Review

Myocarditis and dilated cardiomyopathy: An inflammatory link

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Received 10 February 2003; received in revised form 28 April 2003; accepted 9 May 2003

Abstract

Myocarditis is a complex disease because multiple pathogenetic mechanisms play a role. While these mechanisms appear to act in a chronological cascade, they undoubtedly overlap in some cases, rendering diagnosis and treatment difficult. Ultimately, dilated cardiomyopathy (DCM) may result. A multitude of still-circumstantial evidence points to a major role of viral myocarditis in the etiology of DCM. The common presence of viral genetic material and viral proteins in the myocardium of patients with DCM provides the most compelling evidence, but proof of causality is still lacking. Nevertheless, because of the striking increase in heart failure prevalence in recent years, anti-viral and anti-inflammatory therapies should be developed for their potential to prevent or ameliorate DCM.

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Keywords: Myocarditis; Dilated cardiomyopathy; Autoimmunity; Heart failure; Immunosuppression

1. Introduction

Myocarditis is, by definition, an inflammatory disorder, while dilated cardiomyopathy (DCM) is, in most cases, idiopathic. However, accumulating data has revealed an important inflammatory component in the pathogenesis of DCM, and there is growing evidence that myocarditis and DCM are closely related. The purpose of this review is to demonstrate the interrelationship between the two. This topic was authoritatively reviewed in 1999 by Kawai [1]. By examining the pathogenesis of myocarditis we will consider mechanisms by which viral myocarditis might cause dilated cardiomyopathy. We will then review the basic and clinical evidence supporting the claim that myocarditis is a common precursor of DCM.

2. Myocarditis: a triphasic disease

It is helpful to recognize myocarditis as a progressive disease with three distinct, chronologically successive stages (Fig. 1). Murine models of myocarditis form the basis for this construct. In the first phase in humans an initial insult to the myocardium occurs. This is believed, but certainly not proven, to be a viral infection in the great majority of cases, and other forms of injury may also trigger the triphasic cascade. In most patients overt congestive heart failure does not occur during phase 1, and the initial insult may go unnoticed. After resolution of the initial injury, the second phase develops as a result of autoimmunity triggered by that injury. Clinically overt congestive heart failure often develops in this phase as a result of extensive additional myocardial injury. In the third phase a typical picture of DCM develops and may progress despite cessation of the first two processes.

![Triphasic Disease Process](image)

**Time for primary review 21 days.**
With these three distinct processes in mind, it is easier to consider diagnostic and therapeutic strategies. Clearly, these will differ for each stage of disease. In the initial phase, evidence of active viral infection will be the most useful finding. A history of recent chemical and toxin exposure may lead to a diagnosis. Therapy in this stage requires removal of the responsible agent. In the case of viral infection, antiviral therapies and support of the immune system may be helpful, though evidence from clinical trial is unavailable. Though there are relatively few relevant therapeutic options today, future possibilities are discussed below (see Section 5).

The second phase of myocarditis has been targeted in most therapy trials to date [2–4]. These studies assumed dominance of autoimmunity as the etiology of ventricular dysfunction. Endomyocardial biopsy showing lymphocytic infiltration and other histological indicators of immune activation were used for diagnosis. None of the studies demonstrated a sustained benefit of immunosuppressive therapy. However, as discussed later, these studies did not use newer diagnostic techniques that might have allowed therapy tailored to the disease state and specific etiology.

In phase 3, after both the infectious and the autoimmune processes have abated, the disease takes on the characteristics of idiopathic dilated cardiomyopathy. Diagnosis is made with the usual imaging methods and therapy is directed at prevention and reversal of adverse remodeling.

In animal models, and surely in humans, separation between the three phases is not always distinct. They may overlap one another chronologically, and phases 1 or 2 may recur after the triphasic cascade has progressed, resulting in multiple cycles of disease occurring simultaneously. Thus, the triphasic model is too simple in some cases to provide appropriate clinical guidance. It is very likely that the immunosuppression trials of the past [2–4] included patients in all three phases of myocarditis, which could explain the failure of therapy to provide a detectable benefit.

While this triphasic model is intended to describe viral myocarditis, at least one other infectious agent, Trypanosoma cruzi, the protozoan responsible for Chagas’ disease, induces an autoimmune phase of disease after the initial injury which later leads to dilated cardiomyopathy [5–7]. This three-stage process may be generalizable to other cardiac infections [8], but little work has been done to substantiate this possibility for bacterial, fungal and other infections.

