Diagnosis of myocarditis: current state and future perspectives

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Chapter 2

ABSTRACT

Myocarditis, i.e. inflammation of the myocardium, is one of the leading causes of sudden cardiac death (SCD) and dilated cardiomyopathy (DCM) in young adults, and is an important cause of symptoms such as chest pain, dyspnoea and palpitations. The pathophysiological process of disease progression leading to DCM involves an ongoing inflammation as a result of a viral-induced auto-immune response or a persisting viral infection. It is therefore crucial to detect the disease early in its course and prevent persisting inflammation that may lead to DCM and end-stage heart failure. Because of the highly variable clinical presentation, ranging from mild symptoms to severe heart failure, and the limited available diagnostic tools, the evaluation of patients with suspected myocarditis represents an important clinical dilemma in cardiology. New approaches for the diagnosis of myocarditis are needed in order to improve recognition, to help unravel its pathophysiology, and to develop new therapeutic strategies to treat the disease. In this review, we give a comprehensive overview of the current diagnostic strategies for patients with suspected myocarditis, and demonstrate several new techniques that may help to improve the diagnostic work-up.
INTRODUCTION

Myocarditis is an inflammation of the myocardium as a result of an infection, autoimmune disease or cardiotoxic agent. This inflammation can lead to acute heart failure, chest pain and life threatening arrhythmias. Cardiac function may rapidly deteriorate and patients may become hemodynamically unstable and require supportive therapy or even cardiac transplantation. Furthermore, patients with myocarditis have an increased risk of sudden cardiac death (SCD) and the development of a dilated cardiomyopathy (DCM). Therefore it is important to detect the disease early in its course. However, myocarditis is one of the most challenging diagnosis in cardiology and is often under-recognized due to the heterogeneity of its clinical presentation that overlaps with other cardiac diseases, such as an acute coronary syndrome. Endomyocardial biopsy (EMB) is the gold standard for diagnosing myocarditis and its underlying cause, and it may contribute to the selection of patients who might benefit from specific therapeutic measures. Although EMB is safe in experienced hands, there is a small risk of potentially serious complications. Sensitivity of EMB is negatively influenced by sampling error, and the (immuno)histochemical assessment of the biopsy material is challenging. Also, EMB cannot be used for risk stratification or to predict the progression to DCM. In addition, prognosis is good in the majority of patients and effective therapy is not available for most causes. EMB is therefore not part of routine clinical practice in patients with suspected myocarditis. Cardiac magnetic resonance (CMR) is a good non-invasive alternative but with current techniques the diagnosis can still be missed. Also, CMR cannot determine the underlying cause of myocarditis, and, so far, cannot be used for risk stratification or prediction of outcome, both crucial for patient management. In this review, we will discuss the current diagnostic approach in patients with suspected myocarditis and demonstrate new techniques that may help to improve the diagnostic work-up and risk stratification.

CLASSIFICATION AND ETIOLOGY

Symptom onset, histological features and underlying etiologic agents may each contribute to the classification of myocarditis into distinct subtypes (Table 2.1). Based on the onset of symptoms, myocarditis is divided into fulminant, acute or chronic myocarditis. The chronic state can be further subdivided according to the stage of inflammation into persistent inflammation, chronic viral infection (with or without inflammation) or healed inflammation (with or without irreversible damage to the heart). The types of infiltrates found in EMB samples can also classify myocarditis, and provide important clues to an underlying etiology. Lymphocytic myocarditis is by far the most common form.
Histological findings may include the presence of multinucleated giant cells, granulomas, neutrophilic or eosinophilic granulocytes. Finally, myocarditis can be categorized by its underlying etiology. There are numerous causes of myocarditis, yet the etiology remains undetermined in most cases. Viral infection of the myocardium is the most common identified cause of myocarditis. There are up to 20 known cardiotropic viruses that may elicit myocarditis. In Europe and North America, viral genomes of parvovirus B19 (PBV19), human herpes virus 6 (HHV6) and enterovirus (EV) are detected in the majority of cases. An immune response against cardiac myocytes is another important cause of myocarditis, which may be triggered by the viral infection, a specific allergenic agent such as medication, or cardiac transplantation, but is also found in systemic autoimmune disorders, such as systemic lupus erythematosus, rheumatoid arthritis and scleroderma. In addition, toxic agents including cocaine, amphetamines and certain cytostatic drugs can lead to myocardial inflammatory disease also. Other less frequent causes of (toxic) myocarditis include animal bites, insect stings and heavy metals.

