Review

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Diagnostic criteria for myocarditis on cardiac magnetic resonance imaging: an educational review

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Abstract

Acute myocarditis represents one of the most mysterious acute cardiovascular diseases due to the great diversity of its clinical presentation, ranging from simple symptoms such as flu-like syndrome to lethal conditions such as cardiogenic shock or sudden cardiac death. The diagnosis will be suspicious in the presence of chest pain in a subject with risk factors, and guided mainly by the ECG, biological markers, trans-thoracic echocardiography, and the cardiac MRI. In this sense, and returning to the pathophysiological bases of this condition, the positive diagnosis will rely mainly on the detection of tissue abnormalities secondary to the myocardial inflammatory storm. Cardiac MRI represents a diagnostic pillar, given the information it can provide, both in analyzing the morphology, and the myocardial function but also tissue abnormalities that represent the main element of the diagnostic criteria of Lake Louisse.

keywords: CMR, early gadolinium enhancement, late gadolinium enhancement, myocarditis, myocardial edema

Introduction

Acute myocarditis represents one of the most mysterious acute cardiovascular diseases, due to the great diversity of its clinical presentation, ranging from simple symptoms such as flu-like syndrome to lethal conditions such as cardiogenic shock or sudden cardiac death, and the nonspecificity of other diagnostic tools routinely performed by the cardiologist like the cardiac biomarkers, which are nonspecific and nonsensitive. In this sense, and returning to the pathophysiological bases of this condition, the positive diagnosis will rely mainly on the detection of tissue abnormalities secondary to the myocardial inflammatory storm, and this is possible only through the realization of an endomyocardial biopsy, the latter of which is practiced only in specific situations, or cardiac imaging by MRI. The latter is an indispensable pillar in the diagnosis of myocarditis. In this educational review, we will detail the different diagnostic criteria to objective in cardiac MRI, the discussion of the modified diagnostic criteria of Lake Louisse, and finally know the practical conduct in front of the suspicion of a case of myocarditis.

HIGHLIGHTS

- Acute myocarditis represents one of the most mysterious acute cardiovascular diseases, due to the great diversity of its clinical presentation, ranging from simple symptoms such as flu-like syndrome to lethal conditions such as cardiogenic shock or sudden cardiac death.
- Cardiac MRI represents a diagnostic pillar, given the information it can provide, both in analyzing the morphology, and the myocardial function but also tissue abnormalities.
- In 2018, an updated version of the original Lake Louisse criteria was published, which incorporated CMR mapping techniques into the diagnostic approach for the first time.

Physiopathological principles

Myocarditis is defined as an acute or chronic inflammation of the cardiac myocardium, apart from an ischemic cause. This inflammation can be due mainly to an infectious cause, but also to other etiologies such as autoimmune diseases, sarcoidosis, toxic intake, and giant cell myocarditis. This inflammation generally goes through three phases[1]:

Phase I: After penetration into the myocyte through specific receptors, viral replication causes a severe cytopathic effect in the intracellular, activating the inflammatory cascade and chemotaxis of inflammatory cells, with vasodilatation causing hyperemia with intracellular edema[2].

Phase II: In this phase, there will be mainly an amplification of the inflammatory response, with a recruitment of macrophages and T lymphocytes CD4+ and CD8+, and as a result at the tissue level, myocyte cell necrosis, which represents one of the

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fundamental signs, objectified in cardiac MRI. The evolution after this phase is varied from one individual to another and according to the genetic profile of the individual[3].

Phase III: This phase determines the long-term evolution of the individual. Two scenarios are possible, the resolution of the inflammation with the elimination of the pathogenic agents, and in this case, we will have a complete cure without evolution towards chronicity. In the other case, there will be a sustained inflammation in the long-term, either by the persistence of the cellular aggression or by the activation of systemic cardiac autoantibodies, which will lead to an inflammatory cardiomyopathy and then to a chronic form of myocarditis.

There are three possible consequences: first tissue, then morphological, and finally functional[4].

