Myocarditis

Invited Editorial
Myocarditis: the last frontier in advanced heart disease - K. L. Baughman

Lead Article
Myocarditis - L. T. Cooper Jr

Expert Answers to Three Key Questions
How does viral infection of the heart cause chest pain, arrhythmias, and heart failure? - U. Kühl
What are the current treatment options for myocarditis? - H.-P. Schultheiss, U. Kühl

Fascinoma Cardiologica
Art and the Heart: Aesthetic rewards in basic research and painting - A. H. Henderson

Summaries of Ten Seminal Papers - L. Blauwet
A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators - J. W. Mason and others
High prevalence of viral genomes and multiple viral infections in the myocardium of adults with “idiopathic” left ventricular dysfunction - U. Kühl and others
The role of endomyocardial biopsy in the management of cardio-vascular disease: a scientific statement form the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology - L. T. Cooper and others
Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy (IMAC-1) - D. M. McNamara and others
Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis - R. E. McCarthy HI and others
Diagnostic performance of cardiovascular magnetic resonance in patients with suspected acute myocarditis: comparison of different approaches - H. Abdel-Aty and others
Idiopathic giant-cell myocarditis—natural history and treatment. Multicenter Giant Cell Myocarditis Study Group Investigators - L. T. Cooper and others
A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogenetic features at diagnosis - A. L. Cofioia and others
Autoimmunity in Coxsackievirus infection - N. R. Rose
Complication rate of right ventricular endomyocardial biopsy via the femoral approach: a retrospective and prospective study analyzing 3048 diagnostic procedures over an 11-year period - M. Holzmann and others

Bibliography of One Hundred Key Papers

The incidence of congestive heart failure (CHF) is increasing dramatically and CHF is now the most common diagnosis-related group for patients over 65 years of age admitted to hospital. Determining the etiology of heart failure is critical, as this defines the patient's natural history and treatment options. Despite a full evaluation of patients with new-onset or progressive heart failure utilizing traditional techniques, including endomyocardial biopsy (EMB), approximately 50% of patients are deemed “idiopathic” in origin. A “virus” is suspected as the cause of most cases of nonischemic cardiomyopathy and, if true, viral myocarditis diagnosis and treatment represent a remarkable opportunity to alter the observed increase in cardiac dysfunction and heart failure. In this issue of Dialogues in Cardiovascular Medicine, the world’s experts in myocarditis address our current understanding of the pathophysiology and treatment of this disorder.

Dr Cooper addresses nonviral causes of myocarditis, including giant cell myocarditis, sarcoidosis, and hypersensitivity eosinophilic myocarditis. While the etiology of each of these nonviral disorders is unclear, the pathophysiology, as currently defined (immune, inflammatory, and allergic), does allow appropriate management. Each of these disorders is relatively rare and accounts for only a small portion of those patients in the idiopathic cardiomyopathy category.

Viral or postviral autoimmune myocarditis is much more likely to be responsible for a large proportion of those patients with heart dysfunction of unknown etiology. Kühl identifies mechanisms by which cardiotropic viruses or postviral autoimmune processes may damage the heart, including the site of viral infection. Endothelial infection and secondary dysfunction may cause vasospasm or vascular occlusion, resulting in chest...
pain or myocardial infarction. Interstitial invasion could result in diastolic or systolic dysfunction. Myocardial invasion results in cardiac dysfunction through several mechanisms, including direct viral damage to the myocyte, innate and adaptive immune response, and cytokine production, all of which cause direct or secondary myocardial deterioration. Therefore, the effect of a virus on the heart may be dependent on its predilection for endothelial, interstitial, or myocardial invasion and the nature of the immune response.

The diagnosis of myocarditis is difficult as the signs, symptoms, electrocardiographic changes, biomarkers, echocardiograms, and other noninvasive studies are nonspecific. Mahrholdt and Sechtem specifically address the value of EMB vs cardiac magnetic resonance imaging in establishing a diagnosis. The authors have identified the limitations of the Dallas criteria for diagnosing myocarditis by heart biopsy: focal myocardial inflammation; interobserver variability in the histopathologic interpretation of biopsy results; lack of correlation between myocardial invasion with cardiotropic viruses and myocardial inflammation; and poor correlation of Dallas criteria myocarditis with treatment outcomes. Nonetheless, EMB is the only technique capable of definitively diagnosing myocardial inflammation and its etiology.

The authors identify what they currently consider a “complete” EMB should include: obtaining six samples from both right and left ventricles from each patient; and a pathology analysis that includes histology, immunopathology, and DNA and RNA studies for nested polymerase chain reaction (PCR) and reverse transcriptase PCR evaluation of viral genomes.

Magnetic resonance imaging is noninvasive, does not expose the patient to radiation, and is associated with limited risk. Newer techniques and use of gadolinium contrast have allowed investigators to identify focal areas of myocardial inflammation during the acute process or scar tissue in the recovery phase. Both are of value in diagnosing myocarditis. In addition, magnetic resonance imaging may identify extra cardiac disease processes, which may help establish other diagnoses. It is likely that a thorough EMB, in addition to cardiac magnetic resonance imaging (CMR) to establish a diagnosis and define the area to be biopsied, will result in a higher yield of areas of myocardial inflammation. However, CMR may be less sensitive for diffuse forms of myocardial inflammation.

Treatment of myocarditis, and presumably prevention of the advancement of heart disease, is highly dependent on understanding the pathophysiology of the underlying disorder. Cooper, Schultheiss, and Kühl review what is known about current treatment options. Standard therapy includes: lifestyle alterations and avoidance of exercise in the short term; consideration of β-blocker and angiotensin-converting enzyme inhibitor use;
appropriate use of pacemakers for heart block; implantable cardioverter-defibrillators for malignant arrhythmias; as well as ventricular assist device support and transplant for patients with refractory symptoms. It seems clear from the data thus far available that patients with fulminant myocarditis should be supported without immunosuppressive therapy, while patients with giant cell myocarditis and acute necrotizing eosinophilic myocarditis need high-dose immunosuppressive therapy, perhaps long-term.

Patients with sarcoidosis and hypersensitivity or eosinophilic-related myocarditis also appear to respond to immunosuppressive agents. What is less clear is the appropriate therapies for patients with viral infection or the postviral immune cardiac response. Utilizing the PCR methodologies noted above, viral pathogens have been detected in EMBs of patients with cardiomyopathy and/or heart failure. It is yet to be determined whether or not these viral pathogens are in the endothelium, interstitium, or myocardium and whether or not localization provides additional diagnostic information beyond that of their presence in heart tissue. Increasingly, it appears that patients with viral persistence have a worse prognosis than those with spontaneous viral clearance or those who have no evidence of viral infection. It is also becoming increasingly clear that patients who do not have viral persistence, but have anticardiac antibodies may be more responsive to immunoadsorption or immunosuppressive therapies.

Over the next several years, the authors and further investigations will define the degree to which myocarditis is responsible for the large number of patients who have heart muscle dysfunction of unknown etiology. We finally have, in our grasp, molecular and genetic techniques that significantly enhance our ability to diagnose myocarditis and its viral or immune causes. The recently released guidelines of indications for EMB\(^1\) will allow investigators to identify differences in the clinical subsets being investigated. With these clinicopathologic descriptions and techniques defining the presence and etiology of myocarditis, treatment trials may be possible. With our current enhanced techniques and worldwide attention being paid to myocarditis, idiopathic cardiomyopathy, the last frontier in advanced heart disease, will be conquered.

REFERENCE

Myocarditis

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Viral myocarditis and the subsequent immune response to injury it elicits are a major cause of acute and chronic nonischemic dilated cardiomyopathy. Clinical presentation in myocarditis varies widely from asymptomatic electrocardiographic or laboratory findings to fulminant heart failure. Although histological examination, usually of myocardium obtained by endomyocardial biopsy, is required to confirm a diagnosis of myocarditis, patients may at times be treated based on a possible or probable diagnosis. Cardiac magnetic resonance imaging using a combination of T2- and T1-weighted sequences has a high sensitivity and specificity for myocarditis. Patients with acute myocarditis frequently improve with standard heart failure care, but occasionally require mechanical circulatory support. There is a growing interest in and use of immunomodulatory and antiviral therapies for select patients with chronic symptomatic cardiomyopathy despite optimal medical management.

Pathologists first recognized that the immune system could injure as well as heal the heart in the late 1800s. The description of an association between lymphocytes and damaged myocardial cells was called myocarditis, and, over the next century and a half, many infectious agents, systemic diseases, and toxins were associated with this histopathology. In 1948, a polio-like enterovirus, later called coxsackievirus B (CVB), was found to be an important cause of acute myocarditis and dilated cardiomyopathy, and much of our subsequent understanding of the molecular pathogenesis of the disease derives from inbred rodent strains that are susceptible to cardiovirulent CVB species. Recent experiments utilizing transgenic mouse models and isolated cell systems coupled with clinical observations have greatly expanded our understanding of the interaction of the immune system with the heart. Numerous clinical studies of cardiomyopathy have used molecular diagnostic techniques to support

SELECTED ABBREVIATIONS AND ACRONYMS

- ACE: angiotensin-converting enzyme
- ARB: angiotensin receptor blocker
- CAD: coronary artery disease
- CK-MB: myocardial creatinine kinase
- CMR: cardiac magnetic resonance imaging
- cTnI: cardiac troponin I
- CVB: coxsackievirus B
- ECG: electrocardiogram
- EMB: endomyocardial biopsy
- GCM: giant cell myocarditis
- IL: interleukin
- IMAC: Immune Modulation for Acute Cardiomyopathy
- MTT: Myocarditis Treatment Trial
- VAD: ventricular assist device

Keywords: myocarditis; dilated cardiomyopathy; endomyocardial biopsy; noninvasive imaging; heart failure

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The concept that viral and postviral autoimmune myocarditis are a major cause of acute and chronic nonischemic dilated cardiomyopathy and sudden death. This issue of Dialogues in Cardiovascular Medicine contains four articles that together aim to present the current understanding of the etiology, pathogenesis, diagnosis, and treatment of myocarditis. This lead article focuses on nonviral myocarditis in order to complement the other articles in this issue that discuss viral genome analysis and the treatment of virus-associated myocarditis. Accordingly, I have included separate sections on uncommon entities: giant cell myocarditis (GCM), cardiac sarcoidosis, and eosinophilic cardiomyopathies. I have not discussed the toxic myocarditis seen after chemotherapy with anthracyclines or nonviral infections that can affect the heart, such as Chagas disease, human immunodeficiency virus–associated cardiomyopathy, and Lyme disease. The article on cardiac magnetic resonance imaging (CMR) covers the topic in such depth that further comment in the lead article would also be redundant.

**DEFINITION**

The histological standard for the diagnosis of myocarditis is the presence of lymphocytes and other inflammatory cells associated with myocyte damage (Figure 1). Many experts contend that these findings have little clinical utility because of low sensitivity and an inconsistent correlation with meaningful clinical outcomes. Newer histological criteria that rely on specific cell stains have greater sensitivity and probably greater prognostic value. For example, Kindermann et al recently demonstrated in a case series of 181 patients with acute dilated cardiomyopathy that the presence of greater than 14 inflammatory cells per high power field on immunohistology was predictive of death or transplantation over the subsequent 10 years.

Molecular analysis of myocardium obtained from biopsy has revealed that viral genomes are common in acute and chronic dilated cardiomyopathy. Myocarditis is no longer synonymous with acute viral infection. Inflammation in the setting of acute dilated cardiomyopathy often results from recent viral injury, but the differential diagnosis includes a large number of uncommon, but clinically important disorders that may have specific treatments (Table I). Viruses may also

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**Table 1. Major etiologies of myocarditis.**

<table>
<thead>
<tr>
<th>Viral</th>
<th>Toxins</th>
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<tbody>
<tr>
<td>Adenovirus</td>
<td>Anthracyclines</td>
</tr>
<tr>
<td>Coxsackievirus</td>
<td>Cocaine</td>
</tr>
<tr>
<td>HCV</td>
<td>Interleukin 2</td>
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<tr>
<td>HIV</td>
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<thead>
<tr>
<th>Bacterial</th>
<th>Hypersensitivity</th>
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<tbody>
<tr>
<td>Mycobacteria</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Streptococcal species</td>
<td>Cefalosporins</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td>Digoxin</td>
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<table>
<thead>
<tr>
<th>Fungal</th>
<th>Tricyclic antidepressants</th>
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<tbody>
<tr>
<td>Aspergillus</td>
<td></td>
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<tr>
<td>Candida</td>
<td></td>
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<tr>
<td>Coccidiodes</td>
<td></td>
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<tr>
<td>Cryptococcus</td>
<td></td>
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<td>Histoplasma</td>
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<table>
<thead>
<tr>
<th>Protozoal</th>
<th>Dobutamine</th>
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<tr>
<td>Trypanosoma cruzi</td>
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<thead>
<tr>
<th>Parasitic</th>
<th>Immunologic syndromes</th>
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<tbody>
<tr>
<td>Schistosomiasis</td>
<td>Chung-Strauss</td>
</tr>
<tr>
<td>Larva migrans</td>
<td>Inflammatory bowel disease</td>
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</table>

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.

cause myocardial damage without histological inflammation. In contrast to cardiovirulent CVB strains that cause acute lymphocytic myocarditis within days to weeks of infection, parvovirus B19 and adenovirus cause relatively little cellular inflammation. CVB can also persist in an attenuated form at low levels, impairing heart function through cleavage of host proteins, rather than causing cell lysis and autoimmunity.

Although histological examination, usually of myocardium obtained by endomyocardial biopsy (EMB), is required to confirm the diagnosis of myocarditis, confirmation is not always required for optimal clinical care and is infeasible in epidemiologic studies. Clinicians and researchers may categorize patients with possible or probable acute myocarditis using modified case definitions from the smallpox vaccine program (Table II).

Table II. Clinical classification for acute myocarditis based on level of diagnostic certainty.

<table>
<thead>
<tr>
<th>Level of suspicion</th>
<th>Description of criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible myocarditis</td>
<td>1) Symptoms (dyspnea, palpitations, or chest pain)</td>
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<tr>
<td></td>
<td>2) ECG abnormalities beyond normal variants, not documented previously (ST/T abnormality, paroxysmal supraventricular tachycardia, ventricular tachycardia, atrioventricular block, or frequent atrial or ventricular ectopy), or focal or diffuse depressed LV function of uncertain age by an imaging study</td>
</tr>
<tr>
<td></td>
<td>3) Absence of evidence of any other likely cause</td>
</tr>
<tr>
<td>Probable myocarditis</td>
<td>1) Meets criteria for possible myocarditis</td>
</tr>
<tr>
<td></td>
<td>2) In addition, meets one of the following elevated levels of cardiac enzymes (creatine kinase-MB fraction or troponin T or I), new onset of depressed LV function by imaging, or abnormal imaging consistent with myocarditis (MRI with gadolinium, gallium (67Ga) scanning, or antimyosin antibody scanning)</td>
</tr>
<tr>
<td>Confirmed myocarditis</td>
<td>1) Histopathologic evidence of myocarditis by endomyocardial biopsy or on autopsy</td>
</tr>
</tbody>
</table>

Mild forms of myocarditis probably occur in the absence of symptoms. Screening of asymptomatic patients with electrocardiogram (ECG) or troponin following influenza revealed abnormalities suggestive of subclinical myocarditis. Similar observations have been reported from screening of asymptomatic military recruits following smallpox vaccination. Thus, in the appropriate clinical scenario, a variety of historical, imaging, and clinical criteria with particular strengths and weaknesses may be combined to define myocarditis.

The clinical presentation in myocarditis varies widely from asymptomatic ECG or laboratory findings to fulminant heart failure. Cardiac symptoms are nonspecific and include fatigue, decreased exercise tolerance, palpitations, precordial chest pain, and syncope. Thus, the clinician should consider myocarditis in the differential diagnosis of many cardiovascular syndromes. Of the 3055 patients in the European Study of Epidemiology and Treatment of Cardiac Inflammatory Disease (ESETCID) study, 72% had dyspnea, 33% had chest pain, and 18% had arrhythmic events. A prodrome of fever, myalgias, and gastrointestinal or respiratory symptoms is variably reported and may reflect systemic effects of acute viral infection. Men are affected slightly more often than women, probably due to protective antiviral effects of estrogenic hormones. For example, 62% of the 111 patients enrolled in the Myocarditis Treatment Trial (MTT) were male.

