Cardiomyopathies are defined as diseases of the heart muscle (myocardium) associated with cardiac dysfunction. They are classified into five major forms by their central haemodynamics and macropathology: dilated, hypertrophic, restrictive, right ventricular, and non-classifiable cardiomyopathies. In 1995, a Task Force of the World Health Organisation and the International Society and Federation of Cardiology (ISFC, presently the World Heart Federation: WHF) introduced several changes in the definition and classification of heart muscle disease. Previously the cardiomyopathies were defined as heart muscle diseases of unknown aetiology and were differentiated from the specific heart muscle diseases with known aetiology. With the increasing understanding of their aetopathogenesis, the difference between cardiomyopathies and specific heart muscle diseases has become indistinct. The term cardiomyopathy is now no longer reserved for the idiopathic forms but can be used interchangeably with the term heart muscle diseases. Right ventricular, valvular, hypertensive, ischaemic and inflammatory cardiomyopathy have been introduced as specific cardiomyopathies.

This new WHO/ISFC definition also comprises inflammatory cardiomyopathy as a distinct entity among the specific heart muscle diseases. The inflammatory cardiomyopathy is defined by myocarditis in association with cardiac dysfunction. Myocarditis is an inflammatory disease of the heart muscle and is diagnosed by established histological, immunological and immunohistochemical criteria. Idiopathic, autoimmune, and infectious subtypes were recognised.Viral cardiomyopathy is defined as viral persistence in a dilated heart. It may be accompanied by myocardial inflammation and is then termed inflammatory viral cardiomyopathy. The term viral cardiomyopathy or viral persistence in dilated cardiomyopathy should be applied if only viral RNA or DNA without inflammation is present. If both viral nucleic acid and inflammation are present, then the correct term is viral inflammatory cardiomyopathy.3 If no viral or bacterial RNA or DNA is detected but inflammatory processes with preserved cardiac function are present, the correct term is autoreactive myocarditis. Both myocarditis and inflammatory cardiomyopathy reflect an inflammatory process in cardiac tissue.4 Inflammation plays an important role in the pathogenesis of many common cardiovascular diseases. In most cases, the role of inflammation is a natural response to injury and an important mechanism for healing and tissue repair. However, the inflammatory reaction can be inadequate or overwhelming, leading to direct injury and severe host disease. Accumulating data show that inflammation is an important component in the pathogenesis of dilated cardiomyopathy. There is also growing evidence that...
myocarditis is a precursor of dilated cardiomyopathy. Myocarditis can result in dilated cardiomyopathy with progression to heart failure in up to 30% of cases, where prognosis is poor, with a survival rate less than 40% after 10 years.  

Post-mortem studies suggest that myocarditis is a major cause of sudden unexpected death in young adults less than 40 years of age, accounting for up to 20% in the population of those who die from cardiovascular causes. In 1980, the introduction of the endomyocardial biopsy provided a method for assessing the presence of myocarditis and inflammation in the human heart. However, early biopsy studies had highly variable results, with the incidence of myocarditis ranging from 0-80%. To resolve this problem arising from differences between the methods of diagnostic evaluation the Dallas criteria for the histological diagnosis of myocarditis by haematoxylin and eosin staining were introduced in 1987.

**Causes of myocarditis**

A large variety of infectious agents, systemic diseases, drugs and toxins have been associated with the development of myocarditis. However, the aetiology of myocarditis often remains unknown. The spectrum of the infectious agents varies with the geographical region, the age of the patient, application of different therapeutic procedures and additional diseases. In general, viruses such as parvovirus B19, enteroviruses and adenoviruses represent the most commonly identified aetiological agents of viral cardiomyopathy. In addition, bacteria such as *borrelia burgdorferi* and *chlamydia pneumoniae*, protozoa and even fungi can also cause myocarditis (Table 1). In our area Parvo B19, sometimes with double infections including herpes viruses, is the leading aetiological agent. We regularly carry out a review of the most frequent cardiotoxic viruses, including: Parvo B19, enteroviruses, CMV, EBV, influenza, herpes, in addition to *chlamydia pneumoniae* and *borrelia burgdorferi*. In our registry a rise of Parvo B19 to around 30% of the biopsied dilated cardiomyopathy and inflammatory dilated cardiomyopathy / myocarditis patients can be observed. An example of a positive polymerase chain reaction (PCR) is given in Figure 1.

Viral infections are postulated to be the most common cause of myocarditis in Europe and North America. Initially, rising antibody titres against specific viruses in the serum of patients during acute myocarditis and reconvalescence were used to demonstrate aetiological relevance. Recently, genomes of parvovirus B19, enterovirus, cytomegalovirus, influenza virus and hepatitis C virus have been identified in endomyocardial biopsies in patients with myocarditis and dilated cardiomyopathy using PCR. However, the association of specific viruses with the pathogenesis of myocarditis remain controversial. In various investigations viral genomes were found in endomyocardial tissue in less then 40%, so that autoreactive forms still appear to be the most frequent subgroup.

