Hepatitis C Virus Infection and Cardiomyopathies

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Cardiomyopathies may present as idiopathic dilated, hypertrophic, or restrictive disease, arrhythmogenic right ventricular cardiomyopathy (ARVC), and various other distinct disorders of the heart muscle. They constitute a heterogeneous group of myocardial diseases of multifactorial etiologies, including genetic anomalies and acquired immune factors, such as viral infections. The myocardium may be infected by a wide variety of viruses, although most commonly by enteroviruses, coxsackievirus B in particular. However, in many cases, when myocarditis has been diagnosed on the basis of clinical manifestations, a viral origin cannot be confirmed, despite extensive laboratory investigations.

The clinical presentation of viral myocarditis is variable. When myocardial necrosis is diffuse, congestive heart failure develops, and growing evidence now links viral myocarditis with dilated cardiomyopathy. Localized myocardial lesions may result in thining or aneurysms of the ventricular wall which, in the case of ARVC, are complicated by arrhythmias. When myocardial necrosis is limited to the subendocardium, restrictive cardiomyopathy may develop. Finally, although it has not been established that hypertrophic cardiomyopathy is a complication of viral myocarditis, asymmetrical septal hypertrophy has been observed in some patients with myocarditis.

A high prevalence of hepatitis C virus (HCV) infection has recently been noted in patients with hypertrophic cardiomyopathy, dilated cardiomyopathy, and myocarditis (Figure 1). In this issue of Circulation Research, Omura et al report that mice transgenic for the HCV-core gene develop ventricular dilatation, cardiac dysfunction, and myocardial fibrosis at 12 months, similar to the pathological manifestations observed in human dilated cardiomyopathy. Although HCV infection may be the cause of several phenotypically different cardiomyopathies, mild inflammation with mononuclear cell infiltration has also been observed with HCV infection in humans. However, no lymphocytic infiltration was observed in these HCV-core transgenic mice. Furthermore, cardiomyocyte hypertrophy and disarray of the myofibers are typical characteristics of human hypertrophic cardiomyopathy, but the wall thickness of the HCV-core mice was not increased. Therefore, although the HCV-core mice did not have all the phenotypical manifestations of human cardiomyopathies, the observations made by Omura et al are nevertheless relevant, because they show that the expression of the HCV-core is associated with the long-term development of myocardial disease. They also found that the expression of atrial and brain natriuretic polypeptides was enhanced, and that activator protein-1 (AP-1) was activated in the heart. However, nuclear factor-κB (NF-κB) was not activated. The authors state that the activation of myocardial AP-1 by HCV-core is an important pathway toward cardiomyopathic changes, although it has not been shown that blocking this pathway changes the disease phenotype. Whereas AP-1 is activated in transgenic mice of HCV core protein, the latter interferes with the activation of AP-1 in human macrophages. Furthermore, HCV core protein inhibits AP-1, and activates extracellular signal-regulated kinase (ERK), C-jun N-terminal kinase (JNK), and p38 mitogen-activated protein (MAP) kinase. Although, HCV core protein is known to activate NF-κB, the authors found no changes in NF-κB. Therefore, further studies will be necessary to clarify the molecular pathogenetic changes observed in HCV-core transgenic mice.

Phenotypes of HCV Cardiomyopathies

In a collaborative research project of the Committees for the Study of Idiopathic Cardiomyopathy in Japan, HCV antibodies were found in 74 of 697 patients (10.6%) with hypertrophic cardiomyopathy and in 42 of 633 patients (6.3%) with dilated cardiomyopathy, significantly more prevalent than the 2.4% observed in age-matched volunteer blood donors in Japan. In an initial study, we evaluated 31 patients with cardiomyopathy and myocarditis and found HCV RNA by polymerase chain reaction in the hearts of 6 patients (19.4%) with dilated cardiomyopathy. Over a 10-year period, we identified 19 among 191 patients with dilated cardiomyopathy (9.9%) who had evidence of HCV infection, in contrast to only 1 of 40 patients with ischemic heart disease (2.5%). No patient with dilated cardiomyopathy and positive HCV antibody had a history of blood transfusion or intravenous drug use, three had a history of hepatitis, mildly elevated serum amino-transferase were present in 10, and nine patients had normal liver function tests. The main clinical manifestations at initial presentation were heart failure and cardiac arrhythmias. Among these patients with HCV antibodies, 10 had HCV RNA in the serum, and six patients had type 1b HCV. HCV RNA was found in the heart of eight patients, and negative strands of HCV RNA were detected in the heart of two patients. Although negative RNA molecules are inter-
During the same period, we identified 16 of 113 patients with hypertrophic cardiomyopathy (14.1%) with evidence of HCV infection. None of these 16 patients had a family history of hypertrophic cardiomyopathy. Seven patients had hematomas, four had received blood transfusions, and 10 patients had mildly elevated serum amino-transferase. Apical hypertrophic cardiomyopathy was diagnosed in nine patients who had ace of spade–shaped deformities of the left ventricle, with an apical/mid anterior free wall thickness ratio >1.3. Histopathological studies showed mild to severe degrees of myocyte hypertrophy in the right or left ventricle, mild to moderate fibrosis, and mild cellular infiltration. Type 1b HCV RNA was detected in the serum of seven patients, HCV RNA in biopsy specimens of six, and negative strands of HCV RNA was detected in the biopsied hearts of two patients. Analysis by fluorescent single-stand conformation polymorphism showed the presence of multiple clones in the sera of patients with hypertrophic cardiomyopathy. Teragaki and coworkers recently found 18 of 80 Japanese patients with hypertrophic cardiomyopathy (22.5%) with positive HCV antibodies, a prevalence significantly higher than in controls, and higher than in our study. In their study, seven patients had type 1b, and five patients had type 2a HCV.

