REVIEWS

Viral myocarditis and dilated cardiomyopathy: mechanisms, manifestations, and management

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Abstract

Viral infection of the heart is relatively common and usually of little consequence. It can, however, lead to substantial cardiac damage and severe acute heart failure. It can also evolve into the progressive syndrome of chronic heart failure. Recent studies have gone some way towards unravelling the complex mechanisms underlying the heart muscle damage that occurs after viral infection. These studies have lent support to both immune and viral mediated (independent of an immune response) cardiac damage. Acute myocarditis can present in various ways, and it may be a cause of sudden death in an otherwise healthy young adult. New treatments for viral heart disease are awaited. In the meanwhile, the haemodynamic support of patients with acute left ventricular failure caused by myocarditis should be aggressive, to allow for the possibility of spontaneous recovery. Contemporary trials of treatment in chronic heart failure secondary to dilated cardiomyopathy support the use of angiotensin converting enzyme inhibitors, β adrenoceptor blockers, and spironolactone in such patients.

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Despite significant progress in the prevention and treatment of cardiovascular disease, the incidence and prevalence of chronic heart failure continue to rise. Whatever the underlying aetiology, severe heart failure can have a mortality of up to 50% within one year of diagnosis.[1] In the United Kingdom the evaluation and care of patients with chronic heart failure, not taking into account lost wages and productivity, is estimated to cost the NHS over £1 million a day.[2]

Myocarditis is a common cause of dilated cardiomyopathy, which in the western world is the underlying aetiology in about 45% of patients undergoing heart transplantation.[3] A relation between infection and chronic heart disease was suggested as early as 1806, when Corvisart described a cardiac inflammatory disorder that could result in progressive abnormalities of cardiac function after all evidence of the infective agent had disappeared.[4] Myocarditis can be initiated by several different infective agents, including viruses, parasites, protozoa, and fungi.

Viruses causing myocarditis
- Coxsackie (A, B)
- Adenovirus
- Influenza (A, B)
- Herpes simplex
- Cytomegalovirus
- Varicella-zoster virus
- Epstein-Barr virus
- Mumps
- Rubella
- Rubeola
- Vaccinia
- Rabies
- Coronavirus
- Hepatitis B
- HIV

Viral infection is thought to be the most common cause of myocarditis and in this review we will focus on viral myocarditis, its progression to dilated cardiomyopathy, and the current treatment of dilated cardiomyopathy.

Aetiology and pathophysiology

VIRUSES CAUSING MYOCARDITIS

Viruses known to cause myocarditis are listed in box 1. HIV is an important cause of heart muscle disease but a full review is beyond the scope of this article (for a review, see Barbaro[5]). Coxsackie B virus is most often associated with myocarditis. It is a member of the picornavirus family and the enterovirus genus, and is closely related to other enteroviruses such as echovirus, poliovirus, and rhinovirus. Most adults have at some time been infected with this cardiotropic virus. In a series of healthy adults, neutralising antibody against two serotypes of coxsackie B was detected in sera from 86% of those tested.[6]

PATHOGENESIS

With the application of cellular and molecular biological approaches to the investigation of mechanisms of viral myocardial damage, our understanding of myocarditis and its progression to dilated cardiomyopathy has increased substantially. A clear understanding of the pathophysiology of progression of heart muscle damage and the development of dilated cardiomyopathy is important in the management of this often fluctuating disease.

It is likely that both immune mediated and direct viral cytotoxic mechanisms of myocar-

dial tissue destruction are important in the pathogenesis of viral heart disease (for reviews see Kawai[7] and Knowlton and Bardorff[8]).

IMMUNE MECHANISMS OF MYOCARDIAL DAMAGE

In the immunocompetent patient, the immune response stimulated by viral proteins limits viral replication, and in the majority of patients clears the virus from the host. However, the immune response itself can cause damage to the myocardium, and the balance between beneficial and detrimental effects of the response significantly influences the extent of cardiac cell loss.