**Histology of inflammatory cardiomyopathy**

In 1999, the WHF/ISFC updated the conventional histological criteria for the diagnosis of inflammatory cardiomyopathy/myocarditis according to the Dallas classification by the introduction of immunohistochemical methods (Table 2). Myocarditis was defined as a process characterised by an inflammatory

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Table 1. Infective agents of myocarditis.

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Enterovirus, rhinovirus, influenza A B, rubeola, mumps, HIV-1, hepatitis C virus, adenovirus, cytomegalovirus, Epstein-Barr virus, varicella-zoster, Parvovirus B19, human herpes 6 virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>Staphylococcus, streptococcus, pneumococcus, meningococcus, gonococcus, salmonella, corynebacterium diphtheriae, haemophilus influenzae, mycoplasma pneumoniae, brucella</td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>Tuberculosis, avium intracellulare</td>
</tr>
<tr>
<td>Fungi</td>
<td>Aspergillus, candida, actinomyces, blastomyces, cryptococcus, histoplasma</td>
</tr>
<tr>
<td>Protozoa</td>
<td>Toxoplasma gondii, trypanosoma cruzi</td>
</tr>
<tr>
<td>Rickettsiae</td>
<td>Coxiella burnetti (Q fever), rickettsia rickettsii,</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>Trachomatis, psittaci</td>
</tr>
<tr>
<td>Parasitic</td>
<td>Trichinella spiralis</td>
</tr>
</tbody>
</table>
infiltrate of the myocardium. The inflammatory infiltrate should be subclassified as lymphocytic, eosinophilic, neutrophilic, giant cell, granulomatous or mixed. The distribution of the infiltrate should be classified as focal, confluent or diffuse. In acute myocarditis necrosis and or degeneration of adjacent myocytes is required. In chronic myocarditis necrosis of myocytes is not obligatory.

The WHF committee chose a minimum of 14 infiltrating leukocytes/mm² for the definition of myocarditis, preferably activated leukocytes (CD45ro) or T-lymphocytes (e.g. CD3)+. Up to 4 macrophages may be included in this total amount. In case of nests of leukocytes (>3 lymphocytes, preferably T-cells) located outside the lumen of a vessel, a focal inflammatory process (myocarditis) is diagnosed. If those foci are present, myocarditis can be diagnosed due to the nature of the infiltrate even when the critical number of 14 leukocytes is not reached. If the focal or diffused leukocytes are localised in fibrotic areas the process may be termed reparative.²⁰

The amount of fibrosis should also be classified as none (grade 0), mild (grade 1), moderate (grade 2) or severe (grade 3). The distribution of the fibrosis should be described as endocardial, replacement or interstitial.

The following terminology has been suggested:²⁰,²¹

**First biopsy:**

1. *Acute (active) myocarditis:* a clear-cut infiltrate (diffuse, focal or confluent) of ≥14 leukocytes (preferably activated T-cells) and macrophages/mm² (Figure 2). Quantification of the amount of the infiltrate should be made with immunohistochemical methods. Necrosis and degeneration are mandatory. Fibrosis may be absent or present and should be graded.

2. *Chronic myocarditis:* an infiltrate of ≥14 leukocytes and macrophages/mm² (diffuse, focal or confluent, preferably activated T-cells) quantitated by immunohistochemistry. Necrosis or degeneration are usually not evident. Fibrosis should be graded if present.

3. *No myocarditis:* no infiltrating cells or <14 leukocytes/mm².

**Subsequent biopsies:**

1. *Ongoing (persistent) myocarditis:* Criteria as in 1 or 2 above (features of an acute or chronic myocarditis).

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### Table 2. Histological criteria for the diagnosis of myocarditis according to the Dallas classification³ and WHF.²⁰,²¹

<table>
<thead>
<tr>
<th>Dallas terminology</th>
<th>Histopathology</th>
<th>WHF terminology</th>
<th>Immunohistochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infiltrate</td>
<td>Myocyteolysis</td>
<td>Oedema</td>
</tr>
<tr>
<td><strong>First biopsy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active myocarditis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Borderline myocarditis</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Second biopsy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing myocarditis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Resolving/healing myocarditis</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Resolved myocarditis</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Immunohistochemistry aids in subclassification of infiltrating cells. DCMI – inflammatory dilated cardiomyopathy.
2. Resolving (healing) myocarditis: Criteria as in 1 or 2 above, but the immunologic processes are sparser than in the first biopsy.