Prolonged Persistence of Hepatitis C Virus Genomes in Paraffin-Embedded Hearts

A multicenter study was conducted by the Scientific Council on Cardiomyopathies of the World Heart Federation (Bernhard Maisch, MD, Chairman) to test the reproducibility of detection of viral genomes, such as enterovirus, adenovirus, cytomegalovirus, and HCV in formalin-fixed tissues. The detection of viral genomes, such as enteroviruses, adenovirus, cytomegalovirus, and HCV in formalin-fixed tissues is less sensitive than in frozen sections of two patients. Analysis by fluorescent single-stand conformation polymorphism showed the presence of multiple clones in the sera of patients with hypertrophic cardiomyopathy. Teragaki and coworkers recently found 18 of 80 Japanese patients with hypertrophic cardiomyopathy (22.5%) with positive HCV antibodies, a prevalence significantly higher than in controls, and higher than in our study. In their study, seven patients had type 1b, and five patients had type 2a HCV.

Genes of the Major Histocompatibility Complex Class II May Influence the Development of Different Phenotypes of HCV Cardiomyopathies

The human major histocompatibility complex (MHC) is located on the short arm of chromosome 6 and encodes for several protein products involved in immune function, including complement, TNF-α, and the human leukocyte antigen (HLA) complex, the polymorphisms of which are often proposed as determinants for the susceptibility to various diseases. Recent studies on HCV hepatitis showed that DQB1*0301 was associated with clearance of the virus. DRB1*1101, which is also in linkage disequilibrium with DQB1*0301, was associated with clearance. Several other studies have examined the association of MHC alleles with diseases. Recent studies on HCV hepatitis showed that DQB1*0301 was associated with clearance of the virus. DRB1*1101, which is also in linkage disequilibrium with DQB1*0301, was associated with clearance. Several other studies have examined the association of MHC alleles with diseases. Recent studies on HCV hepatitis showed that DQB1*0301 was associated with clearance of the virus. DRB1*1101, which is also in linkage disequilibrium with DQB1*0301, was associated with clearance. Several other studies have examined the association of MHC alleles with diseases. Recent studies on HCV hepatitis showed that DQB1*0301 was associated with clearance of the virus. DRB1*1101, which is also in linkage disequilibrium with DQB1*0301, was associated with clearance. Several other studies have examined the association of MHC alleles with diseases. Recent studies on HCV hepatitis showed that DQB1*0301 was associated with clearance of the virus. DRB1*1101, which is also in linkage disequilibrium with DQB1*0301, was associated with clearance. Several other studies have examined the association of MHC alleles with diseases.
patients with hypertrophic cardiomyopathy. In contrast, there was no increase in either allele in patients experiencing dilated cardiomyopathy. HLA-DRB1*1201 was slightly increased in patients with dilated cardiomyopathy, but not in patients with hypertrophic disease (Figure 2).15 MHC class II genes may play a role in the clearance of, and susceptibility to HCV infection, and may influence the development of different phenotypes of cardiomyopathy.

**Treatment of HCV Cardiomyopathies**

In patients with HCV hepatitis, the success of treatment can be measured by the biochemical and virological responses. However, therapeutic markers have not been introduced in clinical practice to follow HCV cardiomyopathies. We have examined the effects of interferon on myocardial injury associated with active HCV hepatitis in collaboration with colleagues from Shimane University.11 We used TL-201-SPECT, because it is more sensitive than electrocardiography or echocardiography to detect myocardial injury induced by HCV. The SPECT scores decreased in 8 of 15 patients (53%) in whom interferon treatment was completed. Circulating HCV disappeared after interferon therapy in all patients who had a decrease or no change in SPECT scores, and HCV genomes persisted in the blood of two patients whose clinical status worsened.11 This preliminary study suggests that interferon is a promising treatment for myocardial injury induced by hepatitis C virus and interferon therapy [Abstract].

We would like to propose a collaborative study of myocarditis/cardiomypathies, based on a global network, to clarify the prevalence of cardiac involvement in HCV infection and to conduct a therapeutic trial.

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**References**


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