The electrocardiogram in acute myocarditis may be normal or have nonspecific ST-segment and T-wave abnormalities. Sinus tachycardia may reflect decreased stroke volume. Occasionally, the electrocardiogram changes are suggestive of an acute myocardial infarction and may include ST-segment elevation in two or more contiguous leads (54%), widespread ST-segment depressions (18%), and pathological Q waves (18% to 27%). Q waves are associated with a poor prognosis.
in acute myocarditis. Not infrequently, the electrocardiogram may have PR-segment depression that signifies coexistent pericarditis. In a small proportion of patients, various degrees of heart block or ventricular tachycardia may occur. High-degree heart block or sustained ventricular arrhythmias should raise suspicion of cardiac sarcoidosis or giant cell myocarditis (Figure 2).20,21

Biomarkers of cardiac injury are elevated in a minority of patients with acute myocarditis. Troponin I has a high specificity (89%), but low sensitivity (34%) for myocarditis. Biomarkers are more likely to be elevated in patients with less than 4 weeks of symptoms.22 Clinical and experimental data suggest that cardiac troponin I (cTnI) is increased much more frequently than myocardial creatinine kinase (CK-MB) in patients with myocarditis.23 Several other circulating biomarkers including cytokines, markers of apoptosis, and antiheter antibodies have been used to estimate prognosis in acute myocarditis. Fuse et al demonstrated that higher levels of sFAS and sFAS-ligand, markers for apoptosis, are associated with decreased survival in acute myocarditis. Similarly, Siwa et al demonstrated that in women with peripartum cardiomyopathy, sFAS/APO-1 levels were significantly higher in those who died compared with survivors (8.98+/−4.5 vs 5.33+/−3 U/mL, **P=0.02**).24 High levels of interleukin 10 (IL-10), a cytokine that is elevated in models of myocarditis, are associated with an increased risk of death in acute myocarditis.25 These novel biomarkers are not in widespread clinical use, but they may have clinical value in medical centers where they are available.

Echocardiography is useful for excluding valvular, pericardial, and congenital causes of cardiomyopathy; however, the findings in acute myocarditis are not specific. Echocardiographic patterns of dilated, hypertrophic, restrictive, and ischemic cardiomyopathies have been described in histologically proven myocarditis. Segmental or global wall motion abnormalities can simulate myocardial infarction in myocarditis. Patients with fulminant myocarditis may have normal left ventricular size and increased wall thickness, presumably due to edema, because the wall thickness decreases with the resolution of myocarditis. Left ventricular cavity size may be normal in early myocarditis and increase over time due to remodeling. In the MTT, increased sphericity and left ventricular volume characterized acute myocarditis.26

Cardiac magnetic resonance imaging (CMR) is an increasingly common diagnostic test for suspected acute myocarditis. As of 2008, eight controlled studies on the use of CMR for the diagnosis of myocarditis have been published.27 The accompanying article by Mahrholdt et al covers the role of CMR in depth, but a few points are worth emphasizing here. CMR may differentiate ischemic from nonischemic cardiomyopathy. Subendocardial or transmural enhancement is typical of ischemic cardiomyopathy. In contrast, nonischemic dilated cardiomyopathy may have three patterns of enhancement: no enhancement, myocardial enhancement (indistinguishable from patients with coronary artery disease [CAD]), and patchy or longitudinal mid-wall enhancement.28 Mahrholdt et al demonstrated that CMR may be used to direct biopsies to regions of active myocarditis.29 Importantly, a combination of T2- and T1-weighted imaging is necessary to achieve the best sensitivity and specificity for myocarditis.27

The gold standard for the diagnosis of myocarditis remains histopathology, usually from myocardium obtained using EMB. The 2007 American Heart Association/American College of Cardiology Foundation/European Society of Cardiology joint scientific statement on the role of endomyocardial biopsy in cardio-

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**Figure 2.** Electrocardiogram of a woman with acute giant cell myocarditis. Note the 2:1 AV-node block, right bundle-branch block, and Q waves in the anterior leads. Modified from reference 21: Cooper L, Hare J, Tazelaar H, et al. Usefulness of immunosuppression for giant cell myocarditis. Am J Cardiol. 2008;102:1535-1539. Copyright © 2008, Elsevier Inc.
vascular disease lists 14 clinical scenarios in which EMB may be considered (Table III). For the 2 clinical scenarios with class I indication, the clinician should perform EMB because of the likelihood that a specific disorder would be found that would meaningfully change prognosis or treatment. If a patient with an indication for EMB presents at a medical center where expertise in EMB is unavailable, transfer of the patient to a medical center with such expertise should be strongly considered.

The role of EMB may expand because the risks associated with EMBs using the newer, flexible biopsy tools with smaller jaws seem to be lower than those associated with the Stanford-Caves type biopsy tools that have been in widespread use for decades. Furthermore, newer diagnostic criteria that rely on immunoperoxidase techniques are coming into broader clinical use. For example, expression of CD3 (for lymphocytes), CD68 (for macrophages), or major histocompatibility complex antigens are more sensitive markers than the Dallas criteria for myocardial inflammation. In an accompanying article, Kühl et al discuss the clinical value of viral genomes detected in myocardium in depth.

### PROGNOSIS

Several clinical, hemodynamic, functional, and histological variables predict the risk of death or heart transplantation in acute myocarditis. In a series from Massachusetts General Hospital, syncope was associated with increased risk. In that series and in the US MTT, lower ejection fraction was predictive. The likelihood of death or need for cardiac transplantation is

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<table>
<thead>
<tr>
<th>Scenario number</th>
<th>Clinical scenario</th>
<th>Class of recommendation (I, IIa, IIb, or III)</th>
<th>Level of evidence (A, B, or C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>New-onset heart failure of &lt;2 weeks’ duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>2</td>
<td>New-onset heart failure of 2 weeks’ to 3 months’ duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>3</td>
<td>Heart failure of &gt;3 months’ duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1 to 2 weeks</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>4</td>
<td>Heart failure associated with a DCM of any duration associated with suspected allergic reaction and/or eosinophilia</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>Heart failure associated with suspected anthracycline cardiomyopathy</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>6</td>
<td>Heart failure associated with unexplained restrictive cardiomyopathy</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>7</td>
<td>Suspected cardiac tumors</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>8</td>
<td>Unexplained cardiomyopathy in children</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>9</td>
<td>New-onset heart failure of 2 weeks’ to 3 months’ duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>10</td>
<td>Heart failure of &gt;3 months’ duration associated with a dilated left ventricle, without new ventricular arrhythmias or second- or third-degree heart block, that responds to usual care within 1 to 2 weeks</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>11</td>
<td>Heart failure associated with unexplained HCM</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>12</td>
<td>Suspected ARVD/ARVC</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>13</td>
<td>Unexplained ventricular arrhythmias</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>14</td>
<td>Unexplained atrial fibrillation</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>

Table III. The role of endomyocardial biopsy in 14 clinical scenarios.

Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; ARVD, arrhythmogenic right ventricular dysplasia; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy.
significantly greater in patients with abnormal right ventricular systolic function (right ventricular descent \(<1.7\) cm) than in patients with normal right ventricular systolic function (right ventricular descent \(>1.7\) cm) \((P < 0.03)\). In accord with this observation, the series from Johns Hopkins Hospital reported that higher pulmonary artery pressures were associated with increased risk. As referenced above, sFAS and IL-10 are the two serologic biomarkers reported. The histological finding that is universally recognized as having poor prognosis is GCM. Recently, it was found that patients with immunohistologic (CD3 or CD68) criteria had higher risk than those who did not have positive immunohistochemical staining.8

The natural history of acute myocarditis in children is generally good in the short term, but there is a long-term risk of death or transplantation. In one relatively large study of 41 children with acute myocarditis, 27 (66%) made a complete recovery, 4 (10%) made an incomplete recovery, and 10 (24%) either died (5) or underwent transplantation (5). A recent long-term study of pediatric myocarditis demonstrated that the greatest burden of myocarditis may not be apparent until 6 to 12 years after diagnosis, when children die or need to undergo heart transplantation for chronic dilated cardiomyopathy. In a posttransplantation study, 19 children with myocarditis were compared with 80 control patients without histologic evidence of myocarditis on explanted heart tissue. The patients with myocarditis required more aggressive maintenance immunosuppression following transplantation, but overall survival between the groups was similar.36

Nonviral causes of myocarditis and their management

**Giant cell myocarditis**

Giant cell myocarditis (GCM) is a rare, but usually fatal, autoimmune form of myocarditis, histologically defined by the presence of giant cells associated with myocyte necrosis and usually eosinophils. Well-formed granulomas are absent, and fibrosis is absent to minimal (Figure 3). In contrast to acute lymphocytic myocarditis, autoimmune disorders such as inflammatory bowel disease occur in approximately 20% or more of GCM patients and viral genomes are rare. Only one case of GCM has been described in association with coxsackievirus infection. Also supporting a primary autoimmune etiology, GCM-like inflammation can be induced in the Lewis rat by immunization with cardiac myosin. GCM is rare. In a Japanese autopsy registry from 1958 to 1977, the prevalence of giant cell myocarditis was 0.007% (25 out of 377 841 cases). The prevalence of idiopathic GCM in necropsies performed between 1950 and 1963 at Oxford Infirmary was a similarly low 3 out of 12 815. The clinical course is usually one of rapid deterioration over days to weeks, with frequent ventricular arrhythmias and sometimes heart block. The prognosis in GCM is significantly worse than that for lymphocytic myocarditis, with a median survival of 5.5 months from the onset of symptoms and an overall 89% rate of death or cardiac transplantation. Unlike typical myocarditis, GCM usually improves with cyclosporine-based immunosuppression. In a recent prospective, multicenter study of cyclosporine and steroids for acute GCM, 11 subjects received high-dose...
steroids, cyclosporine, and, in 9 cases, muromonab-CD3 in a standard protocol. During one year of treatment, only one subject died of respiratory complications and 2 subjects received heart transplantations. Serial EMBs revealed that, after 4 weeks of treatment, the degree of necrosis, cellular inflammation, and number of giant cells decreased (Figure 4). One subject, who completed the trial, subsequently died of GCM recurrence after immunosuppression was discontinued. Her case demonstrates that there is a risk of recurrent, sometimes fatal GCM after cessation of immunosuppression.

**Cardiac sarcoidosis**

Sarcoidosis is an idiopathic, multisystem, granulomatous disease that may affect the heart in isolation or as part of a multisystem process. The first case of cardiac sarcoidosis was reported 79 years ago by Berenstein, Konzelmann, and Sidlick. The disease is uncommon, with an estimated incidence of 10.9 per 100 000 in Caucasians and 35.5 per 100 000 in African-Americans in the United States. In Europe, however, Scandinavians have the highest incidence rates at 50-60 cases per 100 000.

Autopsy studies estimate the prevalence of cardiac involvement in about 25% of patients with sarcoidosis; however, cardiac sarcoidosis accounts for a disproportional number of deaths from the disease. In a large series from Baltimore, the rate of extrathoracic sarcoid was higher in African-American than in Caucasian patients (2.15 vs 1.20 manifestations per patient, respectively). From comparative autopsy data, the rate of cardiac involvement in sarcoid patients is higher in Japanese than in US patients.

As with more common etiologies of myocarditis, patients with cardiac sarcoidosis may present with a wide variety of signs and symptoms, ranging from asymptomatic ECG abnormalities to sudden death. Initial presenting symptoms depend on the underlying pathology and may include dyspnea, palpitations, syncope, dizziness, chest pain, orthopnea, or peripheral edema. The clinical manifestations are related to the location and extent of disease involvement. Congestive heart failure is common and may result from granulomatous involvement of the myocardium or secondary right ventricular failure from pulmonary disease. Ventricular dysfunction can be due to systolic or diastolic dysfunction. Ventricular aneurysms can develop from large regions of scar, and ventricular arrhythmias and heart block are relatively common.

Confirmation of cardiac sarcoidosis is challenging because the sensitivity of EMB is about 25%. In one study by Uemura et al, only 5 out of 26 (19.2%) patients with clinical sarcoidosis and suspected cardiac involvement had diagnostic endomyocardial biopsies. Once a granulomatous infiltrate is confirmed in a patient with suspected cardiac sarcoidosis, other causes of granulomatous lesion must be excluded by appropriate serologic studies and special stains. The clinical utility of serum angiotensin-converting enzyme (ACE) as a diagnostic tool in cardiac sarcoidosis is limited because ACE may also be elevated in other granulomatous disorders and diabetes. Furthermore, although ACE levels may drop with steroid treatment, this decrease does not always correlate with clinical improvement in pulmonary sarcoidosis.

CMR has been used to diagnose cardiac sarcoid in patients with systemic sarcoidosis. In one recent study, the sensitivity and specificity of CMR were 100% and 78% and the positive and negative predictive values were 55% and 100%, yielding an overall accuracy of 83%. Quantitative enhancement using T2 imaging may be more sensitive than T1 imaging for suspected acute sarcoidosis. As with lymphocytic myocarditis,
the diagnostic yield of EMB might be improved if the location of biopsy sites could be determined by regions of abnormal signal on CMR. Today, in the patient with suspected cardiac sarcoidosis, a positive CMR with confirmed extracardiac disease may have the best diagnostic certainty.

Hypersensitivity and eosinophilic myocarditis

Adverse drug effects on the myocardium may be classified into toxic and hypersensitivity forms of myocarditis. French and Weller, who described 126 patients with eosinophilic interstitial myocarditis after sulfonamide administration, made the earliest report of drug-associated myocarditis in 1942. Patients with drug-induced hypersensitivity reactions can present with heart failure or arrhythmias due to myocarditis. Numerous medications, including some antidepressants, antibiotics, and antipsychotics, have been implicated in hypersensitivity myocarditis. Compared with postviral lymphocytic myocarditis, patients are generally older and are often on multiple medications. The presentation may be acute or more chronic and associated with rash, fever, and occasionally liver function test abnormalities. ECG changes are similar to those with lymphocytic myocarditis and include sinus tachycardia, nonspecific T-wave abnormalities, and ST-elevations. Hypersensitivity myocarditis is the most common form of allergic drug-induced heart disease. Classically, it is not dose-dependent and may occur at anytime after treatment is initiated. The histopathological features of hypersensitivity myocarditis consist of eosinophils, histocytes, and T cells within the subendocardial, interstitial, and perivascular tissues of the heart. In hypersensitivity myocarditis, myocyte necrosis is absent or sparse and lesions are at a similar stage of evolution. Necrotizing vasculitis, fibrosis, and myocardial scar formation are not seen in hypersensitivity myocarditis, but infiltration of vessel walls by inflammatory cells may be.

There are large gaps in the knowledge of hypersensitivity myocarditis treatment because most reports consist of autopsy series and isolated cases. The offending agent should be withdrawn and a high dose of corticosteroids given. Despite these interventions, patients may have delayed recovery or die. A case has been reported in which the disease responded to treatment with intravenously administered immunoglobulin and a high dose of corticosteroids given. Besides these interventions, patients may have delayed recovery or die. A case has been reported in which the disease responded to treatment with intravenously administered immunoglobulin and a high dose of corticosteroids given. Besides these interventions, patients may have delayed recovery or die. A case has been reported in which the disease responded to treatment with intravenously administered immunoglobulin and a high dose of corticosteroids given. Besides these interventions, patients may have delayed recovery or die. 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<th>Endocardial fibrosis</th>
<th>Myocardial fibrosis</th>
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<td>Antimony</td>
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<td>Arsenicals</td>
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<td>Barbiturates</td>
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*In transplanted hearts only.
forms of eosinophilic myocarditis include endocardial fibrosis, fibrosis of the cardiac valves leading to regurgitation, right and left congestive heart failure, and formation of thrombi on the endocardial surface. Acute necrotizing eosinophilic myocarditis is an aggressive form of eosinophilic myocarditis with acute onset and high mortality rates.

Similar to the treatment of hypersensitivity myocarditis, the treatment for other forms of eosinophilic myocarditis depends on the underlying cause. The approach to the patient with suspected eosinophilic myocarditis should begin with diagnosis and treatment of the hypereosinophilic syndrome, multisystem inflammatory disorder, or underlying infection. High-dose corticosteroids may be beneficial in the setting of systemic disease–associated eosinophilic myocarditis, while surgical treatment may also play a role in the management of endomyocardial fibrosis.