3. Resolved (healed) myocarditis: Criteria corresponding to the Dallas classification.

With the introduction of these quantitative criteria consensus could be reached in a large majority of cases of inflammatory cardiomyopathy.

Pathophysiology of inflammatory cardiomyopathy/myocarditis

Our understanding of the pathophysiology of myocarditis stems largely from murine studies. With the application of cellular and molecular biological methods our understanding of myocarditis and its progression to dilated cardiomyopathy has increased remarkably. A clarification of the pathophysiology of induction and development of heart muscle damage and progression to dilated cardiomyopathy is important for diagnosis and therapy of the disease.

Myocarditis is a continuum of three distinct disease processes, one evolving into the other with transitional periods of overlapping. Pathogenesis, diagnosis and management differ for each of the three processes. Precise knowledge of the point to which the patient’s myocarditis has evolved in this triphasic continuum is essential for diagnostic and therapeutic strategies. In the majority of cases of myocarditis, except in countries in which Chagas’ disease or diphtheria is common, viral infection triggers the triphasic cascade, which may progress to an autoimmune phase after the initial infection and then finally progress to dilated cardiomyopathy. However, other forms of injury may also trigger the triphasic cascade, e.g. systemic diseases, chemicals and toxins.

In the first phase (initial myocardial injury by viral infection) an initial insult to the myocardium occurs. During phase I overt congestive heart failure does not occur in most cases and the initial injury may go unnoticed, unless fulminant myocarditis arises. In the second phase an autoimmune myocardial injury occurs, triggered by the initial injury despite elimination of the virus. Congestive heart failure often develops in this phase. In the third phase the typical clinical picture of dilated cardiomyopathy develops independently after the other two processes (infection and autoimmunity) have abated.

Phase I: Initial myocardial injury

The first phase is believed to be induced by infections (most commonly viral) in the majority of cases. During this phase in most patients severe heart failure does not occur and the initial myocardial injury may go unnoticed. Only in a few cases fulminant myocarditis arises, induced by direct myocytolysis of the normally replicating virus in the absence of a specific immune response. Complete recovery from the disease in this phase depends on an effective immune response in the absence of subsequent autoimmune processes or viral persistence. In addition, the effectiveness of the immune response regulates the severity of virus-induced damage to the heart. The factors responsible for clearance of the infectious agent on the one hand and the myocardial damage on the other are, first of all, cytotoxic T-lymphocytes (CD4+ and/or CD8+). Second, lymphocyte-derived perforins and serin esterases may be responsible for inducing apoptosis. Third, the different cytokines play a role in the initial myocardial injury. Recent evidence suggests that both B- and T-cells, natural killer and dendritic cells are involved in the production of polarising cytokines.

Inactivation of T-cells and associated cytokines after clearance of the infectious agent is necessary for complete recovery from the disease. Molecular mimicry, production of cross-reacting antibodies, or further activation of virally induced killer T-cells may give rise to the extension of myocarditis into the second phase of autoimmune myocardial injury.

Phase II: Autoimmune myocardial injury

The immune system (cellular and humoral), normally
down regulates to a resting state once viral proliferation is controlled. However, if the immune response continues despite elimination of the virus, autoimmune disease may result, initiating the second phase of the disease. In fact, the secondary immune response probably plays a greater role in disease pathogenesis than the primary infection. Important mechanisms of the cellular immune response which may trigger pathogenic heart-specific autoreactivity are:

1. **Activation by a foreign antigen:** Processing of a foreign antigen might result in the presentation of an epitope highly homologous to cardiac myosin and other myocardial proteins. This leads to activation of cross-reactive T-cells.

2. **Increased presentation of self peptides:** Viral infection and necrosis of myocytes may lead to the release of intracellular antigens, extracellular concentrations of which are normally very low. Release of these proteins in large quantities increases the threshold necessary for an immune response, resulting in activation of self-reacting T-cells.

3. **Presentation of cryptic self-peptides:** In addition, altered processing of intracellular localised proteins might occur, resulting in activation of self-reactive T-cells. This mechanism may then propagate an immune response to a cardiac antigen in the absence of further infectious triggers.

The role of the humoral immune response includes, first, the activation of cross-reactive antibodies, which alone are known to induce autoimmune inflammatory heart disease in animals. Auto-antibodies belong to the effector mechanisms of the immune system responsible for tissue damage in various autoimmune disorders. These auto-antibodies are produced as a result of failure or breakdown of the mechanisms normally responsible for maintaining self-tolerance. Patients with myocarditis display serum antibodies to a number of cardiac antigens (Table 3). Occurrence of these antibodies in sera of patients correlates with the extent of inflammation in the myocardium. Antibodies induce cytotoxicity in vitro, with or without complement, and binding of antibodies is inhibited by absorption with viral proteins indicating cross-reactivity. However, it is now widely accepted that the majority of antibodies directed against cardiac antigens found in the serum of patients with inflammatory cardiomyopathy do not play a major pathogenetic role but are indicative of damage to cardiac tissue and show a tendency to autoimmune disease.

