

Non-invasive imaging in the diagnosis of acute viral myocarditis

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Abstract Autopsy series of consecutive cases have demonstrated an incidence of myocarditis at approximately 1–10%; on the contrary, myocarditis is seriously underdiagnosed clinically. In a traditional view, the gold standard has been myocardial biopsy. However, it is generally specific but invasive and less sensitive, mostly because of the focal nature of the disease. Thus, non-invasive approaches to detect myocarditis are necessary. The traditional diagnostic tools are electrocardiography, laboratory values, especially troponin T or I, creatine kinase and echocardiography. For a long period, nuclear technique with indium-111 antimyosin antibody has been used as a diagnostic approach. In the last years, the use of this technique has declined because of radiation exposure and 48-h delay in obtaining imaging after injection to prevent blood pool effect. Thus, a non-invasive diagnostic approach without radiation and online image availability has been awaited. Cardiac magnetic resonance imaging has

these promising characteristics. With this technique, it is possible to analyse inflammation, oedema and necrosis in addition to functional parameters such as left ventricular function, regional wall motion and dimensions. Thus, cardiovascular magnetic resonance imaging has emerged as the most important imaging tool in the diagnostic procedure and the review focus on this field. But there are also advances in echocardiography and computer tomography, which are described in detail.

Keywords Myocarditis · Magnetic resonance · Non-invasive imaging · Echocardiography · Nuclear medicine · Computer tomography

Introduction

Acute myocarditis may cause substantial myocardial damage and can lead to arrhythmias, sudden cardiac death in the acute phase and to dilated cardiomyopathy in the acute and chronic phase [1, 2]. Therefore, early diagnosis is of particular clinical importance. Myocarditis can be diagnosed with certainty only by endomyocardial biopsy, which must be examined by histological, immunohistological and molecular techniques to obtain maximal sensitivity. Due to the often focal localisation of the disease, sampling error may occur. Furthermore, myocardial biopsy is in practise used only rarely, despite a low complication rate [3]. Thus, the diagnosis of myocarditis is often based merely on suspicion.

Viral myocarditis is found after respiratory or gastrointestinal infection with a wide range of viruses. In the seventies, the RNA virus coxsackie B was the most common cause [4]. Other viruses included adeno-, varicella zoster, cytomegalie and Epstein–Barr. In the presence,

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parvovirus B19 and human herpesvirus 6 are increasingly found in endomyocardial biopsies [5–10].

Clinical symptoms, the course and diagnostic approach in patients with suspected myocarditis

Clinical symptoms, such as weakness, palpitations, fatigue, are often minor and are mistaken in many cases as part of the previous infection or delayed convalescence. However, sudden cardiac death in persons active in sports—especially with people younger than 35 years—is often due to non-detected acute myocarditis [11].

In virus myocarditis, the acute phase of the disease is triggered by the entry and proliferation in the myocardium of the causative virus. Various cytokines are activated. Circulating levels of plasma tumour necrosis factor and various interleukins are elevated [12, 13]. Infiltrating T lymphocytes and macrophages can be detected in the acute and chronic phase by biopsy [14]. The acute phase of myocarditis is characterised by myocyte necrosis and cellular infiltrates in the myocardium whereas in case of chronic myocarditis no myocyte necrosis but cellular infiltrates could be detected. Not only in the chronic phase but also in the acute phase, deterioration of the left function and dilated cardiomyopathy may occur [13]. Kühl et al. [5] demonstrated that patients with persisting viral genomes detected by myocardial biopsy showed a progressive impairment of left ventricular function, whereas spontaneous viral elimination was associated with a significant improvement in left ventricular function. In contrast to this finding, Kindermann et al. [15] found in 181 consecutive patients who underwent endomyocardial biopsy as part of an evaluation for clinically suspected myocarditis that for the primary end point of cardiac death or heart transplantation, NYHA functional classes III and IV, high values of the left ventricular end-diastolic diameter index and pressure, a low ejection fraction, and immunohistological detection of inflammation were shown to be significant predictors of poor outcome in the univariate analysis, whereas the Dallas criteria and viral genome detection were not significantly related to outcome. The difference might be due to patient population, sample collection and the fact that in the study by Kühl et al. [5] the patients were reanalysed by endomyocardial biopsy at a median period of 6.8 months (range 5.4–11.9) which was not performed in the study by Kindermann et al. [15]. Thus, it is not known in which patients a clearance of the viral genomes occurred.

