Differentiating infarction from myocarditis

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Abstract

Myocarditis can resemble an acute coronary syndrome (ACS), even an ST-segment elevation myocardial infarction. Furthermore, when a coronary angiogram reveals no significant disease, differential diagnosis can be challenging. Endomyocardial biopsy is still the gold standard for the diagnosis of myocarditis; however, its invasive character and limited sensitivity restrict its generalized application to all patients. Both echocardiography and cardiac serum biomarkers may be normal in the setting of ACS or myocarditis, and when abnormal lack enough specificity to differentiate reliably between the two entities. Nuclear techniques have high sensitivity but modest specificity for the detection of myocarditis, and have the additional limitations of availability and radiation exposure. Cardiac magnetic resonance (CMR) has emerged as a leading modality in the noninvasive diagnosis of myocarditis due to its ability to detect myocardial edema, hyperemia, necrosis and fibrosis in a safe and reproducible fashion. In patients with an ACS-like presentation but normal coronary arteries, CMR is useful not only to differentiate acute myocarditis from an ischemic event but also to identify alternative etiologies. ■ Heart Metab; 2014;62:13–17

Keywords: Cardiac imaging techniques; cardiac magnetic resonance; differential diagnosis; myocardial infarction; myocarditis.

General considerations

Clinical manifestations of myocarditis range from the absence of symptoms to cardiogenic shock, including acute myocardial infarction (MI)-like syndrome. Given the availability of highly effective strategies in acute coronary syndrome (ACS), it is mandatory to rule out coronary artery disease as a potential cause, commonly with invasive angiography. However, the presence of normal coronary arteries neither confirms the diagnosis of myocarditis nor rules out ACS. The gold standard for the diagnosis of myocarditis is endomyocardial biopsy (EMB) [1]. Nonetheless, major disadvantages include its invasive character and poor sensitivity, probably related to patchy sampling and imperfect reproducibility of histological criteria [2].

These limitations highlight the need for reliable noninvasive diagnostic tools; however, the most common approaches lack enough specificity to warrant dependable differential diagnosis. Electrocardiographic findings are neither specific nor sensitive, and myocarditis can be accompanied by ST-segment elevation mimicking an acute MI as well as other ST-segment and T-wave changes, Q-waves, ventricular arrhythmias, or conduction abnormalities [3]. Serum biomarkers of myocardial injury may or may not be elevated in either syndrome, depending on the severity of myocardial damage and the time of testing in relation to the course of the disease. Additional serological testing if infectious or immune myocarditis is suspected also has limited diagnostic value [1].

Abbreviations

ACS: acute coronary syndrome; **CMR:** cardiac magnetic resonance; **EGE:** early gadolinium enhancement; **EMB:** endomyocardial biopsy; **^{67}Ga:** gallium-67; **^{111}In:** indium-111; **LGE:** late gadolinium enhancement; **LV:** left ventricular; **MI:** myocardial infarction

Imaging techniques play an important role in the diagnosis of acute myocarditis and its differentiation from ACS. Cardiac magnetic resonance (CMR) in particular has emerged as the most reliable modality due to the combination of tissue characterization capabilities and a good safety profile.

Echocardiography

The role of echocardiography is limited as there are no specific signs of myocarditis, and segmental wall motion abnormalities resembling ACS may be detected [4]. Nonetheless, echocardiography can still provide relevant information beyond biventricular function. While increased sphericity and left ventricular (LV) volume are common in active acute myocarditis, fulminant forms usually demonstrate normal LV diameter with increased wall thickness [5]. A transient increase in LV wall thickness during the acute phase has been correlated with the presence of myocardial edema in histopathology [6].

Nuclear imaging

There are limited data regarding the diagnostic accuracy of nuclear imaging in myocarditis, with overall high sensitivity although modest specificity. Radionuclide examinations have been largely replaced by CMR due to restricted availability, poorer spatial resolution and the inherent risk from radiation exposure.

