Special Article

Imaging in Inflammatory Heart Disease: From the Past to Current Clinical Practice

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Key words:
Myocarditis, inflammation, imaging, cardiovascular magnetic resonance.

Manuscript received:
June 20, 2009;
Accepted:
July 15, 2009.

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The human heart has been a fascinating organ throughout human history. The Greek philosopher Aristotle (384–322 BC) considered the human heart to be the most important organ of the body. In his belief, the human heart was "the seat of intelligence, motion and sensation", while the other organs surrounding the heart only existed to cool the heart.[1] A few centuries later, the Greek scholar Galen (129–216 AD) described the human heart as the source of the body's innate heat and stated that "the heart is a hard flesh, not easily injured". During the Renaissance, Leonardo da Vinci (1452–1519) stated that "the heart is of such density that fire can scarcely damage it."[2] Taken together, ancient scholars consistently believed that a) the human heart is an outstanding organ, and b) it is robust and can hardly be damaged.

However, today cardiovascular diseases represent the number one cause of morbidity and mortality in western societies and we know that even a tiny pathogen like a virus can cause lethal damage to the heart. Amongst cardiac diseases, inflammatory heart disease is gaining increasing importance, since new imaging techniques enable the non-invasive detection of inflamed or "overheated" myocardium in various diseases. Only through an accurate diagnosis of myocardial inflammation can successful implementation of appropriate therapies be achieved. Therefore, this review will focus on imaging modalities currently used to detect myocardial inflammation, after briefly looking at the historical origins of inflammatory heart disease and related diagnostic techniques (Table 1).

Definition of myocardial inflammation

The word "inflammation" is derived from the Latin term *inflamatio*, which implies to set something on fire. Myocardial inflammation describes a non-specific yet sophisticated biological process involving the teamwork of different cell types and serum factors, and is initiated in response to stimuli that disturb normal cell or tissue haemostasis.[3,4] In principle, inflammation initially occurs at the site of injury in order to eliminate or at least to limit the disturbing stimulus. This process can be induced either by exogenous pathogens (such as bacteria, viruses or parasites), or endogenous factors (such as in autoimmune processes or storage diseases).[4] In response to such adverse stimuli, "acute" inflammation is the initial reaction of the body, which is characterised by the accumulation of leukocytes and specific serum factors at the site of injury. If the innate defence mechanisms are not successful in quickly eliminating the respective pathogen or non-physiological stimulus, then "chronic" inflammation may persist for weeks, months, or even years, and essential-

Table 1. Short history of groundbreaking technical developments in diagnosing heart disease.

1900	1902: first electrocardiogram (ECG) recorded by Einthoven using a string galvanometer
	1929: first right heart catheterisation of a living human's heart (his own!) by Forssmann
	1930s-40s: essential developments in heart catheterisation by Coumand and Richards
	1941: construction of the first magnetic resonance imaging (MRI) machine by Block
	1954: introduction of M-mode echocardiography by Eder
	1962: introduction of emission reconstruction tomography (later known as SPECT and PET) by Kuhl
	1962: introduction of the first biopsy catheter enabling sampling EMBs by Sakakibara and Konno
	1970s: first clinical utilisation of M-mode and Doppler echocardiography
	1971: introduction of the first practical 2D echocardiography scanner by Born and Hugenholtz
	1972: first development of computed tomography by Hounsfield
	1972: development of a new percutaneous, flexible biopsy forceps for serial RV-EMB
	1973: first successful magnetic resonance image produced by Lauterbur
	1973: first computed tomography system from a medical equipment manufacturer
	1975: first successful implementation of SPECT by Kuhl
	1977: first human scan with the first MRI prototype by Damadian
	1981: Schering applied for a patent for the first magnetic resonance contrast agent (Gd-DTPA)
2000	1983: Toshiba obtained approval for the first commercial magnetic resonance imaging system

EMB – endomyocardial biopsy

ly influence not only (coronary or myocardial) structures at the site that had initially been "set on fire", but also surrounding tissues or even remote biological processes.

Based on animal studies, the pathogenesis of myocarditis is believed to comprise three interleaved phases.[4] At first, specific pathogens, such as viruses or bacteria, proliferate and cause myocardial infection, thereby triggering an immunological response that leads to myocardial inflammation and potential myocardial damage with release of cardiac troponins. Chronic inflammation in turn is followed by ventricular remodelling and myocardial fibrosis. The mechanisms involved in human myocarditis are comparable and include host immune activation in response to viral triggers, such as enteroviruses, parvovirus B19 (PVB19), and human herpes virus type 6 (HHV6)[5] (Table 2). Cytokine activation and cross-reacting antibodies may further accelerate and aggravate myocardial destruction. Various cytokines are known to activate matrix metalloproteinases and death-domain or ceramide-mediated signalling pathways, which in turn lead to matrix degradation and play a major role in adverse remodelling. This immune activation may be deleterious and lead to further myocyte destruction and finally to dilated cardiomyopathy.[4]

History of diagnosing "inflammation"

