

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.¹ 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.^{2,3} Localized myocardial lesions may result in thinning or aneurysms of the ventricular wall which, in the case of ARVC, are complicated by arrhythmias.⁴ 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.⁵

A high prevalence of hepatitis C virus (HCV) infection has recently been noted in patients with hypertrophic cardiomyopathy, dilated cardiomyopathy, and myocarditis (Figure 1).^{6–15} In this issue of *Circulation Research*, Omura et al¹⁶ 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.^{6,7,9} 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 cardio-

myopathy, 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- κ B (NF- κ B) 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,¹⁷ the latter interferes with the activation of AP-1 in human macrophages.¹⁸ Furthermore, HCV core protein inhibits AP-1,¹⁹ and activates extracellular signal-regulated kinase (ERK), C-jun N-terminal kinase (JNK), and p38 mitogen-activated protein (MAP) kinase.²⁰ Although, HCV core protein is known to activate NF- κ B,²¹ the authors found no changes in NF- κ B. 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,²² 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.⁶ 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.²³ Because negative RNA molecules are intermediates in the replication of the HCV genome, we presume that HCV replicates in myocardial tissues.

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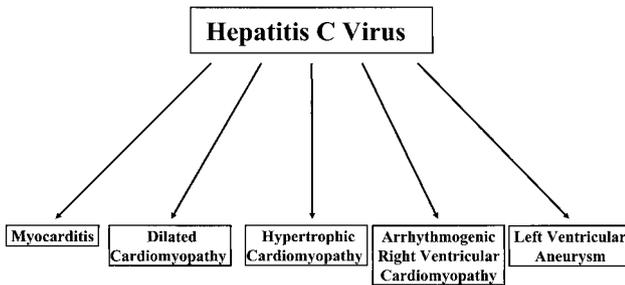


Figure 1. Hepatitis C virus causes various heart diseases.

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 hepatomas, 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 hepatitis C virus RNA in the biopsied hearts of two patients. Analysis by fluorescent single-strand conformation polymorphism showed the presence of multiple clones in the sera of patients with hypertrophic cardiomyopathy.²³ Teragaki and coworkers²⁴ 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 enteroviruses, adenovirus, cytomegalovirus, and HCV in formalin-fixed tissues. The autopsy and biopsy materials were analyzed blindly. We found HCV genomes in 2 of 11 hearts (18%) of patients with dilated cardiomyopathy and myocarditis from Italy, and in 4 of 11 hearts (36%) from the United States, two from patients with myocarditis and two with ARVC,²³ which suggests that HCV may cause ARVC. Because the detection of HCV genomes in formalin-fixed sections is less sensitive than in frozen sections, HCV infection may be a more common cause of myocardial diseases.

In collaboration with the National Cardiovascular Center and Juntendo University, we have detected HCV RNA in paraffin sections of autopsied hearts from six patients with hypertrophic cardiomyopathy (26.0%), three patients with dilated cardiomyopathy (11.5%), and four patients with myocarditis (33.3%). These samples were harvested between 1979 and 1990, confirming that HCV RNA can be amplified from paraffin-embedded

hearts preserved for many years.¹⁴ We also examined autopsied hearts from patients with dilated cardiomyopathy in a collaborative study with the University of Utah and found HCV RNA in 8 of 23 hearts (35%) with positive actin genes. The sequences of HCV genomes recovered from these hearts were highly homologous to the standard strain of HCV.²³ However, the rates of HCV genomes detection in the hearts of patients with cardiomyopathies varied widely among different regions of the world. For example, no HCV genome was detected among 24 hearts obtained from St Paul's Hospital, in Vancouver, Canada. These observations suggest that the frequency of cardiomyopathy caused by HCV infection may be different in different regions or different populations. Some European investigators have even reported negative associations between HCV infection and dilated cardiomyopathy, although these discordant results may be attributable to inappropriate controls, incomplete clinical investigation, or other factors such as regional or racial differences.

