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Clinical Perspective

Postviral autoimmune heart disease — fact or fiction?

Introduction

In 1995, the World Health Organization/International Society and Federation of Cardiology Task Force on cardiomyopathies classified cardiomyopathies, whenever possible, by aetiological/pathogenetic factors[1]. The term 'specific cardiomyopathies' now applies to the conditions previously defined as specific heart muscle diseases. Among these, inflammatory cardiomyopathy, e.g. myocarditis in association with cardiac dysfunction, divided into idiopathic, autoimmune or infectious forms, is considered to be involved in the pathogenesis of dilated cardiomyopathy. Although it is stated that myocarditis is diagnosed by established histological, immunological and immunohistochemical criteria[1], with the exception of the Dallas criteria, the remaining 'immunological and immunohistochemical criteria' remain to be specified, possibly by future Task Forces.

According to the new classification, chronic viral, post-infectious autoimmune and primary autoimmune forms of dilated cardiomyopathy are recognizable. Since the same applies to the entity named 'inflammatory cardiomyopathy', which is said to be involved in the pathogenesis of dilated cardiomyopathy, it may be redundant to have two labels for the same disorder. The classification gives credit to both the 'autoimmune'[2], the 'viral persistence'[3] and the unifying 'virus-immune' hypotheses (Figs 1–3), according to which dilated cardiomyopathy could result from an autoimmune process caused by viral myocarditis[4]. There is undoubtedly a subset of patients in whom acute myocarditis is caused by viruses and other infectious agents[5–7], but do we have conclusive proof of viral aetiology and of postviral autoimmunity in dilated cardiomyopathy? We will summarize the available data, the majority being on enteroviruses.

Indirect evidence of viral aetiology in dilated cardiomyopathy

The indirect evidence implicating enteroviruses as causative agents in dilated cardiomyopathy relies largely on the following: (1) experimental models of viral-induced myocarditis progressing to a chronic stage which resembles human dilated cardiomyopathy[5]; (2) apparent progression to chronic heart failure in some patients with clinical diagnosis of myocarditis[5]; (3) increased enteroviral antibody titres, especially to members of the Coxsackievirus group B (types 1 to 6) serotypes in patients with dilated cardiomyopathy[8].

The following limitation should be taken into account: (1) that the relevance of the experimental models in human disease in uncertain; (2) although clinical and aetiological diagnoses of myocarditis are both difficult, the vast majority of patients with dilated cardiomyopathy do not have previously documented episodes of possible viral myocarditis; (3) the interpretation of the enteroviral serology data is problematic. In particular, infection with any enteroviral serotype commonly induces both IgM and IgG antibody production against many additional enteroviral serotypes (multitypic response)[8,9]. Such antibodies often persist for long periods even in the absence of active infection, and their presence does not necessarily indicate recent infection. In addition, enteroviruses are common environmental agents and are transmitted by close contact. Thus, it is clearly important that control subjects in studies on viral serology share the patient's environment (the household and/or the local community) and that sera from patients and controls are taken over the same time period. The majority of previous workers did not use such controls[8,9]. A recent study failed to document an increased frequency of positive enteroviral serology in dilated cardiomyopathy compared to environmentally matched controls studied over the same time period[10].

Direct evidence of viral aetiology in dilated cardiomyopathy

A definitive proof of viral aetiology in dilated cardiomyopathy according to Koch's postulates would require the isolation of infectious virus from heart tissue, but this has been achieved in only a few cases of acute fulminant myocarditis in infants/neonates[5,6]. Given these limitations and the

Correspondence: Alida L. P. Caforio, MD, PhD, FESC, Department of Clinical and Experimental Medicine, Division of Cardiology, University of Padova, Policlinico Universitario, via Giustiniani, 2, 35128 Padova, Italy.

