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# Diagnostic and prognostic role of cardiac magnetic resonance in acute myocarditis

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**Abstract**
Acute myocarditis (AM) is commonly found in everyday clinical practice. Differential diagnosis between various causes of myocardial damage with non-obstructive coronary arteries can be cumbersome for clinician. Moreover, AM may be provoked by a number of different causes and clinical presentation can be heterogeneous with potential overlap going from asymptomatic or subclinical to severe heart failure, arrhythmias, and death. Cardiac magnetic resonance (CMR) over the last decades has proven to be the diagnostic technique of choice since it allows identifying AM with excellent diagnostic accuracy. Latest technological advancement with parametric imaging such as T1 and T2 mapping further increases sensitivity and provides additional help towards a correct diagnosis. CMR however is no longer to be considered as a mere diagnostic tool but also as a powerful source of prognostic information. Scientific evidence has corroborated CMR's role beyond diagnosis demonstrating how late gadolinium enhancement (LGE) presence is a powerful predictor of cardiac events and how the presence of septal LGE is to be considered of worst prognosis regardless of LGE extension even in patients with preserved global systolic function. CMR should be routinely performed in all patients with AM suspicion since its diagnostic and prognostic role is of paramount important and could modify therapeutic strategy and subsequent clinical decisions.

**Keywords** Myocarditis · Cardiac magnetic resonance · Myocardial oedema · Myocardial fibrosis · Late gadolinium enhancement · Prognosis

## Introduction

### Definition and historical background

Myocarditis, according to the World Health Organization classification of cardiomyopathies, is an "inflammatory disease of the myocardium diagnosed by established histological, immunological and immunohistochemical criteria [1]. First description of an inflammatory process involving the heart goes back to 1806 when Corvisart detected a connection between cardiac inflammation and chronic cardiac dysfunction [2]. It was not however until almost 100 years later when a German physician named Fielder defined the existence of an acute interstitial myocarditis of unknown origin. He described and published in 1899, a case series of young patients with heart failure (HF), sometimes with a fatal conclusion, following a period of fever with a subsequent autoptic evidence of acute myocardial inflammation confined only to myocardium and not affecting pericardium or endocardium [3]. In the following years, the role and importance of coronary circulation became clearer and the pathophysiological distinction between ischaemic and non-ischaemic origin of HF better understood. This scientific progression made the patency of coronary arteries a "sine qua non" condition for forms of non-coronary cardiomyopathies such as myocarditis [4].

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### Epidemiology

The real incidence of acute myocarditis (AM) is unknown but recent epidemiological studies suggest that it is rather frequent. In 2013, AM was diagnosed in over 1.5 million people worldwide [5]. It is being diagnosed usually in young subjects [6, 7] and is detected more frequently in male individuals [8].

This increased myocarditic susceptibility for male subjects, may be due to different immune systems between male and female with a protective effect of female hormones [9].

## Etiopathogenesis

Main causes of AM may be divided in idiopathic, autoimmune and infective even though other forms also exist. Among most common causative agents, we find toxins and drugs [10] even though in Europe and Nord America the predominant cause is infection and especially viral. Among virus, parvovirus B19 (PVB19), coxsackie B virus, human herpesvirus 6 (HV6) type B and adenovirus are the most frequently detected [11].

## Pathophysiology

Myocarditis comprises three different phases with a partial overlap among them. The first phase is characterized by virus-induced cardiomyocyte destruction whereas during the second phase, a specific host's immune response is being activated as well that causes T cells to detect and extinguish infected cardiomyocytes through cytokine secretion [12]. Unfortunately, these mechanisms may destroy healthy cardiomyocytes as well, when an excessive response of the immune system coexists and hence a sustained inflammatory response self-perpetuates. In the third phase, acute inflammatory process progressively disappears and damaged cardiomyocytes are being replaced by collagen with a reparative diffuse fibrosis taking place, switching therefore from an acute to a chronic status of the disease.

