Hepatitis C Virus and Cardiomyopathy

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Abstract

The importance of hepatitis C virus infection has been recently noted in patients with hypertrophic cardiomyopathy or dilated cardiomyopathy. In a collaborative research project of the Committees for the Study of Idiopathic Cardiomyopathy, hepatitis C virus antibody was found in 74 of 697 patients (10.6%) with hypertrophic cardiomyopathy and in 42 of 663 patients (6.3%) with dilated cardiomyopathy; these prevalences were significantly higher than that found in volunteer blood donors in Japan. Hepatitis C virus antibody was detected in 650 of 11,967 patients (5.4%) seeking care in 5 academic hospitals. Various cardiac abnormalities were found, and arrhythmias were the most frequent. These observations suggest that hepatitis C virus infection is an important cause of a variety of otherwise unexplained heart diseases.

As a collaborative research with National Cardiovascular Center and Juntendo University, we tried to detect hepatitis C virus genomes using paraffin sections of autopsied hearts. Among 106 hearts examined, β-actin gene was amplified in 61 hearts (52.6%). Among these, hepatitis C virus RNA was detected in 13 hearts (21.3%), and negative strands in 4 hearts (6.6%). Hepatitis C virus RNA was found in 6 hearts (26.0%) with hypertrophic cardiomyopathy, 3 hearts (11.5%) with dilated cardiomyopathy, 4 hearts (33.3%) with myocarditis. These hepatitis C virus RNA positive samples were obtained between 1979 and 1990, indicating that hepatitis C virus RNA can be amplified from paraffin-embedded hearts preserved for many years.

More recently, we examined the effect of interferon on myocardial injury associated with active hepatitis C. As TL-201-SPECT was a more sensitive method to detect myocardial injury induced by hepatitis C virus than electrocardiography or echocardiography, we used Tl-SPECT scores to evaluate the effect of interferon on myocardial injury. SPECT scores improved in 8 patients (53%) out of 15 patients in whom interferon therapy was completed. Circulating hepatitis C virus disappeared after interferon therapy in all 11 patients with improvement or no change, but hepatitis C virus genomes persisted in the blood in 2 aggravated patients. Although this study is preliminary, interferon therapy is a promising treatment for myocardial diseases caused by hepatitis C virus infection.

Key Words: Cardiomyopathy · Myocarditis · Virus · Hepatitis C · Interferon · Hypertrophy · Heart failure

Hepatitis-C-Virus und Kardiomyopathie

Zusammenfassung

Der Zusammenhang zwischen einer Hepatitis-C-Virus-Infektion und dem Auftreten einer hypertrophischen und einer dilatativen Kardiomyopathie wurde erst vor kurzem erkannt. In einem gemeinsamen Forschungsprojekt der „Committees for the Study of Idiopathic Cardiomyopathy" wurden Hepatitis-C-Virus-Antikörper bei 74 (10,6%) von 697 Patienten mit hypertrophischer Kardiomyopathie und bei 42 (6,3%) von 663 Patienten mit dilatativer Kardiomyopathie gefunden, wobei diese Prävalenz signifikant höher ist als bei freiwilligen Blutspendern in Japan. Hepatitis-C-Virus-Antikörper wurden bei 650 (5,4%) von 11 967 Patienten, die zur Behandlung in fünf Universitätskliniken waren, gefunden. Verschiedene kardiale Veränderungen wurden beobachtet, wobei Arrhythmien am häufigsten auftraten. Diese Beobachtungen legen nahe, daß eine Hepatitis-C-Virus-Infektion eine wichtige Ursache für eine Reihe bisher ungeklärter Herzerkrankungen ist.

In einem gemeinsamen Forschungsprojekt mit dem „National Cardiovascular Center" und der Juntendo-Universität versuchten wir Hepatitis-C-Virus-Genome in Paraffinschnitten von autoptischen Herzen nachzuweisen. Von 106 untersuchten Herzen wurde das β-Aktin Gen bei 61 Herzen (52,6%) nachgewiesen. Bei diesen Proben wurden die Hepatitis-C-Virus-RNA in 13 Herzen (21,3%) und Negativstränge bei vier Herzen (6,6%) gefunden. Eine Hepatitis-C-Virus-RNA wurde bei sechs Herzen (26,0%) mit hypertrophischer Kardiomyopathie, drei Herzen (11,5%) mit dilatativer Kardiomyopathie und bei vier Herzen (33,3%) mit Myokarditis identifiziert. Diese Hepatitis-C-Virus-RNA-positiven Proben wurden zwischen 1979 und 1990 eingebettet, und daher kann gefolgert werden, dass Hepatitis-C-Virus-RNA noch aus paraffineingebettetem Gewebe, das mehrere Jahre gelagert wurde, amplifiziert werden kann.