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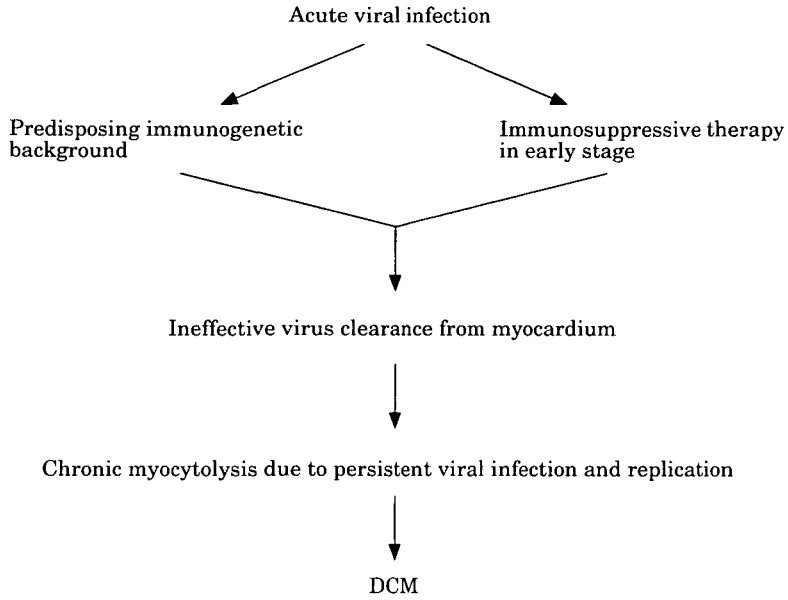

Figure 1 **Schematic sequence of pathogenetic events in dilated cardiomyopathy (DCM) according to the viral hypothesis. Following acute myocarditis, due to genetic predisposition or inappropriate immunosuppression given at an early stage, some patients would develop chronic myocytolysis due to persistent viral infection and replication within the cells, leading to dilated cardiomyopathy.**

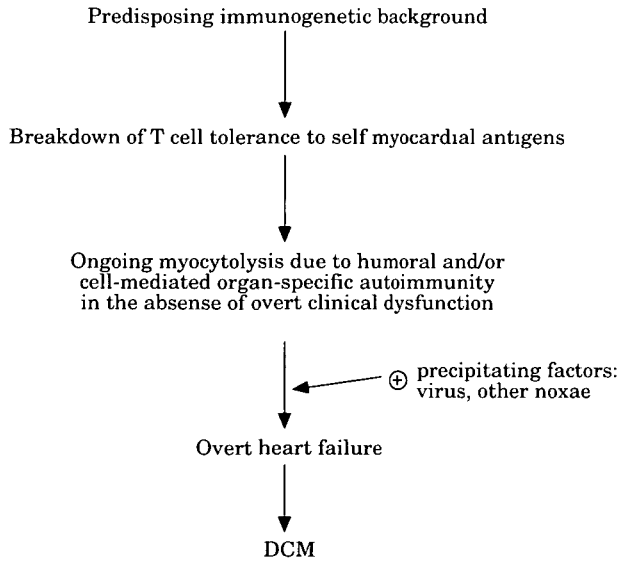

Figure 2 **Schematic sequence of pathogenetic events in dilated cardiomyopathy (DCM) according to the autoimmune hypothesis. Myocarditis and dilated cardiomyopathy would represent the acute and chronic phases of an organ-specific autoimmune disease of the heart, in subjects with a predisposing immunogenetic background. There would be a long pre-clinical stage of ongoing myocardial tissue damage probably mediated by T cells, resulting in detectable immune activation in situ (e.g. presence of activated inflammatory cells, HLA and adhesion molecules, in the myocardium) and in the periphery (circulating cardiac autoantibodies, elevated cytokine levels). Viral infections may or may not have a role in precipitating the onset of heart failure symptoms.**

developments in molecular biology, enteroviral genome hybridization techniques have been applied to further elucidate the role of these viruses in the aetiology of dilated cardiomyopathy. In an initial study[11], it was reported that Coxsackie virus-specific sequences were detected in about 40% of human hearts with histologically proven active or healing myocarditis or cardiomyopathy. A slot blot hybridization assay was used. This technique has relatively low specificity and hybridization artifacts are a concern[9]. This led subsequent workers to use the more sensitive and specific polymerase chain reaction; unfortunately, this approach raised more questions than answers. Enteroviral genomic sequences were detected in the myocardium of 8 to 70% of patients with active myocarditis, 0 to 45% of those with dilated cardiomyopathy and in 0 to 70% of controls with other cardiac conditions; average frequencies, derived from all published studies, are of 25% in myocarditis and 15% in dilated cardiomyopathy, not significantly different from the frequency of 15% among controls[4]. Using an in-situ hybridization, which is technically more difficult than polymerase chain reaction, some reported a higher frequency of enteroviral material in myocarditis (20–30%) and in dilated cardiomyopathy (17–30%) than in controls (0%)[3,4], others obtained similar incidences among the study groups, with a frequency of 13% in controls[12]. Although differences in hybridization