## Clinical presentation

Clinical presentation of AM is extremely heterogeneous. In the majority of cases, it has a subtle presentation or even completely asymptomatic that follows a feverish period and is usually self-limiting. It may as well however present as a recent-onset HF, with arrhythmic events, or with infarct-like symptoms [13]. Most of the times, AM presentation does not compromises haemodynamic stability and symptoms, if any, resolve after a few days. Unfortunately in some cases, presentation may be more complicated, especially when AM is fulminant and severe acute HF with haemodynamic instability and high mortality may be found [14].

## Diagnostic conundrum of AM

From all the abovementioned evidence, it is clear that AM diagnosis may be cumbersome for clinicians. Many different causes and clinical presentations with potential pathophysiological overlap between acute and chronic forms may occur making diagnosis complex and in many cases challenging. A number of non-invasive diagnostic tools are available such as electrocardiogram, biomarkers (e.g. troponin) and various non-invasive imaging techniques such as echocardiography and more recently positron emitting tomography among others but none of them allows neither a definite diagnosis of myocarditis nor a differential one among ischaemic and non-ischaemic causes for cardiac damage. Description of strengths and pitfalls of each technique goes beyond the scope of this review and readers should consult other publications for this matter [15]. Definite diagnosis is supposed to be provided by endomyocardial biopsy (EMB). Universally accepted Dallas Criteria [16] require histopathologic documentation of a myocardial inflammatory infiltrate of non-ischaemic origin with or without degeneration of adjacent myocytes. EMB, even though considered to be the gold standard for AM diagnosis is being rarely performed, since accepted indications are rarely to be found in real life cases. EMB according to guidelines is indicated either to exclude fulminant myocarditis when unexplained, new-onset HF of less than 2 weeks duration with haemodynamic compromise occurs or to exclude giant cell myocarditis when unexplained, new-onset HF of more than 2 weeks with a dilated left ventricle and associated brady- or tachy-arrhythmias is seen [17]. Patients with subclinical presentation and haemodynamic stability as the typical AM patients are not appropriate candidates for EMB and referring physicians are not keen on having it routinely performed since it is an invasive procedure with potentially serious complications [17]. Moreover, even when EMB is performed it lacks of sufficient sensitivity. Postmortem EMB in patients deceased of myocarditis, diagnosed 25% of samples when a single specimen was performed [18]. Even when 10 biopsy specimens per ventricle were evaluated, the frequency of false-negative results was extremely high, being 45% for the left and 37% for the right ventricle [19]. In addition and in the minority of cases, where sampling is correctly and safely performed in the inflamed myocardial area, diagnosis once again is limited by poor inter-observer agreement of histologic findings [20]. It is clear therefore that EMB is neither sensible nor specific enough and not indicated for routine AM diagnosis and therefore a different diagnostic approach accurate, safe and especially non-invasive is necessary in everyday clinical practice.

## Cardiac magnetic resonance for AM diagnosis

Cardiac magnetic resonance (CMR) is a non-invasive, non-ionizing, safe imaging technique that is considered to be currently the best available tool not only for cardiac chamber volumes and function quantification [21], but also for valves regurgitation assessment [22] as well as for an accurate myocardial tissue characterization [23, 24]. Over the last decades, CMR's clinical application and diagnostic power has constantly risen. Even though it is considered to be a relatively new imaging technique, it has been more than 25 years ago