The Roman writer Celsus (25 BC–50 AD) introduced the first four of five cardinal clinical signs of "acute inflammation":[6] I) "rubor" (redness), as well as II) "calor" (increased heat), were believed to be caused by increased blood flow at the site of inflammation, whereas III) "tumour" (swelling) was the result of increased fluid accumulation and IV) "dolour" (pain) had different potential reasons. Later, the Greek scholar Galen (129–216 AD) added the fifth cardinal sign of inflammation: *functio laesa* (disturbance of function).[6] However, since the human heart is localised inside the human chest, clinical evaluation of those cardinal signs of inflammation in the case of the heart was impossible in living humans for quite a long time, and was confined to *post mortem* analysis by pathologists. Not until 1812 did Corvisart describe cardiac enlargement as a characteristic feature of myocardial disease in clinical terms for the first time.[7] With technical advances and the development of sophisticated cardiac imaging modalities, appropriate and progressively more precise and detailed evaluation of myocardial inflammation became possible *in vivo*. However, despite all advances, today's modern non-invasive cardiac imaging techniques still aim at assessing some of those cardinal signs of inflammation, such as "tumour" (swelling) of cardiomyocytes, or *functio laesa* (disturbance of function) of left or right ventricular function, or even "rubor" (redness) and "calor" (increased heat) by evaluation of myocardial perfusion.

Formation of the term "myocarditis"

Only after the year 1819, when the French physician Laennec (1781–1826 AD) introduced the stethoscope,

did a better non-invasive evaluation of cardiac diseases, enabling the differentiation between valvular and non-valvular diseases, become possible.[8] At that time, the term "carditis" (later gradually replaced by the term "myocarditis") was used to describe various non-valvular diseases that were characterised by cardiac dysfunction, which in turn was believed to be caused by either coronary or myocardial inflammatory processes.[9] The German scholar Virchow introduced the term "chronic myocarditis" for these aforementioned non-valvular diseases. In his opinion "chronic myocarditis" defined a heart muscle disease exclusively caused by myocardial inflammation.[9] However, in the following years, the term "chronic myocarditis" was widely, but inconsistently used and comprised various diseases, such as hypertension or coronary artery disease (CAD), since those diseases were believed to result in "chronic myocarditis".

Progress in electrocardiography in the first half of the 20th century resulted in the identification of CAD as an important reason for cardiac dysfunction and was followed by a shift in the meaning of the term "myocarditis" to those diseases with myocardial inflammation mostly caused by infectious pathogens.[10] As discussed in more detail by Silverman et al, specific aetiologies of myocarditis, such as rheumatic fever, diphtheria, syphilis, endocarditis, viral, rickettsial and parasitic diseases, were recognised around the mid 20th century.[11] The advances in diagnostic techniques following the 1950s repeatedly forced the scientific world to reassess their respective classification of cardiomyopathies, including various forms of myocarditis. At that time, the term "primary myocardial disease" as well as "non-coronary cardiomyopathy" were introduced to describe myocardial diseases of different origin that had no relationship to hypertension or CAD.[11]

Introduction of endomyocardial biopsy sampling

In 1962, Sakakibara and Konno introduced the first biopsy catheter, which enabled the *in vivo* sampling of endomyocardial specimens in suspected myocardial disease.[12,13] However, the sampling of endomyocardial biopsies (EMB) was not commonly used until major advances in cardiac transplantation required appropriate and easy tools for monitoring potential graft rejection. Only after 1972, when a new percutaneous and flexible bioptome was developed that allowed serial right ventricular EMBs to be obtained after heart transplantation, did the procedure of obtaining EMBs in order to evaluate myocardial disease become popular and widely used.[14] In the following years, the necessity of adopting objective and comparable histopathological criteria in the evaluation of EMBs became evident. Thus, in 1986 the Dallas criteria were proposed in order to provide a universally accepted histopathological classification of myocarditis.[15] According to this classification, the diagnosis of myocarditis is based on the detection of myocardial cellular infiltration with myocyte necrosis, with or without fibrosis, while borderline myocarditis is diagnosed in the case of myocardial cellular infiltration without myocyte necrosis, again with or without fibrosis (Figure 1). Moreover, if follow-up EMBs are obtained in a patient who has a previous histopathological diagnosis of myocarditis, then the progression

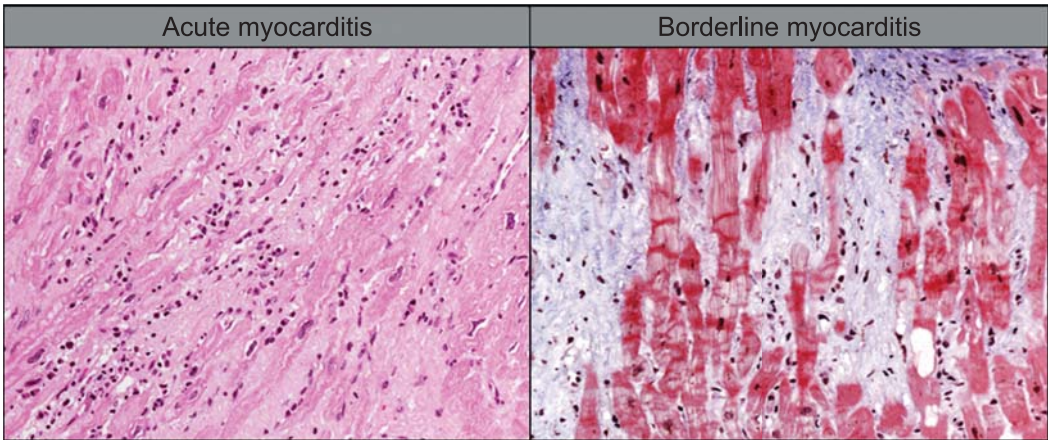

Figure 1. Histopathological evaluation of endomyocardial biopsy demonstrating extensive myocyte necrosis and inflammation in acute myocarditis (HE stain) and fibrosis (blue areas) and sparse inflammation in borderline myocarditis (Masson Trichrom stain).