GENERAL PRINCIPLES IN THE TREATMENT OF MYOCARDITIS

With the exception of specific therapies for uncommon histologic forms of myocarditis, such as GCM, treatment of the patient with myocarditis is supportive and largely based on heart failure and arrhythmia guidelines. The American Heart Association/American College of Cardiology Foundation, the European Society of Cardiology, and the Heart Failure Society of America heart failure guidelines are all relevant to patients with dilated cardiomyopathy due to myocarditis. The 2006 American Heart Association/American College of Cardiology Foundation/European Society of Cardiology guidelines for the management of ventricular arrhythmias and the prevention of sudden cardiac death recommend that ventricular arrhythmias be managed conventionally in the setting of myocarditis. Patients with symptomatic or sustained ventricular arrhythmias may respond to amiodarone. Temporary pacemakers may be required for patients with symptomatic bradycardia or complete heart block who have acute myocarditis.

Lifestyle

Because mice that are forced to exercise during acute viral myocarditis have a high risk of death, most experts suggest that patients with acute myocarditis avoid high levels of physical activity and competitive sports for at least the first month after symptom onset. Some patients with clinically severe myocarditis may require longer periods for recovery. Exercise may be gradually reintroduced at a rate tailored to the patient’s tolerance. The resumption of aerobic physical activity should be delayed if echocardiographic measures of left ventricular function are persistently abnormal, clinically relevant arrhythmias are present, or if serum biomarkers of cardiac injury are elevated.

β-Adrenergic receptor blockers

β-Adrenergic receptor blockers can improve survival in patients with heart failure and an ejection fraction less than 40%. However, there have been no clinical trials of β-blockers for the treatment of heart failure due to myocarditis. Carteolol, a nonselective β-blocker, decreased inflammation, necrosis, fibrosis, and ventricular wall thickness in a murine model of CVB myocarditis. However, metoprolol increased mortality (60% vs 0%), necrosis, and viral replication when given to mice with acute viral myocarditis. These studies are consistent with the clinical observation that β-blockade can cause cardiopulmonary congestion if given before volume status has been optimized. In myocarditis, as with other forms of heart failure with left ventricular systolic dysfunction, β-blockers should be initiated at low doses and gradually titrated to target doses.

Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers

Data on ACE inhibitor and angiotensin receptor blocker (ARB) treatment of heart failure due to myocarditis is based on animal models. Captopril reduces inflammation, necrosis, and left ventricular mass in a murine model of myocarditis, while candesartan improved survival (60% versus 18%) in a murine model of viral myocarditis. However, the data on ARB treatment are mixed because, in a separate study, losartan did not decrease inflammation or necrosis following viral infection.

These studies suggest that the use of ACE inhibitors, captopril in particular, may improve heart failure due to myocarditis by reducing inflammation as well as by neurohumoral inhibition. In the absence of human studies, it is reasonable to extrapolate the trial experience from patients with nonischemic cardiomyopathy and reduced left ventricular systolic function to similar patients with myocarditis.

Implantable defibrillators and pacemakers

The indications for elective implantable defibrillator and pacemaker placement differ somewhat for myocarditis compared with chronic nonischemic dilated cardio-
myocarditis. Heart block and ventricular arrhythmias often resolve after acute inflammation has subsided. Therefore, temporary pacemakers should be considered in acute myocarditis for patients with symptomatic bradycardia or complete heart block. Implantable defibrillator implantation is not generally recommended for patients with acute myocarditis and life-threatening ventricular arrhythmias. However, implantable defibrillator therapy may be appropriate if arrhythmias persist after the acute phase of myocarditis, despite optimal medical therapy. Patients with persistent ventricular arrhythmias may require heart transplantation.

**Mechanical circulatory support**

Mechanical circulatory support, including ventricular assist devices (VADs) or extracorporeal membrane oxygenation, is indicated for patients who deteriorate despite optimal medical management and may serve as a bridge to transplantation or recovery. Successful weaning from VAD or extracorporeal membrane oxygenation with recovery of ventricular function in fulminant myocarditis can occur although death from multiorgan failure or sepsis has also been described. In 4 children with fulminant myocarditis supported with VAD, cardiac function improved in 3, and VADs were removed. In the fourth patient, no myocardial recovery occurred after a period of 20 days, and transplantation was performed with an uneventful postoperative course. In a separate study, seven of nine patients (78%) with GCM were bridged with VADs to heart transplantation. However, the only predictor of recurrent GCM following transplantation in this series was the use of a VAD or intra-aortic balloon pump before transplantation. Interpretation of these data is that the more severe the native heart GCM, the more likely posttransplantation recurrence will occur.

**Heart transplantation**

Patient survival following cardiac transplantation for myocarditis is similar to survival following transplantation for other causes. The incidence of patients undergoing transplantation for myocarditis ranges from 1% to 8%. O’Connell et al reported the United Network for Organ Sharing registry outcomes for 14,055 adult patients transplanted between January 1968 and December 1993. Patients with biopsy-proven myocarditis (n=142) had a better posttransplantation survival rate than a comparison group transplanted for other causes (including coronary artery disease, valvular heart disease, congenital heart disease, and restrictive cardiomyopathy, P=0.037 by log-rank test).

Heart transplantation is also an effective treatment for GCM, although GCM recurs in 20% to 25% of transplanted hearts. In a series of 34 GCM patients who underwent heart transplantation, 9 patients had recurrence of GCM at a mean of 3 years following transplantation (range: 3 weeks to 9 years). Only 3 of these patients had symptoms and signs of left ventricular failure. One of these 3 symptomatic patients died of recurrent GCM 3.5 years after transplantation, despite aggressive immunosuppression. In the remaining 2 patients, the giant-cell infiltrate and symptoms resolved with heightened immunosuppressive therapy. Five of the 6 asymptomatic patients were well 2.1 years after surgery (the sixth died of squamous cell carcinoma of the lung). Similar data were reported in a review of 340 heart transplant patients from Ottawa. In that report, GCM was identified at explant in 7 patients and asymptomatic GCM recurred in 3 patients between 5 to 13 months after transplantation and in 1 patient, 30 months after surgery. All recurrent GCM cases resolved with augmented immunosuppression.

**Anti-inflammatory and antiviral treatment**

Antiviral and immunomodulatory effects of intravenous immunoglobulin suggest that it might improve left ventricular function and decrease the risk of death or transplantation in patients with acute viral myocarditis. However, a recent systematic review concluded that there is insufficient evidence to recommend its use in acute myocarditis. In the Immune Modulation for Acute Cardiomyopathy (IMAC) trial, patients with recent-onset myocarditis or dilated cardiomyopathy (less than 6 months in duration) were randomized to intravenous immunoglobulin or to placebo. The ejection fraction of both the treatment and placebo groups improved from 25% to 40%. In contrast to acute cardiomyopathy, there may be a role for intravenous immunoglobulin in patients with peripartum cardiomyopathy or with chronic dilated cardiomyopathy.

Most treatment trials of immunosuppression in acute myocarditis have reported negative results. In the US MTT, 111 patients with heart failure of less than 2 years duration, myocarditis (according to the Dallas criteria), and ejection fraction less than 45% were randomized to three treatment groups: prednisone/azathioprine, prednisone/cyclosporine, and placebo. Both the pooled immunosuppression and placebo-treated groups improved ejection fraction from an average of 25% to 34%. There was also no difference between the groups in death or transplantation after 5 years. These studies suggest that immunosuppression is not beneficial.
in the routine treatment of acute myocarditis. In contrast, immunosuppression with azathioprine and prednisone may have role in the management of patients with inflammatory cardiomyopathy, especially if there is no evidence of viral infection.\textsuperscript{75,76}

**Antiviral therapy**

A separate article in this issue addresses the evidence for antiviral therapy in patients with acute or chronic dilated cardiomyopathy and evidence of viral genomes in heart tissue. In one study by Kühl et al, 22 patients with persistent left ventricular dysfunction, symptomatic heart failure, and evidence of myocardial persistence of enteroviral or adenoviral genome by polymerase chain reaction were treated with interferon-beta for 24 weeks.\textsuperscript{77} In this uncontrolled case series, interferon-beta treatment was associated with improved ventricular function and viral clearance. A randomized, double-blind phase 2 study of 143 chronic heart failure patients at 31 medical centers demonstrated that New York Heart Association functional classification improved in 38.6% of the interferon-beta patients compared with 18.6% of those in the placebo group after 12 weeks of treatment. Interferon-beta treatment was associated with clearance of viral genomes as well. A phase 3 trial is under design to confirm these results.\textsuperscript{78}

**THREE KEY QUESTIONS**

Certainly, clinical and translational discoveries in the last decade have advanced our understanding and influenced the management of patients with myocarditis. However, several key questions remain subjects of heated debate within the specialty. Perhaps the most exciting, but controversial subject is the role of viral infection in acute and chronic dilated cardiomyopathy. In the first expert article, Dr Uwe Kühl, a pioneer in the field of viral cardiomyopathy, will answer the question, “How does viral infection of the heart cause chest pain, arrhythmias, and heart failure?” The use of noninvasive and invasive procedures for the diagnosis of myocarditis varies widely even between centers of excellence. To address the controversies regarding diagnosis of myocarditis, Udo Sechtem, Heiko Maharholdt, and Ali Yilmaz will answer the question, “How do you best diagnose myocarditis?” The third expert article will focus on the central clinical question of what is the best treatment for myocarditis. Professor Heinz-Peter Schultheiss, who arguably has the largest range of experience of anyone in cardiomyopathy, together with Dr Kühl will address the question, “What are the current treatment options for myocarditis?”

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In: American Heart Association Annual Scientific Sessions; 2008; New Orleans, LA. Abstract.
Myocarditis

*Expert Answers to Three Key Questions*

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1. How does viral infection of the heart cause chest pain, arrhythmias, and heart failure?
   
   *U. Kühl*

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2. Imaging versus biopsy—how do you best diagnose myocarditis?
   
   *H. Mahrholdt, A. Yilmaz, U. Sechtem*

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3. What are the current treatment options for myocarditis?
   
   *H.-P. Schultheiss, U. Kühl*
Although myocarditis and inflammatory cardiomyopathy may result from virtually any infectious agent or be a part of an underlying inflammatory or autoimmune process, viral infections and antiviral immune responses are considered the most frequent causes.

The histological and clinical presentation of virus-associated heart disease depends on the nature of the offending infectious agent and the host's resulting immune response. Cardiotropic viruses (Table I) may infect different cells of heart tissue, such as cardiomyocytes, fibroblasts, or vascular endothelial cells. For many viruses, the exact site of cardiac infection is unknown. Acute and chronic myocardial injury and subsequent cardiac symptoms result from either direct virus-mediated lytic processes or occur as a result of innate or adaptive antiviral immune responses. Patients' complaints are nonspecific and include fatigue and weakness, palpitations, chest pain or dyspnea (caused by low cardiac output), arrhythmia, ischemia, vasospasms, pericarditic involvement, or elevated filling pressures as a consequence of systolic, diastolic, or endothelial dysfunction. The prevailing symptoms develop after a variable delay following viral illness and depend on the cardiac structures affected and the severity of early myocardial lesions. Depending on the structures affected, symptoms may persist even after clearance of the virus and decline of the inflammatory processes. Direct viral-induced myocyte damage may provoke the release of intracellular proteins and trigger immune responses responsible for immunopathic mechanisms in the context of genetic predisposition. These mechanisms cause ongoing myopericardial damage and persisting complaints, even in the absence of viral genome.

Keywords: myocarditis; inflammatory cardiomyopathy; viral heart disease; chest pain; arrhythmias; heart failure; endothelial dysfunction

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Table I. Cardiotropic viruses.
CHEST PAIN

Viral myocarditis may mimic acute myocardial infarction. Patients present with acute ischemia-like angina, variable ST-wave and T-wave changes, arrhythmias, elevated cardiac enzyme levels, and regional or global wall-motion abnormalities without any coronary disease detectable on catheterization. Mostly, the clinical symptoms recede more or less completely within a few hours, days, or weeks, and long-term prognosis is generally excellent in patients without persisting heart failure, but chest pain may persist chronically, regardless of whether a structural or functional abnormality can be identified.

Pericardial involvement

In clinical practice, pericardial involvement occurs frequently in myocarditis because, anatomically, the pericardium and myocardium are closely related and often share similar or common etiologic agents. Viral infections are the most common cause of perimyocarditis, with enteroviral infections predominating in the etiopathogenesis of acute myocarditis. Cardiotoxic viruses invade both the pericardium and myocardium hematogenously and cause inflammation of both structures simultaneously, although one of the two components usually dominates the clinical and pathological presentation. Typical pericarditic chest discomfort differs from the chest pain typical of viral heart disease in its pleuritic and positional character.

Endothelial dysfunction and ischemia

Virus-related chest pain is often associated with direct infection of vascular endothelial cells. Erythrovirus genomes have been localized in endothelial cells (ECs) of venules, small arteries, or arterioles in fulminant myocarditis or sudden-onset heart failure. In chronic inflammatory cardiomyopathy, erythrovirus genotype 1/parvovirus B19 (PVB19) infection is predominantly detected in the ECs of small capillaries. Viral infection of the vascular endothelium is often associated with endothelial and diastolic cardiac dysfunction, and endothelium-dependent flow-mediated vasodilatation becomes impaired in patients with myocardial virus persistence. Although endothelial dysfunction in patients with myocardial virus persistence can occur independently of myocardial inflammation/endothelial activation, it is more pronounced in patients with concurrent inflammation and depicts an adverse correlation with the number of infiltrating T cells.

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SELECTED ABBREVIATIONS AND ACRONYMS

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<td>EBV</td>
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</tr>
<tr>
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<td>electrocardiogram</td>
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<tr>
<td>EF</td>
<td>ejection fraction</td>
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<td>HHV</td>
<td>human herpesvirus</td>
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<td>IFN</td>
<td>interferon</td>
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<td>IL</td>
<td>interleukin</td>
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<td>LVEF</td>
<td>left ventricular ejection fraction</td>
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<td>PVB19</td>
<td>Parvovirus B19</td>
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<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
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Myocardial ischemia can also be caused by microvascular obstruction when circulating inflammatory cells adhere to virus-activated or inflammation-activated vascular endothelium or by coronary spasms, which can be induced on damaged vascular endothelium (eg, by a viral infection) by a variety of stimuli, including inflammation. Yilmaz et al recently demonstrated pathological biopsy results showing myocardial inflammation and/or detection of viral genomes in 55/85 (64.7%) patients presenting with clinically suspected myocarditis and chest pain symptoms. Coronary vaso-spasm was demonstrated in 71% of patients with pathological biopsies compared with only 40.0% of patients with normal biopsy results. Patients with isolated PVB19 infection demonstrated a significantly higher incidence of coronary vaso-spasm compared with those with isolated human herpesvirus 6 (HHV-6) infection and those with normal biopsy results (86.4% vs 40.0%).

Furthermore, cardiac pain has been attributed to microvascular dysfunction. It has been hypothesized that repeated subclinical episodes of myocardial ischemia may alter the nociceptive afferent or sympathetic afferent endings of cardiac nerve fibers. An alternative relationship, however, is also possible. In the case of primary abnormality of nerve fibers caused by, for example, inflammatory processes or an infection by neurotropic HHV-6, the efferent arm of the cardiac nerve adversely affects microvascular function.

ARRHYTHMIAS

In patients with acute or chronic viral cardiomyopathy, arrhythmias are common and often the only clinical symptom. Tachyarrhythmias and bradyarrhythmias are of particular significance in the differential diagnosis of sudden cardiac death. The factors responsible for the increased incidence of cardiac arrhythmias are structural changes, parameters of ventricular dynamics, and vascular changes.

Fibrosis and scarring of the myocardial tissue and myocyte atrophy favor the development of ectopic pacemakers, late potentials, and reentry as a result of inhomogeneous stimulus conduction. Furthermore, virus-associated inflammatory processes can lead directly to fluctuations in membrane potentials of arterial and ventricular myocytes.

Focal accumulation of inflammatory cells are a hallmark of early antiviral immune responses when virus-infected cells are destroyed by effectors of the innate and adaptive inflammatory processes. Focal lymphocytic infiltrations with myocyte necrosis are, however, not restricted to the ventricular myocardium. Similar myocarditic lesions have also been detected in 66% of right atrial septum biopsies of patients with paroxysmal left atrial fibrillation refractory to conventional antiarrhythmic treatment. Although viral involvement was not analyzed in that study, it may be speculated that similar microlesions resulting from antiviral immune processes may constitute focal starting points of both atrial and ventricular focal or multifocal arrhythmias in viral heart disease.

In addition to microlesions and extended areas of replacement fibrosis, parameters of ventricular dynamics, such as increased wall tension, increased myocardial oxygen consumption, and diminished coronary reserve in the case of disturbed systolic or diastolic left ventricular function, may also contribute to the increased incidence of arrhythmias. Furthermore, vascular factors can increase the arrhythmogenicity of the inflamed myocardium through the disturbance of microvascular and macrovascular perfusion and the resulting myocardial ischemia.