### Table 2.1: Classification of myocarditis

<table>
<thead>
<tr>
<th>Clinicopathology</th>
<th>Histology</th>
<th>Etiology</th>
</tr>
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<tbody>
<tr>
<td>Fulminant</td>
<td>Lymphocytic</td>
<td>Infectious: viral, bacterial, spirochaetal, fungal, protozoal, parasitic, and rickettsial</td>
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<tr>
<td>Acute</td>
<td>Giant cell</td>
<td>Autoimmune: allergens, alloantigens, and autoantigens</td>
</tr>
<tr>
<td>Chronic</td>
<td>Granulomatous</td>
<td>Toxic agents: drugs, alcohol, radiation, and chemicals</td>
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<tr>
<td>Persistent inflammation</td>
<td>Eosinophilic</td>
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<tr>
<td>Viral infection with or without inflammation</td>
<td>Neutrophilic</td>
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<tr>
<td>Healed inflammation with or without irreversible damage to the heart</td>
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**CLINICAL PRESENTATIONS, DIFFERENTIAL DIAGNOSIS AND INITIAL EVALUATION**

Myocarditis has a heterogeneous clinical manifestation which can be divided into the following presentation types: acute coronary syndrome like (ACS-like) symptoms, new-
onset heart failure, life threatening arrhythmias and chronic heart failure. Symptoms or signs are not unique to myocarditis and initial evaluation using ECG, blood studies and echocardiography are not specific. Clinical clues to the disease include elevated inflammatory markers and gastrointestinal or respiratory infection preceding the onset of symptoms, however these may all be absent. Also, viral serology cannot be used for the diagnosis of myocardial infection.

**ACS-like presentation**

A large proportion of patients with myocarditis presents with ACS-like symptoms. Differentiating between myocarditis and acute myocardial infarction (AMI) presents a clinical dilemma because both can present with ST-segment elevation, regional myocardial dysfunction and cardiac enzyme release. The clinical challenge is further illustrated by the fact that even if coronary angiography (CAG) reveals unobstructed coronary arteries, AMI secondary to vasospasm or embolism is often assumed to be the case in clinical practice. However, several studies using CMR demonstrated that myocarditis was the correct diagnosis in the majority of these patients, and not AMI. Pericarditis often coincides with myocarditis. In this spectrum, perimyocarditis refers to acute pericarditis with signs of myocarditis demonstrated by troponin release or myocardial dysfunction.

**New onset heart failure**

Patients with myocarditis may also present with symptoms and signs of heart failure. The suspicion of myocarditis is generally raised when more common causes of heart failure like ischemic, valvular and hypertensive heart disease are excluded. Echocardiography typically shows global impairment of cardiac systolic function and in some cases a thickened ventricular wall as a result of oedema can be seen. In patients with fulminant myocarditis, cardiac function may rapidly deteriorate leading to hemodynamic instability that requires supportive therapy, whereas patients with nonfulminant myocarditis usually have a more gradual course.

**Life threatening arrhythmias**

Myocarditis can also result in arrhythmias and conduction disturbances, that may be severe and life threatening, such as atrioventricular (AV) blocks, ventricular fibrillation/flutters and sustained ventricular tachycardia. Myocarditis is one of the most common findings at autopsy in young adults who died of sudden cardiac death. Although a viral syndrome is sometimes reported, these individuals are usually asymptomatic until death.
In general, the diagnostic evaluation of life-threatening arrhythmias includes 12 lead ECG, echocardiography and in some cases CAG. Myocarditis may be suspected when there is no evidence of coronary artery disease or distinct electrophysiological abnormalities.