After viral invasion of the myocardium, the first wave of infiltrating immune cells consists of natural killer (NK) cells. NK cells are thought to have a cardioprotective effect by limiting virus replication. There is evidence in murine models of myocarditis that mice deficient in NK cell responses have a more severe myocarditis.[9] NK cell infiltration is accompanied by the production of various cytokines including interleukin (IL)-1β, tumour necrosis factor α (TNFα), γ interferon, and IL-2β. These cytokines may have both beneficial and deleterious effects on myocardial function (for review, see Matsumori[10]). Experimental studies have reported beneficial effects of IL-10 on survival and subsequent myocardial function in a murine model of myocarditis,[11] and there are convincing data showing a detrimental effect of TNFα in myocarditis.[12] There are also recent data showing that the vasoconstrictor substance endothelin plays a role in the pathogenesis of myocarditis.[13]

At the same time as the first wave of NK cells, there are also NK-like cells, which, unlike NK cells, cause myocardial damage by the release of perforin molecules. These form circular pore-like lesions on the membrane surface of cardiac myocytes, and contribute to myocardial cytoskeletal disruption.[14]

The second wave of cells seen in the myocardium are T lymphocytes, which peak at 7–14 days after virus inoculation. This coincides with the most severe phase of myocardial damage.[15] T cells are thought to play an important role in both viral clearance and immune mediated cardiac damage. T cells have been shown to be capable of destroying virus infected cardiocytes in vitro.[16] It has been proposed that these cells may injure virally infected myocytes because of molecular mimicry—that is, myocardial antigens that bear similarities to viral protein cause T lymphocytes originally aimed at the virus to cross react with host antigen and produce myocyte damage. The products of cardiac cell destruction themselves may then stimulate further cell lysis by T cells.[17]

The balance between the beneficial and detrimental effects of the immune response in humans is less clear. A large trial of immunosuppressive treatment in patients with myocarditis failed to show a beneficial effect in patients receiving immunosuppresion.[18] However, in a smaller trial there was a beneficial effect of giving immune globulin to patients with myocarditis.[19]

A recent study has shed some light on this dichotomy[20] (for a review, see Knowlton and Bardorff[8]). In coxsackie B virus infected knockout mice lacking different components of the cellular immune system, Opavsky *et al* showed that the activity of different T cell subtypes was an important determinant of myocardial damage.[20] They demonstrated that the absence of both CD4+ and CD8+ T lymphocytes markedly reduced cellular inflammation and mortality caused by coxsackie B infection. Hence selective treatment targeting subsets of immune cells may be a more effective intervention in acute viral heart disease. The timing of any treatment is also likely to be an important determinant of efficacy.

ROLE OF NITRIC OXIDE IN THE PATHOGENESIS OF ACUTE MYOCARDITIS

There has been much interest recently in the role of nitric oxide synthase (NOS) in acute myocarditis. In the healthy heart, nitric oxide derived from endothelial cells modulates myocardial relaxation and diastolic function[21 22] and the Frank-Starling response,[23] and improves energetic efficiency.[24] Nitric oxide may also influence excitation–contraction coupling, heart rate, and β adrenoceptor responsiveness.[25] During acute myocarditis, there is significant expression of the inducible isoform of NOS (iNOS), both in infiltrating inflammatory cells[25] and in cardiac myocytes,[26] which generates large amounts of nitric oxide and the radical peroxynitrite.[27] iNOS expression is probably induced by cytokines such as TNFα and IL-1β.[25] iNOS derived nitric oxide may have beneficial effects because of its antiviral activity.[28] On the other hand, excessive nitric oxide production, especially in the context of increased oxidative stress, may be detrimental—for example, by causing myocardial depression, apoptosis, and necrosis.[29 30] The balance between beneficial and detrimental effects is likely to depend on the spatial and temporal patterns of iNOS expression during the course of the disease.

VIRAL MECHANISMS OF MYOCARDIAL DAMAGE

The direct effects of virus mediated toxicity include focal necrosis of myocytes in the absence of an inflammatory cell infiltrate within three days of infection. At the same time as NK cells, protective antiviral antibodies and infiltrating macrophages begin to clear the virus from the myocardium, with or without the aid of cytokines. Despite these defence mechanisms, acute viral replication may—depending on the circumstances of the patient—cause rapid and severe cardiac decompensation. In experimental models of myocarditis the virulence of cardiotropic viruses is increased by malnutrition,[31] age,[32] and exercise.[33] A study of animals forced to perform regular physical exercise following infection with a cardiotropic virus showed an increase in cardiac necrosis and mortality. Sex hormone status also contributes to the outcome of viral infection of the heart, pregnancy being a particularly potent predisposing factor.[34–36] The

most important factor, though, is immune status. If the initial immune response is ineffective and the virus is not eliminated, chronic myocarditis can evolve, with the potential development of dilated cardiomyopathy.

