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Viral Myocarditis
Diagnosis, Aetiology and Management

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Abstract

Myocarditis is an inflammatory disease of the cardiac muscle caused by myocardial infiltration of immunocompetent cells following any kind of cardiac injury. Classic myocarditis mainly occurs as a result 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 therapy. Chronic inflammatory events may survive successful clearance of initial cardiotoxic agents, be triggered or amplified by autoimmunological processes, or develop in the context of systemic diseases. If the underlying infectious or immune-mediated causes of the disease are carefully defined by clinical and biopsy-based tools, specific immunosuppressive and antiviral treatment options may improve the prognosis of patients with acute and chronic disease.

Viral myocarditis is a non-ischaemic inflammatory disease of the myocardium that may be associated with severe cardiac dysfunction. It can result from virtually any infectious agent; however, viral infections that cause common infectious illnesses are considered the most frequent

cause.[1] The type and extent of acute and chronic myocardial compromise depend on the nature of the offending infectious agent, the affected cardiac structures and myocardial lesions caused by the cytolytic viruses, or lesions caused by the innate and adaptive anti-infectious immune response.[1]

In the past decade, molecular biological studies have identified a number of different viruses and virus subtypes in myocardial tissues of patients with myocarditis and dilated cardiomyopathy (DCM) presenting with acute, chronic and end-stage disease, and virus persistence has recently been identified as a univariate predictor of adverse outcome.[2,3] Symptomatic heart failure therapy may improve clinical symptoms and haemodynamic compromise, but it does not affect the underlying viral cause of the disease. For assessment of the prognosis and an indication of any specific treatment strategy, a reliable diagnosis is mandatory, which can only be reached by direct analysis of myocardial tissue obtained by biopsy.[4] Recent data suggest that patients with heart failure and persisting viral infections may benefit from antiviral therapy if the patients have been carefully characterized and if the treatment is administered in time, before myocardial tissue has been damaged irreversibly by the virus or virus-associated immune mechanisms.

This article focuses on the current consensus on epidemiology, aetiology, diagnosis and treatment of viral myocarditis. Current differential diagnostics have consistently improved over the years and provide the basis for first successful treatment studies in well characterized subgroups of patients. This article discusses these, bearing in mind that the causes leading to acute or chronic myocardial damage in viral myocarditis, responsible for heart failure, arrhythmias and developing cardiomyopathy, are not yet precisely defined for all of the discussed infectious pathogens.

1. Incidence

In the past, viral myocarditis and chronic viral heart disease have been more often a clinically derived diagnosis of exclusion, rather than a specifically proven diagnosis. In an homogeneous population of young military service men, the incidence of myocarditis was reported as 0.17 per 1000 man-years,[5] but the real numbers are expected to be substantially higher because of the often subclinical presentation of acute myocarditis and misinterpretation of unspecific symptoms. The overall incidence of myocarditis in viral infections is estimated at 3–6%.[6] If the substantial number of cases involving recent onset of arrhythmia, contraction disorders and cardiac enlargement is included, the figures are likely to be even higher.[7,8]

The actual incidence of virus-induced cardiomyopathy is not well established because viral myocarditis can be unapparent, and it is difficult to diagnose and may differ as a function of circulating virus populations. The prevailing symptoms can develop with a variable delay after the viral illness, and fatigue, weakness, chest pain or dyspnoea are often not recognized as symptoms of a delayed-onset heart disease. Since the introduction of sensitive and rapid molecular biological techniques applied to endomyocardial biopsy specimens (EMB) of patients with clinically suspected myocarditis and dilated cardiomyopathy (DCM), the incidence of detected viral genomes has increased continuously in these clinical settings and viral genomes have been detected in 30–50% of patients with geographical, temporary and quantitative changes.[9-18]

2. Aetiology and Prognosis

Apart from enteroviruses, which traditionally have been considered the most common agent in myocarditis and acute or end-stage DCM, distinct genotypes of erythroviruses, human herpesvirus type 6 (HHV6), adenoviruses, HIV, cytomegalovirus, herpes simplex type 2 virus and hepatitis C virus have been identified with varying degrees of frequency.[9-33]

Case reports documented so far indicate that 12% of patients with clinically suspected myocarditis and 40% of patients with biopsy-proven myocarditis develop DCM.[34-36] DCM is one of the most common cardiomyopathy entities. Its yearly incidence accounts for 5–8 cases per 100 000, the age-corrected prevalence accounts for

36 cases, and 17 hospitalizations and 3.8 deaths per 100 000 per year are due to DCM.[37] DCM affects males more frequently with a sex ratio of 2 : 1, and manifests predominantly between the third and fifth decade.[37] DCM patients have a 5-year survival rate of 55% when receiving contemporary heart failure treatment, which substantiates its socioeconomic impact.[38,39] Prospective studies have also revealed a grave prognosis for myocarditis patients, with a 5- to 10-year survival rate of 25–46%, mostly due to manifestation of DCM and sudden cardiac death.[2,3,19,40]

3. Pathogenesis

Studies from animal models of different genetic backgrounds have provided evidence that the pathogenesis of viral myocarditis is a multifactorial process involving host genetics, viral genetics and the environment in which they interact. Certain human lymphocyte antigen (HLA)-haplotypes have been associated with clearance or persistence of different viruses when, for example, polymorphisms of major histocompatibility complex (MHC)-II loci influence the affinity of epitopes to bind to different viral peptides. This may be relevant to both antigen presentation and antiviral immune response. Currently described genetic defects in components of immune pathways or chemokine/cytokine receptors (e.g. interleukin [IL]-17, CCR2, CCR5, IL-23R) interfere with certain human autoimmune diseases, but have not yet been characterized in viral or inflammatory cardiomyopathy. Defects in those components also influence the course of viral myocarditis in animal models; however, respective data demonstrating that genetic predisposition influences cardiac infection or immune responses are still lacking in humans.