### 3. Multiple mechanisms of viral and immune injury

There is a stunning array of mechanisms by which cardiotropic viruses can cause congestive heart failure. These are listed in Table 1. Myocytolysis by replicating virus in the absence of a specific immune response is well-documented [9] in animal models. This phenomenon may play a role in fulminant myocarditis in humans, and an effective immune response, without subsequent autoimmunity and viral persistence, may account for the high recovery rate [10]. During phase 1 the immune response is a necessary path to recovery. This was demonstrated in the US myocarditis treatment trial [4] in which markers of an effective immune response, such as anti-cardiac IgG, correlated with a better outcome (Fig. 2). However, the immune response during phase 1 may add to the severity of virus-induced injury by destroying or disabling virus-

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![Fig. 2. Cardiac IgG. In the US myocarditis treatment trial patients with high levels of circulating cardiac-specific IgG had better survival than those with low levels, independent of treatment assignment [4]. This observation is consistent with a beneficial effect of an early, vigorous humoral immune response in myocarditis. Adapted with permission from the Journal of Cardiac Failure.](https://academic.oup.com/cardiovascres/article-abstract/60/1/5/322628)
myocytes, Binah recently reviewed the basic mechanisms by which cytotoxic T lymphocytes (CD4+ and CD8+) may injure myocytes through the normal immune response [11]. It appears that lymphocyte-derived perforins and serine esterases may be responsible for initiating apoptosis leading to death of targeted cells. In addition, the Fas ligand/Fas receptor pathway may bring T-lymphocytes and myocytes together and cause ion channel disturbances as well as apoptosis. Cytokines also contribute both to recovery [12] from infection and to worsened cellular injury [13,14] during phase 1, as well as later phases. Increased levels of cytokines have been found in humans with myocarditis and diluted cardiomyopathy [15]. In a murine myocarditis model in which marked activation of tumor necrosis factor-alpha is present, administration of antibody directed at the cytokine reduced the severity of disease [14].

When T-cell and associated cytokine mechanisms fail to inactivate, myocarditis extends into phase 2. This extension may result, in part, from molecular mimicry [16] or from virally-induced killer T cell activation [17].

As noted above, humoral immune responses during phase 1 may improve outcome, but these responses may be harmful during phase 2. Cross reacting antibodies alone may induce autoimmune myocarditis in animals [18]. Numerous cardiac autoantibodies have been detected in patients [19], including antibodies to heart muscle components, such as anti-sarcolemmal antibody and anti-myosin alpha and beta heavy chains, antibodies against mitochondrial proteins, such as the adenine nucleotide translocator and, antibodies directed at membrane receptors such as the beta-1 receptor. Furthermore, the presence of organ-specific cardiac antibodies in symptom-free relatives of patients with dilated cardiomyopathy is predictive of progression [19].

The importance of latent or persistent virus in pathogenesis of heart failure in phases 2 and 3 is uncertain, but probably considerable. Latent viruses may induce chronic, direct immune and autoimmune injury by low-level or intermittent replication. As demonstrated by Lenzo et al. [20], persistent cytomegalovirus in murine hearts can, indeed, induce chronic inflammation. In a fascinating study, Wessely et al. [21] demonstrated that the mere presence of the Coxsackievirus B3 genome within myocytes, in the absence of both replication and immune activation, can cause atrial and ventricular dilatation and failure.

By virtue of the injury induced in earlier phases, viruses may also worsen heart failure by prompting adverse remodeling in phase 3. It is not clear if the remodeling process itself is different when viral infection is the initiating event, but the study of Wessely et al. suggests that it might be and that the possibility should be further explored.

4. Inflammation and infection in dilated cardiomyopathy

Investigators have speculated for decades on the possibility that myocarditis is a common forerunner of ‘idiopathic’ dilated cardiomyopathy. Table 2 lists several lines of evidence supporting this speculation. Perhaps the first evidence favoring this possibility was presented by Orinius [22], who found cardiac disease in humans many years after apparently uncomplicated Coxsackievirus infection. With the use of endomyocardial biopsy to prove the presence of virus-associated myocardial inflammation prior to therapy [23], it became apparent that at least some patients who ultimately developed typical dilated cardiomyopathy did so as a result of myocarditis. Considerable support for the hypothesis that myocarditis can lead to dilated cardiomyopathy is provided by the many murine models of viral and other forms of myocarditis that unequivocally progress to cardiac dilatation. However, experimental and clinical studies focused on myocarditis cannot inform us of the proportion of cases of DCM that result from a preceding inflammatory insult in humans.

Bowles et al., using a slot-blot hybridization technique on human endomyocardial biopsy tissue, provided the first convincing evidence for viral presence in DCM [24]. They found viral signals in 50% of cases. More recent studies, employing PCR and more specific probes, have reported rates around 35% [25–33]. It is important to recognize that these data may underestimate the actual frequency of viral material in diseased cardiac tissue. All biopsy techniques, including endomyocardial biopsy, are subject to sampling error. In addition, the viral probes used in these studies do

| Table 2 |
| Indirect evidence for a viral etiology of DCM |

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<th>Late development of cardiac abnormalities after Coxsackievirus infection</th>
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not cover all potential viral pathogens. For example, no early studies included primers for hepatitis C virus, which is now known to be present in relatively high frequency [34]. In addition, the literature makes it clear that there is large regional variability in prevalence of known viral pathogens [28,35]. Knowledge of regional and chronological variations in viral prevalence should be incorporated into the selection of PCR probes.