HEART FAILURE

Acute myocardial injury

Patients presenting with viral heart disease can be categorized, based on left ventricular function at the time of presentation, into subjects with preserved systolic function, impaired diastolic function, segmental or compensated left ventricular dysfunction, and acute systolic left ventricular compromise. The kind and extent of myocardial compromise depends on the affected cardiac structures and resulting myocardial lesions. Infection of cardiomyocytes is often associated with systolic ventricular dysfunction, while infection of vascular endothelial cells is a frequent cause of endothelial or diastolic dysfunction with preserved systolic ventricular function.

Viral myocarditis develops in distinct phases (Figure 2, page 174). A direct virus-related cytolysis of cardiomyocytes appears to be decisive in fulminant cases of myocarditis. The resulting myocyte necrosis may cause a significant loss of contractile tissue, which is accompanied by rapidly developing cardiac failure and early death of the host. Early antiviral defense mechanisms of the innate immune system are triggered by the ubiquitous toll-like receptors, through immune responses to the foreign molecular antigens. Cytokines released by macrophages and activation of natural killer cells, which kill virus-infected heart cells directly through perforin and granzyme-mediated lysis, contribute to
The activation of antigen-specific cell-mediated immunity initiates a second phase of virus clearance. Because virus-infected cells are destroyed by the immune effector cells of the adaptive inflammatory response, virus clearance occurs at the expense of further loss of infected myocytes. The ensuing myocardial damage depends on the scale of the cellular virus infection and increases with growing virus dispersion, which, in addition to the early virus-mediated and innate immune-mediated injury (phase 1), contributes to tissue remodeling and the progression of heart failure. Thus, the healing process results primarily from a partial destruction of myocardial tissue that is not capable of regeneration.

If antiviral immunity has developed fast and efficiently with a subsequent rapid decline in the cellular immune processes, residual damage to the myocardium may be negligible and the remaining myocardium can compensate sufficiently for the partial loss of contractile tissue. Consequently, these patients may recover completely with no or only minor residual clinical signs of heart injury. Depending on the severity of the initial cardiac damage, other patients may have residual myocardial damage. Moderate loss of contractile tissue with more pronounced remodeling of the myocardial matrix accounts for the course of patients who only partially recover. Weeks or months after the acute onset of disease, these patients may experience significant improvement of myocardial function and symptoms, although complete recovery is rare. It is difficult to estimate whether such an improvement represents true myocardial recovery at the cellular level or whether the clinical course should be attributed to the newly administered heart failure medication. In the long run, some of these patients experience a progression of heart failure, despite regular heart failure medication. Patients with extended myocardial injury and severe hemodynamic compromise at first presentation often develop irreversible left ventricular dysfunction, and this acute dilated cardiomyopathy (DCM) will progress, irrespective of any symptomatic or specific medical therapy. Both early mortality and long-term prognosis are impaired considerably.
Chronic myocardial injury

The transition of myocarditis into DCM, following direct virus-mediated or immune-mediated myocardial damage leading to early myocardial injury, is generally accepted and supported by literature. In contrast to animal models, continuous myocardial damage caused by persisting virus infection and/or ongoing immune processes has not been proven unambiguously in the human disease. There are, however, an increasing number of sound clinical reports that underline the fact that such mechanisms may also contribute to the progression of heart failure and adverse prognosis in human disease.

Caforio et al reported on the follow-up of patients with active and borderline myocarditis in which virus persistence was a univariate predictor of adverse prognosis in addition to antihuman autoantibodies and clinical signs/symptoms of left and right heart failure. Under certain circumstances, viruses may persist and chronic immune stimulation or autoimmunity may result from incompletely cleared virus infection or in response to virus-mediated and immune-mediated chronic tissue damage, respectively. A number of viruses have been implicated in the induction of apoptosis, including Epstein-Barr virus (EBV) and adenovirus. Focal areas of apoptotic myocytes, endothelial cells, and infiltrating inflammatory cells have been detected in tissue sections from patients with adenovirus-associated myocarditis and DCM. These data suggest a relationship between myocardial virus infection and the

**Figure 3. Virus-mediated impairment of myocardial function.**

*Abbreviations: CTL, cytotoxic T lymphocyte; LV, left ventricular; MMP, matrix metalloproteinase.*
The virus-induced innate and adaptive inflammatory responses are associated with increased systemic and/or local cytokine production, and tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β) are released in large amounts by human monocytes. These cytokines promote cardiac fibroblast activity and it has been speculated that local secretion of cytokines in the myocardium perpetuates the inflammatory process that secondarily leads to the fibrosis associated with DCM and a resultant deterioration of cardiac function. Some of the inflammatory cytokines, eg, TNF-α, IL-1, IL-6, or interferon gamma (IFN-γ), are cardiodepressive and may actually cause a direct negative inotropic response. Chronic immune stimulation with ongoing production of these cytokines may be responsible for persisting regional or global ventricular dysfunction. Wall motion abnormalities will recover, however, if the effects of virus-associated inflammatory processes recede.

Murine models suggest that cytokine-mediated modulation of the immune response to viral infection may lead to induction of autoimmune myocarditis. Among their many immunomodulatory activities, cytokines contribute to the regulation of antibody production. Additionally, cardiodepressive autoantibodies may directly influence cardiomyocyte function.

To meet the energy demand of the heart, normal cardiac function depends on a permanent, adequate production of adenosine triphosphate (ATP). This process is achieved through different metabolic pathways, including glycolysis, β-oxidation, and oxidative phosphorylation. Animal models suggest that many of the steps of ATP generation are disturbed in failing virus-infected hearts, leading to an insufficient supply of energy, oxidative stress, and cell damage that contribute to the dysfunction of the heart.

In addition to these virus-related factors, host-specific differences may influence the course of viral heart disease. There is evidence of a familial disease in at least 25% of DCM patients in Western populations. In this context, the genetic background may be responsible for immune alterations and thereby influence antiviral immunity. The clinical effects of mutations of myocardial proteins, such as actin or dystrophin, may lead to induction of autoimmunity. Murine models suggest that many of these cytokines may be responsible for persisting regional or global ventricular dysfunction. Wall motion abnormalities will recover, however, if the effects of virus-associated inflammatory processes recede.

In a recent biopsy-based 6-month follow-up study, spontaneous virus clearance was found in 36% of patients with chronic viral heart disease. While LVEF of patients with persisting viral infections did not improve, complete clearance of viral genome was associated with an overall improvement in LVEF of 8%, and EF improved by 14% in patients who presented with an EF below 45%. Similarly, symptomatic and hemodynamic improvement occurred in patients whose enteroviral and adenoviral infections cleared with interferon beta treatment. This indicates that virus-associated chronic ventricular dysfunction is not generally caused by an irreversible myocardial injury and that myocardial function can recover if the myocardial infection itself and the cardiodepressive effects of the viral infection disappear.

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Viral persistence in the myocardium is associated with progressive cardiac dysfunction. 

Inhibition of urikinase-type plasminogen activator or matrix metalloproteinases prevents cardiac injury and dysfunction during viral myocarditis. 

Interferon-beta treatment eliminates cardiotoxic viruses and improves left ventricular function in patients with myocardial persistence of viral genomes and left ventricular dysfunction. 
Myocarditis is usually diagnosed by a combination of clinical and/or pathological criteria. However, the diagnosis remains difficult to achieve, mainly due to the heterogeneous clinical presentations of myocarditis patients and the limitations of the diagnostic tests available. Thus, the true incidence of myocarditis remains unclear. According to the literature, myocarditis has been found in between 1% and 9% of routine autopsy cases and in up to 21% of autopsies performed for unexplained sudden cardiac death in young individuals.

From the clinical point of view, there are two components to the diagnosis of myocarditis: when should it be suspected; and how should the final diagnosis be achieved. Thus, we will describe the most common clinical presentations of myocarditis, in the first part of this article, followed by a review of the most relevant diagnostic procedures and the clinical implications, in the second part.

**MOST COMMON CLINICAL PRESENTATIONS**

Unfortunately, there is no population-based epidemiologic study that has defined the presenting symptoms of myocarditis. Thus, the following description is based on the experiences of our myocarditis clinic in southern Germany together with the literature available.

Many cases of myocarditis are subclinical or only mildly symptomatic and have a benign course. In this patient group, the manifestation is completely variable and may in part reflect the variability of disease severity. In the group of more symptomatic patients, however, five different forms of clinical presentation can be described.

The first form is presentation with symptoms of acute myocardial infarction in the absence of coronary artery disease. In these patients, chest pain is usually severe and/or reoccurring, forcing patients to seek medical attention early after onset. Interestingly, in many cases presenting like this, the ventricle is not severely dilated, and patients have nearly normal left ventricular function.

The second form of clinical presentation is subacute new-onset heart failure, often in combination with malaise and bundle-branch block.

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CMR</td>
<td>cardiovascular magnetic resonance imaging</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<tr>
<td>EMB</td>
<td>endomyocardial biopsy</td>
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<tr>
<td>LGE</td>
<td>late gadolinium contrast enhancement</td>
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<tr>
<td>LV</td>
<td>left ventricular</td>
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<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
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<td>RV</td>
<td>right ventricular</td>
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These are patients who have typically not fully recovered from an initial respiratory or gastrointestinal infection and who finally seek medical attention because of persisting dyspnea and increasing peripheral edema. Chest pain also occurs, but is usually not severe enough to lead to hospital admission.4

Patients with inflammatory dilated cardiomyopathy (DCM) also present with heart failure, but in contrast to the patients with subacute new-onset heart failure described above, they have several previous episodes of overt heart failure in their medical history.1 Thus, reoccurring episodes of overt heart failure should be regarded as the third form of clinical presentation.

The fourth form of clinical presentation is best described as a combination of palpitations, fatigue, dyspnea on exertion, and chest discomfort (that can last for several months). These patients are frequently female, do not have impaired ejection fraction or enlarged ventricles, and their B-type natriuretic peptide (BNP) values are normal in most cases.

Finally, the initial manifestation of myocarditis can be sudden cardiac death due to malignant arrhythmias in previously healthy individuals, which is the fifth form of clinical presentation.1

**DIAGNOSTIC PROCEDURES**

**Electrocardiography**

An electrocardiogram (ECG) is still a frontline diagnostic procedure for clinically suspected myocarditis. ECG abnormalities can be found in most patients with biopsy-proven viral myocarditis on initial presentation (77%).5 The abnormalities are nonspecific (Figure 1), unless there is pericardial involvement including various ST-segment abnormalities, ectopic beats, ventricular arrhythmias, bundle-branch block, or, rarely, atrial fibrillation.6 However, as with suspected acute myocardial infarction, a normal ECG does not rule out myocarditis.

**Laboratory testing**

Routine laboratory studies of blood and urine are usually normal or reveal nonspecific abnormalities. Elevated cardiac enzyme levels may reflect myocardial necrosis, but are not seen in all myocarditis patients,5 which may be explained in part by the heterogeneity of clinical presentations and the diagnostic window for enzyme testing.

Serologic studies for detecting infections of cardiotropic viruses or certain bacteria are also frequently performed as part of the clinical routine. A fourfold rise in IgG antibody levels and/or the detection of IgM is considered diagnostic for an infection. However, concordance between the results of serology and the results of endomyocardial biopsy (EMB) occurs in only about 10% of cases.8 This may be explained by the limited diagnostic window of serologic tests (since symptoms of myocarditis may emerge months after seroconversion), serologic cross-reactions, as well as the fact that there is a high prevalence of IgG of most cardiotropic viruses in the general population. Additional microbiological investigation is of clin-
ical importance for certain types of bacterial disease, such as borreliosis or mycobacterial myocarditis. Nevertheless, myocarditis cannot be diagnosed on the basis of laboratory results alone, since myocardial inflammation itself cannot be detected in peripheral blood samples, but in EMB specimens only.

**Echocardiography**

The echocardiogram (ECHO) is one of the most valuable means of detecting clues in suspected myocarditis, even when patients are only mildly symptomatic. Unfortunately, like ECG and laboratory testing, the most common echocardiographic features of myocarditis, such as segmental wall-motion abnormalities, global left ventricular dilatation and dysfunction, ventricular thrombi, as well as pericardial effusion, are completely nonspecific. Thus, a final diagnosis cannot be achieved with this technique.

**Nuclear medicine**

Nuclear techniques, such as gallium citrate ($^{67}$Ga) scintigraphy or indium ($^{111}$In) antimyosin antibody imaging shows some promise as a noninvasive investigation for myocarditis. However, since the availability of these techniques is very limited, we will not provide a detailed assessment in this article.

**Coronary angiography**

Depending on the clinical presentation, myocarditis may mimic acute coronary syndrome. In these patients, coronary angiography is helpful for ruling out relevant coronary stenosis. Intracoronary acetylcholine testing may provide additional clues for coronary spasm caused by viral infection of the coronary endothelium (Figure 2). Furthermore, coronary angiography is needed to exclude ischemic cardiomyopathy in patients presenting with new-onset heart failure. However, myocardial inflammation cannot be detected by angiography.

**Endomyocardial biopsy**

In contrast with all the other diagnostic procedures, EMB can directly diagnose myocardial inflammation in vivo. Biopsy samples can be safely obtained from the left ventricle with a rate of severe complications that is not significantly different from the complication rate of standard coronary angiography (about 0.1% in experienced centers). In 1986, a consensus group proposed the “Dallas criteria” and provided a histopathological categorization by which the diagnosis of myocarditis could be established. Dallas criteria myocarditis requires an inflammatory infiltrate and associated myocyte necrosis or damage not characteristic of an ischemic event. These criteria, which have been used by investigators over the last two decades, are highly specific, but only have a sensitivity of 10% to 22%. The lack of sensitivity arises from sampling error caused by patchy involvement of the myocardium as well as high interobserver variability in interpretation. These limitations in combination with variance be-

![Figure 2. Coronary angiograms of the left coronary artery (LCA). (Panels A and B) In a patient with parvovirus B19-myocarditis, after significant coronary vasospasm was provoked in the left anterior descending coronary artery (LAD) and the left circumflex coronary artery (LCX) with acetylcholine (ACh) (A) compared with a relaxed state after nitroglycerin infusion (B). (Panels C and D) No significant vasoreaction was detected in a patient with normal biopsy findings in response to ACh (C) when compared with the coronary status after nitroglycerin infusion (D).](image-url)
How best to diagnose myocarditis - Mahroldt and others

Cardiovascular magnetic resonance imaging

Friedrich et al were the first to propose cardiovascular magnetic resonance imaging (CMR) for the non-invasive diagnosis of clinically acute myocarditis. They observed that the myocardium of patients with clinical manifestations of myocarditis showed hyperenhancement compared to skeletal muscle on T1-weighted images (Figure 3). However, the imaging protocol used in that study yielded a low contrast between inflamed and normal myocardium and suffered from image artifacts.

New contrast-enhanced CMR techniques, such as the one employed for infarct imaging, have improved the contrast between diseased and normal myocardium by up to 500% when compared with the protocol used by Friedrich et al. When these new inversion recovery gradient echo techniques are used in patients with clinically suspected myocarditis (history of respiratory or gastrointestinal symptoms within 8 weeks of admission in combination with fatigue/malaise, chest pain, dyspnea, or tachycardia plus ECG changes, such as conduction block, ST abnormalities, supraventricular tachyarrhythmia, or ventricular tachycardia), late gadolinium contrast enhancement (LGE) is found in up to 90% of the patients.

Regions of LGE have a patchy distribution throughout the left ventricle. They are frequently located in the lateral free wall (Figure 4, page 182) and originate from the epicardial quartile of that wall. Another frequently seen pattern is the midwall stria pattern in the basal interventricular septum in patients with chronic myocarditis.

Biopsies obtained from the area of LGE show acute or borderline myocarditis in the study by Mahroldt et al. Thus, CMR-guided biopsy in the right or the left ventricles may result in a higher yield of positive findings than routine right ventricular biopsy (Figure 5, page 182).