Genetic predisposition may not only alter antiviral immunity, but also influence the course and severity of a myocarditis if a viral component (e.g. the enteroviral protease 2A) interferes with a predisposed genetic defect as seen in the dystrophinopathies.[41] Nevertheless, the clinical importance of a genetic predisposition of the human disease is currently not well understood, despite the fact that frequent familial occurrence has been recognized and genetic factors are therefore strongly suspected.

Viral infections of the heart develop within pathologically distinct phases (figure 1).[1,42] Most information on this issue is known from enteroviral or adenoviral infections that enter the host through the gastrointestinal or respiratory tract, and can reside in the reticuloendothelial system as an extracardiac reservoir. They may enter the heart as a secondary target organ and infect cardiomyocytes after binding to a tight junctional protein, the coxsackie adenoviral receptor (CAR) and the decay accelerating factor (DAF, CD55). The co-localization of CAR with the co-receptors for adenovirus internalization $\alpha v\beta 3$ and $\alpha v\beta 5$ at the myocyte surface suggests that it is an important molecular determinant for the cardiotropism of both viruses in viral heart disease.[43,44] Erythroviruses and HHV6 genomes, on the other hand, infect vascular endothelial cells and/or other cardiac cells including myocytes (HHV-6).[15,45,46] These different infection sites in cardiac tissue, in addition to different virus variants and viral loads, may explain the heterogeneity of viral heart disease with respect to the expression of its phenotype, clinical presentation and prognosis.

Patients presenting with viral heart disease can be categorized based on left ventricular function at the time of presentation into individuals with preserved systolic function, impaired diastolic function, segmental or compensated left ventricular dysfunction, and acute systolic left ventricular compromise. The type and extent of myocardial compromise depends on the affected cardiac structures and resulting myocardial lesions. Systolic dysfunction following cardiomyocyte infection (e.g. entero- and adenoviruses) and degeneration may either result from disturbance of elements that are responsible for force generation and force transmission (partly reversible), or be caused by an irreversible loss of contractile tissue (figure 1).[41,47] Infection of endothelial cells (e.g. by erythroviruses or HHV-6) is more often associated with endothelial or diastolic dysfunction, but preserved systolic function.[31,48,49]

The emerging innate and adaptive immune responses initiate a further step in the development of