The mechanisms involved in the transition from viral myocarditis to dilated cardiomyopathy have been difficult to elucidate. Until recently there was controversy as to whether the presence of enteroviral genomes in the heart is significant in the aetiology of chronic disease or whether they simply represent remnants of previous infection. Two studies came to opposite conclusions. Figulla *et al* suggested that the presence of enteroviral RNA in endomyocardial biopsies is a positive prognostic factor with respect to haemodynamic and clinical outcome,[37] while a prospective study from our own institution showed that the presence of enteroviral RNA in the myocardium of patients with myocarditis or dilated cardiomyopathy was an independent predictor of an *adverse* prognosis.[38]

Persistent enteroviral and adenoviral genomes have been identified by polymerase chain reaction (PCR) and in situ hybridisation of the heart. In a recent study, Pauschinger *et al* showed that 22% of patients with left ventricular dysfunction and clinically suspected myocarditis had active enteroviral RNA replication in the myocardium.[39] In that study reverse transcriptase PCR was used to detect minus strand RNA. Transcription of minus strand RNA from the plus strand enteroviral template is the essential first step in enteroviral replication and is an indication of the active RNA replication of enteroviral genomes.

The key question was whether or not this replication could produce new antigenic non-infective viral protein sufficient to cause ongoing myocardial injury. In an elegant in vitro experiment, Wessely *et al* explored the effects of low level restricted replication of enteroviral genomes in isolated cardiac myocytes, in a pattern similar to that observed in hearts with persistent viral infection.[40] The presence of viral genetic material was enough to induce cardiac filament disruption and other features of myocardial injury independent of host cell immune effects. In a similar experiment the same group produced persuasive data supporting a role for enteroviral protease mediated disruption of the cardiac cell cytoskeleton, a recognised feature of dilated cardiomyopathy.[41]

Subsequently the same group showed that transgenic mice with cardiac specific expression of full length copy of the coxsackie B virus genome developed morphological changes and abnormal excitation–contraction coupling similar to those observed in dilated cardiomyopathy. The hearts of these mice had molecular, histological, and functional features resembling human dilated cardiomyopathy, with an increase in left ventricular end diastolic and systolic dimensions, and reduced left ventricular fractional shortening. Histological examination revealed myocyte fibrosis and degeneration.[42] These studies lend convincing support to the hypothesis that low level expression of viral genome—in the absence of maturation of infectious virus progeny—can induce chronic dynamic myocardial injury.

Box 2: Clinical characteristics of patients with active myocarditis[18]

- Age, 42 (14) years (mean (SD))
- Sex, 62% male
- Flu-like symptoms, 60%
- Chest pain, 35%
- Raised white cell count, 24%
- Increased erythrocyte sedimentation rate, 60%
- Fever, 18%

Clinical manifestations

The clinical characteristics of patients with active myocarditis are summarised in box 2. The majority of patients with myocarditis remain asymptomatic, as the cardiac sequelae are often subclinical and self limiting. However, myocarditis can occasionally be a devastating illness that evolves into a chronic progressive disease. Its clinical manifestations are variable and reflect abnormalities in left ventricular systolic and diastolic function and electrical activation, leading to arrhythmias or conduction defects. Mason *et al* carried out the largest prospective study of patients with myocarditis,[18] evaluating a series of 111 patients with dilated hearts, histological evidence of myocarditis, and a left ventricular ejection fraction of less than 45%. They produced some important clinical data about the natural history of myocarditis and showed that mortality (taken as death or the need for a heart transplant) was 20% at one year and 56% at four years. In an earlier study, data from our group showed that at six months after the index episode of acute myocarditis, 50% of patients will develop dilated cardiomyopathy; if left ventricular function was improving or normal, the prognosis was good, whereas residual left ventricular impairment was associated with a poor outcome.[43]

Mason *et al* found that 60% of patients with myocarditis have antecedent flu-like symptoms. An interesting study which reflects these findings—in a series of patients with influenza of sufficient severity to warrant being seen by a doctor—showed that ECG abnormalities were present in about 10% of patients.[44 45] Chest pain is also a common manifestation of myocarditis. Patients can present with a clinical syndrome mimicking that of acute myocardial infarction, with chest pain, left ventricular dysfunction, and ECG evidence of myocardial injury. Subsequent necropsy examination usually shows normal coronary arteries.[46] Another not uncommon feature of myocarditis is systemic or pulmonary thromboemboli.[47 48] The mechanism of the disturbance of the coagulation pathway is unclear, but in 15% of patients with myocarditis ventricular thrombus can be detected on transthoracic echocardiography.[49] The electrical sequelae of myocarditis may become manifest as syncope, palpitations, sudden death from tachyarrhythmias (see illustrative case study, box 4), or heart block. In a