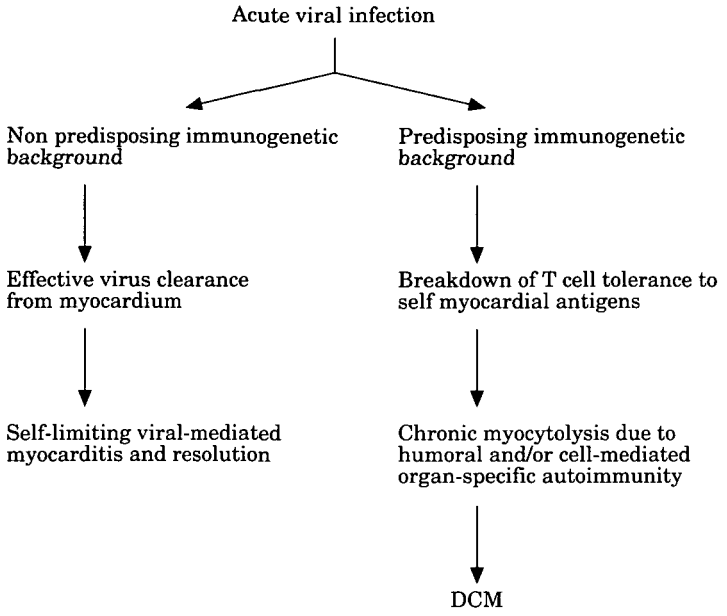

Figure 3 **Schematic sequence of pathogenetic events in dilated cardiomyopathy (DCM) according to the virus-immune hypothesis. Following acute viral myocarditis, subjects who are not genetically predisposed to autoimmunity would develop self-limited disease and recover completely. Conversely, in some susceptible individuals, viral infection would initiate a chronic autoimmune myocarditis leading to dilated cardiomyopathy.**

protocols and experimental procedures among workers could account for some discrepancy among the reported frequencies, overall there is no evidence for an association between enteroviruses and dilated cardiomyopathy in the vast majority of patients. In addition, the presence of viral genome does not imply active infection or pathogenicity; the finding of positive hybridization results in a small proportion of both patients with dilated cardiomyopathy and controls may be a marker for previous infection or relate to a defective non-infectious mutant[4,9]. Such defective particles and whole competent infectious virus would be indistinguishable by in-situ hybridization[9]. Persistence of defective non-pathogenic virus might account for the extreme paucity of reports documenting isolation of infectious enteroviruses from the heart[5,6].

Evidence for post-viral autoimmune heart disease

Data suggesting a post-infectious autoimmune pathogenesis in dilated cardiomyopathy come mainly from studies on experimental Coxsackievirus-B3 induced murine myocarditis[2,5]. Following experimental inoculation with Coxsackie B virus, only certain strains of mice (A-J background) were susceptible to acute myocarditis; the same mouse strains developed a more chronic sequela resembling dilated cardiomyopathy. In this late-phase autoimmune myocarditis, no infectious virus was detectable, by conventional virus culture and isolation methods, in the heart of the affected mice. These mice developed autoantibodies to cardiac myosin[13]. Immunization of A-J normal mice with cardiac myosin alone, without virus, induced histologically and immunologically identical disease[14]. Humoral and cellular transfer experiments in this autoimmune model demonstrated that the myocarditis process was transferable only by T cells[15]. These studies demonstrated that the chronic form of murine myocarditis was a virus-triggered T-cell mediated autoimmune disease in animals with a predisposing genetic background. Since autoimmune myocarditis was produced following stimulation of the immune system with complete Freund's adjuvant and autoantigen (myosin), not only viral infection but other external pro-inflammatory agents could trigger or precipitate autoimmunity in genetically predisposed animals or humans.