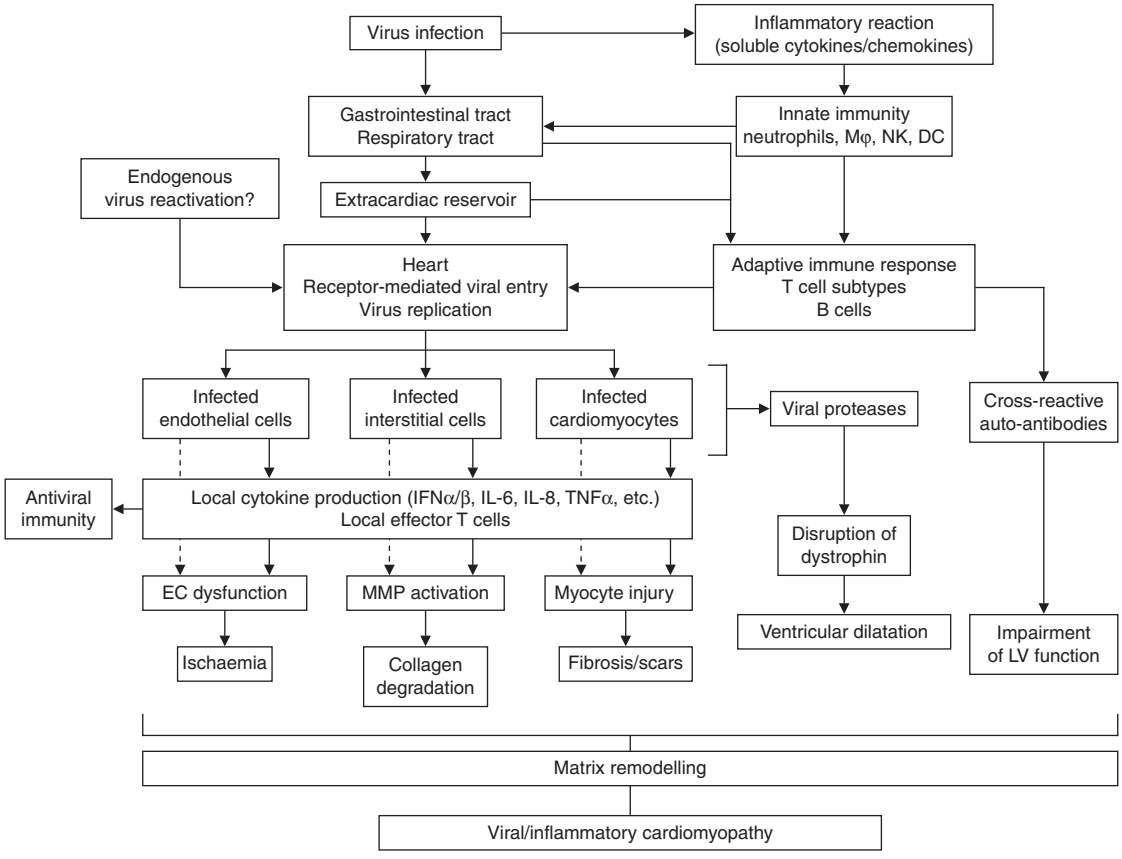

Fig. 1. Causes of myocardial injury in viral and post-infectious heart disease. Myocardial tissue injury emerges during different phases of infectious myocarditis from direct virus-associated and/or immune-mediated tissue injury. **DC** = dendritic cells; **EC** = endothelial cells; **IFN** = interferon; **IL** = interleukin; **LV** = left ventricular; **Mφ** = monocytes; **MMP** = matrix metalloproteinase; **NK** = natural killer cells; **TNFα** = tumour necrosis factor-α.

viral heart disease (figure 2). Virus-infected cardiac cells are destroyed by immune effector cells at the expense of further loss of infected myocytes. The ensuing myocardial damage depends on the scale of the cellular viral infection and increases with growing virus dispersion which, in addition to the early virus-mediated injury, contributes to later tissue remodelling and possible progression of the disease (figure 2). Viral clearance from infected cardiomyocytes therefore takes place at the expense of a partial destruction of myocardial tissue that is not capable of regeneration.

Under certain circumstances, ongoing myocardial injury may result from chronic immune stimulation induced by incompletely cleared viruses or post-infectious autoimmune processes.[50] Continuously synthesized viral proteins, intracellular proteins released from necrotic or apoptotic myocardial cells or matrix alterations with reparative fibroses and scar formation induced by activated matrix-degrading proteases may initially damage some individual cells within restricted areas, but ultimately affect the whole myocardium (figure 1).[2,34,41,50-54] This may finally account for a clinical picture that is consistent with DCM (figure 2).

3.1 Interferons in Antiviral Immunity

After internalization and migration to the appropriate cellular compartment, the viral genome

is transcribed, translated and replicated to permit the assembly and export of new virions so that the infection can spread to additional susceptible cells of the host. Most cell types respond to an incoming viral infection by rapidly secreting antiviral cytokines, such as type I interferons (IFN)-α/β, IL-1, -6, -18, or tumour necrosis factor-α (figure 1). IFNα/β have long been known to inhibit the replication of many viruses *in vitro*, including cardiotropic picornaviruses, influenza viruses, herpes viruses adenoviruses and others. Many viruses are sensitive to the antiviral activity of IFNα/β *in vivo*, although it is important to note that different viruses and even different strains of the same virus can be differently sensitive to IFNα/β. Response to IFNα/β also depends on the type of infected cell. Although interferons can trigger a number of nonlytic intracellular antiviral pathways to challenge the infection, complete viral clearance often requires additional functions of the immune response.

However, the virus may escape immune surveillance and induce persistent myocardial viral infection (figures 1 and 2). The strategies, by which primarily lytic viruses adopt a nonlytic mode of replication to achieve persistence in the host differ greatly among viruses and have not been established for most viral infections in humans.

For most viral infections it is difficult to determine whether IFNα/β controls viral infection by direct antiviral activities or by modulating the innate and adaptive immune response. Recent data indicate that an imbalance of the developing antiviral IFN response may be responsible for the lack of enterovirus clearance in myocyte culture experiments and myocarditis animal models.[55-58] The observation that the course of human virus-induced cardiomyopathy correlates with the spontaneous course of the different viruses, including enteroviruses, has stimulated specific antiviral treatment trials in patients with chronic cardiac viral infections.[19,31,59]

4. Diagnosis

4.1 Noninvasive Diagnosis

If the symptoms are so pronounced that the patient visits the physician during the first days of viral myocarditis, sinus tachycardia that is out of proportion to fever, arrhythmias and ECG abnormalities are documented. Creatine kinase

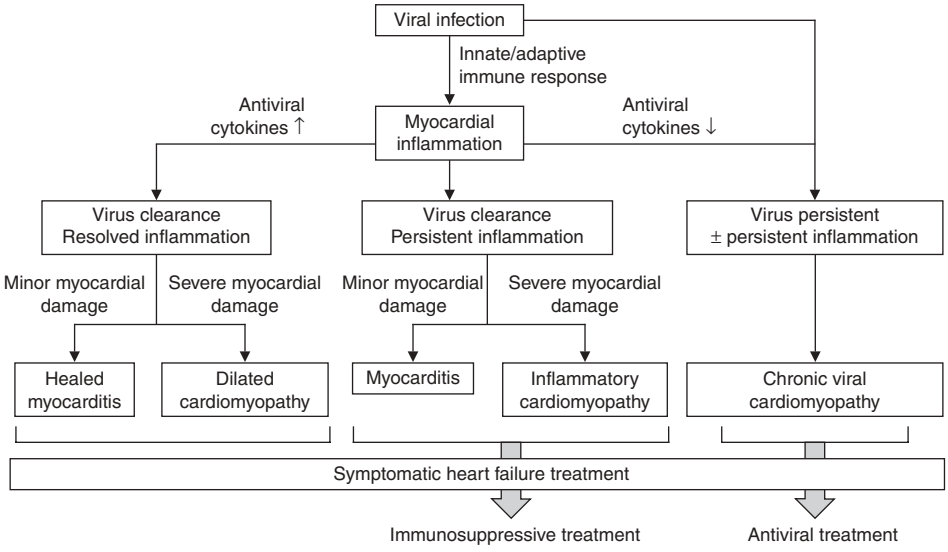

Fig. 2. Development of virus-induced heart disease and stage-dependent therapeutic interventions. ↓ indicates decrease; ↑ indicates increase.