**Chronic heart failure**

DCM, i.e. LV systolic dysfunction with an associated LV dilatation, may be the first manifestation of late-stage myocarditis. DCM is considered to be the chronic component of myocarditis which develops when the disease progresses to a persistent state of inflammation. These patients typically present to the outpatient clinic with gradual progression of heart failure. The acute phase of myocarditis may have passed unnoticed or with mild symptoms only. Next to myocarditis, DCM can be the result of various other causes, and the differential diagnosis is therefore extensive. Although clinical features can provide clues to the underlying cause, without EMB and/or genetic testing the cause of DCM remains unknown in up to half of the cases.

**DIAGNOSIS**

**Endomyocardial biopsy**

EMB may provide information about the presence of viral genome, fibrosis, cell death, the type of inflammatory infiltration and the deposition of iron, proteins or lipids. The underlying cause of myocarditis can only be determined by an EMB because non-invasive tests are limited in their ability to assess these features. EMB is required before targeted therapy can be initiated. Immunosuppression proved to be beneficial in autoimmune mediated myocarditis but detrimental in viral myocarditis. EMB is considered to be a relative safe procedure when performed by an experienced physician. Risks of major complications are comparable between right sided EMB (RV-EMB) and left sided EMB (LV-EMB), although the types of complication are different. RV-EMB is associated with a higher risk of cardiac perforation while LV-EMB has a higher risk of stroke. There is still controversy in many medical centres about the role of EMB in the diagnosis and treatment of myocarditis, mostly because the procedural risks do not always outweigh the incremental value of EMB, as the majority of myocarditis patients have a good prognosis. The highest yield of EMB is reached in myocarditis patients who present with acute heart failure. In these patients, EMB can exclude more aggressive disorders like giant cell myocarditis or necrotizing granulomatous myocarditis and can guide treatment. In order to improve recognition, understanding and, ultimately, management of myocarditis, an
ESC working group recently proposed to perform EMB in all patients with suspected myocarditis, irrespective of clinical presentation type 17.

**Histology, immunology and immunohistochemistry**

Traditionally, the histological diagnosis of myocarditis was established according to the Dallas Criteria that were proposed in 1986 49. These criteria were based on the detection of inflammatory infiltrates in hematoxylin-eosin stained biopsy samples. The diagnosis of acute myocarditis required both inflammatory infiltrates and myocyte damage of non-ischaemic origin (Figure 2.1). Borderline myocarditis was diagnosed when infiltrates were not accompanied by myocyte damage. The introduction of immunohistochemistry (IHC) enabled a more detailed characterization of the inflammatory infiltrates using antibodies against leukocytes (CD45), T lymphocytes (CD3), macrophages (CD68) and together

![Figure 2.1: Histo- and immunopathology of heart tissues.](image)

Upper left: anti-CD45 antibody staining for lymphocytes (400x), showing acute lymphocytic myocarditis with aggregates of extravascular lymphocytes adherent to cardiomyocytes. Upper right image: anti-C3d antibody staining for myocyte damage (400x), demonstrating cell death of cardiomyocytes. Lower left image: haematoxylin-eosin (HE) staining (200x), showing giant cell myocarditis with diffuse inflammatory infiltrates and multinucleated giant cells. Lower right image: HE staining (400x), demonstrating eosinophilic myocarditis with inflammatory infiltrates composed predominantly of eosinophilic granulocytes.
with immune activation markers (anti-HLA-DR) \(^{50,52}\). Myocarditis is currently diagnosed when ≥14 leukocytes are detected per 1 mm\(^2\) in addition to enhanced HLA expression and adjacent myocytolysis \(^{10,53}\). The diagnostic potential of EMB was further enhanced by the introduction of molecular biology methods such as polymerase chain reaction (PCR), which enables the sensitive detection of viral genomes in biopsy samples \(^{54}\). The use of PCR brought new challenges as PVB19 genomes are not only found in myocarditis patients, but also in healthy controls \(^{55-57}\). However, using quantitative PCR (qPCR), Bock et al. \(^{58}\) showed that PVB19 viral load in biopsy samples are significantly higher in patients with acute myocarditis in comparison to patients with chronic myocarditis or healthy controls. This suggests that qPCR may aid in differentiating between active and latent PVB19 infection of the myocardium.