or regression of the myocardial disease can be assessed using the terms "persistent" (ongoing), "healing" (resolving), or "healed" (resolved) myocarditis.[15]

Refining endomyocardial biopsy analysis

In parallel with these developments in obtaining EMBs safely, essential advances were achieved in the detection of specific antigens at the molecular level, using labelled or enzyme-bound antibodies: a technique called immunohistochemistry. After the first application of immunohistochemistry to frozen sections in 1940 by Coon,[16] Taylor and Burns were the first to succeed in applying this method to formalin-fixed, paraffin-embedded tissue sections in 1974.[17] Further advances in the following years made immunohistochemistry a highly valuable and accurate tool for the detection of antigens at the molecular level, thereby enabling more sophisticated diagnoses. Considering the workup of myocardial inflammation in EMBs (in the case of suspected myocarditis), immunohistochemical techniques today offer the detection of low grade inflammation and, moreover, the differentiation of subtle differences in the severity of inflammation[18-20] (Figure 2). Previous studies that evaluated the sensitivity of EMB in diagnosing myocarditis were primarily based on histopathological analyses according to the Dallas criteria. However, as recently discussed by Baughman,[21] because of their low sensitivity the Dallas criteria should now be regarded as outdated and no longer adequate for the workup of EMBs in patients with suspected myocarditis. Immunohistochemical and molecular pathological methods—comprising PCR-based evaluation of virus genomes—were shown to be more sensitive for the diagnosis of myocardial inflammation and/or infection, even in the absence of focal cellular infiltration, and have been successfully used to identify patients who respond to immunomodulatory therapy, independently of the Dallas criteria.[22,23]

Limitations of endomyocardial biopsy necessitating new imaging modalities

Although the workup of EMBs still constitutes the gold standard in the diagnosis of myocarditis and is the only way to directly detect inflammatory infiltrates in the myocardium,[24] the more frequent and common use of this method is hampered by the following limitations: a) sampling error resulting in a sensitivity that is still low; b) its invasive nature with the risk of complications; and c) delayed timing of biopsy resulting in missing of transient antecedent inflammation.

The lack of sufficient sensitivity of EMBs in the diagnosis of myocarditis arises from sampling error caused by patchy involvement of the myocardium, as well as high inter-observer variability in the interpretation of histopathological stains. The degree of sampling error depends on the number of biopsies taken per patient and on the methods applied for *ex vivo* analysis. Critics of EMB often refer to Hauck et al,[25] who demonstrated in *post mortem* tissue of patients with histologically proven lymphocytic myocarditis that, from the evaluation of five biopsies, the histological diagnosis of myocarditis/borderline myocarditis showed false nega-

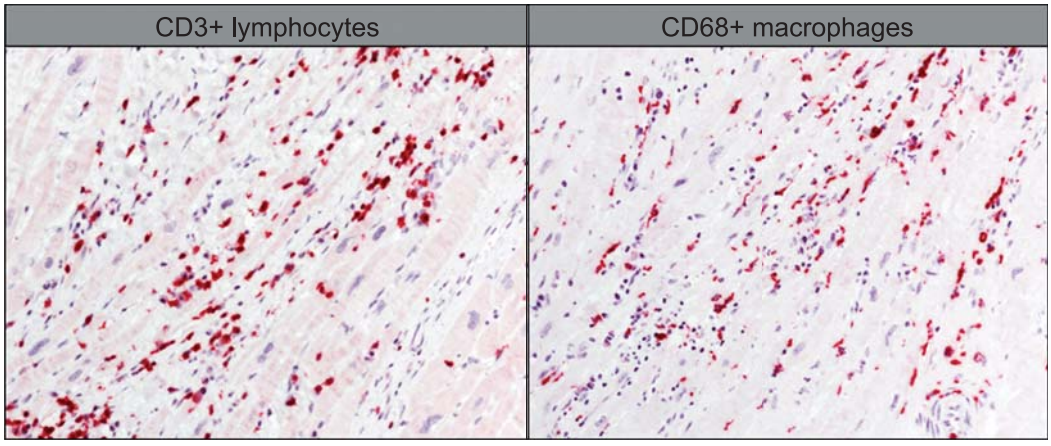

Figure 2. Immunohistochemical detection of CD3+ T-lymphocytes and CD68+ macrophages in the endomyocardial biopsy of Figure 1 (HE stain) demonstrates the typical distribution of mononuclear inflammatory cells in the heart observed in acute viral myocarditis.

tive results in up to 55% of the cases. However, previous studies (including the study by Hauck et al[25]) evaluating the sensitivity of EMB in diagnosing myocarditis were primarily based on histological analyses according to the Dallas criteria.[21] Today immunohistochemical methods are routinely used and have materially increased the diagnostic performance of EMB.[22,23]