Electrocardiography and laboratory values

ST segment and T-wave abnormalities are the typical electrocardiographic patterns, but they are usually

transient. Other electrocardiographic abnormalities include atrial and ventricular arrhythmias, AV and intraventricular conduction defects and variant early repolarisation [16, 17]. But there exist several patients without electrocardiographic abnormalities. Eckart et al. [17] found in patients with vaccinia-associated myopericarditis despite markedly elevated cardiac enzymes in 25% a normal electrocardiogram. Routine laboratory investigations include troponin T or I, myoglobine, and creatine kinase levels. Raised troponin levels reflect myocardial necrosis [18]. There are a large number of causes of an elevated troponin, which include acute coronary syndrome, myocarditis, cardiomyopathy, cardiac contusion, aortic dissection, congestive heart failure, amyloidosis and non-cardiac causes including pulmonary embolism, sepsis and renal failure [19–21]. In patients with acute chest pain, elevated troponin and unobstructed coronary arteries, myocarditis is a common cause [14, 22]. But there are several patients with normal electrocardiogram and negative troponin or creatine kinase levels but suspected myocarditis especially after or during a viral infection of the respiratory or gastrointestinal tract. Carniel et al. [23] found in a consecutive series of autopsies of fatal myocarditis an elevated creatine kinase only in 18% of the patients. In addition, even in patients with ECG changes, these are non-specific for myocarditis [3].

Echocardiography

Traditional echocardiographic findings are left ventricular regional or global dysfunction, and left ventricular dilatation. Pinamonti et al. [24] found in 41 patients with histologically proven myocarditis left ventricular dysfunction in 69%, right ventricular dysfunction in 23%, asynergic ventricular areas in 64%, left ventricular “hypertrophy” sometimes reversible in 20%, ventricular thrombi in 15% and “restrictive” ventricular filling in 7% of his patients.

Right ventricular function is an independent predictor of outcome. Mendes et al. [25] assessed the predictive value of right ventricular systolic function in patients with active myocarditis in 23 patients with biopsy-confirmed myocarditis. Initial left ventricular ejection fraction was significantly lower in patients with depressed right ventricular function ($27.5 \pm 4.9\%$) compared with that in patients with normal right ventricular function ($47.5 \pm 6.3\%$) ($P = 0.01$). The likelihood of an adverse outcome, defined as death or need for cardiac transplantation, was greater in patients with abnormal right ventricular function.

The presence of myocardial interstitial oedema in acute myocarditis leads to thickening of the ventricular wall, which can be detected by echocardiography [26]. Felker et al. [27] distinguished fulminant myocarditis with rapid onset of illness with severe haemodynamic compromise

from acute myocarditis by echocardiographic criteria of septal thickness and left ventricular dimensions. Patients with fulminant myocarditis had near normal left ventricular dimensions (5.3 ± 0.9 cm) but increased septal thickness (1.2 ± 0.2 cm) at presentation, while those with acute myocarditis had increased diastolic dimensions (6.1 ± 0.8 cm, $P < 0.01$ vs. fulminant) but normal septal thickness (1.0 ± 0.1 cm, $P = 0.01$ vs. fulminant). Fulminant myocarditis has a better long-term prognosis than acute myocarditis as shown in the clinical study of McCarthy et al. [28].

There are few case reports of detecting myocarditis by novel echocardiographic modalities such as tissue Doppler, strain and strain rates or three-dimensional echocardiography [29–31]. Di Bella et al. [29] report a case where strain Doppler echocardiography was able to identify longitudinal segmental myocardial dysfunction derived from oedema in the acute phase of myocarditis. Smedema [30] demonstrates in a case report the value of tissue Doppler echocardiography and contrast-enhanced cardiac magnetic resonance imaging (CMRI) in the diagnosis and management of patients with myocarditis. Tissue Doppler imaging demonstrated abnormalities suggestive of myocardial scar, which was confirmed by magnetic resonance. Thuny et al. [31] revealed by real-time two- and three-dimensional echocardiography in a 43-year-old man with myocarditis a dilated and hypokinetic left ventricle and massive biventricular thrombosis that was better assessed by real-time, three-dimensional transthoracic echocardiogram.