Box 3: Electrocardiographic findings in patients with myocarditis
- Sinus tachycardia
- Diffuse ST-T wave abnormalities
- Prolonged QT interval
- Bundle branch block (LBBB found in 20%)
- Myocardial infarction pattern
- Complete heart block
- Supraventricular tachyarrhythmias
- Ventricular tachyarrhythmias

Box 4: Illustrative case report

A 42 year old West African man was admitted unconscious to the intensive care unit, after an out of hospital cardiac arrest and resuscitation by a friend. He had little medical history of note other than that he had had a recent upper respiratory tract infection. There were no risk factors for HIV infection. While on intensive care he had recurrent episodes of ventricular fibrillation requiring multiple dc shocks, but ultimately settled on treatment with intravenous lignocaine (lidocaine), amiodarone, and overdrive pacing. His resting ECG showed non-specific T wave changes (fig 1) and he intermittently had non-sustained episodes of a broad complex, irregular tachycardia (fig 2). Full blood count, urea and electrolytes, and liver function tests were normal. Transthoracic echocardiography showed normal left ventricular function and size. He gradually recovered without any sequelae. Electrophysiological testing revealed inducible non-sustained polymorphic ventricular tachycardia. Coronary angiography was entirely normal. A right ventricular biopsy was taken which subsequently showed healing myocarditis (fig 3). The patient declined to have an implantable cardioverter/defibrillator and was discharged on oral amiodarone.

series of 162 subjects under the age of 40 who had sudden unexpected death, myocarditis accounted for 22% of the deaths in those under the age of 30 and 11% in those between 30 and 40.[50] Mason *et al* also evaluated the effect of immunosuppressive treatment with cyclosporin and prednisolone on left ventricular function and mortality in this patient group. This trial showed that features consistent with a stronger immune response were associated with less severe initial disease, supporting the view that in patients with myocarditis a prominent immunological response may be beneficial rather than detrimental. However, there are caveats to these conclusions, as the trial did not involve early immunosuppression, and the agents used may not necessarily have been targeted at the appropriate point in the immune response.

Investigation of patients with acute myocarditis

BLOOD TESTS

All patients with suspected myocarditis should have blood taken for erythrocyte sedimentation rate and C reactive protein determination (raised in 60%), and white blood cell count (raised in 25%). Raised titres of antibodies to enterovirus may be present but simply denote infection at some time. A fourfold rise in IgG titre over a four week period is necessary to establish acute infection. Where there is significant risk, an HIV test should be carried out. Involvement of a microbiologist or virologist is advisable. In 12% of patients there can be a rise in creatine kinase which may provide further support for an incorrect diagnosis of acute myocardial infarction.

ELECTROCARDIOGRAPHY

Electrocardiographic abnormalities are common in acute myocarditis (box 3). Diffuse T wave abnormalities are a frequent feature on the 12 lead ECG,[51] while 20% of patients develop left bundle branch block.[52] Complete heart block is also common but is usually transient and rarely requires the implantation of a permanent pacemaker. Supraventricular arrhythmias are common in patients with myo-

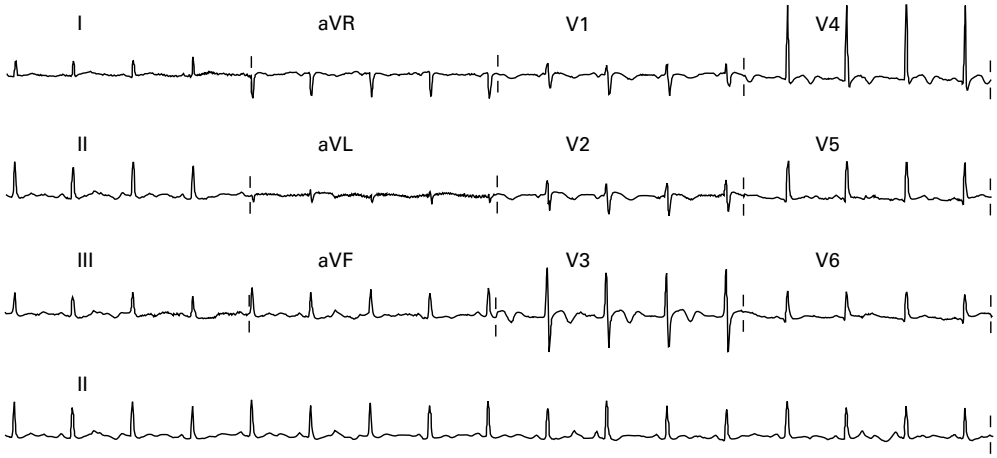

Figure 1 ECG of patient admitted after sudden cardiac arrest: note T wave abnormalities in chest leads. Subsequent biopsy showed healing myocarditis.