(CK) and CK-MB, frequently raised by a factor of 2 to 5, and a raised troponin T test suggest myocardial cell damage. It is not possible to distinguish these patients from those with acute myocardial infarction, neither electrocardiographically nor chemically. Other laboratory parameters such as erythrocyte sedimentation rate or transaminases are often increased, but this is rather an effect of the underlying infection and does not allow conclusions to be made regarding myocardial involvement. Ventricular contractility might be unaffected during the early stage, but regional or, less frequently, global wall motion abnormalities can be shown echocardiographically in >50% of patients.

After a period of about 1–2 weeks, the acute laboratory chemistry test and ECG changes characteristic of the early phase of the disease have receded. Myocardial contractile dysfunction recedes at a significantly slower pace, although it does normalize in many patients. ECG findings for this follow-up phase (14 days after appearance of cardiac symptoms) include nonspecific changes in ST segments or T inversion, sinus tachycardia or a slow normalization of the pulse following stress, supraventricular and ventricular immature beats, and conduction system abnormalities.

Echocardiographically, regional left ventricular wall motion abnormalities of varying scope are particularly discernible. Global systolic myocardial function is often unremarkable, at least during the early phase of the myocarditis, whereas an early diastolic dysfunction often exists. Increase of wall diameters (pseudohypertrophy due to increased interstitial water content), corresponding with the proof of early enhancement of T2-weighted imaging in the cardiac magnetic imaging (CMR) analysis, may be present during the first weeks of acute myocarditis. During later stages, echocardiography is useful as a follow-up imaging modality to monitor the natural history of a patient's ventricular function or in response to treatment. T2-relaxation parameters in CMR characterize myocardial tissue according to water content and changes in contrast kinetics by local changes in membrane permeability, tissue oedema and, ultimately, tissue fibrosis or scar formation in association with inflammatory events.[60] Extracellular contrast agents such as gadolinium diethylenetriamine penta-acetic acid differentially distributes between inflamed and scarred tissue leading to delayed enhancement on T1-weighted images.

Nuclear medicine techniques can demonstrate myocardial damage. Necrosis of myocardial cells can be detected using antimyosin scintigraphy, although such findings are not specific to myocarditis. Radionuclide ventriculography during exertion reveals latent myocardial damage by demonstrating significantly reduced or absent pumping reserves. However, abnormal nuclear studies and imaging techniques cannot distinguish between different inflammatory effector cells, virus types or patients with or without a viral infection and, therefore, do not allow a specific diagnosis.

4.2 Invasive Diagnostic Techniques

Differentiation from other cardiac diseases that evoke similar clinical symptoms is important (figure 3). Valvular heart disease can be identified using echocardiography. The differentiation of inflammatory cardiomyopathy from ischaemic cardiomyopathy is not possible noninvasively, even with the aid of stress echocardiography, because stress-induced regional dysfunction in ventricular walls can also occur in viral myocarditis. After exclusion of other causes of heart failure, cardiomyopathy or myocarditis may be assumed. It is important to remember that none of the noninvasively obtained diagnostic parameters allow an unequivocal diagnosis of myocardial inflammation (myocarditis or inflammatory cardiomyopathy) or viral infection. Because of the low specificity of noninvasive examination methods, subsequent invasive approaches are necessary and indicated, especially in patients with overt heart failure (figure 3).[4] The diagnosis of myocardial viral infection and associated inflammatory processes can only be confirmed by the analysis of EMB.

4.2.1 Molecular Biological Virus Detection

The low diagnostic accuracy of standard virological methods has promoted the development