Nuclear medicine techniques

Gallium-67

In the early 80 s, scintigraphy has been used in evaluating myocarditis. O'Connell et al. [32] evaluated the applicability of gallium-67 myocardial imaging as an adjunct to endomyocardial biopsy in the diagnosis of myocarditis in 68 patients with dilated cardiomyopathy. Histologic myocarditis was identified in only 8% of biopsy specimens. Five of six biopsy samples (87%) with myocarditis showed dense gallium-67 uptake, whereas only 9 of 65 negative biopsy samples (14%) were paired with equivocally positive gallium-67 scans ($P < 0.001$). The introduction of single photon emission computed tomography (SPECT) improved the differentiation between pericardial and myocardial localisation which was difficult with planar images alone [33, 34]. The use of gallium imaging has diminished over time mainly because of a lack of specificity [35].

Indium-111

In 1976, Khaw et al. [36] reported a specific localisation of a purified antibody against cardiac myosin. Intravenously

administered radioiodine-labelled antimyosin was selectively localised in infarcted myocardium of seven dogs 24 h after coronary occlusion. Yasuda et al. [37] were the first who reported the use of an indium 111-monoclonal antimyosin antibody imaging in the diagnosis of acute myocarditis. Because indium 111-monoclonal antimyosin antibody imaging can be used to detect myocardial necrosis, they performed this procedure on 28 patients clinically suspected of having myocarditis, and compared the results with those of right ventricular biopsy performed within 48 h of the scan. Antimyosin scans were positive in 17 patients and negative in 11. Biopsy was positive in nine patients and negative in six. The remaining showed non-specific changes. All patients with biopsy-proven myocarditis had positive antimyosin scans. In addition, eight patients with no evidence of myocarditis on biopsy had positive antimyosin scans. On the basis of a right ventricular biopsy standard, the sensitivity of this method was 100%, the specificity 58%. Kühl et al. [38] compared the results of antimyosin scintigraphy in patients with clinically suspected myocarditis with histologic and immunohistologic findings in the endomyocardial biopsy. They found that, with immunohistologic analysis as the reference method, antimyosin scintigraphy had a high specificity but a lower sensitivity for the detection of myocarditis. During the following years, the results were confirmed by others [39–42]. During more than 20 years, antimyosin scans remained an important cornerstone in the diagnosis of myocarditis [43].

Other tracers

Myocardial perfusion imaging with technetium-99 m-labelled methoxyisobutyl isonitrile SPECT (99mTc-MIBI SPECT) has proven to be an important clinical procedure in assessing the severity of myocardial ischaemia [44]. The uptake and clearance of 99mTc-MIBI by the myocardium is affected by cell viability and membrane integrity. Consequently, infectious diseases, such as myocarditis, may also affect myocardial perfusion by inducing local inflammation and necrosis. Sun et al. [44] compared 99mTc-MIBI SPECT with other heart monitoring methods in order to assess its value in the diagnosis of children with Coxsackie viral myocarditis. The results of their study suggest that the presence of myocardial uptake of 99mTc-MIBI may be a marker of myocardial inflammation and necrosis. Thallium-201 myocardial perfusion defects at rest, suggestive of fibrosis evoked by myocarditis, were examined in orienteers and athletes [45], but no differences were found. These and other tracers have not often been used in clinical practise.

In conclusion, indium-111 antimyosin antibody imaging has been intensively used during more than two decades for

diagnosis of myocarditis. Limitation of this technique includes its current limited availability in the US [46] radiation exposure, which is especially of concern in younger patients and 48-h delay in obtaining imaging after injection to prevent blood pool effects. Therefore, the application has diminished over the last years

Cardiac magnetic resonance imaging

During the passed decade, CMRI has emerged as an important procedure in the investigation of cardiovascular disease. With this technique, it is possible to analyse functional parameters such as left ventricular function, regional wall motion, dimensions and flow properties. In addition, it can characterise tissue to a greater degree than other imaging modalities and detect focal or global inflammation [6, 47].

T1-weighted images before and after gadolinium enhancement

Gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) is an approved extracellular T1-enhancing contrast agent [48] which enhances membrane permeability and capillary blood flow resulting in an increase in volume of distribution. Tissue hyperemia is an integral component of the acute inflammatory reaction of the myocardium. Diffuse myocyte injury can also increase the volume of distribution and subsequently the extraction fraction of extracellular compounds such as Gd-DTPA, resulting in abnormal myocardial enhancement [47, 49].