In patients with inflammatory dilated cardiomyopathy, immune complexes have been found more frequently than in healthy individuals and in patients with dilated cardiomyopathy without inflammation. These circulating immune complexes consisted of IgG, IgM, C3 and C4; in myocarditis IgM predominated. Up to now, the nature of the soluble antigen (foreign or self?) has not been determined. However, immune complex deposition does not seem to play a major role in the pathogenesis of dilated cardiomyopathy.

In this phase, the importance of latent or persistent virus in the pathogenesis of the disease is uncertain, but considerable. A low level or intermittent replication of persistent or latent viruses may induce chronic, direct immune or autoimmune injury to the myocardium. Ongoing viral persistence is associated with a much worse outcome for the patient (need for heart transplantation or early sudden cardiac death).

### Phase III: Dilated cardiomyopathy

In phase III, after both the infectious and autoimmune processes have abated, the disease shows the characteristics of idiopathic dilated cardiomyopathy. The diagnosis is made by echocardiography, when other causes of dilatation are excluded (e.g. coronary artery disease). The therapy in this stage aims at prevention and reversal of adverse remodelling.

Separation of the three phases is not always possible. The three phases may overlap one another chronologically. Furthermore, phases I and II can recur after the triphasic cascade has progressed to dilated cardiomyopathy, resulting in multiple cycles of disease occurring simultaneously.

### Diagnosis

The clinical characteristics of myocarditis vary. The patients may remain asymptomatic and have electrocardiographic abnormalities. Other patients may show signs and symptoms of chronic heart failure and ventricular dilatation. Some patients may present with fulminant heart failure and severe left ventricular dysfunction, with or without cardiac dilatation. Unfortunately, myocarditis can also result in sudden unexpected death. In fact, myocarditis is the major cause of sudden unexpected death in patients less than 40 years of age. Mason et al found that 60% of patients with myocarditis have antecedent flu-like symptoms. We have to bear in mind that the patients can present with a clinical syndrome mimicking that of an acute myocardial infarction with chest pain, ECG and laboratory find-
ings of myocardial injury. The subsequent angiography shows normal coronary arteries.

This large spectrum of clinical forms depends on several factors, such as genetic determinants of the infective agent, the genetics, age, gender and immunocompetence of the host. To date, with the development of various new diagnostic methods, early and definite diagnosis of dilated inflammatory or infectious cardiomyopathy depends first on the detection of inflammatory infiltrates in the endomyocardial biopsies, according to the WHO/ISFC and the Dallas criteria, using immunohistochemis-

Table 3. Compilation of antibodies to cardiac antigen and their possible cross-reactivity and pathomechanism.