An early study compared gallium-67 (^{67}Ga) scintigraphy to EMB for the detection of myocarditis in 68 patients with dilated cardiomyopathy [7]. ^{67}Ga showed high sensitivity (83%) and specificity (86%), but the positive predictive value was poor (36%), probably due to the low incidence of myocarditis (8%) in this population. In addition, ^{67}Ga can accumulate in acute MI [8], although a small case series has shown the feasibility of detecting acute myocarditis presenting as ACS [9].

The identification of myocyte necrosis using a monoclonal antibody labeled with indium-111 (^{111}In) and directed towards myosin was first validated in MI

[10]. The diagnostic accuracy was then determined in biopsy-confirmed myocarditis [11, 12], showing outstanding sensitivity (83–100%) but limited specificity (31–53%). These results could partly be explained by the high percentage of acute dilated cardiomyopathy without histological evidence of myocarditis that showed a positive scan [13]. Furthermore, antimyosin scintigraphy could demonstrate diffuse, heterogeneous isotope uptake in acute myocarditis versus intense, localized accumulation in MI (*Figure 1*) [14].
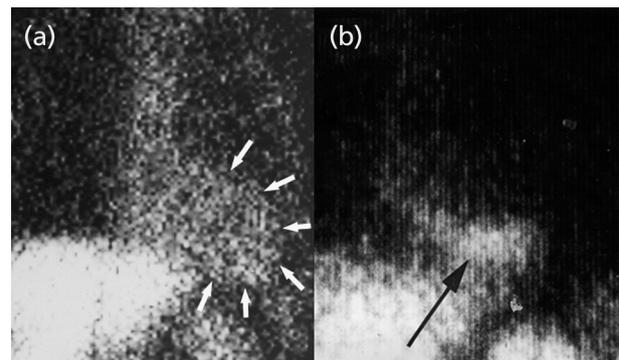

Fig. 1 *Antimyosin scintigraphy. (a) Diffuse isotope uptake (white arrows) is noted in a patient with viral myocarditis. (b) Localized uptake (black arrow) is seen in a patient with an inferior myocardial infarction. Images courtesy of Dr. Jagat Narula, The Mount Sinai Hospital, New York, USA.*

Cardiac magnetic resonance

Cardiac magnetic resonance diagnosis of myocarditis
Beyond the evaluation of global and segmental biventricular function and pericardial effusion, the ability of CMR to characterize histological changes of myocarditis relies on the detection of interstitial edema, hyperemia and capillary leakage, cardiomyocyte necrosis and myocardial fibrosis with specific sequences [15] (*Figure 2*). T2-weighted imaging can be used to detect the presence of myocardial edema both in inflammatory and ischemic diseases. In ACS, edema is typically localized to the territory of the culprit vessel [16]. In myocarditis, edema may be either segmental or diffuse, which justifies the quantification of myocardial signal intensity in comparison with a reference tissue like skeletal muscle [17]. A signal intensity ratio of 2 or greater has shown an average sensitivity, specificity and diagnostic accuracy of 70% [15].

Regarding contrast-enhanced CMR, the presence of vasodilatation, hyperemia and capillary leakage during the acute phase can be evaluated with early gadolinium enhancement (EGE) [18]. A relative increase in myocardial signal intensity early after contrast administration indicates diffuse expansion in the gadolinium volume
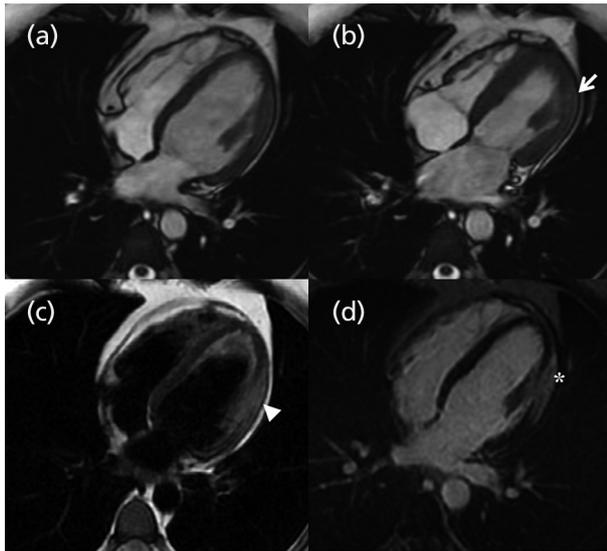
Fig. 2 *CMR features of acute myocarditis. (a) End-diastolic and (b, arrow) end-systolic cine images in a four-chamber view. Localized wall thickening and hypokinesis are noted in the mid lateral wall (b). On T2-weighted imaging (c, arrow head) signal increase representing myocardial edema can be noted in the same location. Final, LGE imaging (d, asterisk) detects the presence of myocardial necrosis/fibrosis in the corresponding area. CMR: cardiac magnetic resonance; LGE: late gadolinium enhancement.*