The group of Friedrich and Schulze-Menger et al. [47, 49] examined T1-weighted images, especially contrast media-enhanced, in comparison to healthy volunteers in patients with suspected myocarditis (acute phase). They found an increased global relative signal enhancement of the left ventricular myocardium compared to skeletal muscle in patients compared to volunteers. Roditi et al. [50] assessed a combination of different techniques including T1 spin echo before and after gadolinium enhancement in 12 patients with suspected acute myocarditis. Ten of 12 patients in the myocarditis group showed focal myocardial enhancement with associated regional wall motion abnormalities. Laissy et al. [51] prospectively compared the value of different CMRI modalities in patients with acute myocarditis. Subtraction Gd-DTPA-enhanced T1-weighted CMRI accurately identified myocardial involvement. Gutberlet et al. [52] retrospectively compared the diagnostic accuracy of three CMRI approaches for the detection of histologic and immunohistologic criteria proved myocardial inflammation in patients clinically suspected of having chronic myocarditis. The sensitivity, specificity and diagnostic accuracy of the

T1-weighted imaging after contrast agent administration compared with the immunohistologic detection of inflammation were 62, 86 and 72%.

The relationship of CMRI findings to long-term outcome was studied in another study [53] by serial CMRI studies in 16 patients with acute myocarditis who were followed for 2–3 years. Myocardial contrast enhancement was monitored using contrast-enhanced T1-weighted fast spin echo images. Contrast enhancement 4 weeks after onset of symptoms was predictive for the functional and clinical long-term outcome.

There are some methodical concerns regarding T1 contrast-enhanced images: first, it is difficult to establish stable conditions after the application of Gd-DTPA. There is a continuous change of the zero run through after the application of the contrast media. Thus, it is a crucial point, at which time the images are performed. Secondly, the T1-weighted images after Gd-DTPA are related to skeletal muscle. Thus, the relative enhancement depends on the assumption that the skeletal muscles exhibit a “normal” pattern of gadolinium enhancement. This assumption is wrong if the inflammatory process involves skeletal muscles as well [49]. Thirdly, T1 contrast-enhanced images in the diagnosis of myocarditis are only published by few investigators. Therefore, before a routine use of this image approach is used in daily practise, more studies from different centres should be performed. A native T1-weighted CMR sequence is, of course, of clinical use in the differentiation of pericardial effusion which may accompany myocarditis.

T2-weighted images

The tissue T2 relaxation time is an indicator of tissue water content, which is increased in inflammation or necrosis, i.e. during early myocardial infarction or myocarditis [49, 54]. Gagliardi et al. [55, 56] published two case series on the use of CMR for non-invasive diagnosis of acute myocarditis. Compared with biopsy, T2-weighted spin echo CMRI sequences were found to have a high sensitivity and specificity. There are some case reports on patients with acute myocarditis using T2-weighted images to visualise tissue oedema [40, 57]. However, Friedrich et al. [47] found no significant myocardial signal increase in conventional T2-weighted images in 44 patients. These images are susceptible to motion, and in native T2-weighted images the image quality of the myocardium is poor. In addition, the protocols were different and he used an 1.0 T hardware. New hard- and software developments, especially a triple inversion press hold sequence with short acquisition time (STIR), have led to a much better image quality.

In the study by Abdel-Aty et al. [49], they used a STIR sequence as well. The increase in T2 signal intensity

demonstrated a good accuracy in distinguishing patients with suspected myocarditis ($n = 25$) from control subjects ($n = 24$). We used in a series of 44 consecutive patients with suspected myocarditis after respiratory tract infection a STIR sequence as well. We found a significant difference between patients and controls in global myocardial signal intensity and in the ratio of global myocardial signal intensity/muscle signal intensity. The sensitivity was 77.8%, the specificity 90.5%, the positive predictive value 93.3%, and the negative predictive value 70.4%, and the diagnostic accuracy 82.5%. In addition, the signal intensity of the septum, anterior and lateral wall was highly significant from controls [58] (Figs. 1, 2). Assomull et al. [22] and Gutberlet et al. [52] used novel T2-weighted sequences as well with good results in detecting myocarditis.

In conclusion, in patients clinically suspected of having myocarditis, a STIR sequence seems to have a good sensitivity, specificity and diagnostic accuracy in detecting tissue oedema, a substantial feature of the inflammatory reaction in the myocardium.

