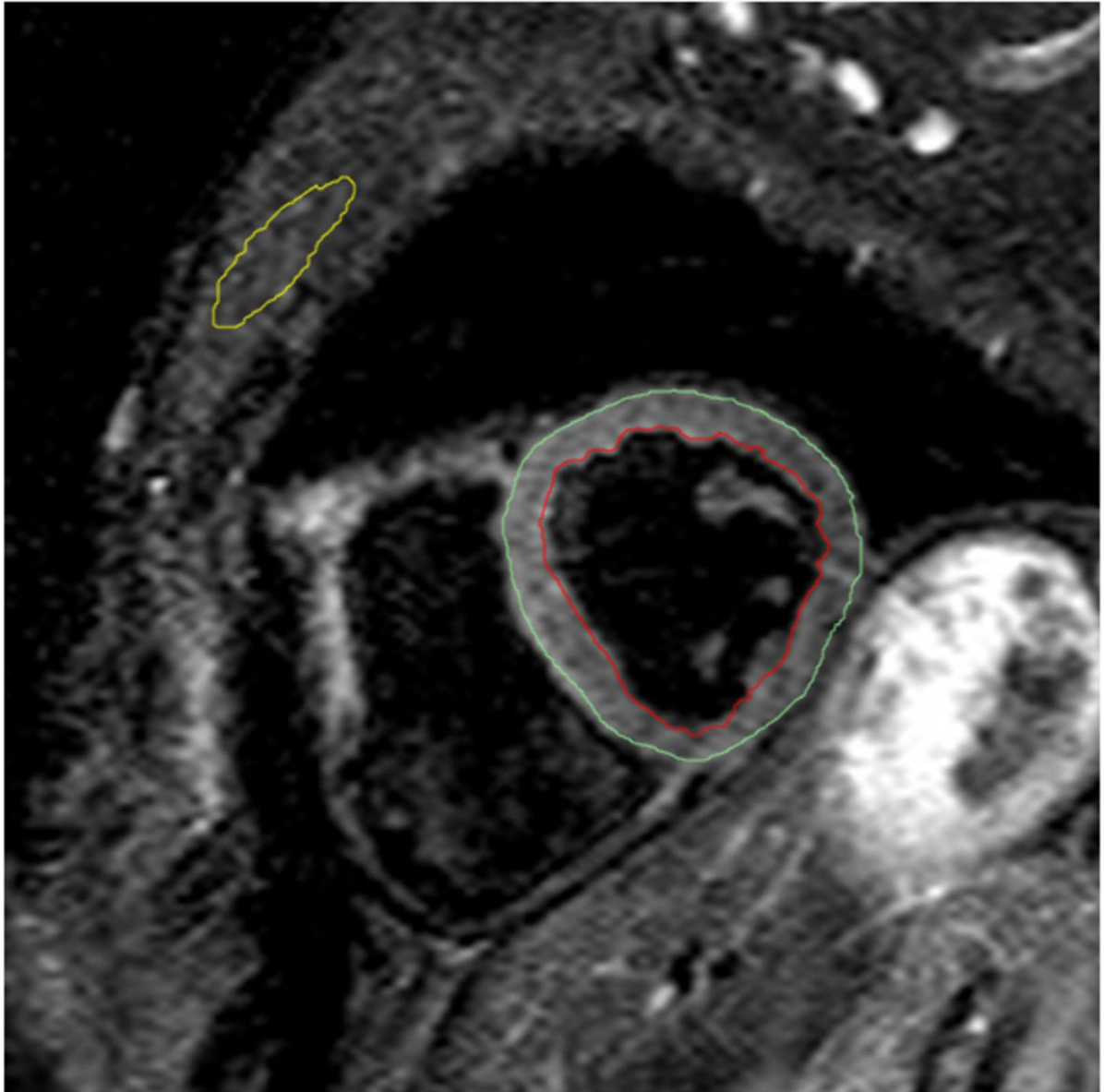
**Figure 2. Late enhancement patterns in myocarditis**

A: Normal myocardium with no evidence of irreversible myocyte injury

B: Regional sub-epicardial enhancement of the lateral wall (arrow)

C: Subepicardial enhancement of lateral and midwall enhancement of the septal wall (arrows)

D: Diffuse sub-epicardial enhancement



**Figure 3. Signal intensity analysis contours for tissue characterization**

T2-weighted image in a short axis orientation with example contours for skeletal muscle (yellow), subepicardial border (green) and subendocardial border (red). The contour for the skeletal muscle was copied from a mid-diastolic SSFP still frame in the same slice position.

**Table 1**  
Published controlled studies on CMR in myocarditis

	Validation	n patients	n controls
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
		<b>289</b>	<b>179</b>

\* Comparison to patients with acute myocardial infarction.

