Cardiac Magnetic Resonance Assessment of Myocarditis

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Symptoms consistent with myocarditis are a frequent cause of medical visits, especially in young and middle-aged patients. Moreover, myocarditis was found to be the most frequent disease in patients with acute coronary syndrome yet normal coronary arteries.[1] Although many causes have been identified, acute cases are mostly because of myocardial involvement in systemic viral disease.[2,3] During the first days of viral myocarditis, there is direct cardiomyocyte injury, accompanied by edema, necrosis, and, depending on its spatial extent, regional, or even global contractile dysfunction. The tissue is typically cleared from the virus within 5 days; yet, reactive inflammation (clean-up) may last for several weeks. In uncomplicated disease, there is full tissue and functional recovery within 3 to 4 weeks, whereas more severe disease necrosis results in myocardial scarring. Prolonged autoimmune response or virus persistence may lead to chronic inflammation and is considered a frequent cause of dilated cardiomyopathy.[3]

Symptoms are not specific; patients may present with chest pain, fatigue, dyspnea, or arrhythmia. ECG findings may include AV block, ventricular or supraventricular arrhythmia, and ST changes, including severe elevation mimicking acute myocardial infarction. Except for more severe cases, echocardiography typically shows normal systolic wall motion or just mild regional dysfunction. Serological markers for cardiomyocyte injury, such as troponin, may be normal.

Because of the nonspecificity of its symptoms, signs and test findings, myocarditis is often diagnosed by exclusion of other cardiac diseases. The specific identification of an active nonischemic inflammatory process, therefore, is a clinical challenge, especially in patients presenting with acute chest pain and heart failure.

Invasive endomyocardial biopsy is only recommended in patients with evidence for heart failure in combination with acute disease (<2 weeks, class I) or left ventricular dilatation (<3 months, class I) or specific other cases of heart failure (class IIa).[4]

While nuclear imaging methods have not been proven useful, echocardiography and contrast-enhanced cardiovascular magnetic resonance (CMR) are standard imaging tools in patients with suspected myocarditis.

Figures 1 to 3 present results of a 31-year-old male patient presenting with acute chest pain and a normal physical examination. Although ECG, coronary angiography, and echocardiography were either normal or nonspecific, CMR provided strong evidence for myocardial edema, hyperemia, and necrosis and thus allowed for establishing the diagnosis of acute myocarditis.

Echocardiography

Echocardiography is a safe, versatile, and widely available technique, which can be used at the bedside at any time and allows for a quick assessment of cardiac chamber dimensions, ventricular wall thickness in addition to global and regional systolic function. It also provides information on cardiac pressures, valvular function, and the presence or absence of pericardial effusion. With respect to myocarditis, however, typically echocardiography findings do not allow for diagnosing myocarditis.[5] The scant published evidence for echocardiography findings in myocarditis includes increased wall thickness and hyperechogenicity, often accompanied by conduction abnormalities[6]; yet, both are not frequently observed in clinical routine. This may be, in part, related to technical factors (such as the acoustic window) and physician-related factors (experience, low index of suspicion). Regional wall motion abnormalities were found in 35% to 70% of patients with myocarditis, with only few studies comparing echocardiography with CMR head to head.[7] Echocardiography-derived signs of right ventricular dysfunction accompanying left ventricular dysfunction carry an adverse prognosis.[8]

Cardiovascular Magnetic Resonance

During the recent decade, CMR (where available) has become the diagnostic tool of choice in tertiary care centers for patients with evidence for acute nonischemic myocardial injury. Suspected myocarditis is one of the most frequent indications for CMR scans and, in Europe, represents about one third of CMR referrals.[9]

CMR allows for targeting several features of myocarditis[10–15]: inflammatory hyperemia and edema, necrosis/scar, contractile dysfunction, and accompanying pericardial effusion can all be