The risk of major and minor procedure-associated complications was recently shown (based on a large study group of more than 3000 patients) to be extremely low in experienced centres.[26] The appropriate timing of biopsy remains a challenge. Animal studies in acute myocarditis have demonstrated that the replication of pathogens (e.g. viruses) and the subsequent immunological response may only be detectable for one or two weeks.[4,27] In humans, these initial phases of myocarditis may result in clinical symptoms for only a few days. Moreover, the histopathological, immunohistochemical and molecular pathological investigation of EMBs represents the only method which allows the differentiation of a myocarditis with respect to its aetiopathogenesis, and is therefore critical for the assessment of severe giant cell myocarditis and necrotic eosinophilic myocarditis.[24] Performing EMB during these acute stages of myocarditis is critical for the detection of the underlying pathogen and the accurate assessment of the severity of acute damage. Of course, initiating EMB in such a short time span requires a high clinical suspicion of the presence of an inflammatory process.

Non-invasive imaging strategies may avoid the above mentioned disadvantages of EMB, offering: 1) provision of the correct diagnosis without the risk of complications; 2) the possibility of assessing the entire myocardium; and 3) repetition of the procedure at any time.

Currently applied imaging techniques for workup of myocarditis

Today, a huge armamentarium of diagnostic (imaging) techniques enable the accurate and non-invasive evaluation of various cardiac diseases associated with or caused by myocardial inflammation.[28,29] Although the spectrum of pathogenetic aetiological factors spans a broad range, nowadays viruses constitute cause number one for the occurrence of both acute and chronic myocarditis (Table 2).

Electrocardiogram (ECG)

In 1902, Einthoven invented an "electrocardiograph machine" using a string galvanometer, which is an instrument capable of detecting and recording the small electrical currents produced by the human heart.[30] With this device the first recording of an ECG was achieved. In the following years, this device was further optimised and successfully used to analyse electrocardiographic features of various cardiovascular diseases. Today a 12-lead ECG is routinely recorded in almost every patient being admitted to hospital. In the case of myocarditis, ECG changes are not uncommon and comprise supraventricular tachycardias, conduction blocks, ST abnormalities or sustained/non-sustained ventricular tachycardias (amongst others).[5,31] Moreover, ECG changes may even represent the first sign of myocarditis in otherwise asymptomatic patients. However, ECG signs are non-specific. Hence, the definitive diagnosis of myocarditis cannot be made based on the ECG.[32]

Echocardiography

M-mode echocardiography was first introduced by

Table 2. Possible causes of myocardial inflammation.

Most common:
- Viral infection (parvovirus B19, human herpes virus, coxsackie viruses, adenovirus, cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus)
- Cardiotoxic drugs (anthracyclines, cyclophosphamide)

Less common:
- Bacterial infection (streptococcus, meningococcus, haemophilus)
- Fungal infection (histoplasmosis, aspergillosis)
- Protozoal infection (Chagas disease, toxoplasmosis)
- Autoimmune diseases (Churg-Strauss syndrome, systemic lupus erythematosus, giant cell myocarditis)
- Systemic storage diseases (sarcoidosis, amyloidosis, cardiac siderosis)
- Genetic diseases with cardiac involvement (muscular dystrophy, mitochondrial myopathy)
- Hypersensitivity reactions (to penicillins, cephalosporins, sulfonamides, tetracyclines)

Edler in 1954.[33] However, only in the early 70s was M-mode echocardiography applied for clinical use. Following the introduction of Doppler and 2-dimensional echocardiography in those years, this technique today has become the most widely used imaging method for the diagnosis of heart disease. In the workup of myocarditis, echocardiography still represents the first-choice imaging modality, since it offers the acquisition of comprehensive anatomic and functional data very quickly at the patient's bedside.[29,34] In the past, the diagnostic value of M-mode and 2-dimensional echocardiography in patients with histologically proven myocarditis was evaluated, and various different echocardiographic patterns resembling dilated, hypertrophic, restrictive, or even ischaemic cardiomyopathy have been described.[35] However, none of these echocardiographic features are specific in comparison to biopsy results. In recent years, new methods, such as tissue Doppler, strain-rate imaging, or contrast-enhanced echocardiography, have broadened the diagnostic possibilities of echocardiography. However, the value of these new echocardiographic imaging techniques in patients with myocarditis is still unknown, as data from larger patient groups are not available.

Nuclear scintigraphic imaging

Although the first X-ray radiographs were already being performed by Roentgen at the end of the 19th century and the first radiotracer studies in animals by Hevesy in 1924,[36] emission reconstruction tomography (later known as SPECT and PET) was introduced by Kuhl only in 1962.[37] The radiotracers that have been successfully used for the evaluation of clinically suspected myocarditis, namely gallium-67 and indium-111,[38,39] were developed in 1969 and 1990, respectively.[40,41] Both have a high sensitivity in the detection of inflamed myocardium. However, data are only available from patients with severe forms of myocarditis. Moreover, the gold standard, against which the sensitivity of the techniques was evaluated, was EMB without the use of immunohistochemistry, which itself suffers from a low sensitivity. Nevertheless, these scintigraphic techniques seem to have a high sensitivity in diagnosing acute inflammation but their specificity is known to be rather low. Due to their limited specificity, their radiation burden and the practical difficulties of myocardial scintigraphy, the use of scintigraphic techniques has declined over the past years.