The diagnosis of myocarditis aims to objectify these morphological, functional, and tissue consequences, and since the morphological change, and the alteration of the systolic or diastolic function is not specific to myocarditis alone, and meet in several cardiac conditions, mainly myocardial ischemia, the characterization of the tissue change represents the main target to diagnose myocarditis. Although, the endomyocardial biopsy represents the best diagnostic means to objectify these tissue changes already mentioned, but given its invasive degree, makes it can be practiced in daily routine, for this, the cardiac MRI will play a very important role in the diagnostic conduct.

Cardiac MRI and the diagnosis of myocarditis

Morphological and functional abnormalities

In terms of analysis of the systolic and diastolic left ventricular function, mainly regarding the possible morphological changes mainly a dilatation of the cardiac chambers, and thus the analysis of the ejection fraction, MRI finds its place, although echocardiography is also sensitive to these changes, but with a lesser accuracy than MRI, especially on the analysis of the kinetics of the inferolateral region, which is the preferential damage of myocarditis, for which MRI finds its place, given its great spatial diversity in terms of analysis compared to TTE[5].

For this reason, balanced steady-state free precession techniques, represents the gold standard for morphological, and functional evaluation of the left ventricle, but also the right, which is poorly explored in echocardiography[6].

In patients with myocarditis, MRI can show morphological changes such as increased myocardial mass secondary to edema, as well as pericardial effusion often localized opposite the inflamed myocardium.

Tissue abnormalities

The following three tissue manifestations, often associated with myocardial inflammation, can be analyzed by MRI:

Hyperemia: Early gadolinium enhancement (EGE)

Inflammated myocardium is characterized by vascular hyperpermeability of the interstitial environment secondary to vascular vasodilatation and cellular necrosis with destruction of myocyte connections. The principle is that after injection of a contrast medium, there will be a rapid uptake of contrast by the myocardium concerned, and this in a rapid way, compared to the healthy myocardium. The increased contrast uptake can be represented by T1-weighted spin echo sequences as a rapid hypersingal (between 20 s and 3 min) after injection of gadolinium at the dose of 0.1 mmol/kg. An EGE ratio of 4 is considered pathological, with healthy skeletal muscle as reference, and the increase in relative myocardial signal intensity greater than 45% suggestive of myocardial inflammation (Fig. 1)[7].

Although this sign was initially included in the diagnostic criteria of Lake Louisse 2009, but given its low sensitivity and specificity, in the order of 70 and 74%, respectively, on a meta-analysis published by Kotanidis *et al*. it is no longer included in the updated criteria for myocarditis published in 2018.

Edema: spontaneous hypersignal

In myocarditis, there will be intracellular edema, which allows for high water permeability, which can be objectified by a spontaneous hypersignal on T2-weighted sequences that is usually performed using short inversion time recovery pulse sequences. These sequences are sensitive to long T2 of water protons to generate images with higher signal intensity of edematous myocardial tissue compared with surrounding healthy muscle tissue.

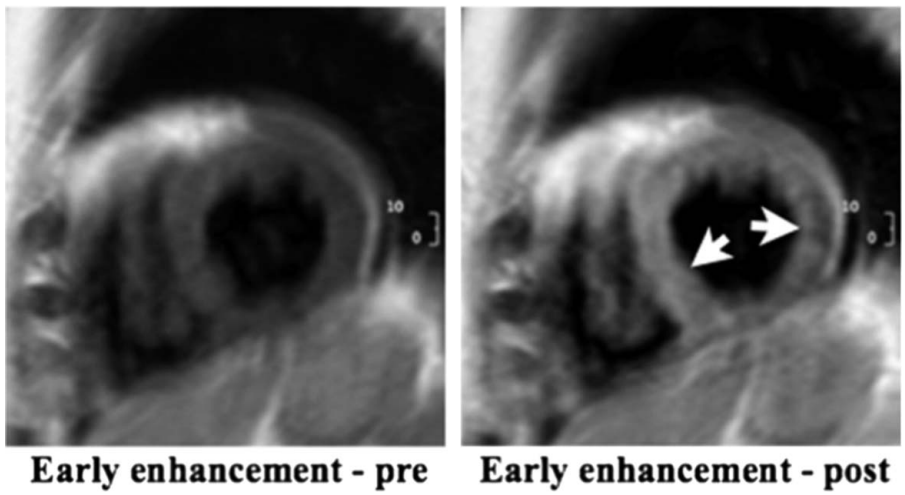

Figure 1. Showed the early gadolinium enhancement (arrow).