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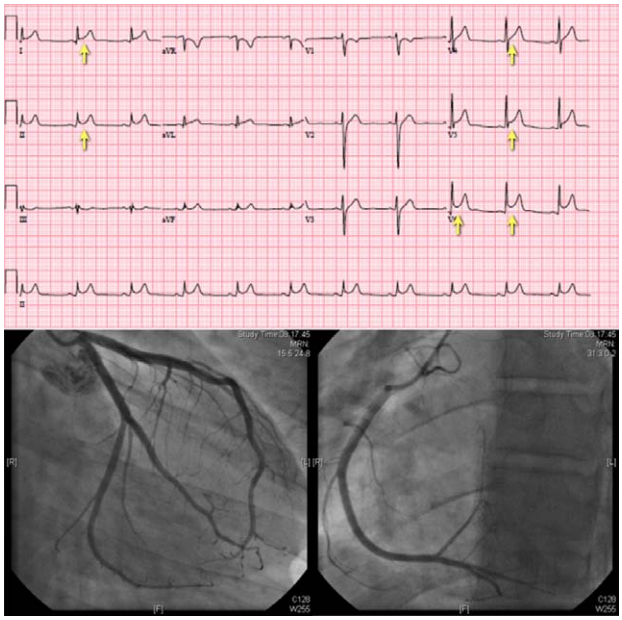

Figure 1. ECG and coronary angiogram still frames of a 31-year-old male patient presenting with acute chest pain. Despite typical ST-segment elevation in lateral leads (**top**), there is no evidence for coronary artery stenosis (bottom panels).

visualized during a single scan with just 4 different protocol components (Table 1).

On the basis of available research and expert consensus, diagnostic CMR criteria have been proposed (Lake Louise Criteria)[16] that are also part of societal publications[17,18] and include CMR criteria for hyperemia, edema, and necrosis (Table 1). If 2 of 3 criteria are positive, the CMR scan is indicative of active myocarditis.[16]

Although more research is required to assess the use of each of the parameters in various clinical settings (clinically acute versus chronic, mild versus moderate, diffuse versus regional) and the effect of the use of CMR in myocarditis on outcomes has not been prospectively studied, the current approach allows for a robust assessment of the extent of injury and dysfunction in clinically acute scenarios. Of note, the presence of necrosis or scar is a strong predictor of prognosis in patients with myocarditis.[14]

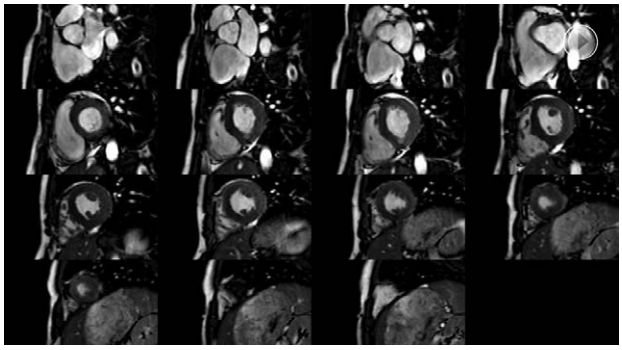

Figure 2. Short-axis stack of systolic cardiovascular magnetic resonance still frames in the same patient confirming normal systolic function. A movie is available in the online-only Data Supplement.

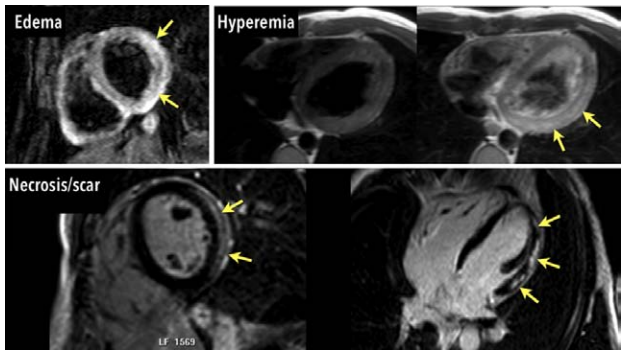

Figure 3. Cardiovascular magnetic resonance criteria for myocarditis (Lake Louise Criteria) in the same patients: regional myocardial edema (**top left**), hyperemia in images acquired early after contrast injection (**top right**), and inflammatory necrosis in images acquired late (>10 minutes) after contrast injection (**bottom**). All 3 criteria are positive.