Despite this wealth of PCR and other evidence for viral involvement, as pointed out by Weiss et al. early on [26], presence of viral genomic material does not prove pathogenesis. Weiss et al. showed that enteroviral RNA is also present in a variety of other cardiac disorders and in normal hearts. Many studies have used patients without cardiac disease as controls. The presence of cardiac muscle disease may increase the likelihood of viral presence. For example, Andreoletti et al. [29] found viral genomic material in endomyocardial biopsies of 36% of patients with DCM and 33% of patients with coronary artery disease as controls. The presence of cardiac muscle disease may increase the likelihood of viral presence. For example, Andreoletti et al. [29] found viral genomic material in endomyocardial biopsies of 36% of patients with DCM and 33% of patients with coronary artery disease, but in none of their 45 healthy heart controls. These findings reemphasize the fact that presence of viral nucleotides in the heart does not establish an etiologic link.

As noted above, there are multiple mechanisms by which persisting virus might induce DCM. Recent studies have shed light on the incidence of active infection as compared to latency. Andreoletti et al. found antigenomic RNA in only three of 46 patients with PCR-positivity, suggesting that the incidence of active infection is low. However, only about half of their population had DCM, while the others had chronic coronary disease. Fujioka et al. [30], on the other hand, reported the presence of negative RNA strands in seven of nine patients with PCR positivity from a group of 26 with DCM.

Deguchi et al. [36] made an interesting recent observation on the physical location of entroviral RNA in patients with DCM. They studied myocardial tissue from 26 patients who underwent partial left ventriculectomy for treatment of heart failure. In patients with positive PCR signals, both positive and negative RNA strands were found within myocardial lesions, localized to degenerating myocytes, inflammatory cells and endothelial cells by in situ hybridization. This provides evidence for active viral infection in some patients with end-stage dilated cardiomyopathy.

A point favoring causal involvement of virus in DCM is the observation by several groups that viral presence confers a poor prognosis [30,36,37]. An alternate interpretation is that viruses gain access more readily to more severely diseased myocardium.

In aggregate, these PCR data must be interpreted with caution because a pathogenetic role of latent or replicating virus in chronic dilated cardiomyopathy is not assured simply by their presence in cardiac tissue. However, data derived from recent therapy trials support the likelihood that viruses play a critical causative role. Two recent studies have demonstrated that removal of immunoglobulins from the plasma of patients with DCM improves ventricular function [38,39]. These studies strongly implicate a causal role of persistent autoimmunity in DCM.

While the possible importance of humoral mechanism is raised by these therapy trials, in and of themselves, they do not directly implicate viruses in DCM. Recent studies help create a potential link between virus and DCM through circulating autoantibodies. Cardiac specific myosin antibodies are present in a large proportion of patients with DCM [40–45]. Several investigators have shown recently that viral infections induce antibodies that cross-react with viral and myosin epitopes [46–48]. Thus, molecular mimicry resulting from viral infection could account for the presence of antimyosin antibodies, which, in turn, are capable of inducing autoimmune myocarditis resulting in dilated cardiomyopathy.

5. Current and future inflammation-based therapy

Heart failure prevalence is increasing in the United States [49,50] and other countries. Idiopathic DCM accounts for a large portion of the cases. The growing evidence for a major role of viral and other inflammatory mechanisms in DCM should prompt new efforts to control those mechanisms, even before all the proof is in. An appealing possibility to consider is widespread childhood vaccination against the most common cardiotropic viruses [51,52]. Strong proof of a link between viral infection and DCM, accounting for the majority of cases, will be needed before a vaccination program could be undertaken because of its great expense and the need for societal and governmental support. Other novel strategies must be pursued in the meantime.

The existence of a common receptor for enteroviruses and adenoviruses [53–55] provides another opportunity for preventive therapy. If the interaction between viruses and their cellular receptor could be prevented, or if the intracellular signaling consequent to that interaction could be altered, infection might not occur. Tyrosine kinase $ps6^{54}$ may be a convenient point of attack with a pharmaceutical agent [56].

New therapies should also be directed at ameliorating disease after the viral pathogen has established itself. In the case of CMV infection, gancyclovir is a proven therapy [57] which is now being evaluated in a prospective trial [58]. Certainly, plasmapheresis strategies should be further documented. Use of hyperimmune globulin [59,60] and of immunosuppressive therapies [61] in patients with proven immune activation should be further evaluated. Anticytokines [12,14,62], T-cell receptor vaccines [63] and myosin-induced tolerance [64] are in the preclinical stage of assessment, and offer promise.

Because of the overlap of pathophysiological stages in myocarditis, design of appropriate therapy is challenging. The appropriate therapy for one stage (e.g. immuno-
suppression in phase 2) may be harmful in another stage (e.g. during active infection in stage 1). Measurement of cardiac gene expression using cDNA array technology offers some hope that the dominant mechanism in a given patient can be discerned and treated [65].

References


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