**Diagnostic performance**

Because EMB is considered to be the gold standard for diagnosing myocarditis, other in-vivo tests cannot be used as a reference of validation. For this reason EMB is compared with autopsy and transplanted hearts. Hauck et al. \(^{14}\) and Chow et al. \(^{15}\) both evaluated the diagnostic performance of EMB by studying ex-vivo hearts that were either obtained at autopsy in patients diagnosed with myocarditis or obtained after cardiac transplantation. In both studies, the diagnosis was still missed in approximately half of the patients with myocarditis, even when 10 biopsy samples were analyzed \(^{14}\). Moreover, 17 biopsies were needed to reach a sensitivity of 80% \(^{15}\), indicating that sampling error of EMB can be explained by the focal nature of inflammation as found in the majority of cases \(^{14}\). In addition, EMB is hampered by high interobserver variability in the interpretation of biopsy samples \(^{13}\). For this reason, Baughman \(^{12}\) proposed to abolish the Dallas criteria and to use both IHC and PCR instead. The incremental diagnostic value of IHC was demonstrated in biopsy samples that were negative according to the Dallas criteria while IHC was able to reveal inflammatory infiltrates in these biopsy samples \(^{45,59}\). Despite the introduction of IHC and PCR, sampling error remains an important limitation of EMB and the sensitivity of EMB is still dependent on the number of biopsy samples. When comparing the diagnostic performance of univentricular EMB and biventricular EMB, the highest diagnostic performance was reached with biventricular EMB \(^{48}\). However, this incremental diagnostic performance may have resulted from the higher number of samples that were taken with biventricular EMB. The sensitivity of univentricular EMB for the detection of inflammation seems to be higher in LV-EMB than RV-EMB, especially when RV function is not affected \(^{11,48,60,61}\). Attempts to improve the diagnostic performance of EMB by CMR guided biopsy failed to succeed \(^{48}\).
Cardiac Magnetic Resonance

CMR is a non-invasive tomographic imaging modality that can be used to assess both the structure and function of the heart with high accuracy. CMR is unique when it comes to its ability to assess the characteristics of the myocardial tissue, making it the noninvasive diagnostic tool of choice in myocarditis. In addition, CMR cine imaging is considered the reference standard for the quantitative assessment of regional and global left and right ventricular function. Using these techniques, CMR is able to demonstrate typical features of acute inflammation such as dysfunction, oedema and necrosis.

Tissue characterization

Tissue characterization by CMR is based on the principle that tissues have different magnetic properties. CMR is able to generate images that that highlight specific soft tissues by using different imaging techniques. With the use of a gadolinium based contrast agent (GBCA) image contrast can be enhanced to provide further detail.

Injured cardiac muscle cells lose their membrane integrity and GBCA that normally remains in the extracellular space, can now freely diffuse into the cell. After 5–15 min, the contrast will have been largely washed out of the normal myocardium but will remain concentrated in the areas of necrosis. GBCA affects the magnetic parameter T1 relaxation time, and regional differences in contrast concentration can be depicted using inversion recovery T1-weighted imaging (late gadolinium enhancement (LGE)). In fibrosis, the mechanism is similar, with the contrast agent accumulating in the increased extracellular space in fibrotic areas. Myocardial necrosis or fibrosis is also seen in ischaemic heart disease and in many other non-ischaemic cardiomyopathies.