Diagnostic Targets and Protocol

Contractile Function

Although systolic dysfunction is not always present and also is not specific to inflammatory causes, knowledge about left ventricular and right ventricular function is important for clinical decision making (eg, the use of heart failure medication). CMR is considered the noninvasive gold standard in the quantitative assessment of systolic ventricular function. Cine imaging is typically performed using a steady-state–free precession gradient echo sequence with 20 to 30 phases per heartbeat. State-of-the-art scanners using parallel imaging can acquire several slices within a single breath hold. A combination of long- and short-axis planes allows for assessing all myocardial segments in 2 perpendicular views (Figure 4) and provides accurate values on left ventricular volumes, mass, and function. The sequence also allows for the reliable detection of pericardial effusion, including its volume and hemodynamic relevance.

Myocardial Edema

CMR is the only imaging modality that allows for assessing myocardial edema, a regular feature of inflammation. Despite scanner- and protocol-dependent variations of image quality, edema-sensitive CMR has shown good diagnostic performance in clinically acute myocarditis.[12,19,20]

Edema in the absence of necrosis or scar represents reversible injury and thus can predict functional recovery.[21,22] Figure 5 shows an example of myocardial edema (water-sensitive T2-weighted sequence) in a patient with clinically acute myocarditis.

Edema may (Figure 6) or may not (Figure 7) be accompanied by colocalized necrosis.

Several technical aspects are important for CMR edema imaging: triple-inversion-recovery spin echocardiography protocols with fat and flow suppression (short inversion time inversion recovery and spectral presaturation with inversion recovery) are especially well suited because of their specific sensitivity to water[23]; yet, the inherently limited signal-to-noise requires a careful setup of protocols. This includes the use of the body coil (or an efficient correction algorithm for surface coils)

Table 1. Diagnostic Targets, Approach, and Sequences Used by CMR in Patients With Suspected Active Myocarditis

Target	Lake Louise Criterion	CMR Approach	CMR Sequence
Function	Supportive only	Cine CMR	Steady-state–free precession
pericardial effusion	Supportive only	Cine CMR	Steady-state–free precession
Edema	Yes	Edema-sensitive CMR	T2-weighted triple inversion recovery or other
Hyperemia	Yes	CMR before and early after contrast injection (early Gd enhancement)	T1-weighted fast spin echo
Necrosis/scar	Yes	CMR late after contrast injection (late Gd enhancement)	Inversion-recovery gradient echo

If 2 Lake Louise Criteria are positive, the CMR is considered indicative of active myocardial inflammation. CMR indicates cardiovascular magnetic resonance; and Gd, gadolinium.

for homogeneous signal distribution, adequate flow suppression, acquisition timing during diastolic diastasis, sufficiently thick slices, and acquisition of data during regular heart rates.[16] Short-axis views are recommended to reduce the issue of artifacts associated with slow transplanar blood flow. On most scanners, a robust image quality can be achieved in ≥80% of patients.

The evaluation may be performed qualitatively if there are clearly visible high–signal intensity areas indicating regional edema; yet, milder forms of myocarditis, which can be observed in women, may be accompanied by global edema and, therefore, a quantitative analysis is recommended, using the global signal intensity ratio of the myocardium normalized to the skeletal muscle in the same slice (typically, values >1.9 are considered pathological) as a criterion.[16]

Studies of edema-sensitive CMR protocols during the course of myocarditis have confirmed that edema imaging is mostly useful in clinically acute settings (ie, during the first 7–14 days of the disease).[24] The extent of myocardial edema may be less in patients with chronic mild myocarditis. Recently, T1 mapping[25] and T2 mapping[20] have been suggested for edema imaging and may increase accuracy when compared with currently used techniques.

Hyperemia

The first contrast-enhanced CMR technique ever applied in patients with acute myocarditis[10] targets myocardial hyperemia as another regular feature of inflammation. The associated increase of the volume of distribution for gadolinium (Gd) can be visualized early after injection using contrast-media–sensitive sequences, typically non–breath hold, T1-weighted, black-blood fast spin echo protocols, performed in short-axis or—with sometimes more robust image quality—axial views.

Comparing the signal intensity in images obtained before and during the first minutes after injection can visualize an increased regional volume of distribution (Figure 3). Using the skeletal muscle as an internal reference, we found that the relative increase of the myocardial uptake can be semiquantitatively assessed.[10] Being one of the three Lake Louise Criteria, early Gd enhancement significantly improves the accuracy of CMR protocols.[12] As a recent study demonstrated, omitting the early enhancement from the Lake Louise Criteria did not affect overall accuracy but was associated with a lower positive likelihood ratio.[15] Interestingly, early enhancement was found to be less prevalent in younger patients (age, <40 years).[26] Early Gd enhancement may not be specific to myocarditis[27]; thus, its discriminatory value in patients with unknown causes may be limited.