when CMR started showing its potential in AM diagnosis. Gagliardi et al. [25] studied a pediatric population with AM diagnosis and described a significant difference in signal intensity between children with and without AM when T2-weighted spin-echo sequences were used. Over the following years, additional steps were made towards a better understanding of the mechanisms and causes of inflammatory myocardial damage and its CMR depiction. Abdel-Aty et al. in 2005 [26] assessed the diagnostic accuracy of available proposed CMR diagnostic approaches and observed how by using T2-weighted imaging and post-contrast imaging with early and late gadolinium enhancement (LGE), allowed to obtain a high diagnostic accuracy in patients with suspected AM. The following year, Mahrholdt et al. [27] elegantly observed and described the association of different clinical presentations and pattern of myocardial damage by analyzing 128 patients with a clinical suspicion of AM. Forty-nine presented as a causative agent a PVB19 infection and 16 patients a HV6 infection. Clinical presentation was different between groups, since PVB19 infections presented predominantly with severe acute chest pain mimicking myocardial infarction, whereas most patients infected by HV6 showed symptoms of subacute new-onset HF, arrhythmias and bundle branch block. LGE in these two subgroups also differed since PVB19 group had had LGE in the infero-lateral segments, whereas HV6 in the intraventricular septum. Authors postulated that different LGE patterns for each virus were due to different viral cardiac tropism. As already known, all Herpes viruses infects T cells and also nervous and cardiac conduction system [28] and hence, a specific tropism for the septal area where electrical conduction system of the heart passes may occur provoking therefore arrhythmias and conduction abnormalities. On the other hand, PVB19 infection by causing endothelial dysfunction of myocardial vessels promotes inflammation and ischaemia mimicking myocardial infarction and due to particular cardiac tropism, initial viremia may lead to pericarditis that can propagate to adjacent myocardium in the lateral free wall of the left ventricle sparing ventricular septum that is not in direct contact with the pericardial layers. These hypotheses however remain so far an interesting possible explanation of these findings without definite confirmation.

From all available evidence such as abovementioned, it is now obvious that AM CMR-driven diagnosis is made after analysis of a series of potential characteristic morphological and functional abnormalities as well as associated comprehensive tissue characterization (Fig. 1) that allows for myocardial oedema, hyperaemia and fibrosis to be detected [30]. A number of available sequences are being used for this purpose. First of all, cine images derived from balanced steady-state free precession sequence (bSSFP) are used for morphological and functional assessment of all cardiac chambers. Available reference values for cardiac volumes and function [21] and CMR's accuracy in volumes and function quantification, allow detecting even mild changes and therefore discover cases of subtle acute myocardial damage. Furthermore, T2-short tau inversion recovery (T2-STIR) pulse sequences may accurately detect waterbound protons in non-blood pool fluids allowing for myocardial oedema to be depicted as hyperintense areas [26]. Moreover, myocardial hyperaemia may be assessed by contrast-enhanced fast spin-echo T1-weighted images acquired during the first minutes after contrast administration [31] or by post-contrast bSSFP sequences as well [29]. Finally, T1-weighted post-contrast sequences, acquired early and late after gadolinium-based contrast agent administration shows high-intensity areas when hyperaemia and/or acute/chronic myocardial damage is present.

Which and how sequences are to be used for AM diagnosis has been established based on CMR recommendations deriving from small studies and are mainly the result of experts' consensus so-called Lake Louise Criteria (LLC) [30]. According to LLC, when myocardial oedema, hyperaemia and LGE are being considered, the presence of at least 2 out of 3 of these tissue markers allows diagnosis with a diagnostic accuracy of 78% [30]. Therefore, in order to formulate a rather convincing diagnosis at least 2 out of 3 element among oedema, hyperaemia and LGE are needed. An additional strength point of sequences focused on oedema, hyperaemia, and LGE detection is the fact that other than diagnosis by repeating CMR over time, monitoring the course of the inflammatory process is feasible, hence allowing for important information regarding the reversibility and the extension of irreversible cardiac damage, to be detected hence differentiating between acute and healed myocarditis [32]. Baccouche et al. [33] by comparing CMR and EMB in consecutive patients with AM, assessed the ability of each technique to provide correct AM diagnosis, documenting an additional diagnostic ability when both techniques were used together in troponin-positive patients without coronary artery disease. In this study, EMB diagnosed a higher number of patients with AM than CMR with the latter being inconclusive in 20% of scans performed versus 12% of inconclusive EMBs. Authors stated that both techniques present some limitations and in order to overcome those, a "diagnostic synergy" needs to be considered between the two techniques, especially when CMR does not provide a definite diagnosis that is clinically needed. Caution must be made when trying to interpret these results. Authors postulated that EMB was diagnostically more sensible especially in cases of subtle or borderline AM. But EMB was considered diagnostic for acute forms of myocarditis also in the sole presence of virus genome without inflammation. Moreover, active inflammation by CMR was assessed only by means of LGE and not by dedicated sequences for myocardial oedema and hyperaemia, making this methodological gap a likely cause for the high number of inconclusive CMRs and missed AM diagnoses. Currently available diagnostic criteria with the use of myocardial oedema, hyperaemia and LGE as well as novel