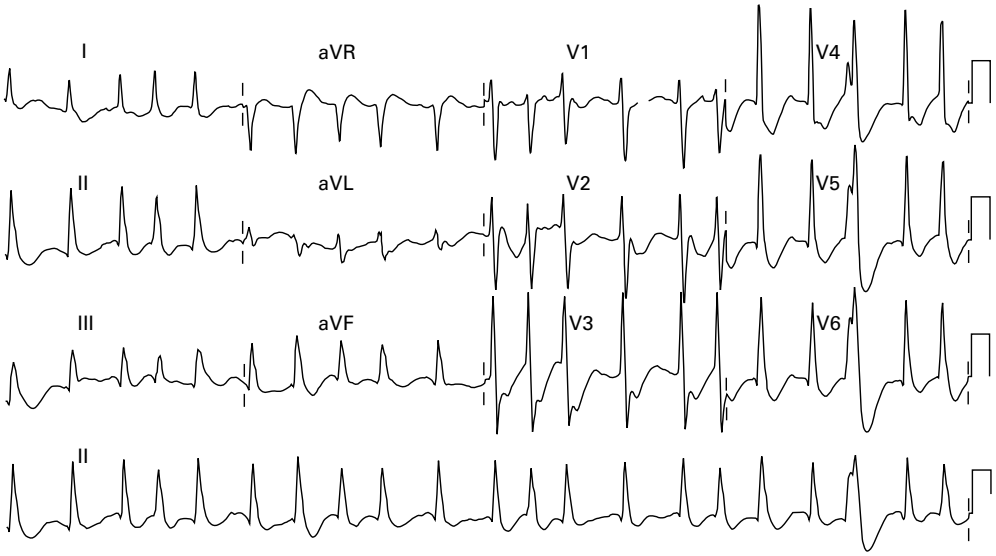

Figure 2 ECG from the same patient as in fig 1, showing irregular broad complex tachycardia.

carditis, and ventricular arrhythmias are not infrequent[53] (see the illustrative case report, box 4).

ECHOCARDIOGRAPHY

Echocardiography may be helpful but is not diagnostic. Left ventricular systolic dysfunction is often seen in patients with acute myocarditis and may be segmental, reflecting the frequently focal nature of the myocarditic process.[54] It can mimic the pattern seen in regional ischaemic damage. Left ventricular dimensions are not usually increased in the acute phase of myocarditis. As discussed above, left ventricular thrombi are often seen. A characteristic trabeculated pattern of ventricular wall thickening may sometimes be found early in the disease process if inflammation is substantial, though this is uncommon.[55]

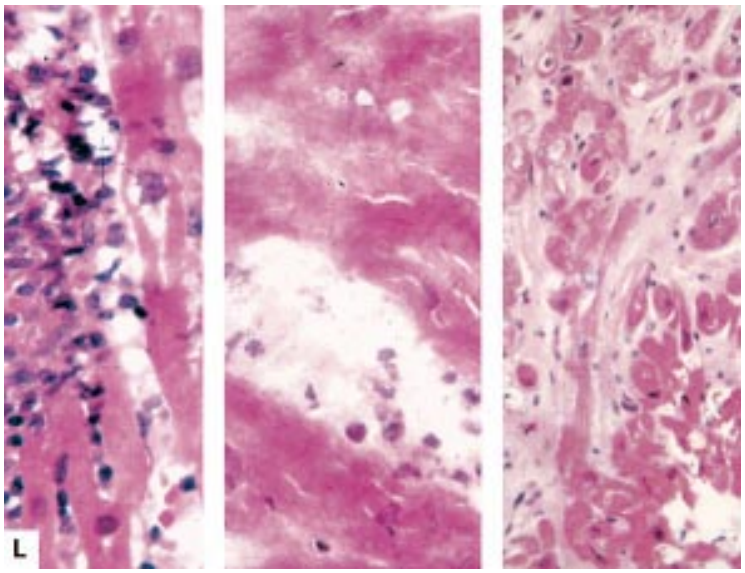

Figure 3 Serial biopsy samples taken from the patient in figs 1 and 2, showing from left to right: acute myocarditis, healing myocarditis, dilated cardiomyopathy. All sections have the same magnification with haematoxylin and eosin stain. Reproduced with permission of E G J Olsen.