There are only few data on the prognostic relevance of early Gd enhancement. Two prospective studies showed that an increased early Gd enhancement ratio (typically, values of ≥4.0) is associated with persisting symptoms[28] and impaired long-term functional outcome.[28,29]

Necrosis and Scar

CMR images using contrast-agent–sensitive sequences acquired ≥10 minutes after injection of Gd (late Gd enhancement imaging) visualize irreversible injury (necrosis in the acute setting and scar at a chronic stage) as areas with high signal intensity. In more severe myocarditis, regional necrosis is frequently observed. The regional distribution is typically distinct from ischemic lesions, which invariably include subendocardial layers, whereas myocarditis typically exclude those zones.

In less severe cases of myocarditis, necrosis may be absent (Figure 7), which explains varying reports on the sensitivity of late Gd enhancement imaging in myocarditis, which varies from 29% to 88%.[16] Even in the presence of extensive necrosis, regional function may be partially or completely preserved (Figure 8).

The presence of necrosis or scar in myocarditis as detected by late Gd enhancement imaging has been associated with higher cardiovascular and overall mortality in myocarditis[14]; yet, confirmative data are not available.

Importantly, in the acute setting of myocardial injury, necrosis is accompanied by edema, and thus the areas appear initially larger than the actually damaged area[20] and may even disappear when the natural process of scar shrinking leads to focal areas too small for being detected in CMR images.

Of note, necrosis was found to be more prevalent in younger patients and in men, potentially indicating a more pronounced immune response with subsequent irreversible tissue injury.[26] It is important to keep in mind that the young male pattern with significant necrosis and often infarct-like presentation is not the typical finding in elderly or female patients, and thus in this population the absence of extensive irreversible injury should not be used as a criterion to rule out myocarditis.

Pericardial Effusion

Although rarely of hemodynamic or prognostic significance, pericardial effusion can be easily verified or excluded in cine CMR images and thus serve as a helpful additional parameter. Although the Lake Louise Criteria consider the presence of pericardial effusion as a supportive criterion only,[16] recent data indicate that the assessment of pericardial effusion may improve the sensitivity of the CMR scan.[13]