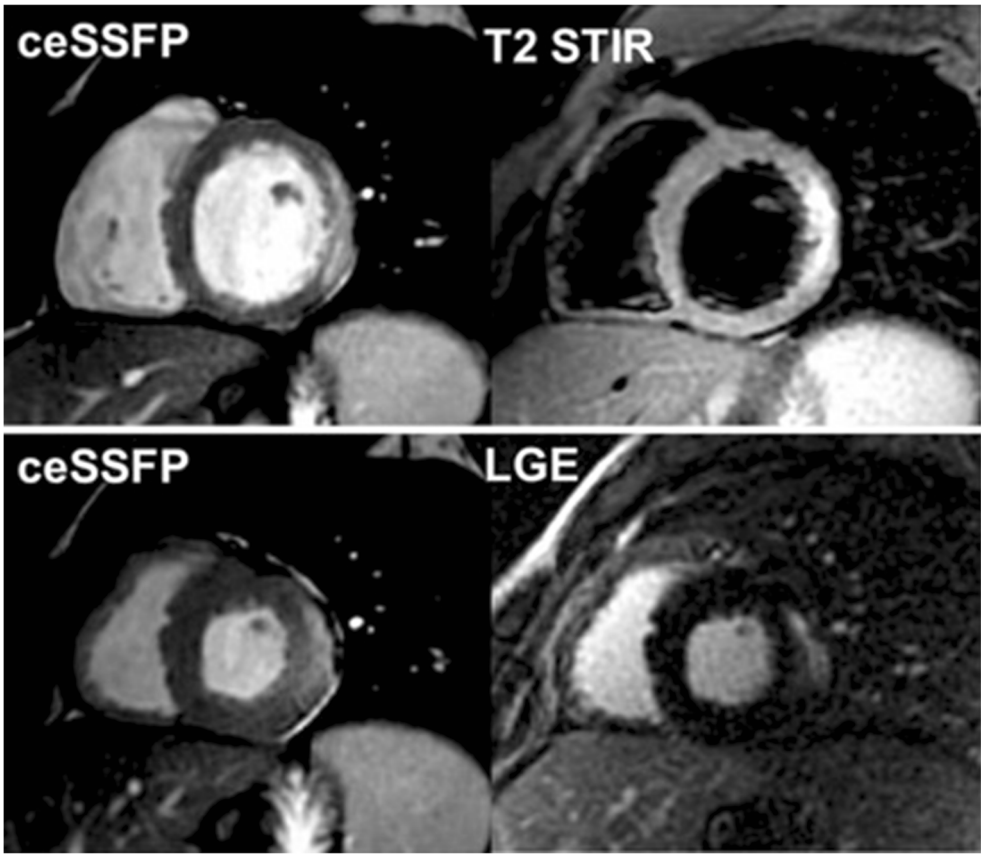


**Fig. 1** Visualization of oedema, late gadolinium enhancement (LGE) and cine short-axis images in a patient with acute myocarditis. The left upper (diastole) and lower (systole) cine images shows, hyperintense lateral area due to hyperaemia, while right upper image shows a hyperintense lateral area in T2-STIR images for myocardial oedema assessment and lower right image shows a small subepicardial lateral area of LGE with a non-ischaemic distribution. Modified by Perfetti et al. [29]. ceSSFP, contrast-enhanced steady-state free precession; T2 STIR, T2 short tau inversion recovery; LGE late gadolinium enhancement

diagnostic techniques discussed further on are definitely increasing CMRs diagnostic accuracy and reduce the cases where EMB is deemed clinically necessary.

LLC presents some limitations, such as the frequent artifacts that may lower diagnostic quality especially when breath-holds are required. Moreover, presence of oedema, hyperaemia and/or LGE may be rather challenging to assess, mostly in cases of subtle diffuse myocardial inflammation with or without concomitant extensive myositis. Even though, and up until updated diagnostic criteria will be available, LLC are to be considered the more appropriate diagnostic algorithm for AM diagnosis.