Late enhancement technique

Cardiac magnetic resonance imaging techniques have been applied to identify viable myocardium and distinguish it

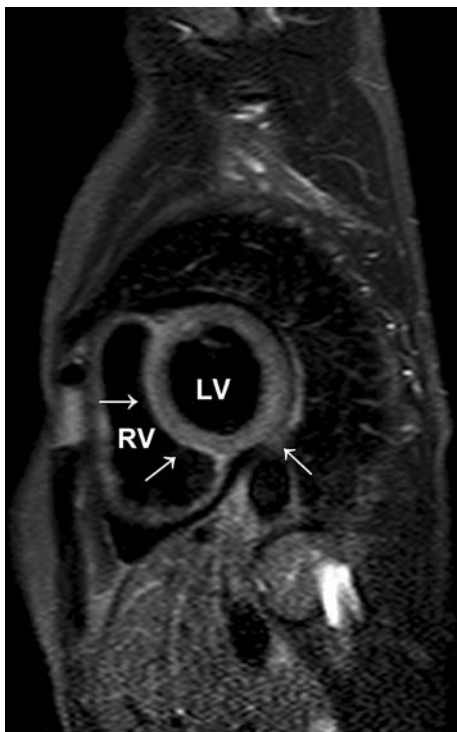


Fig. 1 Cardiovascular magnetic resonance image. Short-axis image of a 54-year-old female patient with acute myocarditis. T2-weighted image showing oedema of the septum, inferior and lateral wall (arrow). The patient had biopsy-proven myocarditis of isolated parvovirus B19 infection. LV Left ventricle. RV right ventricle

from myocardial necrosis [59] (Fig. 3). Normal myocardium does not enhance because extracellular magnetic resonance contrast agents, such as Gd-DTPA, are excluded from the myocyte intracellular space by intact sarcolemmal membranes and also, little interstitial space is available between densely packed myocytes [60]. This technique has been shown to be effective, in both animals and humans, in identifying the presence, location and extent of acute and chronic myocardial infarction [59, 61]. The cellular mechanisms responsible for contrast enhancement have not been fully elucidated. The hypothesis is that in acutely infarcted regions the myocyte membranes are ruptured allowing the cardiovascular magnetic resonance contrast agent to passively diffuse into the intracellular space, resulting in increased tissue-level contrast agent concentration and therefore hyperenhancement [60].

The same mechanism may explain contrast enhancement in the setting of inflammatory heart disease. Images acquired late (10–20 min) after application of paramagnetic contrast agents provide a sensitive tool for detection of myocardial fibrosis, which is distinguished by bright late enhancement regions where the contrast lingers in the extracellular spaces of scarred myocardium [62]. The major difference to infarcted regions is that areas of tissue damage within a myocarditic focus are usually smaller than in infarcts. Islands of necrotic cells are dispersed in a “coguar-like pattern” throughout the focus [52, 63].



Fig. 2 Short-axis T2-weighted image of a control. There is a homogeneous signal of the myocardium. LV Left ventricle. RV right ventricle

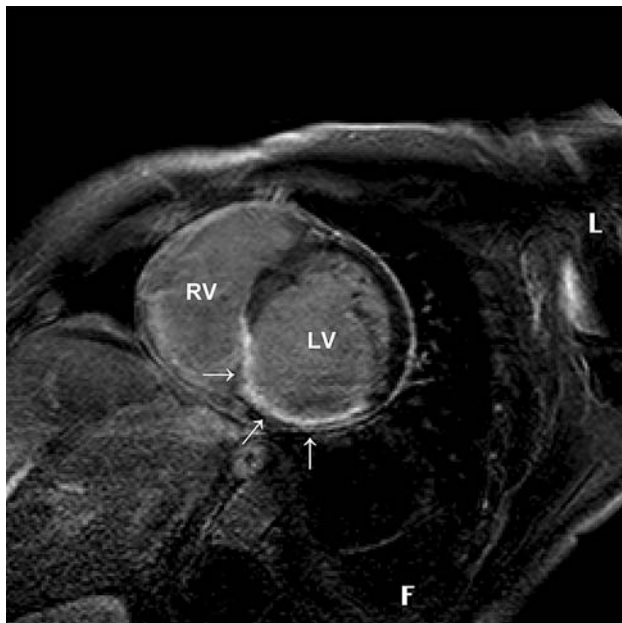


Fig. 3 Delayed enhancement imaging of a 50-year-old male patient with a chronic myocardial infarction. Short-axis view. There is a transmural scar of the inferoseptal wall (*arrow*). *LV* Left ventricle. *RV* right ventricle

In addition, hyper-enhanced myocardial regions can be visualised in patients with hypertrophic or dilatative cardiomyopathy [64]. CMRI has been examined in other cardiac diseases as well [65–69]. There are several case reports of the usefulness of delayed contrast-enhanced magnetic resonance imaging for the detection of myocarditis [70–72]. In controlled studies with patients suspected to have myocarditis, delayed contrast-enhanced cardiac magnetic resonance has been investigated as well [22, 49, 51, 73–75]. A typical subepicardial/midmyocardial late contrast enhancement is highly predictable of myocarditis in suspected patients [48, 75, 76] (Figs. 4, 5).