Cardiovascular magnetic resonance imaging

Like most currently applied imaging techniques, the discovery of the principles of magnetic resonance imaging (MRI) dates back to the first half of the 20th century. In 1941, the American physicist Block constructed the first MRI machine, using physical principles of MRI that were discovered by Rabi in 1939.[42,43] At that time, MRI machines were exclusively used (mostly by physicists) to analyse the subatomic structure of materials and substrates. About a half century later, it was Raymond Damadian who built the first MRI machine for diagnostic purposes in human beings and he performed the first human scan on his machine in 1977.[42,43] In the following years, essential technical progress was made and scan times decreased from hours to a few minutes. Today, MRI techniques are widely used to diagnose diseases of the heart and the blood vessels: cardiovascular magnetic resonance (CMR). Current clinical recommendations for the use of CMR comprise (amongst others) the study of patients with CAD, of patients with congenital disease and of those with myocardial and/or pericardial disease. In particular, the initial changes in myocardial tissue composition during the first phase of myocardial inflammation represent attractive targets for a successful CMR-based imaging approach (Figure 3).

A CMR study in a patient with (clinical) myocarditis was mentioned for the first time in 1984 by Lieberman et al,[44] followed by a case report of two patients with myocarditis by Chandraratna et al.[45] In the latter report regional "myocardial edema", which disappeared with clinical recovery, was described. In the following years, newer and more advanced CMR scanners, coils and pulse sequences enabled a more accurate and differentiated cardiac study in patients with myocarditis. In 1991, Gagliardi et al published their first CMR results for the detection of "myocardial inflammation" in a series of patients with clinical suspicion of myocarditis.[46] Using a T2-weighted spin-echo sequence, they were actually looking for myocardial oedema as an indirect sign of acute myocardial damage. They found a very high sensitivity and specificity for this method when compared to the clinical as well as biopsy-based diagnosis in their patients. In later years, T2-weighted oedema imaging was further optimised and is today routinely used as a tool for evaluating the presence of "acute myocardial inflammation"[47,48] (Figure 4). Although data based on the application of this pulse sequence in patients with biopsy-proven myocarditis are scarce, experience from animal models and patients with a clinical

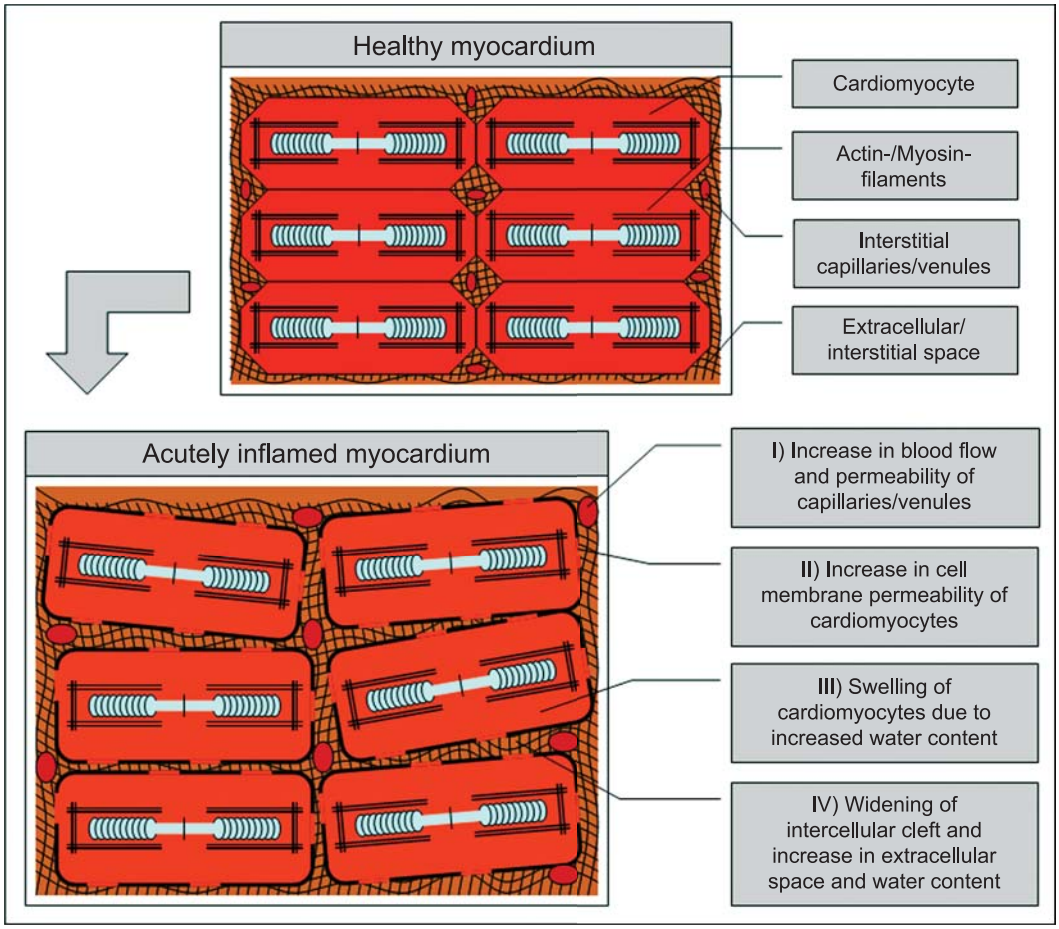

Figure 3. Diagram demonstrating initial changes in myocardial tissue composition during the first phase of myocardial inflammation that represent attractive targets for a successful approach based on cardiovascular magnetic resonance imaging.