## CMR for AM prognosis

Once CMR's ability to correctly diagnose AM had been established, the lack of clear prognostic information became more obvious and the need for data impelling. Available studies were of small numbers, single-center and with limited follow-up and therefore definite prognostic conclusions were hard to be drawn.

More than 10 years ago, Mahrholdt et al. [27] observed that clinical course in PVB19 myocarditis with a laterally located LGE was mostly benign whereas patients affected by HV6 showed predominantly septal LGE and had worse clinical course with half of them not improving after the acute event during the follow-up period. The same group of authors later on [34] studied more than 200 patients with an EMB diagnosis of AM and observed how LGE predicted ventricular remodeling, systolic impairment and worse prognosis. Cardiac death occurred in 28/29 patients with LGE and only in 1 patient without LGE with all deceased patients showing global systolic impairment. Few years later, the same group evaluated a bigger population of patients with AM and found how CMR abnormalities of any type were predictors of outcome [35].

Prognostic indicators and additional data were necessary and just recently two studies with big number of patients enrolled and long enough follow-up were published [36, 37]. The first one enrolled 670 patients with average follow-up of 4.7 years. This is the study with the biggest AM population ever to be enrolled. Authors' confirmed the prognostic role of LGE by finding that LGE more than doubled the risk of adverse cardiac events with midwall septal LGE being the more malignant localization of all. This study delivered important results even though some limitations need to be acknowledged. It was an "all-comer" study with all patients with clinical suspicion of myocarditis being enrolled. Big number of patients enrolled was the result of wide inclusion criteria, since patients were enrolled as long as one of the following three criteria were met: (1) acute chest pain with onset <2 weeks; (2) subacute dyspnea or signs of left ventricular dysfunction; and (3) subacute evidence of ventricular arrhythmias, syncopal

spells or abnormal ECG. Since only a small percentage underwent EMB, the risk of having included false positive AM patients cannot be excluded. Moreover, it was a single-center study and different magnetic field (1.5 and 3 T) scanners were used.

On the same period Aquaro et al. [37] published a multicenter study with a smaller population than the previous mentioned but with stricter enrollment criteria considered. Authors included 374 AM patients excluding all patients with signs of HF, significant arrhythmias and/or global systolic impairment. Study population was formed only by subjects with AM and preserved global systolic function, as the ones routinely found in everyday clinical practice. Median follow-up was of 4.3 years. Patients included showed two different distribution patterns of LGE with subepicardial infero-lateral wall pattern (IL) seen in 41% and midwall anteroseptal (AS) in 36%. AS group had lower values of inflammatory biomarkers such as C-reactive protein than IL group but higher troponin release suggesting, in accordance with previous studies [27, 28], a different kind of myocarditis, with less inflammation but greater myocardial damage. AS distribution showed worse prognosis than IL regardless of LGE extent underlining the higher prognostic significance of LGE localization rather than LGE extension. Among limitations to be considered, first of all was the low number of subjects undergoing EMB. This data could be explained as previously mentioned by the fact that patients with preserved systolic function and haemodynamic stability are not usually candidates for invasive investigations of suspected AM and current guidelines do not justify a routine use of EMB. Moreover, parametric imaging was not included in the performed diagnostic protocol. Authors' justification was that this unavoidable limitation was due to the fact that T1 and T2 mapping techniques became available only recently. Furthermore, in the context of a multicenter study, mapping imaging would have provided different and incomparable results among different centers and therefore it was decided to avoid it.