\*\* Comparison to patients with clinical evidence, but lack of immunohistologic evidence for chronic myocarditis

**Table 2**  
Diagnostic accuracy of LV dysfunction as assessed in controlled trials.

LV dysfunction (EF<55%)	Validation	Sens	Spec	Acc	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%
<b>Pooled data (n=276)</b>		<b>54%</b>	<b>76%</b>	<b>64%</b>	<b>71%</b>	<b>60%</b>

Sens: Sensitivity; Spec: Specificity; Acc: Accuracy; PPV: Positive predictive value; NPV: Negative predictive value.

**Table 3**  
Overview of the diagnostic accuracy of individual tissue criteria as assessed in controlled trials.

Early myocardial gadolinium enhancement	Validation	Sens	Spec	Acc	PPV	NPV
Friedrich et al., Circulation 1998 (9)	Clinical	84%	89%	86%	89%	84%
Laiassy 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%
<b>Pooled data (n=194)</b>		<b>74%</b>	<b>83%</b>	<b>78%</b>	<b>86%</b>	<b>70%</b>
<b>T2</b>	<b>Validation</b>	<b>Sens</b>	<b>Spec</b>	<b>Acc</b>	<b>PPV</b>	<b>NPV</b>
Rieker et al., RoFo 2002 (36)	Clinical	100%	50%	76%	69%	100%
Laiassy 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%
<b>Pooled data (n=178)</b>		<b>70%</b>	<b>71%</b>	<b>70%</b>	<b>77%</b>	<b>63%</b>
<b>Late enhancement</b>	<b>Validation</b>	<b>Sens</b>	<b>Spec</b>	<b>Acc</b>	<b>PPV</b>	<b>NPV</b>
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%
<b>Pooled data (n=336)</b>		<b>59%</b>	<b>86%</b>	<b>68%</b>	<b>89%</b>	<b>53%</b>

Sens: Sensitivity; Spec: Specificity; Acc: Accuracy; PPV: Positive predictive value; NPV: Negative predictive value

**Table 4**  
Overview of the diagnostic accuracy of several combinations of tissue criteria.

T2+LGE	Validation	Sens	Spec	Acc	PPV	NPV
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%
<b>Pooled data (n=130)</b>		<b>25%</b>	<b>95%</b>	<b>56%</b>	<b>86%</b>	<b>50%</b>
<b>T2 and/or LGE</b>	Validation	<b>Sens</b>	<b>Spec</b>	<b>Acc</b>	<b>PPV</b>	<b>NPV</b>
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%
<b>Pooled data (n=130)</b>		<b>60%</b>	<b>66%</b>	<b>62%</b>	<b>79%</b>	<b>43%</b>
<b>Any one of three</b>	Validation	<b>Sens</b>	<b>Spec</b>	<b>Acc</b>	<b>PPV</b>	<b>NPV</b>
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%
<b>Pooled data (n=130)</b>		<b>88%</b>	<b>48%</b>	<b>70%</b>	<b>68%</b>	<b>76%</b>
<b>Any two of three</b>	Validation	<b>Sens</b>	<b>Spec</b>	<b>Acc</b>	<b>PPV</b>	<b>NPV</b>
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%
<b>Pooled data (n=130)</b>		<b>67%</b>	<b>91%</b>	<b>78%</b>	<b>91%</b>	<b>69%</b>

Sens: Sensitivity; Spec: Specificity; Acc: Accuracy; PPV: Positive predictive value; NPV: Negative predictive value

**Table 5**

Indications for CMR in patients with suspected myocarditis.

New onset or persisting symptoms suggestive of myocarditis	<i>plus</i>	Evidence for recent/ongoing myocardial injury	<i>plus</i>	Suspected viral etiology
Dyspnea <i>or</i> orthopnea <i>or</i> palpitations <i>or</i> effort intolerance/malaise <i>or</i> chest pain		Ventricular dysfunction <i>or</i> new or persisting ECG abnormalities <i>or</i> elevated troponin		History of recent systemic viral disease or previous myocarditis <i>or</i> absence of risk factors for coronary artery disease or age of <35y <i>or</i> symptoms not explained by coronary stenosis on coronary angiogram <i>or</i> recent negative ischemic stress test



**Table 6**

Proposed terminologies for describing CMR findings

	normal	CMR findings consistent with myocardial inflammation		
<b>Edema</b>	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
<b>Hyperemia Capillary leak</b>	Lack of evidence for increased myocardial early gadolinium enhancement ratio	Increased myocardial early gadolinium enhancement ratio <sup>‡</sup>		
<b>Irreversible cell injury</b>	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
<b>LV dysfunction</b>	Normal LV function	<b>Supportive CMR findings</b>		
<b>Pericardial effusion</b>	Lack of evidence for pericardial effusion	Regional systolic dysfunction	Moderately large pericardial effusion	Global systolic dysfunction Large pericardial effusion without hemodynamic relevance
		Small pericardial effusion	Large pericardial effusion	Large pericardial effusion with hemodynamic relevance

\* To avoid misinterpretation of artifacts, areas with abnormal SI should consist of at least 10 adjacent pixels to be regarded as relevant.