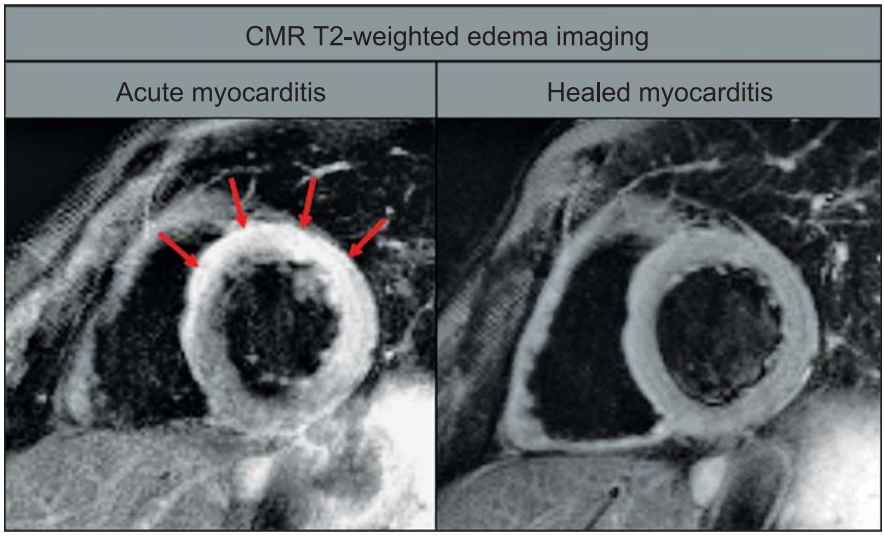

Figure 4. T2-weighted short-axis spin-echo images in a patient with biopsy-proven myocarditis during the acute phase of disease (left) and after three months of recovery (right). High signal intensity in the anteroseptal and anterolateral segments (red arrows) during the acute phase was indicative of myocardial oedema/inflammation and had already disappeared at follow up.

diagnosis of myocarditis have lead to its broad acceptance. Moreover, a group of experts recently recommended employing this CMR imaging method as one of three methods on which the appropriate diagnosis of myocarditis should be based.[28]

Only a few years later, Matsouka et al performed T1-weighted imaging using a contrast agent (gadolinium diethylenetriaminepentaacetic acid, Gd-DTPA) for the first time in two patients with myocarditis.[49] By comparing pre- and post-contrast images they could demonstrate that Gd-DTPA accumulation in regions of suspected myocardial inflammation led to increased signal intensity, thereby causing a clear "contrast enhancement" in comparison to non-inflamed surrounding myocardium. After this first introduction of contrast-enhanced CMR (ceCMR) for the evaluation of myocarditis, Friedrich et al were the first to perform ECG-triggered T1-weighted ceCMR in a series of 44 patients with clinical symptoms of myocarditis in 1998.[50] Since T1-weighted images were obtained both prior to and within 1 min after Gd-DTPA infusion, this sequence was titled "myocardial early gadolinium enhancement" (Figure 5). In subsequent years, other studies have confirmed the diagnostic value of this sequence, although it is prone to severe artefacts that often prevent appropriate analysis.[47] Nevertheless, this CMR imaging method has also been recently included in the three methods whose use is advised for the appropriate diagnosis of myocarditis.[28]

In 2001, Simonetti et al introduced a new pulse-sequence for ceCMR: T1-weighted segmented inversion-recovery gradient-echo (IR-GE).[51] This sequence was superior to others used for contrast enhancement, since it highly improved the difference in signal intensity between myocardial regions with (diseased) and those without (healthy) Gd-DTPA accumulation, thereby leading to a much better contrast. Today, this method is known as "late gadolinium enhancement" (LGE) imaging. It was initially developed for the non-invasive detection of infarcted myocardium. However, it was soon realised that any kind of myocardial necrosis and scar could be nicely visualised using this pulse sequence.[52-54] Rieker et al were the first to apply this pulse sequence to patients with suspected myocarditis.[55] In 2004, Mahrholdt et al used it to detect diseased myocardium in patients with biopsy-proven myocarditis.[56] The distribution of scar as observed in these CMR images differs for different types of cardiac disease. While patients with CAD and myocardial infarctions demonstrated a more subendocardial or transmural distribution of LGE, those with non-ischaemic cardiomyopathies (including myocarditis) demonstrated either an intramural or a subepicardial pattern of LGE, or a subendocardial one that did not coincide with coronary blood supply.[52,57] In the case of myocarditis, LGE imaging revealed two common patterns of myocardial damage: either an intramural, rim-like pattern in the septal wall or a subepicardial (patchy) distribution in the free LV lateral wall[5] (Figure 6). Areas of LGE represent irreversibly injured myocardial tissue and are due to in-