## Novel diagnostic sequences for interstitial myocardial remodelling assessment

Over the last years a significant evolution in CMR's diagnostic armamentarium occurred, offering additional tools in everyday clinical practice. T1 and T2 mapping techniques provide an accurate measurement of T1 and T2 values of the corresponding myocardial area [38]. Pre- and post-contrast T1 mapping allows quantifying the degree of myocardial interstitial remodeling. Myocardial T1 value, assessed by pre-contrast T1 mapping, which is an intrinsic characteristic of the tissue, depends on structural and biochemical composition of both intracellular and extracellular compartment. Therefore, native T1 mapping values increase above normal limits [39] in cases of cardiomyocyte damage, enlarged extracellular space, intramyocardial oedema or fibrosis [40] all seen, among others, in cases of myocardial inflammation [41]. Native T1 mapping is acquired before contrast administration whereas, post-contrast T1 maps assessment is possible in various time points, allowing for myocardial T1 recovery, hence reflecting contrast agent kinetics. Post-contrast T1 time is not an intrinsic property of myocardial tissue, but depends upon the accumulation of contrast agent in the extracellular space. Based on amount of contrast agent concentration in myocardial tissue and when equilibrium is reached with the blood pool, cardiac extracellular volume fraction (ECV) may be estimated [42] allowing for extracellular volume space quantification and accurate myocardial fibrosis correlation [43, 44].

This novel approach may provide aid towards an improved detection of cases of AM, trying to overcome all known limits of LLC such as long acquisition time, frequent artifacts, qualitative and reader-dependent interpretation. Parametric imaging allows for quantification via absolute numbers with validated cutoffs for healthy and diseased myocardium [45]. Moreover, sequences are less prone to artifacts especially for poor breath-holders and significant information may be achieved even without the need for contrast administration.

Given all these strengths, over the last few years a big number of papers on strength and utility of T1 and T2 mapping are being published [46]. To begin with, native pre-contrast T1 mapping has shown to be able to accurately define myocarditis activity by differentiating between active and non-active forms of myocarditis [47]. Moreover, T1 mapping have been shown to outperform traditional T2-weighted sequences for myocardial oedema detection [48] and promising results have been also demonstrated when native T1 mapping was compared to T2-weighted and LGE sequences for AM diagnosis as well [49]. Furthermore by detecting disease progression and activity in a quantitative way, the efficacy of an anti-inflammatory treatment can be assessed and therefore the inflammatory disease monitored [41, 50]. Pre- and post-contrast T1 mapping images in a patient with inferior and infero-lateral AM localization may be seen in Fig. 2.

Unfortunately, an abnormal T1 value does not allow discriminating between various causes of structural or biochemical myocardial alterations and hence differential diagnosis between increased extracellular space, oedema, fibrosis and fatty infiltration is not feasible making impossible a differentiation among different pathological cardiac conditions. For this matter in the absence of clinical data and based exclusively on T1 mapping data, it is not possible to differentiate between acute, subacute and chronic myocarditis. To support a correct differential diagnosis, T2 mapping parametric imaging provides additional information. In Fig. 3, T2 mapping of the same patient with inferior/infero-lateral evidence of increased T1 values and AM diagnosis depicted in Fig. 2 may be seen. T2 mapping increases diagnostic accuracy in AM [51]. When both parametric techniques were used in patients with