Cardiac magnetic resonance imaging studies are mainly performed in the acute phase of myocarditis. Mahrholdt et al. [6] found a pathological late gadolinium enhancement in 83 of 87 patients with confirmed acute myocarditis. Patients without histopathological evidence of myocarditis did not have late gadolinium enhancement except for one patient diagnosed with cardiac amyloidosis. In the setting of parvovirus B19 myocarditis, late gadolinium enhancement was located predominantly in the lateral wall of the left ventricle, typically originating from the epicardial quartile ($n = 49$). This was completely different from patients with human herpesvirus 6 myocarditis ($n = 16$), in whom pathological delayed enhancement was most frequently found in the anteroseptal region, often located intramurally, without any contact with the subepicardial region. In the setting of combined parvovirus B19/human herpesvirus 6 myocarditis, the pattern was similar, not only

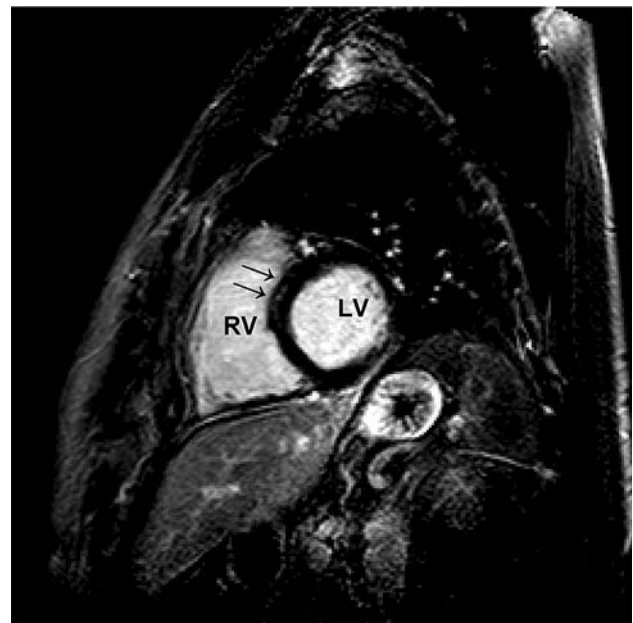


Fig. 4 Delayed enhancement imaging of a 42-year-old male patient with viral myocarditis, exertional dyspnoe after a gastrointestinal infect. Short-axis view demonstrating a small enhanced mid-wall signal intensity of the left ventricular septum (*arrow*). *LV* Left ventricle. *RV* right ventricle

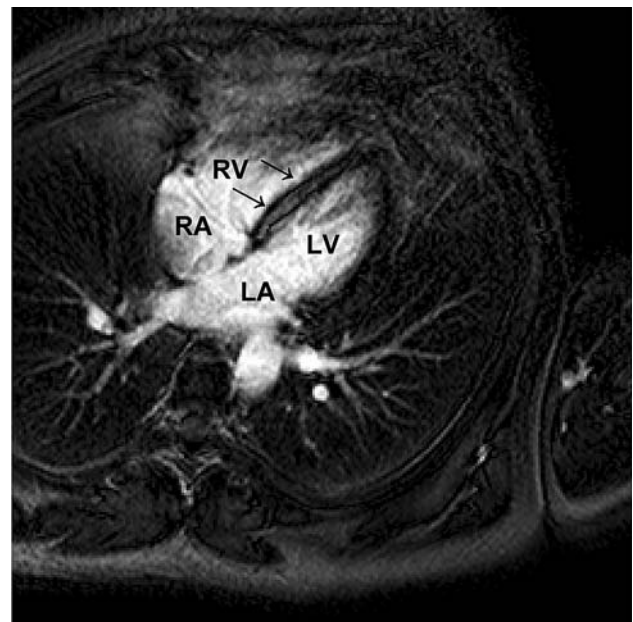


Fig. 5 Delayed enhancement imaging of a 61-year-old male patient with viral myocarditis, fatigue and frequent ventricular premature beats after a respiratory infect. Four-chamber view demonstrating enhanced mid-wall signal intensity of the left ventricular septal myocardium (*arrow*). *LV* Left ventricle. *RV* right ventricle. *LA* Left atrium. *RA* right atrium

affecting the anteroseptal myocardium but also forming a mid-wall area of damage in the entire septum. Myocardial biopsies targeted to areas with late gadolinium

enhancement show histological evidence of myocarditis in patients [6].