Fig. 3 *Differential diagnosis of dilated cardiomyopathy with LGE. In two different cases of dilated cardiomyopathy with similar LV remodeling on cine images (a and b) the pattern of LGE differentiates between ischemic heart disease with a subendocardial and transmural infarction in a coronary artery territory (c, arrow head), and myocarditis with extensive subepicardial LGE (d, arrow). LGE: late gadolinium enhancement; LV: left ventricular.*

of distribution, with an average sensitivity of 74%, specificity of 83% and diagnostic accuracy of 78% [15]. Late gadolinium enhancement (LGE) imaging may reveal focal areas of contrast accumulation secondary to cellular necrosis and/or replacement fibrosis. The characteristic pattern of LGE in myocarditis is patchy or multifocal in a subepicardial or intramyocardial distribution, often involving the lateral wall [19]. This feature is not pathognomonic but is clearly distinct from ischemic heart disease, which typically presents with subendocardial or transmural LGE within a coronary artery territory (*Figure 3*). It should be taken into account that LGE requires a large enough area of focal myocyte necrosis or fibrosis, which probably explains why this technique is less sensitive (59%) but more specific (86%) than edema and EGE imaging [15].

Two studies evaluated the accuracy of individual tissue-based markers (edema, hyperemia and necrosis) or their combinations in patients with clinically diagnosed acute myocarditis compared with healthy controls [17], or patients with suspected chronic myocarditis undergoing EMB [20]. Both investigations concluded that combinations of two CMR criteria increase performance with pooled sensitivity, specificity and accuracy of 67%, 91% and 78%, respectively [15]. Therefore, recommendations for CMR diagnosis of myocarditis, also known as the Lake Louise consensus criteria, have been issued
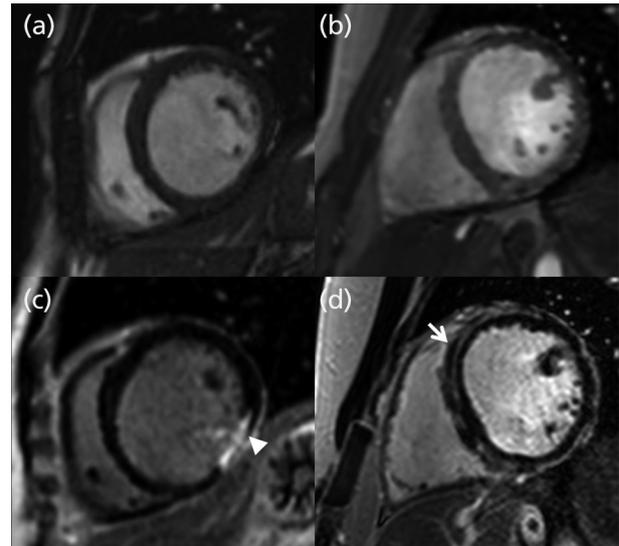
[15], considering a scan positive for myocarditis if two from the three tissue characterization parameters are present *(Table I)*.

In a retrospective analysis of 131 patients with possible acute myocarditis undergoing CMR and EMB, the combination of the three criteria demonstrated a sensitivity of 39%, specificity of 93% and accuracy of 63 % [21]. A recent prospective study [22] in 132 patients with acute or chronic myocarditis tested the Lake Louise criteria using EMB as the reference. A good diagnostic accuracy (79%) was confirmed when the study was performed within the first 14 days after symptom onset, whereas performance decreased to 52% if CMR was carried out later. This finding highlights the relevance of early CMR evaluation if acute myocarditis is clinically suspected.