Regions with signal intensity more than 2 SD greater than the mean of normal-looking myocardial tissue are considered suggestive of regional edema (Fig. 2). The areas examined should not be too small, as signal inhomogeneity on T2 images can be considerable[8].

In terms of efficacy, the sensitivity, specificity, and diagnostic accuracy of T2-weighted imaging in myocarditis (on the basis of qualitative and/or semiquantitative assessment) are 62, 76, and 67%, respectively. When image analysis is based primarily on the calculation of the T2 signal intensity ratio (2.0 is considered pathological), the sensitivity and specificity of the method increase to 68 and 91%, respectively. It is necessary to use as a reference tissue the anterior serratus muscle.

Necrosis: Late gadolinium enhancement (LGE)

Using T1-weighted inversion-recovery gradient echo sequences with inversion times that suppress the signal of healthy myocardial tissue, 10 min after contrast injection, areas that are sites of necrosis with tissue healing, objective an intense signal. This hypersignal is of typical regional localization, initially subepicardial, predominantly on the inferolateral part of the left ventricular wall, and in some cases, at the level of the medial part of the basal segment of the interventricular septum, in patients in the acute phase of myocarditis. The pathophysiological explanation for this hypersignal is that when membrane damage has occurred in early necrosis. Gadolinium molecules enter the intracellular space. This results in an increase in the intratissue distribution volume of gadolinium, with an associated increase in signal intensity. In the chronic phase, the volume of distribution and concentration of intratissue contrast medium is still elevated compared with healthy myocardium, but with a lower intensity than in the acute phase, given the abundance of loose connective tissue in the chronic phase. LGE is detected in nearly 90% of patients, and is still the most widely used approach in the diagnosis of myocarditis and this is reflected in the literature (Fig. 3)[9].

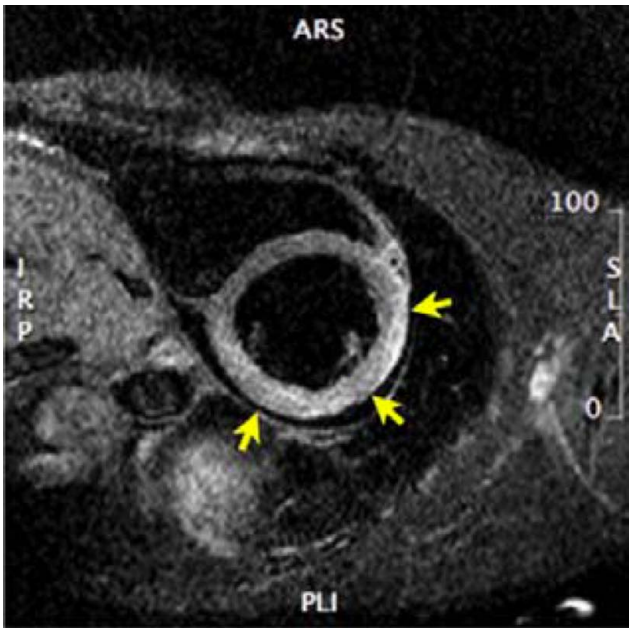

Figure 2. T2-weighted short tau inversion sequence of black blood with clear signs of edema (arrow).

New mapping technique

Conventional methods such as EGE, T2 edema imaging, and T1 LGE indirectly measure the local 'absolute' T1 and T2 relativity of tissue on a pixel-by-pixel level. In particular, the appearance and signal intensity reflect relative changes in relaxivity in pathologic tissue, with an increase in signal intensity between healthy and diseased myocardium after contrast use. Parametric mapping techniques allow objective quantification of T1 and T2 relaxation times, the latter representing the magnetic properties of pathological myocardial tissue[10].