CARDIAC BIOPSY

While first described almost 200 years ago, the diagnosis of myocarditis could not be unequivocally established antemortem until the introduction of the endomyocardial biopsy technique, which was pioneered in the United Kingdom by Richardson at King's College Hospital (London) in the early 1970s.[56] According to the Dallas criteria,[57] biopsy evidence of active myocarditis shows: "*an inflammatory infiltrate of the myocardium with or without degeneration of adjacent myocytes not typical of the ischaemic damage associated with coronary artery disease*." In survivors of acute viral myocarditis the histological features can heal or progress to those of idiopathic dilated cardiomyopathy (fig 3). When carried out in experienced hands both left and right ventricular biopsy techniques are safe. While biopsy data do not necessarily alter management they can establish a clear diagnosis and thus provide detailed prognostic information.

Management of patients with myocarditis

There is no evidence currently to support the routine use of immunosuppressive agents in acute myocarditis.[18] In humans there are data supporting a potential role for the administration of immune globulin to patients with new onset dilated cardiomyopathy secondary to myocarditis.[19] Preliminary data from a small series of patients showed an improvement in ejection fraction from 25% to 41%, and an improvement in function from New York Heart Association class II/IV to I/II. These data are preliminary and a double blinded outcome trial is awaited. Current management of patients with myocarditis and any ensuing left ventricular dysfunction should follow conventional lines.

Patients presenting with acute heart failure secondary to myocarditis should be treated in the same way as one would treat patients presenting with heart failure secondary to

Box 5: Treatment of patients with myocarditis

- There is no evidence for routine use of immunosuppressants
- Immune globulin may be useful
- Treatment of heart failure should follow conventional lines
- Loop diuretics where necessary
- Angiotensin converting enzyme inhibition
- β Adrenoceptor adrenoceptor blockade
- Spironolactone

ischaemic heart disease or other myocardial insults.

In a setting where close haemodynamic monitoring is available, pulmonary oedema should be treated with intravenous loop diuretics, nitrates, and diamorphine. An aggressive approach to the management of cardiogenic shock should be adopted, as functional recovery may occur despite substantial abnormalities of left ventricular function. Thus intravenous inotropes and mechanical ventricular support (for example, an intra-aortic balloon pump) should be used if necessary to allow adequate time for myocardial recovery. Tachyarrhythmias should also be managed in the conventional fashion, exercising caution when using antiarrhythmic agents with negative inotropic properties.

Once the patient is stabilised, and if there is residual left ventricular systolic dysfunction, appropriate conventional treatment should be given. The use of ACE inhibitors unequivocally improves prognosis in patients with heart failure from all causes.[1 58–60] There are also now persuasive data from large trials showing that β adrenoceptor blockers[61 62] and spironolactone[63] improve outcome in heart failure when added to ACE inhibitors. These trials evaluated heart failure from ischaemic and non-ischaemic cardiomyopathies. For instance, the MERIT-HF trial (a large trial of the β adrenoceptor blocker metoprolol) included 1385 patients with non-ischaemic dilated cardiomyopathy (35% of the 3991 patients recruited). Similarly in the RALES study, a trial of spironolactone in severe heart failure, 46% of the 1663 patients studied had non-ischaemic dilated cardiomyopathy.

Because of the potential for gradual recovery of left ventricular function after virus induced dilated cardiomyopathy, it may be possible to reduce or even discontinue these agents if there is clinical and echocardiographic evidence of complete recovery.

The treatment of myocarditis is summarised in box 5.

Conclusions

Cardiac involvement in viral illnesses is common and may often go unnoticed. It can, however, have substantial acute haemodynamic and clinical sequelae and may lead to dilated cardiomyopathy and heart failure. Recent studies have identified key roles for the persistence and replication of viral protein within the myocardium, and for immune mediated cardiac damage in the occasionally progressive nature of the disease. The possible role of inducible nitric oxide synthase remains to be clarified. These pathophysiological studies may ultimately provide new starting points for treatment of this occasionally fatal disease. In the meantime, an aggressive approach to acute decompensation during acute myocarditis, and the use of ACE inhibitors, β adrenoceptor blockers, and spironolactone for the treatment of chronic dilated cardiomyopathy, form the optimal treatments.

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