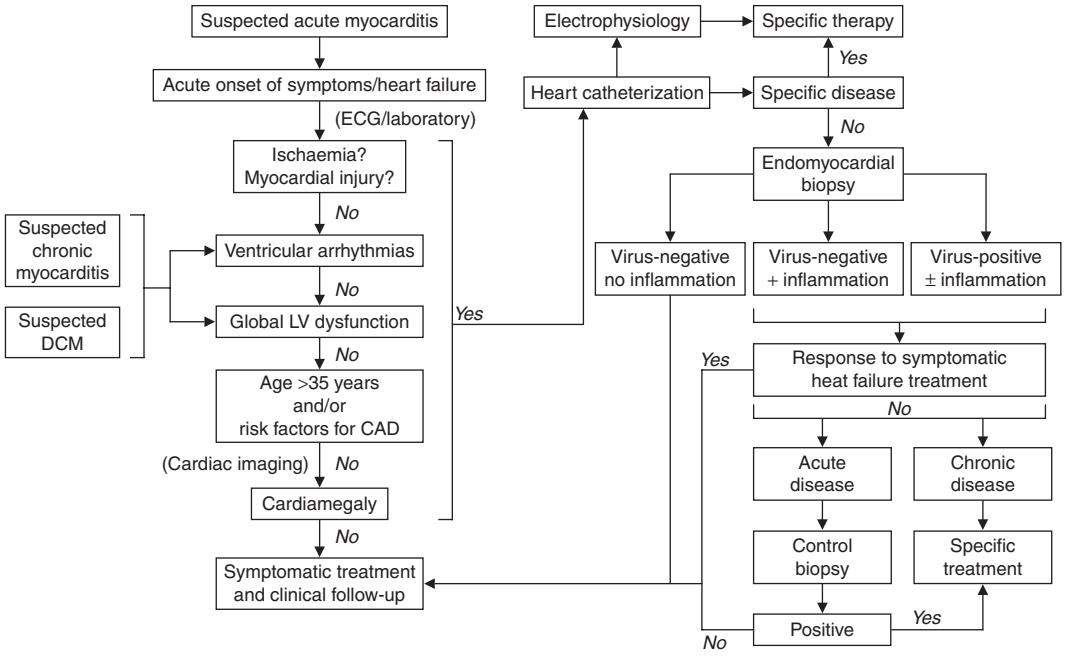

Fig. 3. Diagnostic flow-chart of noninvasive and invasive diagnostic procedures in patients with clinically suspected acute or chronic viral myocarditis. **CAD** = coronary artery disease; **DCM** = dilated cardiomyopathy; **LV** = left ventricular.

of molecular biological detection assays for viral genomes in cardiac tissues of cardiac patients. *In situ* hybridization of enteroviral RNA in EMB was first demonstrated in 1986 by Bowles et al.[61] and Kandolf et al.[62] Apart from the information on direct localization of viral infections, *in situ* hybridization is a time consuming procedure not suitable for obtaining a routine clinical diagnosis, which demands rapid information on the aetiology.

The introduction of the more rapid nested polymerase chain reaction (nPCR) in routine molecular biological analysis of viral infections of the myocardium has substantially increased our information on possible cardiotropic viruses in patients with acquired heart disease (table I). Meanwhile, a quantitative approach to the majority of cardiotropic viruses has been introduced to the routine virological diagnostic sets of specialized laboratories. The quantitative approach and its clinical interpretation is hampered by the fact that actual virus numbers are often misjudged primarily as a result of the sampling error if only a limited number of EMB are analysed in early, focal disease. Furthermore, if timing of biopsy is late with respect to the onset of virus-induced disease, it may only detect residues of incompletely cleared viruses. Because such copy numbers may only be remnants of earlier stages of an infectious disease, low virus copies at diagnosis neither exclude a virus-associated myocardial injury nor do they necessarily correlate with the magnitude of myocardial damage at the timepoint of diagnosis. At present, information on sampling error and follow-up information comparing quantitative virus data and virus-associated myocardial inflammation with the clinical course are not available.

Analysis of virus replication in the myocardium, which can be identified by using plus-minus strand detection methods, have suggested that the clinical course of patients is linked with the course of the viral infection and that persistence of replicating viruses may provide an adverse impact on the prognosis of affected patients.[11,63] This assumption has been questioned by others.[64]

Table I. Virus-associated heart disease[a]

Virus	Cardiotropic subtypes/variants	Treatment[b]
RNA viruses		
Picornavirus		
coxsackie A+B	CVB 1–6, A2, 5	IFNβ
echovirus	Echo 30	
poliovirus		
hepatitis virus	B, C	IFNα and ribavirin
Orthomyxoviren		
influenza	A, B	
Paramyxoviren		
RSV		
mumps		
Togaviruses		
rubella		
Flaviviruses		
Dengue fever		
Yellow fever		
DNA viruses		
Adenovirus	A 1, 2, 3 and 5	IFNβ
Erythrovirus	1 (B19V), 2	
Herpesvirus		
HHV6	A, B	Val-/ganciclovir
CMV		
EBV		
VZV		
Retrovirus		
HIV		
Post-infectious cardiomyopathy		
Autoimmune myocarditis and DCMi		Immunosuppression (corticosteroids, azathioprine, ciclosporin)
Dilated cardiomyopathy		Symptomatic (ACE inhibitors, β-blockers, diuretics)

a Infectious pathogens in acquired viral myocarditis/inflammatory dilated cardiomyopathy (DCMi) and post-infectious of heart failure.

b Plus heart failure therapy.

CMV = cytomegalovirus; **CVB** = coxsackie B virus; **EBV** = Epstein-Barr virus; **HHV** = human herpesvirus; **IFN** = interferon; **RSV** = respiratory syncytial virus; **VZV** = varicella zoster virus.

Of note, we are currently not aware of the replicative pattern or metabolic activity of cardiotropic viruses other than coxsackie B virus.

Another important finding that can be derived from molecular biological virus analysis and subsequent sequencing of the amplification products is the identification of specific virus variants that may have distinct pathogenetic potentials and therefore might explain the often observed discrepancies between PCR results and the unpredictable clinical courses.[33] In human heart disease, it is currently unknown how different virus subtypes or variants may deliver disease-specific cardiac pathogenicity and what determines a cardiovirulant phenotype that can cause overt heart disease.