<sup>†</sup> Global high T2 signal is defined by an SI ratio between myocardium and skeletal muscle of  $\geq 2.0$

<sup>‡</sup> An increased myocardial early gadolinium enhancement ratio is defined by either an SI enhancement ratio between myocardium and skeletal muscle of 4.0 or an absolute myocardial enhancement of  $\geq 45\%$

Proposed diagnostic CMR criteria (Lake Louise Consensus Criteria) for myocarditis

**Table 7**

**In the setting of clinically suspected myocarditis<sup>a</sup>, CMR findings are consistent with myocardial inflammation, if at least two of the following criteria are present:**

- 1 Regional or global myocardial SI increase in T2-weighted images.<sup>b</sup>.
- 2 Increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images.<sup>c</sup>.
- 3 There is at least one focal lesion with non-ischemic regional distribution in IR-prepared gadolinium-enhanced T1-weighted images ("late gadolinium enhancement")<sup>d</sup>.

**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.**

<sup>a</sup>The clinical suspicion for active myocarditis should be based on the criteria listed in table 5.

<sup>b</sup>Images should be obtained using a body coil or a surface coil with an effective surface coil intensity correction algorithm; global SI increase has to be quantified by an SI ratio of myocardium over skeletal muscle of  $\geq 2.0$ ). If the edema is more subendocardial or transmural in combination with a co-localized ischemic (including the subendocardial layer) pattern of late gadolinium enhancement, acute myocardial infarction is more likely and should be reported.

<sup>c</sup>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  $\geq 4.0$  or an absolute myocardial enhancement of  $\geq 45\%$  is consistent with myocarditis.

<sup>d</sup>Images should be obtained at least 5 minutes after gadolinium injection; foci typically exclude the subendocardial layer, are often multi-focal, and involve the subepicardium. If the late gadolinium enhancement pattern clearly indicates myocardial infarction and is co-localized with a transmural regional edema, acute myocardial infarction is more likely and should be reported.

**Table 8**  
Summary of recommended components for the CMR study report

<b>Recommended CMR reports components</b>	
<b>LV volume and function</b>	LV end-diastolic volume and volume index LV end-systolic volume and volume index Ejection fraction Cardiac index LV mass and mass index
<b>Presence or absence of markers for inflammatory activity and injury</b>	<ul style="list-style-type: none"> <li>• T2 signal/edema (regional edema or global T2 ratio)</li> <li>• Calculated global myocardial early gadolinium enhancement ratio</li> <li>• Myocardial late gadolinium enhancement with non-ischemic regional distribution</li> </ul>
<b>Conclusion</b>	Based on the presence or absence of 2 or more criteria, considering additional evidence by the presence of LV dysfunction and/or pericardial effusion
<b>Recommendation for follow-up</b>	Based on clinical setting A follow-up >4 weeks after the onset of symptoms may have prognostic implications and thus is recommended.

**Table 9**  
Recommended sequence parameters for CMR in suspected myocardial inflammation.

	Sequence	Orientation	Slice thickness	Repetition time	Echo time	Flip angle
<b>Function, pericardial effusion</b> (SSFP images)	Steady-state free precession (SSFP)	Multiple short axis <i>or</i> multiple long axis	8mm (+2mm gap) <i>or</i> 10mm (no gap)	<5ms	<2ms	45 to 65°
<b>Edema</b> (T2-weighted images)	Triple-inversion recovery, black-blood fast/turbo spin echo (STIR) <i>For assessing regional edema, the following sequences can be used instead:</i> - ACUT2E TSE SSFP - T2-prepared SSFP - Double-inversion recovery fast/turbo spin echo (DIR)	Multiple short axis and long axis	10 to 15mm	>2000ms	60–70ms	90°
<b>Hyperemia Capillary leak</b> (myocardial early gadolinium enhancement ratio)	Non-breath-hold black-blood fast/turbo (FSE/TSE) spin echo	Multiple short axis <i>or</i> axial	10mm	1 R-R interval	<20ms	
<b>Irreversible cell injury</b> (myocardial late gadolinium enhancement)	T1-weighted, inversion-recovery prepared gradient echo with fat-sat prepulse, if available	Multiple short axis and long axis	6 to 10mm	≥ 2 R-R intervals	<4ms	

SSFP- Steady-state free precession; STIR- Short-TI inversion recovery; ACUT2E TSE- Acquisition for Cardiac Unified T2 Edema.

**Table 10**  
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