It is worth noting, however, that the relevance of experimental models to human autoimmune disease is limited. Although many mechanisms by which viruses could initiate or precipitate an autoimmune process have been hypothesized (Fig. 4), so

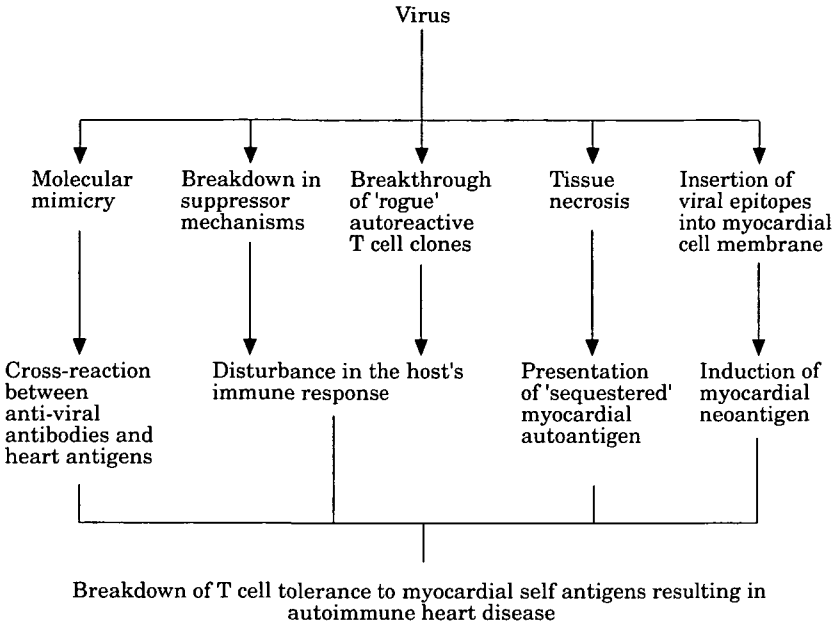

Figure 4 **Hypothetical mechanisms of virus-induced or precipitated autoimmune heart disease. None of these has been proven in patients with other autoimmune conditions.**

far there is no direct evidence of viral aetiopathogenesis in patients with T cell-mediated autoimmune diseases, e.g. multiple sclerosis or Type 1 insulin-dependent diabetes mellitus; conversely, there are data to suggest that infectious agents could have a protective effect[16]. In a cross-sectional study in patients with dilated cardiomyopathy we failed to demonstrate significant associations between positive autoimmune serology, e.g. presence of cardiac autoantibodies, and positive enteroviral serology or polymerase chain reaction results[17].

Future developments

The aetiopathogenetic classification of dilated cardiomyopathy[1] needs both clinical and scientific validation. Although it seems reasonable to postulate that chronic viral and autoimmune myocarditis cause dilated cardiomyopathy in distinct patient subsets, there is no clinical evidence for the occurrence of post-viral autoimmunity in this condition, as in other organ-specific autoimmune diseases. Thus, it is important to define consensus criteria, based upon standard techniques and methodology, to differentiate viral and autoimmune aetiology in the individual patient with myocarditis/dilated cardiomyopathy, and to prove or disprove the occurrence of post-viral autoimmune heart disease[7,9,18,19]. At present, immunological and viral hybridization techniques, protocols, and diagnostic criteria vary even among leading research centres. This results in wide discrepancies in the proportions of patients classified as having viral or autoimmune heart disease and hampers the possibility of designing future multicentre trials in specified subsets (e.g. immunosuppression in the autoimmune cases, anti-viral drugs in chronic viral disease). This is clinically relevant; for example, differential diagnosis of viral vs autoimmune hepatitis is achieved and dictates aetiologically directed treatment with interferon and corticosteroids, respectively; so far, cases of post-viral autoimmune hepatitis have not been documented[20].

Key points

(1) There is no conclusive evidence of an association between enteroviral infection and dilated cardiomyopathy in the vast majority of patients, based upon viral serology and occurrence of viral genome in myocardial tissue by the polymerase chain reaction.

(2) The projected incidence of enteroviral infection among patients with active myocarditis is uncertain, but may be of 20–30%. The role of other viruses has not been thoroughly investigated.

(3) It is unclear whether the detection of enteroviral genomic sequences by molecular hybridization methods is relevant to pathogenesis. It may be a marker of previous infection or relate to a defective non infectious mutant.

(4) There are no prospective data which demonstrate the transition from viral myocarditis to autoimmune dilated cardiomyopathy in patients. This is in keeping with the findings of other organ-specific autoimmune conditions.

A. L. P. CAFORIO*†
C. BABOONIAN†
W. J. MCKENNA†
**University of Padua, Italy*
†St. George's Hospital Medical School
London, U.K.

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