4.2.2 Histological and Immunohistological Analysis of Inflammation

The diagnosis of myocarditis is still largely based on histomorphological criteria according to the Dallas Criteria. Since the majority of patients do not undergo invasive diagnostic techniques and biopsy until reparative processes have

already taken place – because the course of the disease is usually subacute – the histological diagnosis of myocarditis based on the Dallas Criteria is usually no longer suitable for this stage of the disease.[65] Apart from its low sensitivity and specificity, the main disadvantage of histological assessment of myocardial biopsies is the absence of sensitive markers for an active immunological process. In contrast, immunohistological diagnostic techniques offer an enormous diagnostic potential stemming from the multitude of disposable monoclonal antibodies; this potential by far surpasses the possibilities of a purely histological analysis of the inflammatory reaction.[66,67] The differentiation, characterization and quantification of the activated interstitial cells or invading immune cells (e.g. leukocytes, B cells, macrophages, natural killer cells, endothelial cells) allow for a specific assessment of the myocardial inflammatory process (figure 4). Moreover, the homogenous distribution of endothelial cell adhesion molecules that correlates with the number of infiltrating immune cells irrespective of their focal or diffuse distribution, substantially reduces the sampling error (figure 4).[68]

5. Management

Because of the lack of data, evidence-based recommendations for the clinical management at the acute stage of viral myocarditis are difficult to develop. The disease may mimic acute myocardial infarction. These patients present with acute ischaemia-like angina, variable ST and T wave changes by ECG, arrhythmias, elevated cardiac enzymes, and regional or global wall motion abnormalities but without coronary disease by catheterization.[14,69] The clinical symptoms may recede more or less completely within a few hours, days or weeks, without persisting heart failure. Long-term prognosis is generally excellent in most of these patients.

5.1 Symptomatic Treatment

As long as clinical symptoms are mild to moderate and left ventricular function remains practically unaffected, these patients do not need specific medical treatment. Nevertheless, as long as ECG abnormalities and increased levels of troponin I/T or CK isoforms are still recorded, hospitalization and monitoring is recommended to identify and prevent unforeseeable life-threatening arrhythmias or rapid progression of heart failure. Physical activity should be avoided until the viral infection has been cleared (possibly verified by endomyocardial biopsy) and cardiac inflammation has resolved.

Ventricular arrhythmia is common in patients with viral and nonviral myocarditis, but in most cases it does not require specific therapy. If patients present with severe refractory ventricular arrhythmias or atrioventricular blocks, they may require antiarrhythmic medication or insertion of implantable cardioverter-defibrillators or temporary pacemakers, respectively. Because myocarditis may often result in spontaneous remission, antiarrhythmic devices should only be implanted after other methods of controlling arrhythmia have proved to be unsuccessful.

In contrast to patients with arrhythmias or an infarct-like clinical presentation and preserved systolic ventricular function, an adverse prognosis has been reported for those with persisting heart failure.[2,40,70] The treatment of systolic or diastolic heart failure does not depend on the aetiology of the disease and remains primarily supportive. All symptomatic patients should receive optimal heart failure medication including ACE inhibitors, diuretics and β-adrenergic receptor antagonists (β-blockers) according to the guidelines proposed by the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.[71] This background medication should also be maintained if a specific therapy is administered later.

5.2 Specific Treatment Options

Although many patients who present with nonfulminant viral myocarditis or moderate to severe haemodynamic compromise may improve spontaneously within weeks or months with regular heart failure therapy and complete recovery may occur, the overall long-term prognosis of this patient cohort is grave. Adverse prognosis