In a study, Gutberlet et al. [52] analysed 83 patients with chronic myocarditis. They found a lower sensitivity and accuracy of T1- and T2-weighted images. Their specificity was acceptable with 80%. The authors found no association with polymerase chain reaction proof of viral genomes, but a correlation with T1- and T2-weighted images and intra-myocardial inflammation. Thus, CMRI findings have to be interpreted different if it is used in the acute phase or in the chronic phase of myocarditis. In the acute phase, an enhanced signal in T2-weighted images and in T1 contrast-enhanced images is a typical finding whereas this is not the case in chronic myocarditis. At presence, a major limitation of CMRI is that it cannot detect viral persistence.

In conclusion, in patients with suspected myocarditis, cardiovascular magnetic resonance tomography including a high sensitive, specific and robust fast spin echo triple inversion recovery sequence (STIR) is helpful in decision-making. The CMR study should include a late enhancement sequence. T1-weighted native image is recommended in patients with additional pericardial effusion. T1-weighted spin echo after gadolinium injection might be added.

Accuracy of cardiovascular magnetic resonance in relation to biopsy-confirmed cases

The traditional diagnosis of viral myocarditis relies upon the histological (Dallas) criteria. Evaluation of endomyocardial biopsy specimens by use of these criteria may give negative results despite clear clinical evidence for acute myocarditis [3, 49]. There is a sensitivity of only 25–40% reported [3, 77, 78]. To date, techniques, in particular immunohistochemistry and viral polymerase chain reaction, and magnetic resonance guided endomyocardial biopsies have lead to substantial improvement of diagnostic accuracy of endomyocardial biopsy [6, 52, 79]. Thus, endomyocardial biopsy remains the diagnostic gold standard in myocarditis and in viral myocarditis in particular. Table 1 depicts cardiovascular magnetic resonance in relation to biopsy-confirmed cases. The majority of the studies involved only small number of cases. In addition, there are different methods for the evaluation of myocardial oedema used. In older studies, a T1 spin echo or T2 spin echo sequence was used [49, 50, 55]. In some studies, no late enhancement technique was performed [49, 50, 55]. Recent studies compared different cardiovascular magnetic approaches with biopsy results [52, 73], and magnetic resonance guided endomyocardial biopsies [6]. Especially, the latter study has shown a very good accuracy between the late enhancement technique and biopsy-proven myocarditis of 95%. In the study of Gutberlet et al. [52], the diagnostic accuracy was lower (49%). This might be due to

a different state of the patients. A pathological late enhancement occurs in patients with more severe myocarditis which may involve cellular necrosis. Therefore, not all patients with myocarditis present with a positive late enhancement pattern. Gutberlet et al. [52] also compared T1- and T2-weighted images for the diagnosis of myocarditis. The diagnostic accuracy was 72 and 68%. Thus, there is an acceptable concordance between novel magnetic resonance modalities and biopsy results but still further research work has to be performed.

Comparison of echocardiography and cardiovascular magnetic resonance

There are several case reports with normal echocardiographic findings but a diagnosis of myocarditis was confirmed by cardiac magnetic resonance. Marnach et al. [80] describe a case of postpartum myocarditis in a woman with lupus anticoagulant and antiphospholipid syndrome. The diagnosis of myocarditis was confirmed by cardiac magnetic resonance but was not apparent on echocardiography. The myocarditis resolved with steroid therapy. Kontogianni et al. [81] report two male adolescents (15 and 19 years old) who were admitted due to chest pain influenced by the respiratory movements, composing a clinical setting highly indicative of acute myocarditis. The echocardiogram performed in both patients failed to reveal any regional or global wall motion abnormalities or even diastolic dysfunction and remained absolutely normal throughout their 3-month follow-up period. CMRI within 7 days using T2-weighted and gadolinium-enhanced T1-weighted images demonstrated extensive focal contrast enhancement, consistent with acute inflammatory myocardial involvement. The authors conclude that contrast CMRI is a more sensitive method than the echocardiogram for the diagnosis of acute focal myocarditis.