As mentioned above, the inability to demonstrate diffuse myocardial changes, as encountered in diffuse myocarditis with diffuse edema, is a disadvantage of the LGE technique. Localized edema without accompanying myocyte death might not result in enough increase in extracellular space to cause LGE. Thus, the sensitivity of LGE to detect milder forms of myocarditis may...
be suboptimal. Abdel-Aty suggested that CMR optimized for the detection of inflammation or edema may be more sensitive in identifying patients with acute myocarditis. Three different pulse sequences were compared in patients with cardiac symptoms, such as angina, dyspnea, or palpitations, accompanied by ECG changes, such as ST-segment changes or conduction defects and elevated serum markers. A T2-weighted triple inversion recovery pulse sequence showed significantly higher global myocardial signal intensity in patients than in volunteers, although there was overlap. A cut-off value of 1.9 had a sensitivity of 84% and a specificity of 74% in identifying the disease. A T1-weighted spin echo before and shortly after contrast injection (as described by Friedrich et al) yielded a significantly higher global myocardial relative enhancement in patients compared with volunteers. A cut-off value of 4.0 had a sensitivity of 80% and a specificity of 73% in identifying myocarditis. The sensitivity of an inversion recovery gradient echo pulse sequence (LGE sequence) started 10 minutes after contrast injection was lower with only 44% (Figure 6), but the specificity was high (100%). The best diagnostic performance was obtained when any two of the criteria obtained with the three techniques were positive in a given patient. One needs to remember, however, that, in this series of trials, the gold standard for identifying myocarditis was the clinical presentation of the patient and that endomyocardial biopsy was not performed.

**CLINICAL IMPLICATIONS**

Can CMR replace biopsies?

In order to answer the question of whether CMR can replace endomyocardial biopsies in diagnosing...
myocarditis and to give the reader practical recommendations, a thorough consideration and direct comparison of each procedure’s advantages and disadvantages based on their modes of practical implementation is needed.

At our institution, biopsy is performed early in patients presenting with heart failure and/or signs of severe myocardial damage indicated by a preceding CMR study. Biopsy is also performed if patients develop heart failure during clinical follow-up or if their daily life is significantly impaired by persisting symptoms, such as recurring chest pain with no improvement for several weeks. Despite the lack of an evidence-based therapy for viral myocarditis, it is worthwhile establishing a diagnosis in these patients with persistent and often debilitating symptoms. In fact, several experimental therapeutic options are currently available.

Biopsy samples taken at our institution first undergo staining with Masson’s trichrome, as well as Giemsa and examination by light microscopy for evaluation of histological abnormalities. Then, immunohistology using CD3, CD68, and HLA-DR antibodies is performed for the detection of T lymphocytes, macrophages, and professional antigen-presenting immune cells, respectively. In addition, DNA and RNA is extracted followed by nested polymerase chain reaction (PCR)/reverse transcriptase–PCR for the detection of viral genomes. Altogether, these methods provide more detailed information about the nature of the inflammatory process than the comparatively crude method of CMR. In addition, the pathologist is able to distinguish between various degrees of inflammation and to detect the underlying pathogen. Despite the fact that most cases of myocarditis are viral in origin, treatable and prognostically important forms of myocarditis, such as the bacterial, giant cell, or eosinophilic variants, can be identified.

This comprehensive investigation of biopsies was shown to be highly sensitive for the detection of myocardial inflammation (even in the absence of focal lymphocytic inflammation in the biopsies), has been shown repeatedly in the past. Why et al.²⁹ prospectively evaluated 120 patients with clinical suspicion of myocarditis and/or dilated cardiomyopathy and divided them into two groups on the basis of the presence or absence of enteroviral genome in the biopsy samples. Mortality and progression to cardiac transplantation during the follow-up was greater in the enterovirus positive group than in the enterovirus negative group. Furthermore, the detection of enterovirus RNA in the myocardium was shown by multivariate regression analysis to be an independent predictor of clinical outcome. This type of viral persistence without inflammation would obviously be missed by CMR.
The major limitations of endomyocardial biopsy are its associated sampling error and its invasive character with a nonnegligible risk of complications. At our institution, biopsies are taken using a transfemoral biventricular (left ventricular [LV] and right ventricular [RV]) approach targeted towards the area of maximum myocardial damage as indicated by previous CMR. If no signs of myocardial damage are present with CMR (eg, LGE as well as T2-STR [short T1 inversion recovery] imaging are false negative), we obtain at least six biopsy samples from three different locations of the RV septum as well as six additional biopsy samples from three different locations of the LV lateral wall. The degree of sampling error depends on the number of biopsies taken per patient as well as on the methods applied for ex vivo analysis. Critics of endomyocardial biopsy often refer to Hauck et al, 30 who demonstrated in postmortem tissues of patients with histologically proven lymphocytic myocarditis that the evaluation of five biopsies based on Dallas criteria, the histological diagnosis of myocarditis/borderline myocarditis showed false negative results in up to 55% of cases. However, we believe that our biopsy technique comprising both RV and LV biopsies targeted toward the area of myocardial damage as well as the procedures applied for the evaluation of biopsies, minimize the frequency of sampling error. The risk of serious complications, such as complete atrioventricular block with pacemaker implantation, ventricular perforation with hemorrhagic pericardial effusion resulting in pericardiocentesis, or surgical closure of the perforation, is less than 1%. 13-15

On the other hand, CMR is better than EMB at giving additional information about extracardiac diseases, since CMR is able to cover the whole heart and thorax detecting pericarditis or acute aortic syndrome. Our CMR protocol for the investigation of myocarditis comprises assessment of myocardial function, myocardial edema, pericardial effusion, and myocardial damage with LGE imaging in short- as well as long-axis views. Thus, CMR provides highly comprehensive and sensitive information about the (potentially patchy) areas of maximum inflammatory and destructive activity in myocarditis, 31 which cannot be obtained by biopsy. In addition, increased T2 values may indicate a more acute inflammatory process, whereas the presence of LGE is a marker of both acute and chronic myocardial damage. Moreover, the pattern of myocardial involvement may have prognostic implications. 4,19 All this information can be obtained noninvasively and repeatedly without risk, in contrast with invasive procedures.

Recently, our group evaluated the diagnostic performance of both CMR and EMB in the same patients with clinically suspected myocarditis. 32 Our results indicate that biopsy is superior to LGE-based CMR in diagnosing myocarditis because EMB is capable of detecting minor forms of myocarditis, such as borderline myocarditis or virus genome presence, thanks to immunohistochemistry and nested-PCR. LGE-based CMR alone often missed these more subtle forms of myocarditis, possibly due to limited spatial resolution. Interestingly, as in the study by De Cobelli et al, 17 a diagnosis of myocarditis was more frequently made with CMR in patients with severe active myocarditis compared with those with borderline myocarditis. Thus, the value of LGE imaging in CMR-based diagnosis of myocarditis seems to be related to the degree and extent of histological inflammation. Moreover, our data indicate that it is reasonable to perform an initial CMR in patients with clinically suspected myocarditis, since there is high diagnostic conformity between CMR-based and biopsy-based results. If the initial CMR study establishes the diagnosis of myocarditis, additional biopsy is unlikely to change this diagnosis. However, in cases where the initial CMR study is nonconclusive, but a diagnosis is needed, for instance, in a patient with persistent symptoms, a biopsy can be employed as a second step, since a biopsy may potentially spot more subtle forms of myocarditis that would not be detected with CMR. However, although such an algorithm would avoid biopsies in a substantial number of patients and minimize the risk of complications associated with obtaining a diagnosis, it is obviously not a perfect alternative approach. If the diagnosis of myocarditis is merely based on CMR, then there is less detailed information available about the degree of inflammation, the presence of special forms of myocarditis (such as giant cell or eosinophilic myocarditis that require specific therapies), or the presence and type of virus.

There are some merits in using a dual technique approach comprising both procedures (CMR and EMB) in patients with clinically suspected acute myocarditis. When the two techniques are used in combination, the highest number of conclusive diagnoses is achieved in these patients. 32 Since recent data by Kidermann et al 26 indicate that the presence of inflammation in biopsies has prognostic implications and previous data from our group 4 indicate that the presence and distribution of LGE may also have prognostic implications, such a combined approach could also be superior for stratifying future risk and implementing specific therapies.
In summary, we do not believe that CMR can completely replace EMB for the investigation of myocarditis in the near future. Although CMR is capable of diagnosing myocarditis in a very high percentage of patients, it is currently neither able to assess the severity of inflammation nor definitively detect the underlying (mostly viral) pathogens. An exact algorithm specifying when and in which patients different procedures should be preferentially used is not available at the moment. Hence, a decision about whether it is necessary to obtain detailed histopathological information using biopsies following a preceding conclusive CMR has to be taken in consideration of the individual circumstances.

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What are the current treatment options for myocarditis?

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Myocarditis is an inflammatory disease of the cardiac muscle caused by intramyocardial infiltration of immunocompetent cells following any kind of cardiac injury. Classic myocarditis mainly occurs because of the host’s immune response against organisms that cause common infectious illnesses, as a manifestation of hypersensitivity, or as a toxic reaction to drug administration. Chronic inflammatory events may continue after the initial successful clearance of cardiotoxic agents, be triggered or amplified by autoimmunologic processes, or develop in the context of systemic diseases. If the underlying infectious or immune-mediated causes are carefully defined, specific immunosuppressive and antiviral treatment options may improve prognosis of patients with acute and chronic disease.

Keywords: myocarditis; inflammatory cardiomyopathy; viral heart disease; immunosuppressive treatment; antiviral therapy; immunoadsorption; interferon

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Myocarditis is a nonischemic inflammatory disease of the myocardium that may be associated with severe cardiac dysfunction. The inflammatory process occurs because of the host’s immune response to organisms that cause common infectious illnesses, as a manifestation of hypersensitivity responses, or because of an immune-related or autoimmune-related injury. Lymphocytic myocarditis is the most common form of myocarditis reported in the United States and Western Europe, and virus infections are considered the most common cause of this acquired inflammatory heart disease.

Histologically, active myocarditis is characterized by an often focal mononuclear cellular infiltrate with myocytolysis and/or degeneration of adjacent myocytes (Figure 1B, page 188). In addition to lymphocytes, the inflammatory infiltrate may also include mixed types of inflammatory cells. In rare cases, multinucleated giant cells (Figure 1D) or eosinophils (Figure 1C) are predominant in the active inflammatory process.

In the chronic state (inflammatory cardiomyopathy), the diffuse inflammatory infiltrates are less evident, and there is no myocyte necrosis. These chronic inflammatory events can persist after the clearance of cardiotoxic agents, be triggered or amplified by autoimmunologic processes, or develop in the context of a systemic disease.

The causes of acute or chronic myocardial damage in myocarditis, which is responsible for heart failure, arrhythmias, and the development of cardiomyopathy, are not known exactly. Both direct virus-induced myocyte necrosis and emerging innate and cell-mediated antiviral immunity may contribute to early myocyte injury. Chronic immune stimulation and autoimmunity may propagate harmful myocardial changes, regardless of whether the initial trigger, e.g., viruses, still persists or has been cleared. Chronic immune stimulation may arise from synthesized virus proteins of incompletely cleared viruses, the release of intracellular proteins from necrotic or apoptotic myocardial cells, be induced by cross-reacting autoanti-
bodies, or activation of matrix-degrading proteases. All of these factors can influence both prognosis and responsiveness to specific treatment modalities.

Symptomatic heart failure therapy may improve clinical symptoms and hemodynamic compromise, but it does not affect the specific underlying causes of the disease. In contrast with lymphocytic myocarditis, giant cell myocarditis (GCM) is a heterogeneous disorder with variable rates of recurrence and severity that may need instant and often multiple drug regimens in order to improve an otherwise poor prognosis. Mean transplantation-free survival with GCM is 5.5 months and, in comparison with nonfulminant lymphocytic myocarditis, considerably worse 4-year survival rates (11% versus 44%) have been reported. Necrotizing eosinophilic myocarditis is a rare condition with a rapid progression of hemodynamic compromise and a fatal outcome. Prognosis of both diseases is improved by immunosuppressive treatment.

**Treatment**

**Acute fulminant and nonfulminant lymphocytic myocarditis**

Data supporting favorable effects of specific immunosuppressive or antiviral treatment strategies are lacking for both acute conditions, and treatment therefore remains supportive. It may initially require intensive care with intravenous inotropic agents and mechanical assistance for circulatory support in addition to conventional heart failure therapy. If fulminant myocarditis is quickly recognized and patients are given aggressive treatment, more than 90% will recover with minimal long-term sequelae. Nonfulminant patients with more stable conditions should be treated with optimal heart failure medication, including angiotensin-converting enzyme (ACE) inhibitors, β-adrenergic blocking drugs, and diuretics (Figure 2).

Ventricular arrhythmia is common in patients with active myocarditis, but, in most cases, it does not require specific therapy. If patients present with severe refractory ventricular arrhythmias, antiarrhythmic...
treatment with amiodarone or an implantable cardioverter-defibrillator is necessary. Similarly, patients with atrioventricular (AV) block may require insertion of a temporary pacemaker.

Because myocarditis may go into spontaneous remission, antiarrhythmic devices and mechanical devices should only be used after all other methods of controlling arrhythmia and heart failure have proved to be unsuccessful. At present, heart transplantation is the only curative option for the treatment of refractory heart failure.

**Giant cell myocarditis**

Rapid immunosuppression includes cyclosporine (target serum trough level of 150-300 ng/mL) and initial high-dose (10 mg/kg) methylprednisolone daily (Figure 2). After three days, prednisone is titrated weekly from 1 mg/kg to 0.5 mg/kg, 0.25 mg/kg, 15 mg/day and 10 mg/day. In very acute conditions, 5 mg/day of OKT-3 antibodies (muromonab-CD3) with high-dose cortisone premedication may be added for 7 to 10 days.14 Low-dose prednisolone and cyclosporine are maintained for 1 year, but both should be continued in case of recurrence, which may even occur months after the cessation of immunosuppression. Some patients may need lifelong therapy after recurrence (L. Cooper, personal communication).

**Necrotizing eosinophilic myocarditis**

Necrotizing eosinophilic myocarditis (NEM) is a similar severe form of myocarditis. NEM may be caused by different drugs and toxic agents, although not all cases are believed to be triggered by hypersensitivity to drugs. Without rapid recognition and treatment, NEM has a fatal prognosis. Most cases are diagnosed at autopsy. Treatment options are few, but, after immediate cessation of all unnecessary medications, high-dose corticosteroids and azathioprine have been used with limited success in uncontrolled series of trials.14

**Cardiac sarcoidosis**

All patients with progressive cardiac diseases and extensive granulomatous infiltration of the myocardium (10% of cases) should be given the standard medication and devices used for the management of heart failure.

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**Figure 2. Specific treatment options in myocarditis and viral heart disease.**

*Abbreviation: IVIG, intravenous immunoglobulin.*
failure, frequent arrhythmias, and conduction defects. In different series of studies, progressive heart failure accounted for 25% to 75% of cardiac deaths. The role of steroids in cardiac sarcoidosis is well established. Patients should be treated as soon as possible after diagnosis is made for at least 6 months to prevent the progression of myocardial dysfunction by inflammatory processes. If prolonged treatment is required, cyclosporine or methotrexate may be used to prevent steroid side effects. In rare cases of acute heart failure, patients may respond to high-dose steroids, but optimum treatment has not been defined.

**Mild lymphocytic myocarditis**

If clinical symptoms are mild or moderate and left ventricular function remains practically unaffected, patients with active myocarditis do not necessarily need special treatment. During the initial phase of myocarditis, especially while electrocardiogram abnormalities and increased levels of troponin I/T or creatine kinase isoforms can be recorded, hospitalization and monitoring is recommended for identifying and preventing life-threatening arrhythmias and the development of myocardial decompensation. In the subacute stage of the disease, physical activity should be avoided until cardiac inflammation (possibly verified by endomyocardial biopsy) has resolved. The prescription of heart failure medication is determined by the severity of ventricular compromise.

**CHRONIC MYOCARDITIS**

In viral and autoimmune inflammatory cardiomyopathy, the interstitial cellular infiltrates usually contain lymphocytes, leukocytes, and macrophages. Eosinophils constitute the predominant component of the inflammatory infiltrate in a variety of myocardial diseases associated with parasitic infections, hypersensitivity/allergic drug reactions, Churg-Strauss or hypereosinophilic syndromes, and endocardial fibrosis (Loeffler's endocarditis). Organ-specific autoimmunity is characterized by defined self-antigens, activated autoreactive T cells, and/or autoantibodies that can transfer disease. Recently, cardiac specific autoantibodies have been identified as a prognostic factor in myocarditis.

In addition to cellular infiltrates, immunoglobulin and complement deposits or enhanced endothelial expression of different cellular adhesion molecules indicate myocardial inflammatory processes and have been used to characterize the myocardial inflammation and to indicate treatments. If cardiac infiltrates or autoimmune processes contribute to cardiac dysfunction in inflammatory cardiomyopathy, the interruption of the involved immune processes and/or elimination of autoreactive mediators, eg, autoantibodies, should improve clinical outcome or at least prevent progression of the disease.