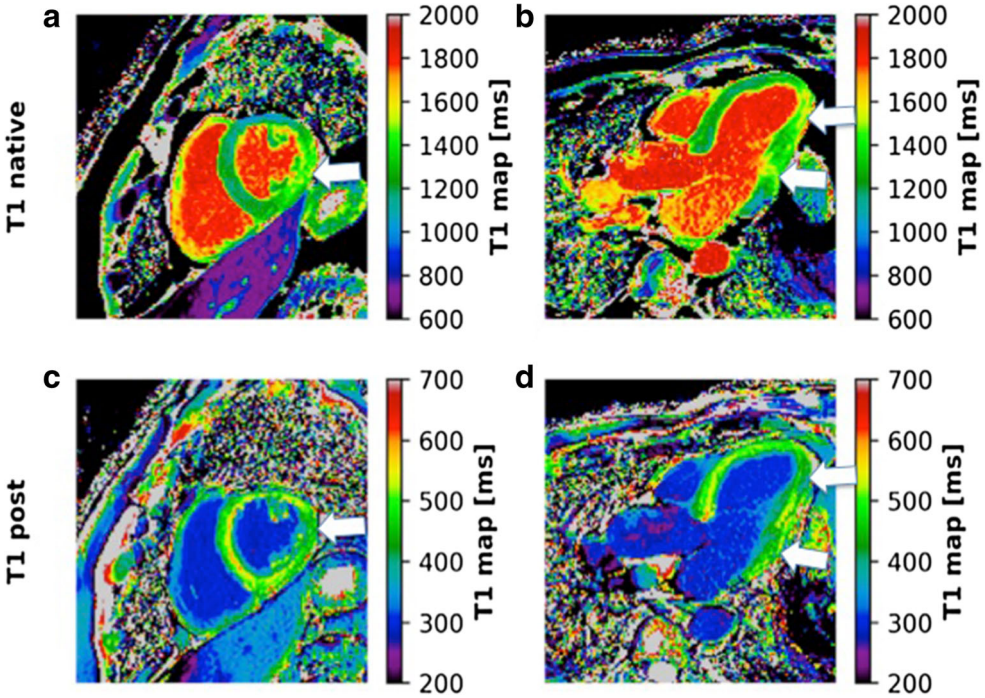


**Fig. 2** Mid short-axis (**a**) and 3-chamber (**b**) pre-contrast T1 mapping of a patient with acute myocarditis and evidence of increased T1 values in the inferior/infero-lateral walls (arrows) with reduced T1 values in the same areas in the post gadolinium-based contrast agent administration T1 mapping sequence (**c**, **d**). Findings in keeping with myocardial damage in the inferior/infero-lateral walls. bSSFP, balanced steady-state free precession; T2-STIR, T2-weighted short-tau inversion recovery; CE, contrast-enhanced; FSE, fast spin-echo; ECV, extracellular volume; LGE, late gadolinium enhancement

suspected AM both of them were useful for confirming or rejecting the diagnosis of myocarditis but only T2 mapping had acceptable diagnostic performance in patients with chronic symptoms [52]. Moreover, T2 mapping has shown to be not only a valuable tool for inflammatory disease detection but also to monitor its evolution in time [53].

Both of these techniques appear promising and soon to be considered irreplaceable in our opinion in routine CMR protocols for AM diagnosis since T1 mapping could permit the detection and quantification of microscopic fibrosis, especially when LGE is non visible, whereas T2 mapping would allow detecting and quantifying myocardial oedema and discriminating between acute and chronic myocardial pathologies making it easier for discrimination between acute and chronic forms of myocarditis. For this reason prospective trials are needed to confirm preliminary evidence in bigger populations reinforcing parametric imaging's clinical utility and prognostic role. This would fill the gap currently representing the biggest limitation of parametric imaging, being the absence of big number, multicenter, multivendor, prospective trials. A final limitation that needs to be acknowledged is the fact that different sequences for obtaining the same information are available such as MOLLI, ShMOLLI, SASHA, and SAPPHIRE. A consensus is needed to define the more appropriate sequence to be used in a constant and reproducible way in order to obtain data and results from scans performed in different centers.

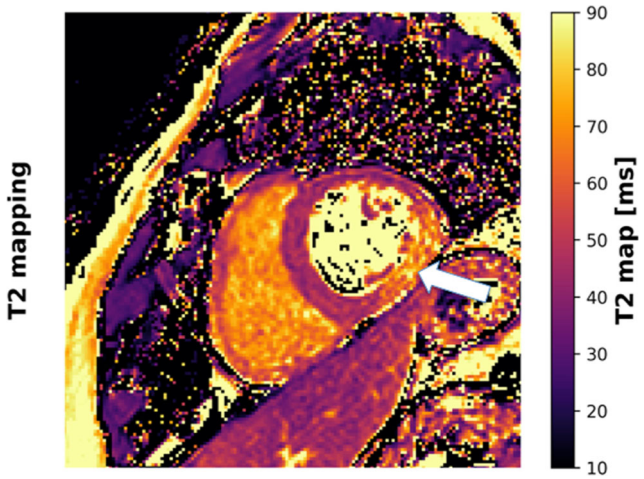


**Fig. 3** Mid short-axis T2 mapping of the same patient of Fig. 2 with evidence of increased T2 values in the inferior/infero-lateral walls (arrow), indicative of myocardial oedema in the same areas that presented increased pre-contrast T1 mapping in Fig. 2

## Proposed CMR protocol for AM diagnosis and algorithmic approach for AM workup

Based on the abovementioned evidence deriving from an extensive literature review and trying to merge available current and emerging techniques, a CMR diagnostic protocol for everyday clinical practice in cases of AM suspicion could be proposed (Fig. 4), starting with preparatory scout sequences and the necessary for planning two chambers, short axis and four chambers bSSFP cine images.