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Antibody</th>
<th>Cross-reactivity with</th>
<th>Pathomechanism</th>
<th>Author (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actin</td>
<td>Anti-actin</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Maisch et al.</td>
</tr>
<tr>
<td>Ach receptor</td>
<td>Anti-Ach</td>
<td>Unknown</td>
<td>Bradycardia</td>
<td>Goin et al.</td>
</tr>
<tr>
<td>AH</td>
<td>Anti-AH</td>
<td>Unknown</td>
<td>Impairment of energy metabolism</td>
<td>Pankuweit et al.</td>
</tr>
<tr>
<td>PK</td>
<td>Anti-PK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLD</td>
<td>Anti-DLD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK</td>
<td>Anti-CK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANT</td>
<td>Anti-ANT</td>
<td>Enterovirus</td>
<td>Impairment of energy metabolism</td>
<td>Schulze and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Schultheiss</td>
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<tr>
<td>b1-receptor</td>
<td>Anti-b1</td>
<td>Enterovirus</td>
<td>Positive chronotropic</td>
<td>Wallukat et al.</td>
</tr>
<tr>
<td>b1-receptor</td>
<td>Anti-b1</td>
<td></td>
<td>Negative inotropic1</td>
<td>Limas et al.</td>
</tr>
<tr>
<td>Ca2+ channel</td>
<td>Anti-Ca2+</td>
<td>ANT Enterovirus</td>
<td>Unknown</td>
<td>Schulze et al.</td>
</tr>
<tr>
<td>Carnitin</td>
<td>Anti-carnitin</td>
<td></td>
<td>Unknown</td>
<td>Otto et al.</td>
</tr>
<tr>
<td>Conduction system</td>
<td>Anti-sinus</td>
<td>Anti-AV node</td>
<td>Conduction defect</td>
<td>Maisch et al.</td>
</tr>
<tr>
<td></td>
<td>Anti-Purkinje</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desmin</td>
<td>Anti-desmin</td>
<td>Unknown</td>
<td></td>
<td>Maisch et al.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Obermayer et al.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Portig et al.</td>
</tr>
<tr>
<td>Hsp60, hsp70, vimentin</td>
<td>Anti-hsp60,</td>
<td>Multiple</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-hsp70,</td>
<td></td>
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<tr>
<td></td>
<td>Anti-vimentin</td>
<td></td>
<td></td>
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<tr>
<td>Laminin</td>
<td>Anti-laminin</td>
<td>Unknown</td>
<td>Inhibition of sarcosin dehydrogenase</td>
<td>Maisch et al.</td>
</tr>
<tr>
<td>Mitochondria/microsomes</td>
<td>AMA-laminin</td>
<td>Multiple</td>
<td></td>
<td>Klein et al.</td>
</tr>
<tr>
<td>Myolemma</td>
<td>AMLA</td>
<td>Enterovirus</td>
<td>Lytic</td>
<td>Pohlner et al.</td>
</tr>
<tr>
<td>Myosin</td>
<td>Anti-myoisin</td>
<td></td>
<td>Negative inotropic</td>
<td>Maisch et al.</td>
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<td>Myosin</td>
<td>Anti-myoisin</td>
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<td>Maisch</td>
</tr>
<tr>
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<td>Anti-NADD</td>
<td>Unknown</td>
<td>Impairment of energy metabolism</td>
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</tr>
<tr>
<td>UCR</td>
<td>Anti-UCR</td>
<td>Unknown</td>
<td>Immune complex-mediated</td>
<td>Naparstek and Polz</td>
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<td></td>
<td></td>
<td></td>
<td>degradation of neutrophils,</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td>AV-block</td>
<td></td>
</tr>
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<td>ENA</td>
<td>ENA</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>ANCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear antigen</td>
<td>ANA</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcolemma</td>
<td>ASA</td>
<td>Enterovirus2</td>
<td>Lytic</td>
<td>Maisch et al.</td>
</tr>
<tr>
<td>SR-Ca-ATPase</td>
<td></td>
<td></td>
<td>Metabolic interactions</td>
<td>Khaw et al.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

From reference 21. Used with permission.

1 Hypothetical.
2 Experimentally proven.

Molecular techniques such as PCR, gene sequencing and real-time PCR, often applied on the same endomyocardial specimen, are essential for the rapid, specific and sensitive identification of the infective agents and discrimination between viral and autoimmune myocarditis. PCR investigation should include the following cardiotropic viruses: enterovirus, Epstein-Barr virus, Parvo B19 virus, adenovirus, cytomegalovirus, human herpes virus 6, hepatitis C virus, and influenza viruses A and B. The advantages of PCR analysis for definitive diagnosis of viral inflammatory cardiomyopathy can be summarized as follows: 1) rapid detection of specific microbial nucleic acid sequences; 2) detection of agents that are difficult to cultivate or cannot be cultivated; 3) detection of latent or active infections; 4) strain typing; and 5) detection of virulence and antimicrobial determinants. The correct application of these methods may allow us to obtain information on epidemiology, risk stratification in a given patient and a more appropriate treatment.

The role of endomyocardial biopsy

Endomyocardial biopsy is the gold standard for the final diagnosis of myocarditis. The major limitation of endomyocardial biopsy remains the low sensitivity due to sampling error, particularly in the presence of focal disease. The size and number of the biopsy specimens, as well as the processing of the specimens, influence the sensitivity of endomyocardial biopsy in the detection of myocarditis. The number of biopsy samples directly increases the likelihood of detecting foci of myocarditis. Furthermore, serial sectioning and multiple level examination of endomyocardial biopsies increase the sensitivity of endomyocardial biopsy in the evaluation of myocarditis, facilitating the diagnosis of focal myocarditis. Some authors have demonstrated that biventricular endomyocardial biopsy, obtaining samples from multiple areas of the left and right ventricles, may increase the sensitivity in detection of myocarditis.

The high morbidity and mortality of myocarditis/inflammatory cardiomyopathy calls for a precise aetiologic diagnosis, which is essential for the optimal treatment of the patient. Aetiological diagnosis of myocarditis can only be achieved with endomyocardial biopsy and subsequent molecular investigation of the biopsy samples.