Autoantibodies are extractable by immunoadsorption (IA). Significant improvement of left ventricular dysfunction and clinical symptoms was reported after IA, in parallel with the elimination of circulating cardiodepressant immunoglobulin (Ig) subclass G3 autoantibodies.

A number of nonrandomized studies have suggested the clinical benefit of immunosuppressive therapies in immune mediated cardiomyopathies, but none of the immunosuppressive agents studied in placebo-controlled clinical trials (corticosteroids, cyclosporine, azathioprine, or intravenous immunoglobulin [IVIG]) have yet demonstrated a clear improvement in mortality. There has only been one randomized controlled trial of IVIG in adults, and no clear benefit was shown since patients improved spontaneously with or without immunoglobulin treatment in the patient cohort with acute-onset dilated cardiomyopathy. For similar reasons, two randomized trials failed to find any benefit of immunosuppressive therapy with steroids in combination with azathioprine or cyclosporine in histologically confirmed myocarditis, according to the Dallas criteria.

Two newer randomized studies, in which patients were characterized by defined immunohistological or molecular biological sets of myocardial markers of inflammation or infectious agents, reported treatment benefit versus placebo. Careful characterization and selection of patients for treatment seem to be of the utmost importance in obtaining a positive outcome and preventing harmful treatment side effects.

**Treatment**

Lymphocytic and eosinophilic myocarditis as well as myocarditis caused by autoimmune or hypersensitivity reactions may well respond to standard immunosuppression. The immunosuppressive treatment regimens in chronic myocarditis/inflammatory cardiomyopathy and autoimmune disorders consist of corticosteroids, azathioprine, or cyclosporine. α-Methylprednisolone is generally given, at a rate of 1 mg/kg body weight (for children, 1-2 mg/kg), initially for 4 weeks. The dosage is titrated monthly in increments of 10 mg until a maintenance dose of 10 mg is reached. The treatment should last for 6 months. In cases of persistent inflammation (35% to 40%
of patients), 50-150 mg/day azathioprine may be administered in addition to the steroid medication.

**Immunoadsorption**

In early studies, IA was performed in a series of one to five courses at one-month intervals. During each course, patients underwent one IA session daily for three to five consecutive days. Using protein A columns, a 40% reduction in total IgG and a >85% reduction in IgG3 was achieved during each session. After the final IA session, the patients received 0.5 g/kg polyclonal IgG over a period of 6 hours in order to restore IgG plasma levels. In subsequent studies, hemodynamic improvement at 6 months was found to be comparable between the single course and repeated course IA treatment strategies. These observations suggest that activation of the humoral immune response could play a functional role in cardiac dysfunction of patients with inflammatory cardiomyopathy. Influencing the humoral immune system using IA may thus provide a therapeutic option for patients with immune-mediated heart failure. This treatment regimen is currently being tested in a randomized clinical trial.

**VIRAL HEART DISEASE**

Molecular biology studies have identified different viral genomes and virus subtypes in myocardial tissues of patients with acute, chronic, and end-stage heart disease, and these observations have led to an assumption that dilated cardiomyopathy may be a late sequel of viral myocarditis, although this assumption has been doubted by others. In most studies, virus persistence has not been proven by follow-up biopsies. In a recent biopsy-based follow-up study, virus elimination was found in 62 of the 172 virus-positive patients (36%). Fifty percent of the enteroviral genome was cleared spontaneously and respective data for adenovirus, parvovirus B19, and herpesvirus 6 were 35.7%, 22.2%, and 44.4%. These data show that spontaneous clearance of the virus infection may occur late in the course of the disease. Therefore, a single biopsy analysis does not prove later virus persistence. The complete clearance of viral genome was associated with an overall improvement of left ventricular ejection fraction (LVEF) of 8%, while ejection fraction (EF) improved by 14% in patients who presented with an EF <45%, indicating that chronic ventricular dysfunction in these patients was not caused by irreversibly damaged myocardium. The LVEF of patients with persistent viral infections did not improve. Spontaneous virus clearance, in addition to the presence of myocarditis and nonmyocarditis virus variants, may thus explain the discrepancy in the findings of the earlier studies.

The clinical importance of persistent enteroviral genomes in the myocardium was also demonstrated by Why et al. who showed a higher mortality at 25 months (25% versus 4%) in 41 patients with persistent enteroviral infection. Two retrospective studies on patients with inflammatory cardiomyopathy point in a similar direction. In one study, nonresponders to immunosuppression were characterized by a high prevalence (85%) of viral genomes and no detectable serum autoantibodies. Conversely, virus-negative, autoantibody-positive patients improved significantly with immunosuppressive treatment. Seven of the nonresponders died or were transplanted within a period of 9 months. Caforio et al. reported a 2-year follow-up of patients with active (n=85) and borderline myocarditis (n=89) in which virus persistence was a univariate predictor of adverse prognosis, in addition to antihuman autoantibodies and clinical signs/symptoms of left and right heart failure.

These and other observations suggest that patients with heart failure and persisting viral infection may benefit from timely antiviral treatment, which should be administered before myocardial tissue has been irreversibly damaged by virus-associated mechanisms.

**Antiviral treatment**

Elimination of viral translation, transcription, and proliferation with the use of antiviral medications that target viral attachment to host-cell receptors, virus entry, or virus uncoating, eg, Pleconaril, WIN 54954, or CAR-Fc, would be effective in the early stages, but, unfortunately, most patients present in the later phases of disease. Agents, therefore, are of limited use in virus-associated heart disease.

Interferons (IFNs) are a natural defense against viral infection, and their innate production is associated with recovery from viral infection, while exogenous administration is protective. Data from randomized studies demonstrating a benefit of a specific antiviral therapy in patients with virus-induced heart muscle disease do not exist so far. An analysis of four patients in one open-label study could not demonstrate a beneficial virus clearance effect of a treatment protocol using 9 million units of IFN-α per week for 6 months. According to animal models and cell culture experiments, IFN-α has an antiviral potency similar to that of IFN-β, so one could assume that the concentration of IFN-α used in this study was insufficient for virus elimination. In a second nonrandomized study, patients with clinical evidence of my-
ocardiitis or dilated cardiomyopathy were treated with IFN-α or thymo-
din. Left ventricular contractility improved after 6 months of
therapy, but, unfortunately, virus infection of the myocardium before
and after treatment was not docu-
mented in this study. Data from an
IFN-β treatment study provided the
first evidence that antiviral IFN-β
therapy effectively clears entero-

viral and adenoviral infections of the
myocardium in patients with chronic
heart failure when given subcuta-

neously every other day in combi-
nation with regular heart failure
medication. The treatment was
administered three times a week
using 6 million units of IFN-β per
subcutaneous injection. This dosage
was well tolerated. After 6 months of
therapy, entero viral RNA and
adenoviral DNA were cleared from
the cardiac tissues of all the pa-
tients analyzed (n=22). Virus clear-
ance was associated with a signifi-
cant improvement in left ventricular
contractility and a decrease in left
ventricular size. No patient deteri-

orated.

While entero viruses and adenovirus-
es seem to respond well to IFN-β
treatment, subsequent open-label
studies have shown that other virus infections respond less well.
Optimal treatment conditions for
viruses other than entovirus and
adenovirus have not yet been de-

fined and, therefore, antiviral thera-

py is still a matter for clinical trials
until transplantation. At present
heart transplantation is the only
curative option for the treatment of
refractory heart failure.

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My route to cardiology was anything but planned. Born in North London in 1930, the older son of an electrical engineer of Scottish descent and a child of the war years, I enjoyed my days at boarding school, which led on to watershed years at Cambridge reading natural sciences. I then switched from a potential botanical career to read medicine and went on to St Thomas’ Hospital for the clinical years—all told, a rich and formative path that embraced friendships, sport, singing, painting, stage, and an appropriate mix of clinical and academic excellence. This flowed fairly seamlessly (after the salutary shock of failing finals!) into a series of junior hospital clinical and research posts in different medical specialties—a luxury of all-round experience sadly no longer practically possible.

Taking stock in 1966 over a cup of tea with a friend, I decided to focus on cardiovascular medicine—about the only medical specialty I had not previously experienced—and a short list of favored research centers. Fate stepped in when a chance dinner invitation the following day led directly to the offer of a Research Fellowship at the Peter Bent Brigham in Boston. Three years of laboratory-based research ensued. Investigating myocardial metabolism with perfused rat hearts was a frustrating but invaluable learning experience into all aspects of cardiac function (no data for 1 year, no publications for 2 years!). Momentum gathered. Studies of myocardial mechanics and excitation-coupling (E-C) in papillary muscle preparations (with Ed Sonnenblick) were more productive, and led to fruitful collaboration with Dirk Brutsaert in Antwerp. I came to realize that the motivations and the aesthetic rewards of recognizing new patterns in basic research and in painting were very similar. And the understandings derived from this basic work provided a useful conceptual framework in clinical cardiology.

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Back in the UK (newly married and devotedly nursed through 2 years *hors de combat* for a bladder cancer and its treatment), I was appointed to the newly established academic department of cardiology in Wales at Cardiff and subsequently to the Chair as Head of Department in 1979. This brought clinical and academic responsibilities that included trying to develop cardiac services throughout Wales with its then scant base of one cardiologist per million population.

A small interdisciplinary (and necessarily interdepartmental) basic research group within the context of the clinical unit was established, with pharmacological, molecular biological, nonlinear mathematical, and imaging expertise. Further work on myocardial E-C coupling included studies providing evidence for dual sources of activating calcium and for the release of intracellular calcium during shortening. We then turned our research focus into the less traveled path of investigating vascular function, clinically relevant as this clearly was. Fortuitously, the team happened upon the phenomenon of endothelium-dependent arterial dilatation (just a week before Bob Furchgott’s classic report of the phenomenon was published!). It was a stroke of rare good fortune to be in at the start of the major new chapter of vascular biology and pathophysiology that this heralded. Limited availability of needed laboratory resources catalyzed a fund-raising exercise to build the Wales Heart Research Institute.

I appreciate how fortunate I was in the breadth of my background experience; in having the privilege of being at the helm for Wales during what was a period of remarkable and exciting growth in cardiovascular science and medicine; in the opportunity to develop a basic research program integrally embedded in the activity of the clinical unit; and in the many outstanding colleagues and good friends I made here and abroad, supported unfailingly throughout by my wife and growing family to keep my feet on the ground.

**ARTIST**

It was my father who introduced me to drawing and painting as a 5-year-old—watercolors on site, mostly landscape. As a medical student, I was encouraged by my then landlord, a Royal Academician, to exhibit (and sell) at the New English Art Club and the Royal West of England Academy. Thereafter, I painted every
year on holiday (of course!), but other-
wise little—enjoying the medium, cal-
ligraphically free and open to its acci-
dents, but holding back from joining
any group for fear of losing such flair
as I might have had, until shortly be-
fore retirement I heard of Robin Child's
Experimental Art Group, which I sam-
pled and have been attending since.
It has been an inspirational introduc-
tion to 20th century art, the art of our
age in all its rich variety, and to the
liberated individuality of its great
artists—how they painted, how they
thought, how they interacted.

All artists are said grow on the shoul-
ders of those who go before (at least
until the shock tactics of much con-
temporary conceptual “art”). And “am-
ateurs borrow, professionals steal!”
[Picasso]. Looking for excuses, I sus-
pect that the rational component of
scientific training makes it difficult to
sideline conscious, analytic thought,
and trust to intuition. Important as
this is in basic research, it is seminal
to painting. Intuitive action and recog-
nition are key to 20th century paint-
ing. The work proceeds from in-built
figurative seeds towards an end as yet
unknown, guided predominantly by
considerations intrinsic to art rather
than to figurative reproduction—con-
siderations that will incorporate the
aesthetic response to the mark, the
stroke, the medium (“me, in action,
now” [Franz Kline]), the underlying
structure and its disbalances, reflec-
tions, and rhythms, its palimpsests
that tell of the work’s genesis, the
planes and tricks of visual perception,
the relativities of the palette with its
warms and cools. There is indeed a
complexity of immeasurable compo-
nents to be learned and embedded
beyond the distracting constraints of
cerebral control (as in driving a car.
Aesthetic rewards in basic research and painting - Henderson

(or executing a cover drive off a fast bowler!) And time is needed to incorporate what is learned, to distil and find one's voice. In practice, aspiration far outruns actualité, and the process faute de mieux has to bring its own reward, with the inestimable advantage of deepening our appreciation of these great painters.

Ivon Hitchens, Keith Vaughan, Bomberg, and Peter Lanyon among British painters have been major influences, with de Stael among Europeans, and Diebenkorn, Joan Mitchell, and Helen Frankenthaler from America. The subject is immaterial: abstract or abstracted figurative, landscape, life, or still life. The medium: whatever works. Every painting is a failure, the next (one has to dream) the maybe masterpiece. The exercise is more difficult than any science (though the root resonances are not dissimilar). Playing is the fallback catalyst—as each work is

**THE CARDIOLOGIST'S SELECT BIBLIOGRAPHY**

an experiment into the unknown, yet paradoxically needing the discipline of a specific viewpoint (which is not easy, given the rich variety of influences to which we have been introduced). Interaction within the group of kindred spirits provides the adrenaline that is elusive when painting alone. In recent years, I have exhibited regularly with the annual Royal College of Physicians show (one painting from medical student days, shown in the first of these exhibitions, unexpectedly appearing in the *Lancet* 1997;350:151), and in galleries locally, in London, and with my art group in Wiltshire.

Why paint? In youth, I just did—now, perhaps, in search of an elusive surrogate grail.
Myocarditis

Summaries of Ten Seminal Papers

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Dialogues Cardiovasc Med. 2009;14:201-211

1. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators

2. High prevalence of viral genomes and multiple viral infections in the myocardium of adults with “idiopathic” left ventricular dysfunction
   U. Kühl and others. Circulation. 2005

3. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement form the American Heart Association, the American College of Cardiology, and the European Society of Cardiology...
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8. A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogenetic features at diagnosis

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10. Complication rate of right ventricular endomyocardial biopsy via the femoral approach: a retrospective and prospective study...
    M. Holzmann and others. Circulation. 2008

Selection of seminal papers by Leslie T. Cooper Jr, MD, FACC, FAHA
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Highlights of the years by Ian Mudway, MD
Lung Biology - Division of Life Sciences Franklin Williams Building
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A clinical trial of immunosuppressive therapy for myocarditis. 
The Myocarditis Treatment Trial Investigators

Myocarditis Treatment Trial Investigators


This paper is of particular importance because it is the largest randomized controlled trial of immunosuppressive therapy in patients with myocarditis. The Myocarditis Treatment Trial was a multicenter clinical trial conducted to determine the efficacy of immunosuppressive therapy for treatment of biopsy-documented myocarditis. It also attempted to improve understanding of the immunological mechanisms involved in the development of myocarditis.

Thirty-one centers in the United States, Canada, Great Britain, and Japan screened patients with heart failure. Over 2000 patients were determined to have unexplained heart failure and underwent endomyocardial biopsy. Patients were enrolled in the trial if the biopsy was positive for myocarditis according to the “Dallas criteria,” the duration of symptoms was less than 2 years, radionuclide left ventricular ejection fraction (LVEF) was less than 45%, and there were no medical exclusions. Exclusion criteria included: age 18 or less; current or potential pregnancy; condition contraindicating immunosuppressive therapy; conditions requiring immunosuppressive therapy; coronary heart disease; treatment with investigational drugs, β-blockers, disopyramide, or calcium antagonist therapy; limited life expectancy, and substance abuse. One hundred and eleven patients were randomized within one week after a positive diagnosis of myocarditis to either receive immunosuppressive therapy or no immunosuppressive therapy.

Patients were allocated to one of three treatment arms during the first 16 months of the trial: (i) “control” limb patients received no immunosuppressive therapy, (ii) patients received azathioprine and prednisone; and (iii) patients were treated with cyclosporine and prednisone. All patients received conventional drug therapy for heart failure according to a standardized algorithm. Immunosuppressive therapy was maintained for 24 weeks, followed by a 28-week follow-up period. Patients were taken off the protocol at the conclusion of week 52 and followed for up to 5 years thereafter. The primary outcome measure was LVEF at 28 weeks. Results showed that in the group as a whole, the mean LVEF improved from 25% at baseline to 34% at week 28. The mean LVEF did not significantly differ between the control group and the groups that received immunosuppressive therapy at baseline, week 28, or week 52. The LVEF improved in both treatment groups during the course of the trial. Positive independent predictors of LVEF at week 28 included higher left ventricular ejection fraction at baseline, less intensive conventional drug therapy at baseline, and a shorter duration of disease. Treatment assignment was not a predictor. The immunosuppression and control groups did not differ significantly in survival at one year or throughout the period of follow-up. The mortality rate for the study population was 20% at one year and 56% at 4.3 years. Baseline LVEF was positively associated with the duration of survival and intensity of conventional therapy at baseline was negatively associated with survival.