Differential diagnosis between myocarditis and acute coronary syndrome

CMR is helpful in differentiating myocarditis from ACS in patients with acute chest pain. In 55 patients with unclear presentation and a final clinical diagnosis, all patients with MI (n = 31) had a subendocardial perfusion defect with a corresponding subendocardial or transmural area of LGE, while all but one patient with myocarditis (n = 24) had normal perfusion and a non-ischemic LGE pattern [23]. In a series of 64 patients with acute presentation and probable myocarditis,

In the setting of clinically suspected myocarditis, CMR findings are consistent with myocardial inflammation if two or more of the following criteria are present:

- Regional or global myocardial signal increase (≥2) on T2-weighted images.
- Increased global enhancement ratio between myocardium and skeletal muscle (≥4) or absolute myocardial enhancement (≥45%) on early gadolinium-enhanced T1-weighted images.
- At least one focal lesion with nonischemic distribution in inversion recovery-prepared T1-weighted LGE sequences (this finding is consistent with myocyte injury or scar).

A repeat CMR study 1 or 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 suspicion.
- Only one of the criteria is present.

Left ventricular dysfunction or pericardial effusion provide additional supportive evidence for myocarditis.

Table I *Lake Louise CMR diagnostic criteria for myocarditis. Adapted from Friedrich et al [15]. CMR: cardiac magnetic resonance; LGE: late gadolinium enhancement*

edema and a typical LGE pattern were detected in 58% and 92% of cases, respectively. Of note, CMR was again more commonly abnormal when performed within 2 weeks after presentation [24]. In 23 patients with a clinical suspicion of myocarditis mimicking acute MI, typical intramyocardial and subepicardial LGE was noted in all cases and "ischemic" LGE in none [25]. Preliminary data also indicate the ability of late enhancement with iodine-based contrast agents using cardiac computed tomography to distinguish myocarditis and MI [26], with the additional potential advantage of simultaneous coronary imaging.

CMR is especially useful in the setting of acute chest pain, positive ECG and/or cardiac enzymes, and normal/inconclusive coronary angiograms [27]. In this setting, a number of studies (*Table II*) [24, 30–35] have demonstrated the ability not only to differentiate ACS from acute myocarditis, but to identify alternative etiologies such as Takotsubo cardiomyopathy or pulmonary embolism. We believe that in such patients a typical CMR is diagnostic for myocarditis and confirmatory EMB can be avoided. Nonetheless, EMB can be considered even in these cases given the relevant information influencing prognosis and therapeutic management that may be derived from tissue analysis [1]. Indeed, CMR and EMB including immunohistochemistry and viral genomic analysis appear to be complementary, and the combination allowed for an etiological diagnosis in 95% of patients in one study [28].

Conclusions

Myocarditis may mimic ACS, and conventional tests lack enough specificity for adequate differential diagnosis. CMR can noninvasively depict distinct abnormal tissue patterns (edema, hyperemia and myocyte necrosis/fibrosis) in each entity. Nuclear imaging is an alternative approach, although hampered by radiation and limited specificity. While beyond the scope of this paper, novel multimodality molecular contrast agents designed to target ligands involved in myocardial metabolism, necrosis, apoptosis and inflammation [29] promise to increase further our ability to detect and differentiate ischemic and inflammatory cardiac disorders in the near future. ■

	n	Myocarditis (%)	ACS (%)	Other (%)	Unknown (%)
Baccouche et al [28]	82	81	4	3	12
Leurent et al [29]	107	60	16	14	10
Assomul et al [30]	64	50	12	3	35
Monney et al [24]	79	81	13	6	–
Gerbaud et al [31]	130	26	29	1	23
Steen et al [32]	29	17	38	38	7
Lauradogoitia et al [33]	80	63	15	16	5
Stensaeth et al [34]	49	29	0	53	18

Table II *Diagnosis in CMR studies for patients with acute chest pain, elevated troponin and no significant coronary stenosis. ACS: acute coronary syndrome; CMR: cardiac magnetic resonance.*

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