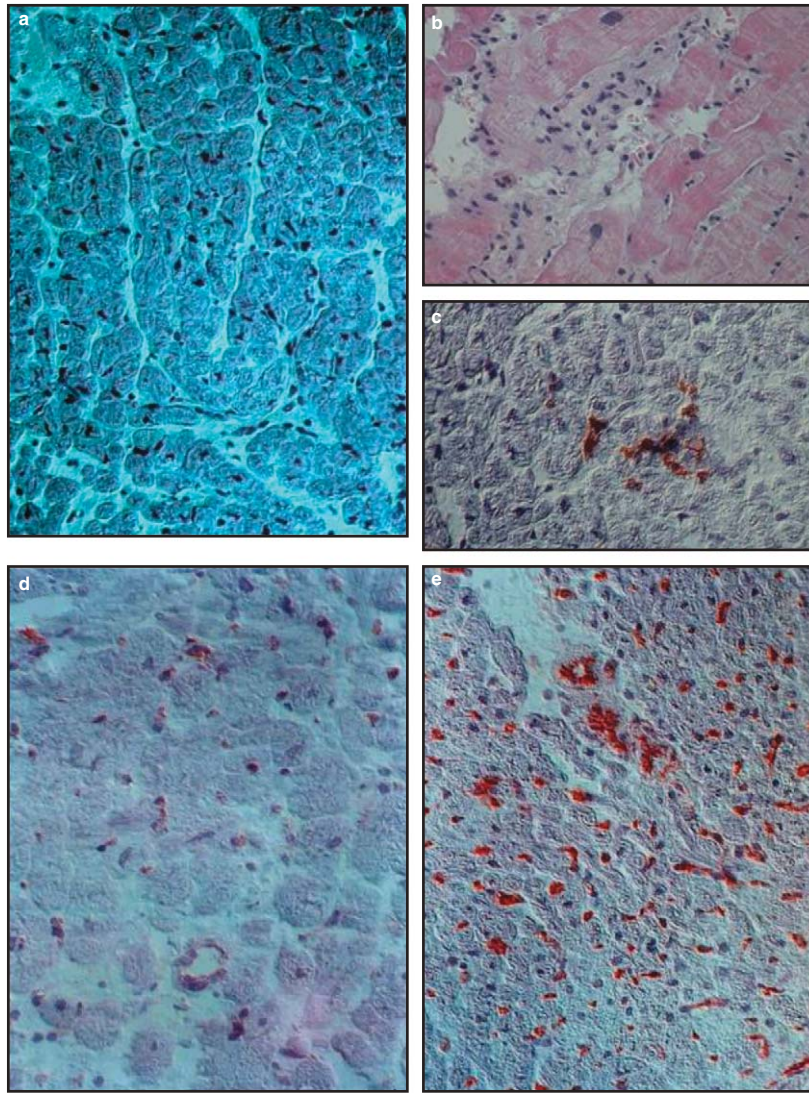

Fig. 4. Histological and immunohistological diagnosis of myocardial inflammation in patients with clinically suspected viral myocarditis or postviral inflammatory cardiomyopathy. (**a**) Non-inflamed myocardial tissue and lack of infiltrating CD3+ lymphocytes. Small myocyte necrosis (**b**) and focal CD3+ lymphocytic infiltrate (**c**) in a patient with a history of viral myocarditis and preserved systolic left ventricular function. Normal (**d**) and enhanced (**e**) adhesion molecule expression (CD54/ICAM-1) in non-inflamed (**d**) and inflamed (**e**) myocardium. **ICAM** = intracellular adhesion molecule.

and lack of recovery are not exclusively caused by the early pathogenetic processes with subsequent ventricular remodelling, but are also associated with a persisting infectious disease.[2,16,19,34,40,72] Both viral infection and associated inflammatory processes have been recognized as independent prognostic parameters, in addition to left and right ventricular dysfunction, in myocarditis and DCM.[2] Therefore, more specific treatment options are needed that directly address the underlying viral or inflammatory causes of the disease.

Available data from different studies have revealed some pitfalls that should be taken into consideration before a decision for any specific treatment is made.

1. Despite the fact that it has been analyzed inconsequently in the past, it has to be assumed that the disease of patients presenting with fulminant or acute heart failure in the context of myocarditis has initially been triggered by a viral infection.[2,3,36,70] If the antiviral immune responses have developed rapidly and efficiently with complete viral clearance and rapid decline of the immune processes, residual damage of the myocardium may be negligible or moderate and the remaining myocardium can compensate for the partial loss of contractile tissue (figure 2).[59] Consequently, these patients may recover with symptomatic heart failure treatment with only minor or moderate residual clinical signs of heart injury, and even survivors of fulminant myocarditis may have a good long-term prognosis.[40,73] Patients with more extended residual myocardial injury may develop irreversible heart failure with progressive left ventricular dysfunction despite early viral clearance and optimal heart failure medication.[34,40] It is important to identify these patients with virus-negative DCM, because they will not respond to specific immunomodulatory therapy (figure 2).
2. In order to prevent excessive tissue damage by an overwhelming or prolonged antiviral immune response, cellular immune processes rapidly decline after successful elimination of the infectious pathogen.[59,74] Under certain circumstances, chronic immune stimulation and autoimmunity may result from molecular mimicry or the virus-mediated chronic tissue alterations, respectively.[50] Immune processes may, thus, be responsible for adverse outcomes in post-viral inflammatory cardiomyopathy.[2,4,70] Several randomized trials have failed to demonstrate a clear benefit of immunoglobulin treatment or immunosuppressive therapy with corticosteroids in combination with azathioprine or ciclosporin in histologically confirmed myocarditis according to the Dallas Criteria, since viral infection had not been taken into consideration and a number of patients in these studies improved spontaneously with or without immumodulatory treatment.[75-77] In contrast, data from recent treatment trials indicate that patients with chronic disease may benefit from immunosuppressive treatment strategies if the target cohort has been exactly characterized and, most importantly, viral persistence has been excluded.[16,72,78-80]
3. Given the fact that viral clearance requires additional functions of the immune response, and that histologically active myocarditis with focal myocyte necrosis represents destruction of virus-infected cells by cytotoxic immune effector cells necessary for viral elimination, any medication that interferes with the antiviral immune responses might perpetuate viral replication and favour viral persistence. This suggestion would be in line with adverse effects observed after early immunosuppression in murine models and of virus-positive patients, in which viral persistence was one of the key discriminators of patients not responding to a 6-month course of immunosuppression.[16] Because data demonstrating the benefit of an early specific antiviral or immunosuppressive treatment in patients with virally induced heart muscle disease do not exist, immunomodulatory treatment should only be administered to non-acute patients with persistent myocardial dysfunction despite receiving heart failure medication.
4. The histological examination of cardiac tissue specimens and noninvasive imaging techniques may detect myocardial inflammation with variable sensitivities, primarily in chronic disease, but none of these diagnostic techniques can record the viral infection.[4,65,81-83] A biopsy-based detailed aetiopathogenic differentiation of the underlying causes of the disease with contemporary diagnostic techniques including immunohistology and PCR amplification of viral genomes is therefore essential for a correct diagnosis and the choice of the most suitable treatment modality.[16,72,74,84,85]

5.3 Antiviral Treatment of Early Disease

In the context of the general viral infection, viruses are processed in lymphoid organs and may proliferate within immune cells such as lymphocytes or macrophages. Subsequently, they constitute target organ infection through haematogenous or lymphangitic spread. Because of a lack of specific symptoms indicating heart involvement, this early phase preceding heart cell infection is generally missed in most patients. Elimination of viral translation, transcription and proliferation with the use of any antiviral medication that targets viral attachment to host cell receptors, virus entry or virus uncoating, such as pleconaril, WIN 54954 or CAR-Fc antibodies, are of limited use in patients with virus-associated heart disease because symptomatic patients generally present when organ infection has already established.[86,87] The current challenge of any antiviral therapy in patients with cardiac viral infections, therefore, is the establishment of treatment strategies that prevent further viral spread and to achieve viral clearance in time before chronically infected heart tissue has been damaged irreversibly.