Echocardiographic findings in myocarditis may provide indirect evidence of inflammation by segmental wall motion abnormality and associated pericardial effusion. Magnetic resonance tomography may also be useful for the non-invasive localization and assessment of the extent of inflammation in patients with myocarditis. Late enhancement may be a sign of interstitial oedema, as is the demonstration of increased pericardial fluid. However, additional studies are required to confirm the usefulness of the procedure.

Treatment

The design of the appropriate therapy for myocarditis is challenging because of the overlap of the pathophysiological stages of the disease. Appropriate therapy requires knowledge of the phase of the disease at the time therapy is applied. Such an evaluation requires immunohistochemical and molecular biological investigations of endomyocardial biopsies in parallel. Phase-specific therapy is important because the appropriate therapy for one stage (e.g. immunosuppression in phase II) may worsen rather than improve myocarditis if administered at another stage (e.g. during active infection in phase I) (Figure 3).

Phase I: Viral infection and replication

Therapy for the first viral or bacterial induced phase requires an effective antiviral or antibacterial treatment, especially as viral infection represents an independent unfavourable prognostic factor in patients. Kühl et al investigated the effects of antiviral IFN-β therapy in patients with myocardial virus persistence, with respect to the safety of the treatment regimen and virus clearance. They included 22 virus-positive patients with a long history of persistent or progressive left ventricular dysfunction despite medication with ACE inhibitors, β-blockers, glycosides and diuretics. They found that a 6-month IFN-β treatment was associated with myocardial virus clearance in all IFN-β treated patients. Virus clearance was associated with haemodynamic improvement in these patients.

Intravenous immunoglobulins have been more often used in the treatment of inflammatory dilated cardiomyopathy. It has been shown that immunoglobulins have both an antimicrobial, that is antiviral, and an anti-inflammatory effect. They prevent the formation of proinflammatory cytokines and downregulate their production, and supposedly reduce oxidative stress. Thus, the use of intravenous immunoglobulin...
may be a therapeutic option in all phases of myocarditis, since it has been shown that they have antiviral and anti-inflammatory effects.

Table 4 gives an overview of all reports on high dose immunoglobulin treatment. Six of them are reported cases,\textsuperscript{50-55} one a series of cases,\textsuperscript{56} one is a retrospective cohort study,\textsuperscript{56} and another is an uncontrolled trial.\textsuperscript{49} Apart from the treatment of Coxsackie virus A19 with intravenous gamma-globulin by Wang et al,\textsuperscript{55} clinical improvement was reported in all cases. It is of note that Drucker et al\textsuperscript{56} compared the outcome and function of 21 children treated with intravenous gamma-globulin to 26 historic controls and found a significant improvement of cardiac function and a trend for improved survival. McNamara’s uncontrolled trial\textsuperscript{49} included ten adults, of whom nine showed considerable improvement of cardiac function and ejection fraction even after 12 months. However, one patient died from heart failure and ventricular arrhythmias.

The only randomised controlled trial evaluating intravenous gammaglobulins in myocarditis was reported by McNamara et al.\textsuperscript{48} Of the 62 adult patients enrolled, only ten demonstrated a cellular infiltrate compatible with active myocarditis according to the Dallas criteria, and three had borderline myocarditis in the respective endomyocardial biopsies. No assessment of viral aetiology was done. Thus the histological entrance criteria varied considerably and most importantly the aetiopathogenesis was unclear. Not unexpectedly, due to the incoherent group of patients with different possible aetiologies, there was no significant difference in event-free survival, nor a significant difference in the improvement of left ventricular ejection fraction for treated cases and controls at six and 12 months. These data are in conflict with an earlier non-randomised, uncontrolled trial by the same authors,\textsuperscript{49} which showed some benefit. We would thus advocate a randomised-placebo controlled trial based on the viral aetiology or autoreactive pathology in patients with inflammatory cardiomyopathy.

In biopsy-proven cytomegalovirus myocarditis, so far one controlled trial has demonstrated the eradication of inflammation and of the virus.\textsuperscript{57} The trial enrolled 35 patients of whom 18 received intravenous cytomegalovirus hyperimmunoglobulin. The control group consisted of 17 patients with cytomegalovirus myocarditis who did not receive the treatment. Comparing the two groups, the effect of cytomegalovirus hyperimmunoglobulin treatment was clear (p<0.05 for

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**Myocarditis: Diagnostic and Treatment Algorithm**

**Diagnostic Approach:**
- Symptomatology: precordial discomfort, dyspnoea, rhythm disturbance (VT, Vfib, VES)
- +/- echocardiography: disturbed global or segmental contraction and relaxation, pericarditis (Horowitz classification B to D)
- + coronary angiography: exclusion of CAD or functional disturbance not explained by CAD