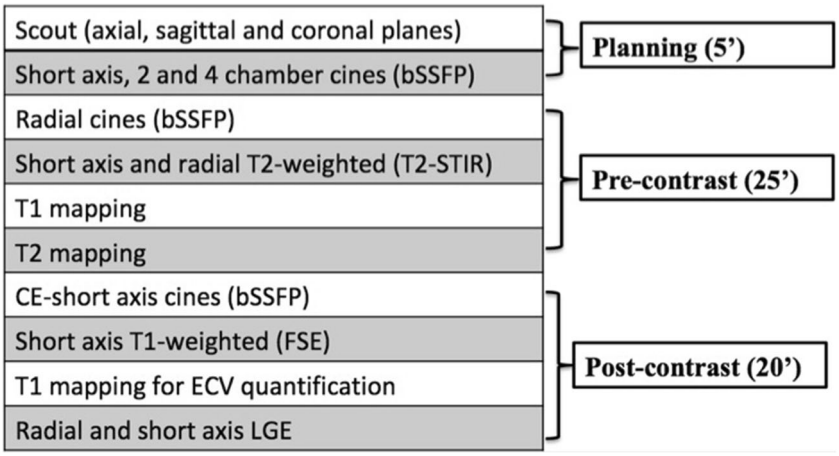


**Fig. 4** Proposed CMR protocol for acute myocarditis diagnosis with order of necessary sequences and approximate scanning time

Then short-axis and radial T2-STIR sequences for oedema detection and parametric imaging with T1 and T2 mapping short-axis images could be acquired. If no additional pre-contrast crosscut images necessary to exclude or confirm diagnostic suspicion, contrast agent could be administered and T1-weighted fast spin-echo sequences in short axis acquired for hyperaemia detection. For the same purpose (and for systolic function assessment) bSSFP cine images could be obtained. T1 mapping sequences at this point could be repeated for additional ECV quantification and finally sequences for LGE in short and radial axis should be acquired.

This protocol could be performed in all cases with a clinical suspicion of AM defined as acute chest pain and at least one between new ECG abnormalities (ST elevation or non ST elevation, T wave inversion, new I-III degree AV-block), troponin increase and regional wall motion abnormalities on echocardiogram or if asymptomatic when at least two of the abovementioned diagnostic criteria met. For both types of patients, the absence of angiographic evidence of significant coronary artery disease would be mandatory except for patients with less than 35 years old and low pre-test probability for ischaemic heart disease. From the proposed CMR protocol, important information would be obtained regarding the evidence of myocardial/pericardial inflammation as well as presence, extend and type (ischaemic or non-ischaemic) of myocardial fibrosis assessed by means of LGE. Moreover, this protocol could be extended in all troponin-positive patients without significant coronary artery disease (documented or suspected) when a clear picture of the cause of troponin rise and/or the extent of cardiac involvement is to be defined. By doing so, appropriate diagnosis, risk-stratification and prognosis of patients with unobstructed coronaries could be obtained, unnecessary coronary angiographies avoided (when AM confirmed) and additional diagnoses of ischaemic heart disease with unobstructed coronaries made (when ischaemic myocardial oedema and LGE detected).

## Conclusions

CMR is the gold standard for AM diagnosis and it should be performed in all patients with suspected AM. CMR findings allow not only obtaining a definite diagnosis in the vast majority of cases but also providing precious prognostic information for the clinician that could modify therapeutic strategy and subsequent clinical decisions. Two predominant different types of AM, based on clinical presentation and CMR findings may be considered. The first one with infarct-like symptoms, high inflammatory response but small myocardial damage and subepicardial lateral wall involvement is to be considered relatively benign whereas the other one with heart failure symptoms, low inflammatory response but big myocardial damage with intramyocardial septal localization is to be considered less benign and associated to adverse cardiac events even when global systolic function is preserved.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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