T1 and T2 relaxation times are displayed as a map and are calculated on a pixel-by-pixel basis, allowing assessment of global or regional myocardial T1 and T2 relaxation times. Each deviation from the normal tissue-specific range of these relaxation times with published values as a reference indicates a change in tissue composition.

One of the advantages of T1 mapping is to know the extracellular volume, which allows the identification of the degree of edema, capillary leakage, and cellular hyperemia, based on the T1 mapping before and after the injection of the contrast medium, provided that the blood hematocrit is known[11].

Overall, mapping techniques show excellent sensitivity, specificity, and diagnostic accuracy in patients with clinically suspected myocarditis. Current evidence suggests that T2 mapping techniques are more specific in detecting acute inflammation than T1 mapping, regardless of the stage of myocarditis. This can be explained by the fact that T1 relaxation time prolongation is caused both in acute inflammation by edema and by increased interstitial space, which is observed in fibrotic states, whereas T2 relaxation time prolongation is observed only in cellular edema. However, T1 and T2 mapping techniques seem to have a complementary diagnostic value (Fig. 4)[12].

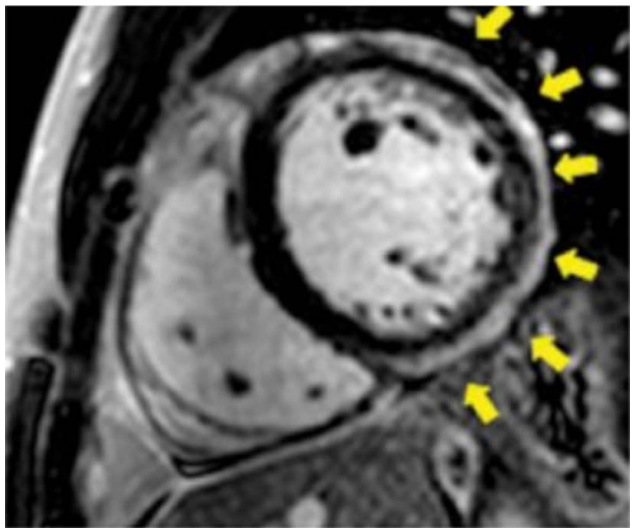

Figure 3. Late gadolinium enhancement in the inferolateral and anterior portion of the subepicardial in a patient with viral myocarditis (arrow).

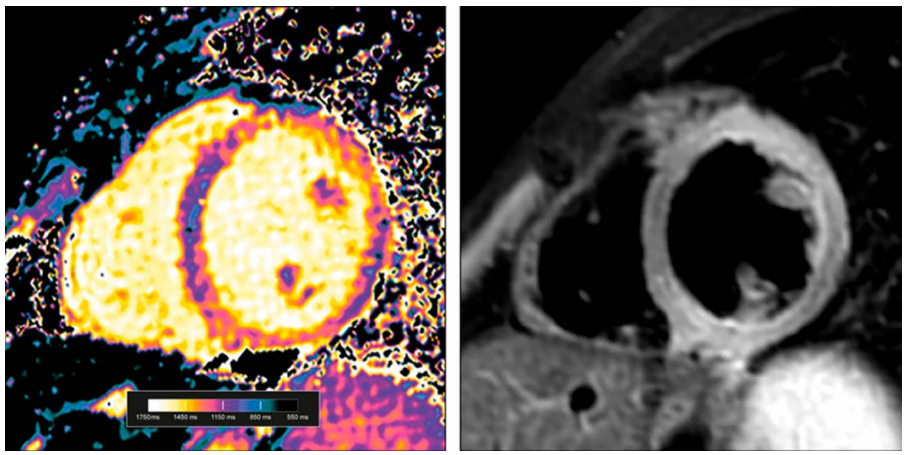

Figure 4. Native T1 map (left) in a patient with acute myocarditis showing prolonged T1 relaxation times in the anterolateral and inferoseptal regions of the left ventricle (1320 ± 43 ms (local reference999 ± 31 ms)). Corresponding T2-weighted black blood short tau inversion recovery sequence (right) with clear signs of edema in the same region.