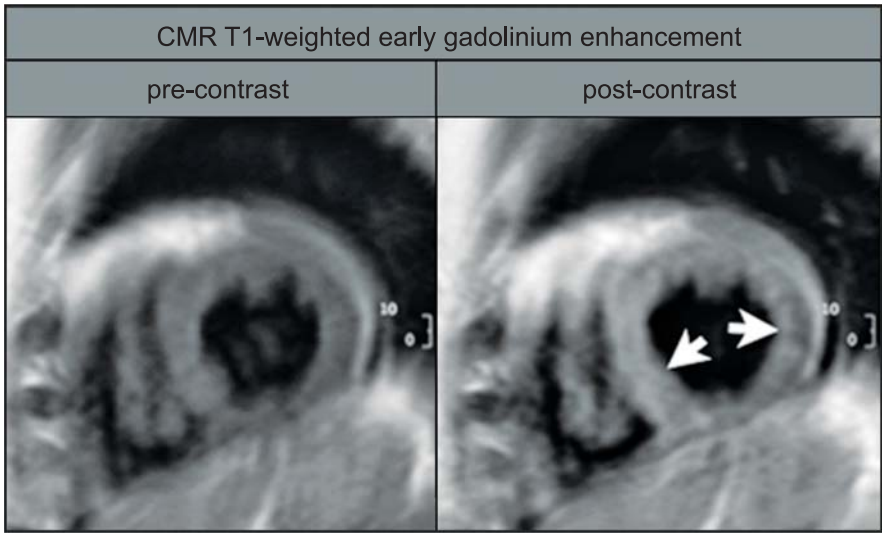

Figure 5. T1-weighted short-axis spin-echo images before (left) and after (right) gadolinium infusion with early gadolinium accumulation in the septum (white arrows) indicative of myocardial inflammation. Reprinted with permission from Friedrich et al.[28]

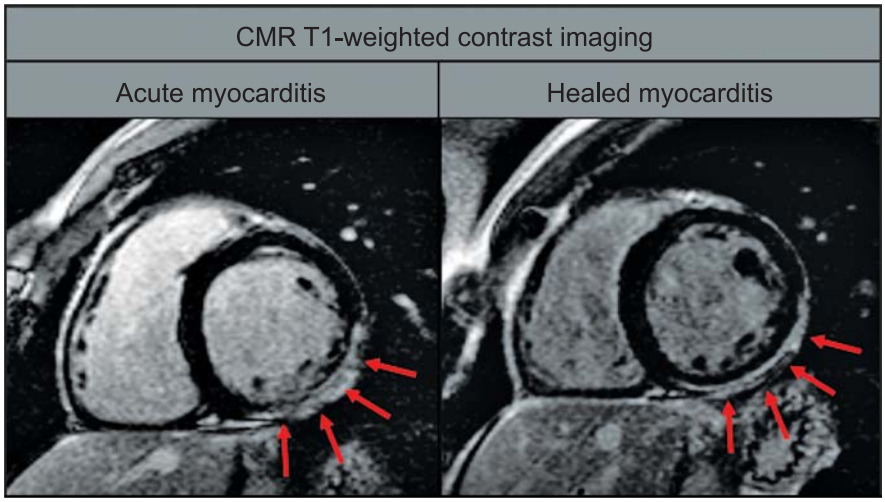

Figure 6. T1-weighted short-axis gradient-echo images in a patient with biopsy-proven myocarditis, demonstrating subepicardial late gadolinium enhancement (LGE, red arrows) in the inferolateral segments during acute presentation (left) indicative of myocardial damage. At follow up after three months a shrinkage in the extent of LGE was observed (right).

creased extracellular/interstitial space as a result of myocardial necrosis and fibrosis. Thus, LGE does not allow the differentiation between acute and chronic inflammation, but represents irreversibly damaged myocardium. Moreover, few data are available regarding a direct comparison of both non-invasive, CMR-based LGE imaging and invasive EMB with respect to the conformity of procedure-derived diagnoses in the same patients. Recently, we evaluated the diagnostic performance of LGE imaging and EMB in patients with troponin-positive acute chest pain in the absence of significant CAD.[58] Our results suggest that CMR and EMB have good diagnostic performances as single techniques in patients with troponin-positive acute chest pain in the absence of CAD. The combined application of CMR and EMB resulted in considerable diagnostic synergy, overcoming some limitations of CMR and EMB as individually applied techniques.