**Endomyocardial biopsy**

- Inflammation (biopsy) >14 ly & Mo/mm\(^2\)
  - PCR for cardiotropic agents positive = virus positive myocarditis
  - Heart failure and antiarrhythmic therapy
- Inflammation (biopsy) >14 ly & Mo/mm\(^2\)
  - PCR for cardiotropic agents negative = autoreactive myocarditis
  - Immunosuppressive or immunomodulatory therapy
- Inflammation (biopsy) <14 ly & Mo/mm\(^2\)
  - PCR for cardiotropic agents positive = viral heart disease
  - Agent specific antiviral therapy
- Inflammation (biopsy) <14 ly & Mo/mm\(^2\)
  - PCR for cardiotropic agents negative = no myocarditis

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**Figure 3.** Recommendation for a rational diagnostic pathway and treatment algorithm in the Marburg University Hospital for a patient admitted with suspected myocarditis (modified from reference 21, used with permission).
cytomegalovirus-elimination and eradication of inflammation), which is in accordance with case reports.58

In summary, whereas in cytomegalovirus myocardi-
tis immunoglobulin data are promising, in merely sus-
ppected but unproven viral myocarditis the data are con-
flicting. A trial taking into account the different aeti-
ologies (different viruses assessed separately versus
non-viral/autoreactive versus placebo) would add im-
portant new information. In the Marburg Registry
data support a positive effect of moderate-dose intra-
venous immunoglobulins (IgG and IgM pentaglobin)
in adenovirus positive myocarditis for clinical im-
provement, eradication of both the inflammation and
the virus. In Parvo B19 myocarditis the same registry
indicates that clinical improvement can be noted, but
only inflammation is successfully eliminated, whereas
Parvo B19 persistence remains a problem in the ma-
jority of patients.59

### Phase II: Autoimmune myocardial injury

Therapy for the second stage is an anti-inflammatory
agent, which may be harmful if the virus persists in
the myocardium. Immunosuppressive therapy has
been demonstrated to be effective only when the au-
toimmune reaction is associated with dilated cardio-
myopathy in the absence of viral genome.60

The only published truly randomised and double-
blind immunosuppression treatment trial in patients
with myocarditis diagnosed according to the Dallas

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**Table 4. Trials and reports on intravenous immunoglobulins in suspected myocarditis.**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>n</th>
<th>Histology</th>
<th>Viral PCR</th>
<th>IvIG dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>McNamara et al, 200148</td>
<td>Randomised, controlled trial</td>
<td>62</td>
<td>Only 10 active and 3 borderline myocarditis</td>
<td>Not done</td>
<td>2 g/kg single shot</td>
<td>No improvement vs. controls</td>
</tr>
<tr>
<td>Drucker et al, Retrospective, cohort study, historical cohort 199456</td>
<td>46 children</td>
<td></td>
<td>Only partly myocarditis</td>
<td>Not done</td>
<td>2 g/kg single dose</td>
<td>Pos. trend in mortality, reduction in LVEDD</td>
</tr>
<tr>
<td>McNamara et al, 199749</td>
<td>Case series</td>
<td>10 adults</td>
<td>Only partly done, few myocarditis</td>
<td>Not done</td>
<td>2 g/kg over 2-4 days</td>
<td>Improvement of EF after 12 months</td>
</tr>
<tr>
<td>Kishimoto et al, 200347</td>
<td>Case report</td>
<td>9 adults</td>
<td>4 myocarditis only</td>
<td>Not done</td>
<td>1-2 g/kg over 2 days</td>
<td>Improvement of NYHA, EF and FS</td>
</tr>
<tr>
<td>Alter et al, 200159</td>
<td>Case report</td>
<td>1</td>
<td>Myocarditis</td>
<td>Varicella</td>
<td>2 g/kg over 2 days</td>
<td>Normalisation</td>
</tr>
<tr>
<td>Takeda et al, 199850</td>
<td>Case report</td>
<td>1</td>
<td>Borderline myocarditis</td>
<td>EBV</td>
<td>2 g/kg over 2 days</td>
<td>Improvement</td>
</tr>
<tr>
<td>Nigro et al, 200051</td>
<td>Case report</td>
<td>1 child</td>
<td>Myocarditis</td>
<td>Parvo B19</td>
<td>2 g/kg over 5 days</td>
<td>Improvement, PCR negative</td>
</tr>
<tr>
<td>Tsai et al, 200152</td>
<td>Case report</td>
<td>1 child</td>
<td>Not done, Myocarditis</td>
<td>Mycoplasma pneumoniae (serology)</td>
<td>2 g/kg over 2 days</td>
<td>Improvement</td>
</tr>
<tr>
<td>Shioji et al, 200253</td>
<td>Case report</td>
<td>1 adult</td>
<td>Fulminant myocarditis</td>
<td>Not done, negative serology</td>
<td>2 g/kg over 2 days</td>
<td>Improvement</td>
</tr>
<tr>
<td>Tedeschi et al, 200254</td>
<td>Case report</td>
<td>1 adult</td>
<td>Not done</td>
<td>Not done, negative serology</td>
<td>2 g/kg over 5 days</td>
<td>Improvement</td>
</tr>
<tr>
<td>Wang et al, 200455</td>
<td>Case report</td>
<td>1 child</td>
<td>Fulminant myocarditis</td>
<td>Coxsackie A16</td>
<td>1 g/kg for 2 days</td>
<td>Patient died</td>
</tr>
</tbody>
</table>