Regional contrast enhancement is therefore not specific for myocarditis. However, the pattern of contrast enhancement varies between cardiac diseases whereby subepicardial or mid-myocardial contrast enhancement is typically seen in myocarditis (Figure 2.2A). LGE imaging has been shown an excellent diagnostic tool in suspected myocarditis and may show regional contrast enhancement even when myocardial function is completely normal.

Acute myocardial inflammation leads to myocardial oedema, which profoundly affects the magnetic properties, especially the T2 relaxation time, and differences between normal and oedematous myocardial tissue can be demonstrated using T2-weighted (T2w) imaging. As with LGE, regional high signal intensity reflecting myocardial oedema typically involves the subepicardial or midwall layer of the myocardium (Figure 2.2B). However, in case of diffuse myocardial involvement with global oedema, T2w imaging will not show regional differences in signal intensity. To overcome this drawback, the signal intensity of the skeletal muscle is used.
muscle may be used as a reference to calculate the oedema ratio (ER), which is considered abnormal when it reaches a value of 2.0 or higher.\textsuperscript{74}

Friedrich et al.\textsuperscript{77} have proposed to use standard T1-weighted imaging before and after contrast administration to demonstrate myocardial hyperemia in actively inflamed myocardium. This so-called early gadolinium enhancement (EGE) technique reflects contrast distribution in the early washout period.\textsuperscript{62,77} The authors showed that the relative increase in signal intensities of the myocardium compared to skeletal muscle was higher in patients with suspected myocarditis than in healthy control patients and proposed a ratio $\geq 4.0$ as diagnostic for myocardial inflammation.\textsuperscript{78} However, practical application of this approach is hindered by suboptimal image quality caused by breathing and motion artifacts with the use of this non-breath-hold imaging sequence.

\textbf{Figure 2.2: LGE, T2w and Cine imaging in acute myocarditis.}\n
Cine, LGE and T2w images both in the same patient with acute myocarditis, demonstrating subepicardial LGE (A), subepicardial oedema (B) and wall motion abnormality in the inferolateral wall (C= diastolic cine image, D= systolic cine image), typical of myocarditis.
**Diagnostic performance**

In order to determine CMR’s diagnostic performance it needs to be compared to the gold standard, i.e. endomyocardial biopsy. Many studies however did not validate CMR findings with histopathology because EMB was not routinely performed. Studies that validate CMR with a biopsy sample report sensitivity rates of 61–76%, 47–64% and 60–74% for respectively EGE, T2w and LGE. The diagnostic performance dramatically drops in the chronic phase of myocarditis and in patients with borderline myocarditis. This, for example, became apparent in a study by Baccouche et al. who performed CMR and EMB in patients with suspected myocarditis and found that 63% of the patients without LGE had borderline myocarditis on biopsy. In 2009 a combined approach was proposed in order to improve CMR’s diagnostic performance. With this combined approach, using EGE, T2w and LGE, myocarditis is diagnosed when 2 out of 3 techniques are positive. In a study by Abdel-Aty et al. this yielded a sensitivity and specificity of respectively 76% and 96% in patients with acute biopsy proven myocarditis. Despite these criteria, the diagnosis may still be missed in a substantial number of patients, especially in the chronic phase of myocarditis.

There are a number of possible explanations for false negative CMR studies. First, the size of small islands of necrosis and oedema may be beyond the detectability limit of CMR. Also imaging artifacts can hamper the diagnostic performance of CMR, which may be prominent in the non-breath hold EGE sequence and in T2w imaging. Furthermore, current CMR techniques only allow for the visualization of regional abnormalities, and cannot demonstrate global myocardial involvement. Ratio’s comparing signal intensity of myocardial and skeletal muscle may overcome this problem in EGE and T2W imaging, however, skeletal muscle may also be involved in the disease. This became apparent in a study by Ferreira et al. who showed that patients were misdiagnosed by their oedema ratio because both myocardium and skeletal muscle were affected.