5.4 Antiviral Treatment of Chronic Viral Heart Disease

Interferons serve as a natural defence against many viral infections. Their innate production is associated with clinical recovery from viral infection and subsequent sequelae, while exogenous administration is protective. Type I interferons therefore constitute a promising choice for treatment.

Analyzing four patients, one open-labelled study could not demonstrate a beneficial effect in terms of viral clearance in patients treated with a protocol IFNα 3×10^6 IU every other day for 6 months.[88] Three patients improved, although the virus persisted in two. Because IFNα displays an antiviral potency similar to that of IFNβ, it can be assumed that the concentration of IFNα used in this study may have been insufficient for viral elimination. In another randomized study, 180 patients with clinical evidence of myocarditis or DCM were treated with IFNα 3–5 $\times10^6$ IU per day for 3 months (n = 97), thymomodulin 10 mg (three times per week) for 2 months (n = 33), or conventional therapy alone (n = 50).[89] Left ventricular function improved after 6 months of treatment in the IFNα group (34.8% vs 50.6 ± 9.6%) and the thymomodulin treated group (no exact data given), but it remained unchanged in the conventionally treated controls (35.3% vs 39.3 ± 13.1%). The beneficial effect on left ventricular ejection fraction and exercise tolerance was reported to remain stable at long-term follow-up after 5–7 years.

Data from an IFNβ phase II study provided first evidence that antiviral IFNβ-1a therapy effectively clears cardiac viral infection in patients with chronic heart failure when given subcutaneously every other day in addition to continued heart failure medication.[74] Twenty-two patients with EMB-proven enteroviral (n = 15) and adenoviral (n = 7) persistence were treated with IFNβ for 24 weeks. The treatment was administered following a stepped regimen in order to limit the IFN-related adverse effects. The patients entered a run-in period to improve tolerance, during which they received IFNβ 2×10^6 IU per administration every other day for 1 week. Within the following 2 weeks, study medication was elevated to IFNβ 4×10^6 IU and 6×10^6 IU, respectively, and continued for the following 21 weeks. This dosage was well tolerated. Complete elimination of viral genome was proven in follow-up biopsies in all patients. This was paralleled by a significant improvement in left ventricular function, decrease in ventricular size, amelioration of heart failure symptoms, and a significant decrease of infiltrating inflammatory cells, while no patient deteriorated. While entero- and adenovirus infections seem to respond well to the IFNβ treatment, subsequent open-labelled studies have shown that other viral infections respond less well with respect to viral clearance, although erythrovirus load decreased and patients improved clinically.[74,85] These data were recently confirmed by the first randomized IFNβ treatment study (BICC [Beta Interferon for Chronic Cardiomyopathy] trial).[85] The other viruses might respond more positively to specific antiviral treatment regimens (table I), but opti-

mal treatment conditions for viruses other than enteroviruses and adenoviruses have not yet been defined. At present, antiviral therapy is still restricted to clinical trials in specialized centres.

5.5 Treatment of Post-Viral Inflammation

Myocardial inflammatory processes or systemic autoimmunity may survive myocardial virus elimination and warrant immunosuppressive treatment in order to prevent later immune-mediated myocardial injury (figures 1 and 2).[72,78,90] Treatment regimens for these patients with post-viral chronic myocarditis/inflammatory cardiomyopathy consist of corticosteroids, azathioprine or ciclosporin, which are administered in addition to regular heart failure medication (table I). Methylprednisolone is generally given at a rate of 1 mg/kg bodyweight (1–2 mg/kg in children) daily, initially for 4 weeks. Depending on bodyweight, azathioprine 100–150 mg is administered daily in addition to the corticosteroid medication. The corticosteroid dosage is titrated monthly in increments of 10 mg until a maintenance dose of 10 mg/day is reached. The treatment should last for 3–6 months. Actual data of first randomized trials confirm efficacy of those treatment regimens in carefully selected patients.[16,72,90]

6. Conclusions

Myocarditis is a non-ischaemic inflammatory disease of the myocardium that can result from virtually any infectious agent, but viral infections are the most frequent cause. The different aetiologies of myocarditis cannot be recognized by noninvasive clinical analyses. The assessment of a reliable diagnosis, the selection of patients who are likely to benefit from immunomodulatory treatment and the choice of the most appropriate treatment regimen can only be reached by a biopsy-based evaluation of myocardial tissue. Symptomatic heart failure therapy may improve clinical symptoms and haemodynamic compromise, but it does not affect the underlying viral or inflammatory cause of the disease. First data from randomized trials indicate that patients with virus-negative myocardial inflammation may benefit from immunosuppressive therapy, whereas, depending on the virus type, virus-positive patients respond favourably to antiviral treatment with IFN. General optimal treatment conditions for both clinical settings have not yet fully been defined and, therefore, immunomodulatory treatment strategies are still restricted to clinical trials in specialized centres.

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