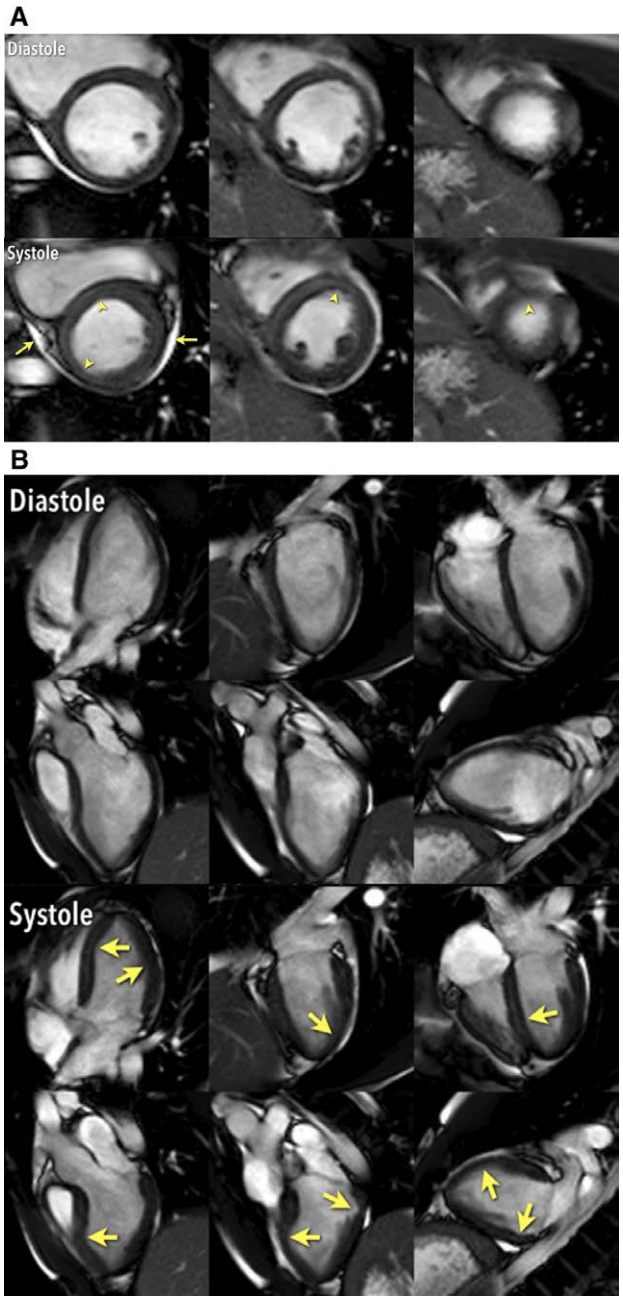

Figure 4. A, Cine cardiovascular magnetic resonance (CMR) images in 3 short-axis views in diastole (**top**) and systole (**bottom**) in a patient with suspected active myocarditis. Note multiregional hypokinesis/lack of systolic wall thickening (arrowheads) and mild pericardial effusion (arrows). A movie is available in the online-only Data Supplement. **B**, Rotational long-axis cine CMR images of the same patient in diastole (**top**) and systole (**bottom**). Arrows indicate areas with regional hypokinesis of various degrees of severity. A movie is available in the online-only Data Supplement.

Important Aspects for CMR in Patients With Suspected Myocarditis

Patient Selection

The main strength of CMR, especially when using the Lake Louise Criteria, is its high specificity and positive predictive value.[16] Thus, it is especially suited for confirming suspected myocarditis in patients with reasonably high pretest likelihood. It is also suitable to rule out myocarditis or other nonischemic myocardial disease if function is normal and there is no evidence for scarring. If combined with perfusion imaging (the early Gd enhancement component would be replaced by a first-pass perfusion sequence during pharmacological vasodilation), it can also rule out significant coronary artery stenosis.

For verifying the diagnosis, it is absolutely important to scan patients within the first 1 to 2 weeks of the onset of the disease. During later time points, the inflammatory markers and even the findings in late Gd enhancement images may disappear.[24]

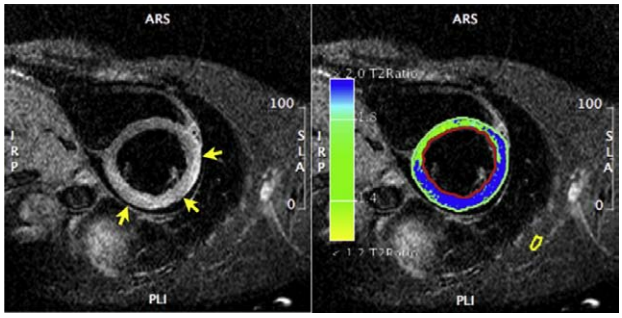

Figure 5. Myocardial edema in a patient with clinically acute myocarditis. **Left**, Water-sensitive cardiovascular magnetic resonance image in a midventricular short-axis view as acquired with the body coil (note the homogeneous signal distribution in the field of view). There is increased signal intensity in the anterior anterolateral, lateral, inferolateral, and inferior segments, which seems more pronounced in the subepicardial layer. **Right**, signal intensity ratio map showing pixels with a ratio of ≥2.0 (compared with the region of interest in the skeletal muscle marked by the yellow contour) as blue. The normal signal intensity in the septal segments (≈1.6) indicates absence of a low–signal intensity artifact. Note that there is mild pericardial effusion that seems black because of the flow suppression pulse of this sequence.