**Diagnostic approach in patients with suspected myocarditis**

Clinically suspected myocarditis requires cardiac signs and/or symptoms in combination with cardiac biomarker release, ECG changes, arrhythmias or LV dysfunction, in the absence of other cardiac causes. CMR should be performed in all patients when clinically possible. CMR can provide strong evidence for the diagnosis of (acute) myocarditis and allows the detailed assessment of other underlying myocardial disease. Effective therapy is only available for a limited number of causes, such as giant cell myocarditis or eosinophilic myocarditis. Since immunosuppressive therapy is potentially detrimental in myocarditis of viral origin, and EMB is the only way to differentiate between viral and autoimmune-related disease, EMB is required in all patients who are hemodynamically unstable. In addition,
its use should be considered in patients with new onset heart failure or arrhythmias whose clinical condition fails to improve or deteriorates, even when CMR does not show signs of myocarditis, given its lower sensitivity in this patient group. Patients with ACS-like presentation generally have excellent prognosis, and, in these, EMB is rarely required although it may be considered with chronic or recurrent symptoms.

In all patients, follow-up CMR should be considered to establish the final recovery status, by showing residual scar and systolic function.

A proposed diagnostic approach for the use of CMR and EMB in clinically suspected myocarditis and based on the type of presentation, is shown in Figure 2.3.

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**Figure 2.3: Proposed diagnostic approach for the use of CMR and EMB in clinically suspected myocarditis.**

ACS = acute coronary syndrome; HF = Heart failure; CMR = Cardiac magnetic resonance; EMB = Endomyocardial biopsy.
FUTURE PERSPECTIVES

EMB and CMR form the backbone of the current diagnostic work-up of patients with suspected myocarditis. However, both EMB and CMR have a number of drawbacks. New diagnostic techniques face challenging requirements: they should be able to detect the disease in an early stage, to determine the degree of inflammatory activity and myocardial involvement, and to identify patients who are at risk for the development of DCM or SCD. In addition, they should be less invasive than EMB and allow the serial assessment of the disease extent to follow the response to putative therapeutic measures.

New CMR techniques: T1 and T2 mapping

Recently, new CMR techniques were introduced that enable a quantitative measurement of magnetic relaxation parameters T1 and T2 superscript 81, 82 (Figure 2.4). Parametric maps encoding these values enable a more detailed tissue characterization and appear to have higher sensitivity for small regions of oedema and necrosis that would be missed by conventional CMR techniques superscript 83-86. Furthermore, T1 values change after contrast, and pre-contrast and post-contrast values can be used together to estimate the myocardial extracellular volume (ECV), i.e. the space that is not occupied by cardiac myocytes and is replaced by collagen matrix. The ECV can be considered a surrogate marker for interstitial fibrosis and is a promising new tool in patients with diffuse myocardial disease superscript 87. Furthermore, studies elaborated to determine the diagnostic values of these techniques, report incremental improvement.

Figure 2.4: Quantitative measurements of myocardial magnetic properties using CMR mapping techniques.

CMR study in a fifty-one year old patient who presented to our hospital with acute heart failure and severe LV dysfunction after a respiratory infection. T2w imaging did not show regional myocardial oedema (left). CMR mapping technique was performed and revealed diffuse and markedly elevated T1 relaxation times of the myocardium suggestive of diffuse myocardial oedema (right). Endomyocardial biopsy was performed and confirmed the diagnosis of myocarditis.
diagnostic value compared to conventional CMR in myocarditis\textsuperscript{80, 88, 89}. Although the first results are promising, there are still some obstacles to overcome before these techniques can be used in clinical practice. For example, the diagnostic value of these techniques in myocarditis still requires validation by EMB. Also, T1- and T2-values vary with the type of scanner, the magnetic field strength and the pulse sequence used, making it difficult to determine its normal range\textsuperscript{85}. Finally, there is ongoing debate on what is the optimal parameter to evaluate myocardial disease (pre-contrast T1 or T2, post-contrast T1, or ECV).