We have recently analyzed sera stored during the Myocarditis Treatment Trial²⁵ of immunosuppression in patients with heart failure and myocarditis. Anti-HCV antibodies were identified in 59 of 1355 patients (4.4%), including 6 of 102 patients (5.9%) with biopsy-proven myocarditis, and 53 of 1253 patients (4.2%) whose biopsy specimens did not satisfy the Dallas criteria. Because, according to the US Center for Disease Control, the prevalence of HCV infection in the general US population is 1.8%,²⁶ HCV infection is more prevalent in patients with heart failure because of myocarditis. Furthermore, variations between 0% and 15% were found in the prevalence of HCV infection among the different medical centers and regions.²⁷ Thus, anti-HCV antibodies were recoverable in sera stored for 13 to 17 years and were more prevalent in patients with myocarditis and heart failure than in the general population. In regions where its prevalence is high, HCV infection may be an important cause of myocarditis and heart failure.

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 the progression of liver disease, and DQB1*0401 and DRB1*0405 were more prevalent among patients who developed chronic liver disease. We have recently performed association analyses of alleles distributions, using frequencies of phenotype in patients with hypertrophic or dilated cardiomyopathy. The frequency prevalence of HLA-DQB1*0303 and HLA-DRB1*0901 was most prominently increased in

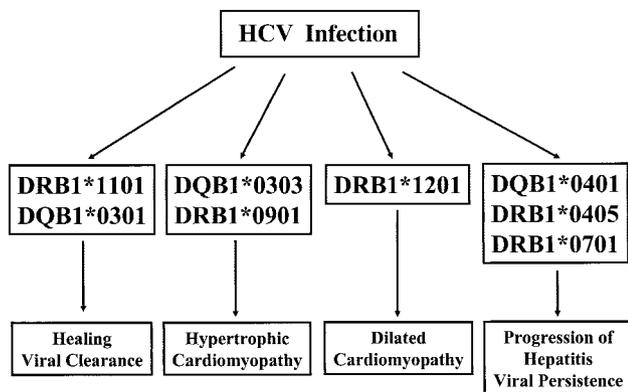


Figure 2. Major histocompatibility complex genes and HCV infection.

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 either 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 diseases caused by HCV. We have also reported the treatment with interferon guided by serial measurements of serum HCV

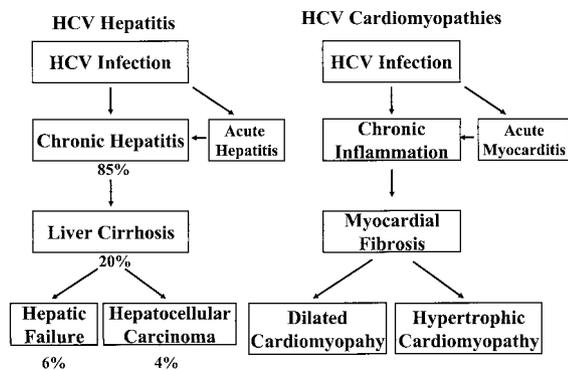


Figure 3. Comparison of the pathogenesis of HCV hepatitis and cardiomyopathies.

RNA and cardiac troponin T in a patient presenting with dilated cardiomyopathy and striated myopathy attributable to HCV infection.¹²

The pathogeneses of HCV hepatitis and cardiomyopathies are compared in Figure 3. In HCV liver disease, most patients develop chronic hepatitis and, years later, liver cirrhosis, hepatic failure, or hepatocellular carcinoma. In HCV heart disease, most patients develop chronic inflammation of the myocardium and, later, dilated cardiomyopathy attributable to necrosis and loss of myocytes. However, because myocytes do not replicate, proliferative stimuli induced by HCV infection may promote myocyte hypertrophy and hypertrophic cardiomyopathy.

We would like to propose a collaborative study of myocarditis/cardiomyopathies, 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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