This study is limited by patient selection in that it potentially excluded patients with nonlymphocytic myocarditis. There was no virology assessment. Finally, only a limited range of possible immunosuppressive therapies was used. Despite these limitations, however, this study suggests that immunosuppressive therapy is not beneficial in most patients with histologically proven acute myocarditis. Patients with a higher LVEF and shorter duration of disease are more likely to improve. The “Dallas criteria” probably have a low sensitivity for the diagnosis of acute myocarditis.

Eduard Shevardnadze, the Georgian head of state, survives an assassination attempt in Tbilisi; Microsoft’s Internet Explorer is released as part of Windows 1995; and Indian astrophysicist and Nobel laureate Subrahmanyan Chandrasekhar dies.
High prevalence of viral genomes and multiple viral infections in the myocardium of adults with “idiopathic” left ventricular dysfunction

U. Kühl, M. Pauschinger, M. Noutsias, B. Seeberg, T. Bock, D. Lassner, W. Poller, R. Kandolf, H.-P. Schultheiss

Circulation. 2005;111:897-893

Viruses are important pathogenic agents in acute myocarditis and have been associated with the development of dilated cardiomyopathy. Enteroviruses have long been considered to be the most important viral pathogen in this disease, but, more recently, other viruses have been implicated as well. Does persistent viral infection with any or several of a wide range of viruses play a role in the transition from acute myocarditis to dilated cardiomyopathy (DCM)? This paper is important because it attempts to answer this question.

Endomyocardial biopsy specimens were obtained from 245 consecutive patients with clinically suggested idiopathic DCM after assessment by both echocardiography and coronary angiography excluded coronary heart disease and other possible causes of cardiac dysfunction. The median left ventricular ejection fraction was 35%. DNA and RNA were extracted from frozen heart muscle tissue probes. Polymerase chain reaction (PCR)/reverse transcription PCR (RT-PCR) was performed for the detection of enteroviruses (EVs), including coxsackievirus and echovirus, adenovirus (ADV), parvovirus B19 (PVB19), human herpesvirus type 6 (HHV-6), Epstein-Barr virus (EBV), human cytomegalovirus (HCMV), influenza viruses A and B, herpes simplex viruses 1 and 2 (HSV-1 and HSV-2), and hepatitis C virus (HCV). Systemic infection with PVB19, EBV, and HHV-6 was excluded by extraction of DNA from peripheral blood cells. Myocardial inflammation was assessed by histological and immunohistological analyses.

Viral genomes could be amplified from endomyocardial biopsies of over two thirds of the 245 DCM patients as follows: EV = 23 (9.4%), ADV = 4 (1.6%), PVB19 = 126 (51.4%), HHV-6 = 53 (21.6%), EBV = 5 (2.0%), and HCV = 2 (0.8%). Influenza A, influenza B, HSV-1, and HCMV genomes were not detected. Forty-five cases (27.3%) had multiple infecions. Histopathological and immunohistological analyses revealed no signs of active or borderline myocarditis in any of the samples analyzed. Lymphocyte and macrophage infiltrates were not significantly different in virus-positive versus virus-negative patients.

These results clearly indicate that there is a high prevalence of viral genomes in the myocardium of patients with DCM. In addition, many of these patients have multiple viral infections. Interestingly, only one fourth of the patients had evidence of EV or ADV infection. In contrast, PVB19 was positively detected in over 50% of cases and HHV-6 in more than 20% of cases.

The high prevalence of viral genomes and multiple viral infections present in this group of DCM patients was unexpected. This may be partially due to the fact that previous studies in the 1980s and 1990s primarily assessed EV and ADV. PVB19 had been reported in cardiomyopathies of childhood, but this is the first of several papers to report PVB19 as a common cause of myocarditis and DCM. Although the detection of viral genomes in this study population does not itself prove causality in the pathogenesis or progression of disease, data from recent publications suggest that PVB19 may play a significant role at some point during the pathogenesis of DCM through various mechanisms. The spectrum of viral infection has changed and patients with dual or multiple viral infections may clear one or more infections while continuing to screen positive for another viral genome in subsequent evaluations. This may account, at least in part, for the variable clinical course of patients with DCM. Pathogenic mechanisms induced during the early stages of unrecognized viral myocarditis may be responsible for later progression to DCM by remodeling or recognition of endogenous epitopes that mimic viral antigens after elimination of the primary viral agent.

The Kyoto Protocol comes into effect, without the support of the United States or Australia; Million Dollar Baby wins the best picture award at the 77th Academy Awards; and Saudi Arabia holds its first ever, male-only municipal elections.
The role of endomyocardial biopsy in the management of cardiovascular disease

A scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Endorsed by the Heart Failure Society of America and the Heart Failure Association of the European Society of Cardiology

L. T. Cooper, K. L. Baughman, A. M. Feldman, A. Frustaci, M. Jessup, U. Kühl, G. N. Levine, J. Narula, R. C. Starling, J. Towbin, R. Virmani; American Heart Association; American College of Cardiology; European Society of Cardiology; Heart Failure Society of America; Heart Failure Association of the European Society of Cardiology

J Am Coll Cardiol. 2007;50:1914-1931

The role of endomyocardial biopsy (EMB) in the diagnosis and treatment of cardiovascular disease is controversial. Who is an appropriate candidate for EMB? This joint scientific statement was written by a multidisciplinary group of experts and endorsed by several cardiovascular medicine associations. Recommendations were derived from a comprehensive review of the published literature on specific cardiomyopathies, arrhythmias, and cardiac tumors.

EMB is not indicated for routine evaluation of heart disease. There are 2 class I recommendations for the performance of an EMB, both in the setting of unexplained, new-onset heart failure: 1) symptoms <2 weeks in duration associated with a normal-size or dilated left ventricle in addition to hemodynamic compromise (suspected lymphocytic myocarditis); and 2) symptoms 2 weeks to 3 months in duration associated with a dilated left ventricle and new ventricular arrhythmias, Mobitz type II second- or third-degree atrioventricular block, or failure to respond to usual care within 1 to 2 weeks (suspected giant cell myocarditis).

The six clinical scenarios in which an EMB is reasonable (class IIa recommendations) are in the setting of: 1) unexplained heart failure of >3 months’ duration associated with a dilated left ventricle, without new ventricular arrhythmias or Mobitz type II second- or third-degree AV heart block, that responds to usual care within 1 to 2 weeks (uncomplicated acute idiopathic dilated cardiomyopathy); 2) unexplained, new-onset heart failure of >3 months’ duration associated with a dilated left ventricle, without new ventricular arrhythmias or Mobitz type II second- or third-degree AV heart block, that responds to usual care within 1 to 2 weeks (chronic symptomatic dilated cardiomyopathy); 3) heart failure associated with unexplained hypertrophic cardiomyopathy; 4) suspected ARVD/C (arhythmogenic right ventricular dysplasia/cardiomyopathy); and 5) unexplained ventricular arrhythmias.

The five clinical scenarios in which EMB may be considered (class IIb recommendations) are in the setting of: 1) unexplained, new-onset heart failure of 2 weeks’ to 3 months’ duration associated with a dilated left ventricle, without new ventricular arrhythmias or Mobitz type II second- or third-degree AV heart block, that responds to usual care within 1 to 2 weeks (uncomplicated acute idiopathic dilated cardiomyopathy); 2) unexplained, new-onset heart failure of >3 months’ duration associated with a dilated left ventricle, without new ventricular arrhythmias or Mobitz type II second- or third-degree AV heart block, that responds to usual care within 1 to 2 weeks (chronic symptomatic dilated cardiomyopathy); 3) heart failure associated with unexplained hypertrophic cardiomyopathy; 4) suspected ARVD/C (arhythmogenic right ventricular dysplasia/cardiomyopathy); and 5) unexplained ventricular arrhythmias.

The single clinical scenario in this document in which EMB should not be performed is unexplained atrial fibrillation (class III recommendation). These recommendations provide a practical guide for the clinician.

The five clinical scenarios in which EMB may be considered (class IIb recommendations) are in the setting of: 1) unexplained, new-onset heart failure of 2 weeks’ to 3 months’ duration associated with a dilated left ventricle, without new ventricular arrhythmias or Mobitz type II second- or third-degree AV heart block, that responds to usual care within 1 to 2 weeks (uncomplicated acute idiopathic dilated cardiomyopathy); 2) unexplained, new-onset heart failure of >3 months’ duration associated with a dilated left ventricle, without new ventricular arrhythmias or Mobitz type II second- or third-degree AV heart block, that responds to usual care within 1 to 2 weeks (chronic symptomatic dilated cardiomyopathy); 3) heart failure associated with unexplained hypertrophic cardiomyopathy; 4) suspected ARVD/C (arhythmogenic right ventricular dysplasia/cardiomyopathy); and 5) unexplained ventricular arrhythmias.

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General Paul Tibbets, the pilot of the Enola Gay, dies; Pakistani President Pervez Musharraf suspends the country’s constitution and declares a state of emergency; and Kaing Guek Eav (alias Duch), who ran the notorious Tuol Sleng prison, is the first Khmer Rouge defendant to appear in court on charges of crimes against humanity.
Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy (IMAC-1)


Circulation. 2001;103:2254-2259

The relationship between myocarditis and idiopathic dilated cardiomyopathy remains elusive, and both viral and autoimmune pathogenic mechanisms continue to be investigated. High dose intravenous immune globulin (IVIG) has both antiviral and immune modulatory effects and has been used to successfully treat children with new-onset dilated cardiomyopathy and myocarditis in children. The aim of this trial was to determine whether or not treatment with IVIG improved left ventricular ejection fraction (LVEF) in adults with a recent onset of idiopathic dilated cardiomyopathy or myocarditis.

The study design was a prospective, randomized, placebo-controlled, double-blind investigation of the addition of IVIG to conventional therapy in adult patients with new-onset dilated cardiomyopathy. Inclusion criteria mandated an LVEF ≤40%, an evaluation consistent with either idiopathic dilated cardiomyopathy or myocarditis, and symptom duration of 6 months or less at the time of randomization. All patients underwent diagnostic coronary angiography or noninvasive stress testing to exclude coronary heart disease and transthoracic echocardiography to rule out significant valvular disease, as well as a right ventricular endomyocardial biopsy prior to enrollment. Exclusion criteria included significant diabetes, significant hypertension, and uncorrected thyroid disease. Patients with evidence of giant cell myocarditis, sarcoidosis, and hemochromatosis were excluded as well.

Patients randomized to treatment received a total of 2 grams/kilogram of IVIG administered each day for 2 consecutive days. Patients randomized to placebo received 0.1% albumin in 10% maltose solution given in an equivalent volume each day for 2 consecutive days. LVEF was assessed at baseline, 6 months, and 12 months by radionuclide angiography. Functional capacity was assessed by metabolic stress testing and a 6-minute walk test. Patients were seen in follow-up at 1, 6, and 12 months after randomization and then every 6 months thereafter. The primary end point of the study was the change in LVEF from baseline to 6 and 12 months. The secondary end points were event-free survival and comparison of functional capacity as assessed by metabolic stress testing.

Sixty-two patients were enrolled in the study. Only 10 (16%) had cellular inflammation on endomyocardial biopsy. Mean duration of symptoms at the time of randomization was 2 months. Overall, mean LVEF improved from 25% at baseline to 41% at six months and 42% at 12 months. There was no significant difference with respect to the change in LVEF between patients treated with IVIG and those who received placebo. The majority of patients experienced a 10% or greater increase in their LVEF at one year and one third of the patients normalized their ejection fraction. Interestingly, there was no association between improvement in LVEF and the presence or absence of cellular inflammation in biopsy, although this may have been due to sampling error and variability in histologic interpretation. Survival was excellent as well, as the transplant-free survival rate was 92% at one year and 88% at 2 years.

These results suggest that IVIG does not add any incremental benefit over conventional therapy in this group of patients. Perhaps more importantly, however, the results indicate that the prognosis for patients with either idiopathic dilated cardiomyopathy or myocarditis is excellent when treated with standard therapies. One explanation for the improved prognosis may be the increased use of β-adrenergic blocking agents in the IMAC-1 study.

The Japanese cities of Urawa, Omiya, and Yono merge to form the city of Saitama; Douglas Adams, the author of the “Hitchhiker’s Guide to the Galaxy,” dies of a heart attack at the age of 49; and Chilean biologist and philosopher Francisco Varela dies.
Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis


Patients with lymphocytic myocarditis have a clinical course that varies greatly. Those with subclinical disease may be asymptomatic, while those with fulminant disease present with severe hemodynamic compromise that not infrequently leads to death. Unfortunately, there are no current clinical criteria that reliably predict outcomes in these patients. The authors of this study hypothesized that patients with fulminant myocarditis have a better long-term prognosis than patients with acute (nonfulminant) myocarditis.

One hundred and forty-seven patients with recent (<12 months) unexplained cardiomyopathy or unexplained ventricular arrhythmias who underwent endomyocardial biopsy (EMB) and met the following criteria were included in the study: evidence of “borderline” or “active” myocarditis on biopsy, according to the Dallas histopathological criteria; absence of any underlying disorder known to be associated with myocarditis; and documented left ventricular dysfunction, defined as an ejection fraction <40%. Patients <15 years of age and patients with chronic active myocarditis were excluded.

The Lieberman criteria (J Am Coll Cardiol. 1991;18:1617-1626) were used to classify patients as having either acute or fulminant myocarditis. Classification of fulminant myocarditis required patients to have severe hemodynamic compromise requiring high doses of vasopressors or a left ventricular assist device and at least two of the following clinical features: fever, rapid onset of heart failure symptoms, and history consistent with the diagnosis of a viral illness within two weeks of symptom onset. Classification of acute myocarditis required patients to have had an indistinct onset of heart failure symptoms, be hemodynamically stable, and remain afebrile.

The end point of the study was death or cardiac transplantation. Mortality data was ascertained by direct contact with the patient or the patient’s family, review of the medical records, search of the National Death Index, or all three. Fifteen patients (10%) had fulminant myocarditis and the rest had active myocarditis. Average follow-up was 5.6 years for the study group. During this time, 48 patients died and 7 received a heart transplant. Overall five-year transplantation-free survival rate was 70%. Only one patient with fulminant myocarditis died. All of the heart transplants occurred in patients with acute myocarditis. Among the patients with fulminant myocarditis, 95% were alive at one year and 93% were still alive at 11 years. In contrast, only 85% of the patients with acute myocarditis were alive without having received a transplant at one year and only 45% were still living without a transplant at the end of 11 years. There was no significant difference in transplant-free survival at one and five years between patients with histologically confirmed borderline myocarditis on EMB and those with active myocarditis. Multivariate analysis demonstrated that fulminant lymphocytic myocarditis was an independent predictor of long-term transplantation-free survival, after adjustments were made for age, severity of inflammation, and hemodynamic variables.

This study is significant in that it shows that patients with fulminant myocarditis have a different clinical course from patients with active lymphocytic myocarditis and, paradoxically, have better long-term transplantation-free survival. Aggressive management of patients with a clinical picture of fulminant myocarditis is warranted. Cardiac transplantation should be avoided in the first few weeks, as left ventricular systolic function is likely to improve and long-term prognosis is excellent.

A top official at Philip Morris states that the company would be open to the limited regulation of nicotine; the United States FDA withdraws the diabetes drug Rezulin because of evidence linking its use to liver failure; and 778 members of a Ugandan doomsday cult, “The Movement for the Restoration of the Ten Commandments,” commit suicide.
Diagnosing acute myocarditis remains challenging, as patients present with a wide array of symptoms that often mimic other disorders. Cardiovascular magnetic resonance imaging (CMR) has become an important tool to help confirm this diagnosis. This study investigates various CMR approaches used in myocarditis in order to propose clear-cut diagnostic criteria that can be used for the assessment of patients with suspected acute myocarditis.

Study methods were simple and straightforward. Twenty-five patients with suspected acute myocarditis and 23 healthy control patients were included in the study. Inclusion criteria for the patients were signs and symptoms of heart disease, evidence of myocardial injury per standard electrocardiogram criteria and elevated cardiac biomarkers, and exclusion of coronary heart disease by angiography or clinical criteria. Exclusion criteria included previous myocardial infarction, chronic myocarditis, and known contraindications to CMR.