Computer tomography with multislice techniques

Computer tomography (CT) with multislice techniques is useful in the diagnosis of coronary artery disease [82]. Brooks and Sane [83] report two patients with clinical myocarditis who had distinctive findings at coronary CT. Both patients demonstrated delayed myocardial enhancement with iodinated contrast. The morphologic features of the enhancement were similar to the myocardial enhancement with gadolinium contrast on magnetic resonance imaging recently described in patients with myocarditis, and different from the enhancement patterns seen in patients with myocardial infarction. Dambrin et al. [84] investigated the diagnostic value of ECG-gated multidetector CT in the early phase of suspected acute myocarditis in 12 consecutive patients admitted for suspected acute

Table 1 Cardiovascular magnetic resonance in comparison to biopsy-confirmed cases

Literature	Number of pts	Myocardial oedema present	Late enhancement present	Biopsy-proven active myocarditis	Accuracy in regions of late enhancement	Accuracy in regions without late enhancement
Gagliardi et al. [55]	11	6 ^a	n.p.	6	n.p.	n.p.
Friedrich et al. [47]	19	16 (84%)	n.p.	4/7 (57%)	n.p.	n.p.
Roditi et al. [50]	20	12 ^b	n.p.	4	100%	n.r.
Mahrholdt et al. [63]	32	n.r.	28 (88%)	20 (62.5%)	19/21 (90%)	1/11 (9%)
De Cobelli et al. [73]	23	5 (22%) ^c	16 (70%)	14 (61%)	12/14 (86%)	n.r.
Mahrholdt et al. [6]	128	n.r.	83 (95%)	87	n.r.	n.r.
Gutberlet et al. [52]	83	72% ^d and 68% ^e	n.r.	49/83 (59%)	49% ^f	49% ^f

n.r. Not reported, n.p. not performed

^a T2 spin echo

^b T1-weighted images before and after contrast agent administration

^c T2-fat saturated black blood image

^d T1-weighted imaging before and after contrast agent administration

^e T2-weighted triple inversion recovery imaging to calculate the oedema ratio

^f Difference not reported

myocarditis less than 10 days after onset of symptoms. All patients had clinical, electrocardiographic signs, and laboratory findings consistent with the diagnosis. They compared the CT results to CMRI using T1-weighted delayed enhancement images after injection of gadolinium. Extent and location of hyperenhancement at CT correlated well with that observed at MR examination. Boussel et al. [85] evaluated the accuracy of delayed-enhanced multidetector computed tomography for differentiating between myocarditis and myocardial infarction in 12 patients with normal X-ray coronary angiography. Final diagnosis between myocarditis and myocardial infarction was identical for delayed-enhanced multidetector computed tomography and magnetic resonance tomography with a significant agreement for number of involved segments and transmural extension. A major limitation of cardiac computed tomography is due to radiation exposure to the patient. The use of lower tube voltages, prospective ECG pulsing and new patients protocols have recently led to dose reduction [86] but still the applied doses remain relatively high [87].

Conclusion

An autopsy series of consecutive cases have demonstrated an incidence of myocarditis at approximately 1–10% [88]; on the contrary, myocarditis is seriously underdiagnosed clinically. In a traditional view, the gold standard has been myocardial biopsy. However, it is generally specific but insensitive for clinical use, mostly because of the focal nature of the disease. The endomyocardial procedure via the femoral vein approach under fluoroscopic guidance has

a very low complication rate of 0.0–0.12% of major and 0.2–5.5% of minor complications when performed by very experienced operators and in a high volume centre [89]. In clinical practice, the overall rate of complications has been reported to range between 1 and 6% [79, 90–92]. The mortality rate has been reported from 0.0 to 0.4% [3, 79, 89–91]. Thus, non-invasive approaches to detect myocarditis are necessary. The traditional diagnostic tools are ECG, laboratory values, especially troponin T or I, creatine kinase and echocardiography. For a long period, nuclear technique with indium-111 antimyosin antibody has been used as a diagnostic approach. In the last years, the use of this technique has declined due to radiation exposure and 48-h delay in obtaining imaging after injection to prevent blood pool effect.

Thus, a non-invasive diagnostic approach without radiation and online image availability has been awaited. Cardiac magnetic resonance has these promising characteristics. With this technique, it is possible to analyse inflammation, oedema and necrosis in addition to functional parameters such as left ventricular function, regional wall motion and dimensions. But still larger studies are warranted to further establish the different CMR modalities in the diagnosis of myocarditis.

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Conflict of interest statement None.

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