In recent years, several studies have evaluated the diagnostic performance of those aforementioned CMR methods in patients with a clinical suspicion of myocarditis.[5,47,59-61] Some of those studies used EMB results as gold standard for the final diagnosis of myocarditis, whereas others were confined to clinical data as the standard of reference. Each individual CMR method seems to have individual advantages but also disadvantages in the diagnosis of myocarditis. Consequently, the combination of these methods is currently regarded as the most appropriate approach in order to make the non-invasive diagnosis of myocarditis with the highest sensitivity and specificity.[28,47] The International Consensus Group on CMR Diagnosis of Myocarditis recently published recommendations with respect to indications for performing CMR in patients with clinically suspected myocarditis, CMR protocol standards, terminology for reporting CMR findings, and diagnostic CMR criteria for myocarditis.[28] Briefly, the combined use of those three aforementioned CMR methods (T2-weighted oedema imaging, T1-weighted early enhancement imaging and T1-weighted LGE imaging) is recommended. It is suggested that, if all those CMR sequences can be performed, and depending on whether two or more of those three CMR sequences result in pathological findings, myocardial inflammation can be predicted or ruled out in the respective patient with a diagnostic accuracy of 78% (pooled data; Table 3, reprinted with permission from Friedrich et al[28]). Moreover, if only LGE imaging is performed, the diagnostic accuracy is said to be 68% (pooled data).

New experimental approaches to imaging myocardial inflammation

Up to now, myocardial inflammation can only be visualised indirectly by means of CMR-based oedema imaging applying T2-weighted sequences[47] or T1-weighted early enhancement imaging.[50] Obviously, these methods are still not sufficient to further differentiate the origin and molecular distinctiveness of causative agent-specific pathology as it can be demonstrated by immunohistochemical and molecular analysis.[19,58] As the predominating forms of myocarditis in humans

Table 3. Diagnostic accuracy of different cardiovascular magnetic resonance imaging methods for myocarditis.

	Validation	Sensitivity (%)	Specificity (%)	Accuracy (%)
Early myocardial gadolinium enhancement				
Friedrich et al, *Circulation* 1998	Clinical	84	89	86
Laissy et al, *Chest* 2002	Clinical	85	100	89
Abdel-Aty et al, *J Am Coll Cardiol* 2005	Clinical	80	68	74
Gutberlet et al, *Radiology* 2008	Histology	63	86	72
Pooled data (n=194)		74	83	78
T2				
Rieker et al, *Rofo* 2002	Clinical	100	50	76
Laissy et al, *Chest* 2002	Clinical	45	100	59
Abdel-Aty et al, *J Am Coll Cardiol* 2005	Clinical	84	74	79
Gutberlet et al, *Radiology* 2008	Histology	67	69	67
Pooled data (n=178)		70	71	70
Late enhancement				
Rieker et al, *Rofo* 2002	Clinical	45	60	52
Abdel-Aty et al, *J Am Coll Cardiol* 2005	Clinical	44	100	71
Mahrholdt et al, *Circulation* 2006	Histology	95	96	96
Gutberlet et al, *Radiology* 2008	Histology	27	80	49
Yilmaz et al, *Heart* 2008	Histology	35	83	51
Pooled data (n=336)		59	86	68

are caused by viral pathogens—and are thus characterised by, for example, macrophage-rich inflammation—efforts are currently being concentrated on *in vivo* CMR of macrophages infiltrating the myocardium or molecular targets over-expressed in myocardial inflammation (such as adhesion molecules). Such "molecular imaging" has yielded promising results in other cardiac applications.[62,63]

One of those new and promising approaches is based on iron-oxide particles of nanoscalar size and with superparamagnetic properties. Such particles have already been used successfully in animal models of inflammation to detect the inflammatory process non-invasively at the molecular level. They have a central core of iron oxide measuring less than 10 nm in diameter and are coated, for example, with polymers, carbohydrates (such as dextrans) or citrate. The particles' respective coating enables the integration of specific ligands, which in turn permit the specific attraction to their molecular targets. Following accumulation of these magnetic nanoparticles, appropriate CMR sequences can be applied in order to detect their organ or tissue distribution by measuring subtle local magnetic field inhomogeneities caused by these superparamagnetic iron-oxides. Some of these contrast agents are already approved and available for clinical use; however, their indications are so far limited to non-cardiac diseases. Nevertheless, Tang et al recently demonstrated that an ultra-small superparamagnetic iron-oxide (USPIO) can be used successfully in humans to image non-invasively the degree of inflammation in carotid atherosclerotic lesions and even to monitor the therapeutic efficiency of anti-inflammatory interventions.[64] Future studies will have to demonstrate the clinical value of such approaches in the workup of myocardial inflammation.

Conclusions

Hallmarks of myocardial inflammation comprising cardiomyocyte swelling, increase in blood flow and vascular permeability, increase in extracellular space and water content, accumulation of inflammatory cells, activation of various inflammatory signalling pathways, potential necrosis or apoptosis of cardiomyocytes, and myocardial remodelling with fibrotic tissue replacement represent different biological targets for the accurate, non-invasive detection of inflammatory heart disease. Imaging techniques for the evaluation of myocardial inflammation that address those aforementioned processes have made impressive progress throughout the last century and currently permit the non-invasive detection of early myocardial tissue changes prior to accumulation of inflammatory cells, primarily based on sophisticated CMR modalities. In particular, CMR-based detection of myocardial oedema and tissue hyperaemia, by T2-weighted oedema imaging or T1-weighted early gadolinium enhancement imaging, and of myocardial

necrosis or fibrosis, by LGE imaging, have been successfully established as the most appropriate methods for the sensitive, specific and safe evaluation of myocardial inflammation today. However, as research and advances in heart imaging are rapidly proceeding, it is hoped that molecular—and thereby more sensitive and timely—diagnosis of myocardial inflammation will be possible in the near future.

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