CMR studies were performed on a 1.5-T system. Each study included the following sequences: (i) T2-weighted triple inversion recovery; (ii) T1-weighted spin echo before and over 4 minutes after gadolinium injection; and (iii) inversion recovery-gradient echo 10 minutes after gadolinium injection. Qualitative and quantitative analysis was performed to assess for: (i) focal and global T2 signal intensity (SI); (ii) myocardial global relative enhancement (gRE); and (iii) areas of late gadolinium enhancement (LGE). Regions of interest covering the left ventricular myocardium and skeletal muscle in the same slice were manually drawn in the precontrast images and copied to the postcontrast images. The myocardial T2-weight signal intensity was related to that of skeletal muscle. High T2 SI and LGE areas (both defined as areas with an SI greater than that of normal myocardium plus two standard deviations) were identified. These areas were manually traced and their volume expressed as a percentage of the total myocardial slice volume.

Global gRE was significantly higher in patients compared with controls. Using a cut-off value of 4.0 resulted in a sensitivity of 80%, specificity of 68%, and diagnostic accuracy of 74.5%. The global T2-weighted SI was also significantly higher in patients compared with controls. A cut-off value of 1.9 yielded a sensitivity of 85%, specificity of 74%, and a diagnostic accuracy of 79%. The sensitivity, specificity, and diagnostic accuracy of LGE were 44%, 100%, and 71%, respectively. Posterolateral and inferior segments were affected in nearly three quarters of the patients, while the anterior and septal segments were affected in only about one third of patients respectively. LGE was always located in the epicardium or midventricular wall and never in the endocardium. The best diagnostic performance was obtained when any two of the three sequences were positive in a given patient (gRE:SI ratio 4.0, T2:SI ratio 1.9; and LGE: presence of visually detected bright areas). This “any two” approach had 76% sensitivity, 95.5% specificity, and 85% accuracy.

The results of this study confirm that CMR is a useful diagnostic tool in assessing patients with suspected acute myocarditis. They also suggest that using the “any two” approach may improve the diagnostic performance of CMR, particularly when patients present with symptoms typical for acute coronary syndrome, which occurs fairly frequently.

In South Africa, Schabir Shaik, a financial advisor to deputy president Jacob Zuma, is found guilty of two counts of corruption and one of fraud; Jamaican Asafa Powell clocks 9.77 seconds for the 100 meters to set a new world record; and a previously unknown poem by the classical Greek lyric poet Sappho is discovered on an Oxyrhynchus papyrus at Cologne University.
Idiopathic giant-cell myocarditis—natural history and treatment.
Multicenter Giant Cell Myocarditis Study Group Investigators

Idiopathic giant cell myocarditis (GCM), is a unique entity that is quite rare and has an extremely poor prognosis. This paper is a landmark study in the field of myocarditis because it outlines the natural history and effect of treatment in patients with this disease. Information on potential study participants was solicited through study announcements in several leading cardiovascular journals published in the United States as well as through direct mailings to the directors of US heart transplantation centers participating in the United Network for Organ Sharing and to major cardiovascular centers worldwide. Using the enrollment criterion of a definite histologic diagnosis of giant cell myocarditis, data on 90 patients from 49 medical centers in 16 countries were reviewed. Detailed case report forms were sent to investigators at each of these sites. A single cardiac pathologist, who was blinded to the patients' histories, reviewed all of the histologic slides and detailed photomicrographs and confirmed 54 cases of giant cell myocarditis. An additional 9 patients were included because the 3 investigators who could not provide pathologic slides reported histologic findings typical of giant cell myocarditis that had been confirmed by experienced cardiac pathologists. This resulted in a total of 63 patients being included in the study population.

The rate of survival for patients with giant cell myocarditis was worse than among the 111 patients in the Myocarditis Treatment Trial (see Seminal Article 1). Among the patients with giant cell myocarditis, the rate of death or cardiac transplantation was 89% and median survival was only 5.5 months from onset of symptoms. In contrast, the mortality rate for patients in the Myocarditis Treatment Trial was only 20% at 1 year and 56% at 4.3 years.

The time from onset of symptoms to the end point of either death, cardiac transplantation, or the end of follow-up was longer for patients treated with combination immunosuppressive therapy than for those who did not receive these combination therapies. One third (22) of the patients were treated with corticosteroids and cyclosporine, azathioprine, or both therapies. These patients survived an average of 12.3 months. Patients treated with cyclosporine in combination with any other immunosuppressive agent had the best survival rate, averaging 12.6 months, while patients treated with corticosteroids alone only had a 3.8-month transplant-free survival period.

The efficacy of cardiac transplantation is uncertain because giant cell myocarditis can recur in the transplanted heart. Transplantation occurred in 34 patients in this study a median of 6 months after onset of symptoms. Nine of them (25%) died during an average follow-up of 3.7 years. Of these patients, 5 died within 30 days of transplantation. Giant cell infiltrate, as identified by endomyocardial biopsy, occurred in 9 of the 34 patients an average of 3.0 years after transplantation (range, 3 weeks to 9 years). Three of these 9 patients had symptoms of left ventricular failure and one of these 3 patients subsequently died, despite receiving aggressive immunosuppressive therapy. The giant cell infiltrate and the symptoms of the other two patients resolved with increased immunosuppressive therapy.

This investigation revealed several important insights regarding giant cell myocarditis. Combined immunosuppressive therapy, particularly if it included cyclosporine, delayed time to death or transplantation. Despite delaying the progression, approximately 50% of the cyclosporine-treated patients ultimately died or required heart transplantation. Although recurrent disease occurs in 25% of transplanted patients, transplantation remains the treatment of choice for many patients with this otherwise frequently fatal disease.

1997/1897

French explorer Jacques-Yves Cousteau dies;
Canadian prime minister Jean Chrétien wins a second consecutive election; and Mary Robinson resigns from her post as president of Ireland to promote civil rights worldwide for the United Nations. She is a barrister and an expert on human rights law.
Despite advances in immunology and virology, establishing the etiopathogenetic features of myocarditis remains a challenging task. Patients present with a broad spectrum of histologic and serologic features that can make it difficult to manage these patients, particularly with regard to treatment and prognosis. These authors propose that assessment of the viral genome and quantitation of antienzyme antibodies (AHAs) in patients with myocarditis will lead to the development of etiologically-driven therapy, which will, in turn, improve prognosis for this potentially devastating disease.

The study population consisted of 174 consecutive symptomatic patients with clinically suspected myocarditis admitted to a tertiary referral center from January 1992 to May 2005. All patients underwent endomyocardial biopsy (EMB). Eighty-five of these patients had histologic evidence of active myocarditis, according to the Dallas criteria, while the remaining 89 patients had evidence of borderline myocarditis (no diffuse or severe inflammation). Immunohistochemistry was used to assess inflammatory infiltrates. Polymerase chain reaction (PCR) and reverse transcriptase PCR were utilized to detect all cardiotropic viral genomes (except parvovirus B19, which was not implemented until 2000). The frequency of positive PCR in myocarditis was compared with that of a control group consisting of 13 patients with histologically confirmed noninflammatory heart disease diagnosed via EMB. Testing for AHA was conducted by standard immunofluorescence of sera from the 130 patients in whom it was available.

IgG class AHAs were detected in 73 (56%) of the study patients. Fifty-four of these (41%) were organ-specific and 19 (15%) were partially organ-specific. Organ-specific AHAs occurred much more frequently in myocarditis patients (41%) than in those with noninflammatory heart disease (1%), ischemic heart disease (1%), or blood donors (2%). Partially organ-specific AHAs also occurred much more frequently in patients with myocarditis. Viral PCR was positive in 31 (25%) of the 120 study patients tested. Of these, 5 were positive for more than one virus. No control patients tested had virus-positive PCR. The most frequently detected virus was enterovirus (15), followed by adenovirus (6), Epstein-Barr virus (5), mumps (3), cytomegalovirus (3), parvovirus B19 (3), hepatitis C virus (2), and herpes simplex virus (1). Myocarditis was classified as autoimmune (positive AHA result and virus-negative PCR) in 47 of the 98 patients in whom combined AHA and PCR was available. Viral myocarditis (virus-positive PCR and negative AHA result) was diagnosed in 9 patients, while 12 patients were diagnosed with viral and immune (virus-positive PCR and positive AHA result) myocarditis and 30 patients (nearly one third) were classified as having idiopathic and/or cell-mediated (virus-negative PCR and negative AHA result) myocarditis.

One hundred and twenty-four patients survived without transplant during follow-up (median duration 23.6 months), 26 either died or received a transplant, and 24 were lost to follow-up. Survival was 87% at 2 years, 80% at 3 years, and 73% at 6 years. Patients with virus-positive PCR had a higher risk of death compared with the group as a whole ($P=0.02$).

AHAs indicated immune-mediated myocarditis in the majority of cases in this study and a virus-positive PCR was a univariate predictor of adverse prognosis in patients with myocarditis. These results are intriguing and suggest that AHA and viral genomic studies may help guide the clinical decision-making process for managing patients with myocarditis.

Austrian politician and former United Nations secretary general Kurt Waldheim dies; Greece’s electricity grid nearly collapses due to record demand for air conditioning during the worst heat wave in a century; and the Valley of Geysers on the Kamchatka Peninsula in the Russian Far East is destroyed by a mudflow.
Autoimmunity in Coxsackievirus infection

N. R. Rose


Viral myocarditis is an entity characterized by a complex interplay between virus-triggered innate and adaptive immune responses resulting in pathogenic autoimmunity. Coxsackie B3 (CB3) is one of the many cardiotropic viruses implicated in this disease. The author of this paper developed a mouse model of autoimmune myocarditis induced by infection with a cardiotropic strain of coxsackievirus B3 (CB3). This paper reviews the results of investigations made with this model, which have helped to delineate the autoimmune response to this viral infection.

Indirect immunofluorescence studies showed the presence of heart-specific antibodies in both the early and late phase of the disease. The presence of cardiac-specific antibodies in the late phase of disease suggested that this may be related to autoimmunity. To establish the autoimmune origin of late phase myocarditis, the disease was reproduced in the mouse model by experimental immunization with cardiac myosin. All of the mouse strains susceptible to CB3-induced late-phase myocarditis developed strong IgG antibodies specific for cardiac myosin and most of the animals developed a histologic picture typical of late-phase myocarditis. No cardiac myosin antibodies were produced in the mice resistant to late-phase myocarditis. This proved that mouse strains susceptible to CB3-induced late-phase myocarditis were also susceptible to autoimmune myocarditis induced by immunization with purified cardiac myosin, leading to the conclusion that the genetic predisposition to developing an immune response to cardiac myosin is critical in determining susceptibility to the late phase of the viral disease.

The investigators used bacterial lipopolysaccharide (LPS), an agent known to augment the innate immune response, to determine what effect early and/or late immunity had on adaptive immunity. LPS treatment of CB3-infected mice normally resistant to autoimmune myocarditis resulted in the production of the typical autoimmune disease. Serum samples of the LPS-treated animals revealed heightened levels of cytokines, particularly interleukin 1β (IL-1β) and tumor necrosis factor α (TNF-α). A large number of leukocytes containing these 2 cytokines were found in the inflamed areas of the myocardium. Subsequent experiments showed that the differential production of IL-1β and TNF-α, as well as IL-18, occurs as early as 6 hours after infection with the CB3 virus, indicating that the very earliest innate immune response to the virus determines the development of a pathogenic autoimmune response.

CD4 T cells play a critical role in the induction of autoimmune myocarditis, as they secrete key cytokines, among them interferon gamma (IFN-γ). This author showed that IFN-γ deficiency promotes severe inflammation and markedly impaired cardiac function, suggesting that severe autoimmune myocarditis is associated with the preferential expansion of certain CD4 T cells (CD25+) and, alternatively, that CD25+ CD4 T cells may slow the development and progression of the disease. Further experiments showed that macrophages play an important role as well, as inhibition of mononuclear cell migration reduced the prevalence and severity of myocarditis. Additional studies confirmed that antibodies are yet another key component.

This paper reviews over 30 years of autoimmune and postviral myocarditis basic research. Collectively, the insights from the studies summarized in this paper constitute the scientific rationale for immunomodulatory therapies including IVIG, immunoadsorption, and plasmapheresis.
Complication rate of right ventricular endomyocardial biopsy via the femoral approach: a retrospective and prospective study analyzing 3048 diagnostic procedures over an 11-year period


_Circulation._ 2008;118:1722-1728

Right ventricular endomyocardial biopsy (EMB) is widely used as a diagnostic tool for assessing patients with known or suspected cardiomyopathies. It remains the gold standard for confirming the diagnosis of myocarditis and ascertaining myocardial viral persistence. Although EMB has been performed for many years and the role of EMB in the management of cardiovascular disease is increasing, concerns about possible complications have hampered the widespread acceptance of this procedure. This study is important because it is the largest investigation to evaluate the incidence of major and minor complications of right ventricular EMB.

This study was both retrospective and prospective. The retrospective part of the study included 1919 consecutive adult patients enrolled over the course of 9 years. The prospective trial enrolled 496 patients over a period of 2 years. None of the patients was in a posttransplant setting. These 2415 patients underwent a total of 3048 EMB procedures over 11 years. The indications for EMB were broad, including evaluation of left ventricular dysfunction, assessment of the effects of immunomodulating therapy in viral myocarditis and inflammatory cardiomyopathy, and investigation of unexplained arrhythmias, neoplastic heart disease, and systemic disease with possible cardiac involvement. All patients underwent echocardiography and coronary angiography.

Major complications included death, urgent cardiac surgery, advance cardiac life support, pericardiocentesis for cardiac tamponade, complete atrioventricular block requiring permanent pacemaker placement, hemothorax, and pneumothorax. Minor complications included pericardial effusion without tamponade, temporary or permanent right bundle-branch block, temporary Mobitz II block requiring atropine, complete heart block requiring either atropine or temporary pacing, nonsustained ventricular tachycardia, and atrial fibrillation lasting <12 hours or cardioversion of atrial fibrillation. EMB procedures were performed by 4 experienced operators using a modified Cordis biotome inserted via the right femoral vein. In the retrospective part of the study, all patients who experienced chest pain, dyspnea, or electrocardiogram (ECG) changes following the EMB procedure underwent echocardiography. In the prospective trial, all patients underwent both ECG and echocardiography testing following the procedure. All adverse EMB procedure-related events were recorded.

No patients died or required emergency cardiac surgery. Major complications were rare in the retrospective part of the study: 2 patients had cardiac tamponade and 1 patient required permanent pacemaker placement for persistent conduction abnormalities. No major complications occurred in the prospective portion of the study. The major complication rate was thus 0.12% in the retrospective study and 0% in the prospective study. Minor complications occurred more frequently. Five patients in the retrospective trial required temporary pacing, for a minor complication rate of 0.20% in this group. The prospective trial had a higher rate of minor complications (5.5%).

The results of this study reveal that the right ventricular EMB procedure is very safe when performed by experienced operators using a modified Cordis biotome inserted via the right femoral vein. Major and minor complications were extremely rare.

President George W. Bush signs the US$ 700 billion bailout bill; the 2008 Nobel Prize in Physiology or Medicine is awarded jointly to Harald zur Hausen (discovery of HPV) and Françoise Barré-Sinoussi and Luc Montagnier (discovery of HIV); and trading is suspended on Russia’s stock exchanges after shares fall almost 20% amid concerns over oil prices and the global economy.
Myocarditis

Bibliography of One Hundred Key Papers

selected by Leslie T. Cooper, MD, FACC, FAHA
Division of Cardiovascular Diseases - Mayo Clinic - Rochester - Minnesota – USA

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Bibliography of One Hundred Key Papers


Dialogues in Cardiovascular Medicine - Vol 14 - No. 3 - 2009

Bibliography of One Hundred Key Papers


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- Manuscripts should be provided on word-processor disks (3.5-in. for IBM, IBM-compatible, or Apple computers) with three hard copies (text and figures) printed on one side of standard-sized white bond paper, double-spaced, with 2.5-cm margins. Pages must be numbered. Standard typed page = 25 lines of 75 characters (including spaces) double-spaced, 2.5-cm margins = a total of 275 words per page.

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Fascinoma Cardiologica articles (A Lexicon of the Heart; Icons of Cardiology; Plants and the Heart; Trails of Discovery, etc) should not exceed 2000 words (8 standard typed pages), should include 3 to 5 illustrations (figures and tables), and cite no more than 15 references. A maximum of 5-10 keywords should be included. No abstract.