Technical Considerations

Important considerations of CMR in clinical settings include adequate training of staff, proper ECG gating, the use of a cardiac phased array coil for functional scans but the body coil for images used for quantitative signal intensity analysis, which is also important to avoid interpretation errors caused by a false high signal intensity in the anteroseptal segments and false low signal in the inferolateral segments. Some vendors

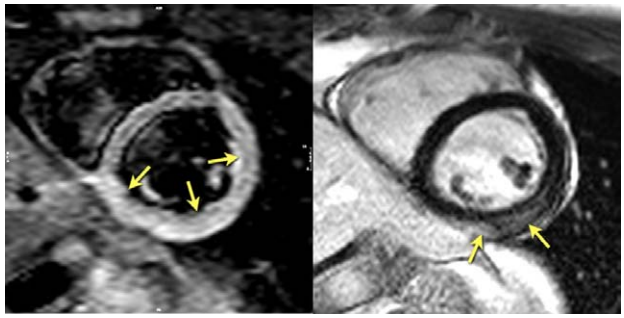

Figure 6. Short-axis views with edema (**left**, arrows) and necrosis (**right**, arrows) in a patient with clinically acute myocarditis. Windowing is optimized to visualize background noise in both high and low–signal intensity regions for avoiding falsely large or small appearing high–signal intensity areas.

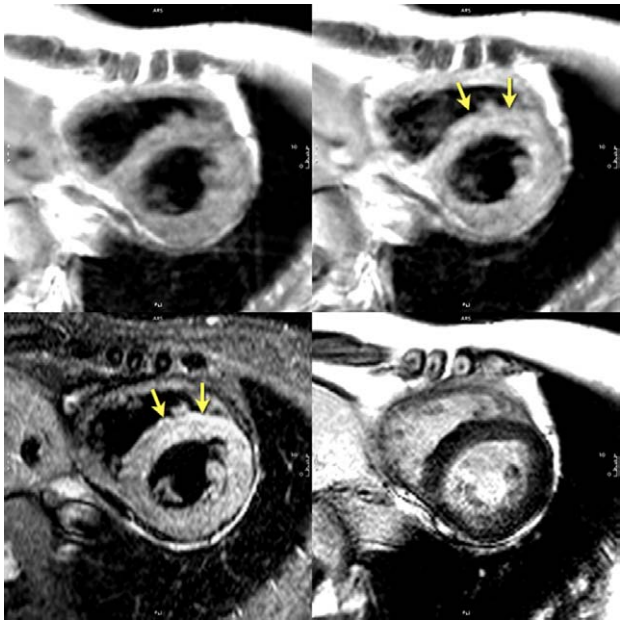

Figure 7. Reversible myocardial injury in a patient with clinically acute myocarditis. **Upper**, short-axis view before (**left**) and early after (**right**) injection of gadolinium showing myocardial hyperemia with regionally more pronounced uptake in the anteroseptal segment (arrows). **Lower**, myocardial edema (arrows; **left**); late gadolinium enhancement image without apparent high–signal intensity areas indicating the absence of necrosis in the edematous regions (**right**). The quantitative evaluation (early gadolinium enhancement ratio) indicated a globally increased early gadolinium uptake. Thus, 2 of 3 Lake Louise Criteria are positive in this patient (regional edema and increased global early gadolinium enhancement ratio).

offer algorithms to correct for the signal intensity gradient of surface coils. Yet, not all of them work well and thus caution is advisable. Correct positioning of slices and parameters settings for the sequences is a key to obtain accurate results. Early Gd enhancement images before and after contrast have to be acquired with the exact same sequence settings. The sequences used for imaging edema and necrosis require special attention. Similar to edema imaging (discussed above), imaging irreversible injury (necrosis, scar, and infiltration) requires a careful tuning of sequence settings, especially the inversion time used to artificially null the myocardial signal. Errors can produce false-positive or false-negative results. A phase-sensitive sequence is recommended to reduce this risk.

Although low volume sites may find it more difficult to provide a consistent image quality with time-efficient protocols, experienced technologists can run a scan within 25 minutes.

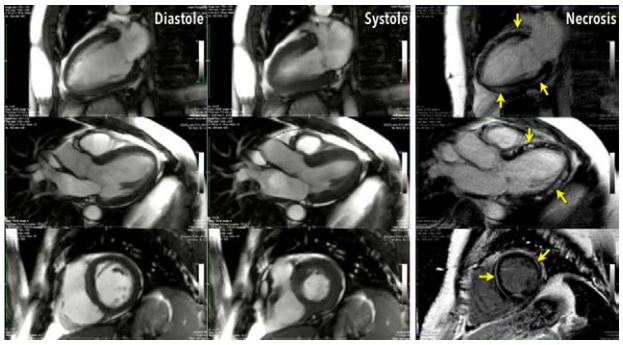

Figure 8. Cardiovascular magnetic resonance (CMR) cine images at diastole (**left**) and systole (**middle**) versus CMR necrosis images (**right**) in a young patient with clinically acute myocarditis. There is a mismatch between a normal systolic function and extensive necrosis (arrows).