Modified diagnostic criteria of Lake Louisse

Given the presence of multiple limitations for each of the imaging signs already detailed, and in order to overcome these limitations, a combination of T2-weighted techniques, T1-weighted early enhancement techniques, and T1-weighted LGE techniques is recommended in 2009, implementing the original version of the diagnostic criteria of Lake Louisse. A meta-analysis by Kotanidis *et al.*[13] reported a sensitivity and specificity of 78 and 88%, respectively.

Lagan *et al.*[14], conducted another meta-analysis having concluded that the sensitivity, specificity, and diagnostic accuracy of the original CLL are 77, 81, and 79%, respectively. Furthermore, both meta-analyses highlight the additional diagnostic potential of parametric mapping techniques as a complement to conventional CMR techniques.

In 2018, an updated version of the original Lake Louisse criteria was published, which incorporated CMR mapping techniques into the diagnostic approach for the first time. This version, which proposes a '2 on 2' approach to objectify both myocardial inflammation on T2 sequences (T2-weighted imaging or T2 mapping) and a T1-based criterion (T1 mapping, extracellular volume, or ECV) must be met.

The diagnosis is then strongly suspected when both a T2 and a T1 marker are positive, whereas the presence of only one positive marker (T2 or T1) makes the diagnosis probable, although with a lower specificity[15].

Le Table 1 shows the updated 2018 Lake Louisse criteria.

Cardiac MRI and follow-up after myocarditis

First, for long-term follow-up of patients with myocarditis using cardiac MRI, the combined approach of a T1-weighted pulse sequence with contrast enhancement a T2-weighted sequence and an LGE pulse sequence can differentiate between reversible myocarditis with elevated T1 gRE and T2 edema ratio that normalizes with time, from irreversible myocardial injury with or without ongoing inflammation (persistent LGE with or without elevated T1 gRE and T2 edema ratio). For this, it is suggested that if none or only one of the T2 or gRE ratios is elevated, may have a very high negative predictive value for excluding active myocarditis. However, data on the value of CMR in identifying cured myocarditis from ongoing active myocarditis are inconclusive[16,17].

In a study by Gutberlet *et al.* of patients with chronic myocarditis suspected clinically by CMR and endomyocardial biopsy, the absence of T2 elevation and the absence of gRE elevation were found in almost 30% of patients whose histology revealed inflammation. Thus, there is persistent inflammation in a subset of patients with elevation of only one of these two CMR parameters.

For long-term prognosis, the ITAMY (ITalian multicenter study on Acute MYocarditis) study of 374 patients with acute myocarditis and preserved left ventricular systolic function demonstrated that patients with LGE in the medial wall of the anterior septum had a worse prognosis than other types of LGE[17,18].

Conclusion

Cardiac MRI remains the cornerstone of the diagnosis of acute myocarditis, firstly because of its advantage of dual analysis, functional and tissular, and secondly because of its noninvasive character.

Table 1

Lake Louisse's updated 2018 diagnostic criteria

Main criteria ('2 out of 2')	T1-based imaging
	a) Regions with high signal intensity in a nonischemic distribution pattern on late gadolinium enhancement images
	b) Regional or global increase in extracellular volume or T1 relaxation times of native myocardium.
	T2-based imaging
	a) Regional area with high T2 signal intensity
	b) Global T2 signal intensity ratio > 2.0 in T2-weighted images
	c) Regional or global increase of myocardial T2 relaxation times
Supportive criteria	Pericarditis
	a) Effusion in cine images or abnormal LGE, T2 or T1
	Systolic LV dysfunction
	a) Regional or global wall motion abnormality

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Consent

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Author contribution

I.J.: study concept or design, data collection, data analysis, or interpretation, writing the paper; N.A.: supervision and data validation; S.N.: supervision and data validation; I.S.: supervision and data validation.

Conflicts of interest disclosure

The authors state that they have no conflicts of interest for this report.

Research registration unique identifying number (UIN)

This is not an original research project involving human participants in an interventional or an observational study but a review. This registration is not required.

Guarantor

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Data availability statement

Data sharing is not applicable.

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