From reference 59, used with permission.
EBV – Epstein-Barr virus; EF – ejection fraction; FS – fractional shortening; IvIG – intravenous immunoglobulin; LVEDD – left ventricular end-diastolic diameter; NYHA – New York Heart Association class; PCR – polymerase chain reaction.
criteria was the Myocarditis Treatment Trial.\textsuperscript{61,62} It
showed neither a benefit nor increased mortality after six months of treatment with cyclosporine A and prednisone. It was underpowered and did not distinguish viral from non-viral disease.

Frustaci et al.\textsuperscript{67} in a retrospective analysis of patients with lymphocytic myocarditis, tried to define the virological and immunological profile of responders and non-responders to immunosuppressive therapy. They found that 85\% of non-responders had viral genomes in the myocardium and no detectable cardiac antibodies in the serum. Conversely, only 14\% of responders had viral particles in the myocardium, but 90\% had cardiac autoantibodies. In conclusion, in patients with active lymphocytic myocarditis, the presence of detectable cardiac autoantibodies and the absence of viral genome in myocardial biopsy specimens represent a strong indication for immunosuppressive strategies.

The European Study on the Epidemiology and Treatment of Cardiac Inflammatory Disease (ESET-CID) is a double-blind, randomised, placebo-controlled three-armed trial with prednisolone and azathioprine for autoreactive (virus-negative) inflammatory dilated cardiomyopathy (DCMi), interferon α for enterovirus positive DCMi, high-dose immunoglobulin for cytomegalovirus and intermediate-dose for adenovirus and Parvo B19 virus DCMi.\textsuperscript{63,64} It has now randomised more than 120 patients to the different arms. Its final results are still awaited. Patients not willing to be randomised in the trial were included in a registry follow-up, which shows improvement of haemodynamic parameters and elimination of the inflammation in the majority of patients.

Since evidence is conflicting, treatment with immunosuppressives in aetiologically undefined myocarditis cannot be generally recommended. We should await further evaluation of double-blind, randomised clinical trials or at least controlled trials and registries. For the treatment of virus-negative (autoreactive) myocarditis it is recommended to await the results of ESET-CID.

Some studies have demonstrated an important role for autoantibodies in the second and third phase of dilated cardiomyopathy and have also introduced a new therapeutic tool with the removal of immunoglobulins from the plasma of patients with dilated cardiomyopathy by immunoadsorption.\textsuperscript{65,66} This new approach has been shown to improve ventricular function,\textsuperscript{65} but the studies were not randomised and only poorly controlled.

### Phase III: Dilated cardiomyopathy

In the absence of chronic, ongoing viral infection or recurrent autoimmune activity, the patients in stage III should be managed in the same way as those with idiopathic dilated cardiomyopathy and congestive heart failure. Further adverse ventricular remodelling may be prevented with β-blockers, angiotensin-converting enzyme inhibitors and spironolactone. However, the facts that each phase may recur when one of the other two phases is well established, and that the virus may persist until phase III, causing further cardiac damage, underlines the need for monitoring for persistent viral infection and replication and recurrent autoimmune.\textsuperscript{26}

### Conclusion

With the introduction of immunohistochemical and molecular biological methods an important improvement in the quantitative diagnosis of inflammatory heart diseases has been achieved. In addition, molecular techniques (e.g. PCR, gene sequencing) for viral genome detection have been introduced. Both methods make endomyocardial biopsy the gold standard for the definite diagnosis of the disease.

Understanding the triphasic nature of myocarditis is the key to the treatment of the disease. However, overlap of the pathophysiological stages requires careful evaluation before the application of any specific therapy. Phase I is dominated by viral infection, phase II by the induction of autoimmune reactions, and phase III by the progression to cardiac dilatation. During phase I appropriate treatment includes eradication of the virus and amelioration of injury caused by the virus. During phase II immunosuppression is the most appropriate therapy. During phase III, dilated cardiomyopathy, though a result of viral and autoimmune injury, may then progress independently.

### References

45. Frustaci A, Bellocci F, Osen EG: Results of biventricular en-