CMR Image Evaluation

In contrast to ischemic damage, the injury does not typically involve the subendocardial layer and is focal or, typical for perimyocarditis, represents a subepicardial layer. The inferolateral segments are predominantly involved. Therefore, lesions are often best seen in 3CV and 4CV views (Figure 4).

Although some of the abnormalities observed in myocarditis are immediately apparent on the images and thus lend themselves for a mere visual analysis, images should also be evaluated quantitatively. This is especially true not only for ventricular volumes, mass, and function, but also for markers of inflammation (hyperemia and edema).

Impact on Patient Management, Prognosis, and Outcome

In clinical applications, CMR has an important role in several scenarios (Table 2). In many patients, it is essential for an informed therapeutic decision making, and thus CMR should be used in all institutions that accept referrals of patients with suspected myocarditis. CMR has a real impact on therapeutic decision making in >50% of these patients and, in ≈11%, provides a new, unexpected diagnosis.[9]

CMR is a predictor of functional and clinical recovery[28,29] and death.[14] With respect to impact on outcome, as true for all other imaging modalities, the lack of specific treatment options for most forms of myocarditis makes it difficult to estimate or assess the effect of CMR.

In the future, it is to be expected that more efficient therapeutic options will be identified to treat patients with ongoing inflammation caused by either virus persistence or

Table 2. Most Important Indications for CMR in Patients With Suspected Myocarditis

Clinical Presentation	Main Diagnostic Goal	Impact on Patient Management
Acute chest pain, normal coronary arteries, recent systemic viral disease, or other potential cause of myocarditis	Rule in/rule out of active inflammation, exclusion of ischemic injury	Modification of treatment (eg, discontinuation of anticoagulation)
Acute or progressive heart failure	Presence and character of myocardial injury (acuity, extent, ischemic vs nonischemic pattern, reversibility)	Gatekeeper for endomyocardial biopsy
Nonspecific cardiac symptoms	Rule in/rule out of myocarditis or other cardiomyopathies	Avoiding further diagnostic tests

CMR indicates cardiovascular magnetic resonance.

autoimmune processes. For clinical scans and pharmaceutical trials alike, the verification of ongoing inflammation is of paramount importance to select patients for an invasive endomyocardial biopsy, which can then clarify the underlying pathophysiology.

Inflammation in Other Myocardial Diseases

Inflammation is a nonspecific tissue response to tissue injury and thus has to be put into clinical context, such as peri-infarct inflammation with edema in reperfused acute myocardial infarction. As a prime example, CMR markers for extensive myocardial inflammation without necrosis or scar have been reported a consistent finding in patients with stress-induced cardiomyopathy.[30] This phenomenon seems consistent with the known proinflammatory effect of catecholamines in this clinical entity.

Limitations

For patients with suspected myocarditis in general, the main limitation of CMR is a lack of availability of an MRI scanner with cardiac software during the acute phase of the disease.

Image quality is not always robust, and consistently good image quality requires knowledge and experience about/in scanning parameters, artifacts, and coil use. Mapping techniques may allow for replacing mere signal intensity–based protocols by the more objective assessment of tissue pathology.[20]

In contrast to its good specificity, the sensitivity of CMR to detect myocarditis is variable[16] and depends on the time point[24] and the protocol of the scan.

Conclusions

Among available imaging techniques, CMR is the most comprehensive and accurate diagnostic tool in patients with suspected myocarditis. It allows for verifying or excluding myocardial inflammation and reversible/irreversible injury and thus assessing the activity and severity of myocarditis. Important roles in clinical routine include the verification of myocarditis in patients with acute cardiac syndromes yet normal coronary arteries or with atypical symptoms, as well as a gatekeeper for endomyocardial biopsy in patients with persisting symptoms and heart failure. Access to CMR scans in tertiary care centers for these purposes is essential.

Ongoing developments include more objective, quantitative tissue markers for inflammation and necrosis or scar and semiautomatic algorithms for image acquisition and evaluation.

Disclosures

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