**Blood biomarkers**

A biomarker is a biological property that can be objectively measured and used as an indicator of pathologic processes\textsuperscript{90}. Blood is highly suitable for the identification of biomarkers because it can be easily obtained. Considerable effort has been devoted to the identification of blood biomarkers that may serve as indicators of prognosis and the response to therapy in myocarditis. In this search, a variety of anti-heart antibodies (AHAs) have been identified in the blood of myocarditis patients and DCM patients. AHAs are presumed to result from (auto)immune processes in the course of an infectious or inflammatory myocardial disease\textsuperscript{17}. Interestingly, patients with circulating AHAs respond favorably to immunosuppression in infection-negative forms of myocarditis\textsuperscript{27}. Also, AHAs have been shown to predict the development of DCM in asymptomatic relatives of DCM patients\textsuperscript{91}. Unfortunately, this type of antibody testing requires highly specialized laboratories and it is not yet accessible for clinical application. The availability of such tests in routine practice will further enhance the clinical implications of AHAs in myocarditis and DCM.

Since several years, there is growing interest in the utility of microRNAs as a diagnostic and prognostic biomarker in myocarditis. MicroRNAs are important regulators of gene expression and are involved in numerous cardiovascular diseases\textsuperscript{92-94}. Several studies have been carried out to determine microRNA expression profiles of EMB tissue in viral myocarditis\textsuperscript{95-97}. In these studies, EMB analysis with microRNA profiling appeared to be a useful marker of adverse outcome and inflammation activity. Recently, studies started to focus on blood microRNA with the intention to replace microRNA profiling in tissue samples. Although this field of research is still in the early stage, first data seem promising as circulating microRNAs appear to be measurable in the blood and seem to be present in a stable form\textsuperscript{98, 99}. However, data of circulating microRNA in viral myocarditis, to our knowledge, are still lacking.
Peripheral muscle biopsy

The concept of skeletal muscle involvement in various cardiomyopathies dates back to the 1970s. In 1997 Arbustini et al. found enteroviral RNA and virus-like particles in the skeletal muscle of a patient with idiopathic DCM. In a subsequent study, they also described enteroviral RNA and virus-like particles in patients with fatal enteroviral myocarditis, suggesting the possibility that skeletal muscle may reflect viral presence in the heart. In addition to viral presence, as already mentioned above, skeletal muscle inflammation has been shown in MRI studies. Results from these small studies suggest that skeletal muscle reflects the pathology of the heart in viral myocarditis. However, the potential of skeletal muscle biopsy as a more accessible diagnostic window to viral myocarditis has never been explored. We recently found increased infiltration of lymphocytes in quadriceps skeletal muscle obtained at autopsy in patients diagnosed with viral myocarditis and in a mouse model for acute CVB3-induced myocarditis. In fact, this infiltration of lymphocytes in the quadriceps muscle appeared to predict viral myocarditis with a sensitivity of 71% and specificity of 100%. Although results are still preliminary, a peripheral muscle biopsy may potentially be used as a much easier and safer alternative to EMB for the detection of inflammation and viral presence in myocarditis, but more research is warranted.

SUMMARY

Because symptoms and initial evaluation are not specific in myocarditis, the evaluation of patients with suspected disease remains challenging. The diagnosis currently relies on CMR and EMB, each with their own benefits and drawbacks. EMB is crucial for a better understanding of pathophysiology and the underlying causative disorder and should be considered as a standard procedure in suspected myocarditis in patients with other than ACS-like presentation types. New diagnostic tools are being developed that may complement and improve on current diagnostic approaches for myocarditis. The focus of newer techniques should include the early (less invasive) detection of disease and both short term and long term risk stratification. This should ultimately allow the identification of the high risk patients in whom aggressive treatment of the disease may prevent SCD and the development of DCM.
REFERENCES

Diagnosis of myocarditis