Vor kurzem untersuchten wir den Einfluss von Interferon auf eine Myokardschädigung, die mit einer akuten Hepatitis C einhergeht. Da TL-201-SPECT sensitiver war als die Elektrokardiographie oder Echokardiographie, um eine Hepatitis-C-Virus-induzierte Myokardschädigung nachzuweisen, ver-

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wandten wir Tl-SPECT-Scores, um den Einfluss von Interferon auf eine Myokardschädigung zu untersuchen. SPECT-Scores verbesserten sich bei acht (53%) von 15 Patienten nach einer Interferonbehandlung. Zirkulierende Hepatitis-C-Viren verschwanden nach einer Interferontherapie bei allen elf Patienten, die entweder eine Besserung oder keine Zustandsveränderung aufwiesen; bei zwei Patienten mit schwerer Erkrankung waren Hepatitis-C-Virus-Genome im Blut noch nachweisbar. Obwohl diese Studie noch vorläufig ist, erscheint eine Interferontherapie erfolgversprechend bei Myokarderkrankungen, die durch eine Hepatitis-C-Virus-Infektion verursacht werden.

Schlüsselwörter: Kardiomyopathie · Myokarditis · Virus · Hepatitis C · Interferon · Hypertrophie · Herzinsuffizienz

The myocardium may be the target of several types of viral infections. Persistent enterovirus infection of the myocardium has been reported, and the existence of a causative role of enteroviruses in acute myocarditis, particularly in children, finds support in a meta-analysis; on the other hand, some of the studies examining the association of enteroviruses with dilated cardiomyopathy have been negative [1]. Etiologic roles for other viruses, particularly the adenovirus [4] and cytomegalovirus [16] has been also published. Recently, the importance of hepatitis C virus infection in patients with dilated and hypertrophic cardiomyopathy, and myocarditis has been noted [9–15]. We will review our recent findings on the role of hepatitis C virus in the pathogenesis of cardiomyopathy and myocarditis.

Hepatitis C Virus Infection and Dilated Cardiomyopathy

We identified 8 of 53 patients (15.1%) with dilated cardiomyopathy who had evidence of hepatitis C virus infection on the basis of a positive immunoradiometric assay (Table 1), whereas only 1 patient (2.5%) of those with ischemic heart disease was positive for the hepatitis C virus antibody. The difference was statistically significant. None of the patients with hepatitis C virus antibody had known risk factors for hepatitis C virus infection, such as a history of intravenous drug use, previous blood transfusions, acute hepatitis, or abnormal liver function. Mildly elevated levels of serum transaminase were found in 5 patients. The primary findings at presentation were congestive heart failure and cardiac arrhythmias. Of the 8 patients with hepatitis C virus antibodies, 5 patients had hepatitis C virus RNA in the serum, and all 5 patients had Type 1b hepatitis C virus.

Hepatitis C virus RNA was found in the autopsied heart of a patient and in the biopsy specimens of 4 patients. Negative strands of hepatitis C virus RNA were detected in the heart of 3 patients. Because negative RNA molecules are considered to be intermediated in the replication of the hepatitis C virus genome, it was supposed that hepatitis C virus replicates in myocardial tissues.

	Case number							
	1	2	3	4	5	6	7	8
Age	54	22	61	66	61	17	62	49
Sex	F	M	M	F	F	F	F	M
NYHA	III	IV	II	III	III	III	II	III
Onset	CHF	CHF	VT	CHF	CHF	CHF	CHF	CHF
LVEF	25	25	26	24	37	26	35	45
AST (11–27 IU/L)	27	57	21	46	42	17	21	41
ALT (6–27 IU/L)	16	75	28	42	50	8	17	35
Outcome	Died of CHF	Died of CHF	Sudden death	CHF	Improved	CHF	CHF	CHF
HCV RNA in serum	+	+	–	+	+	–	+	ND
Type	1b	1b	–	1b	1b	–	1b	ND
Titer	ND	1×10^3	–	2×10^3	8×10^2	–	1.2×10^3	ND
HCV RNA in the heart								
(+) strand	+	+*/–**	–	+	+	–	+	–
(–) strand	+	–	ND	+	–	–	+	–

Table 1
Clinical profiles of patients with dilated cardiomyopathy with positive anti-hepatitis C virus antibody (CHF = congestive heart failure; VT = ventricular tachycardia; AST = aspartate aminotransferase; ALT = alanine aminotransferase; *biopsy specimen; **autopsy specimen; ND = not done).

Tabelle 1
Klinische Befunde bei Patienten mit dilatativer Kardiomyopathie und nachgewiesenen Hepatitis-C-Antikörpern. (CHF = Herzinsuffizienz; VT = Kammertachykardie; AST = Aspartataminotransferase; ALT = Alaninaminotransferase; *Biopsie; **Autopsie; ND = nicht durchgeführt

Hepatitis C Virus Infection and Hypertrophic Cardiomyopathy

Over a 7-year period, 9 of 65 patients (13.8%) with hypertrophic cardiomyopathy were identified who had evidence of hepatitis C virus infection on the basis of positive hepatitis C virus antibody. In contrast, prevalence of positive hepatitis C virus antibody in voluntary blood donors in Japan was 2.41% in subjects 55 to 59 years of age. The difference was statistically significant ($p < 0.0001$) [14].

Of these 9 patients, 3 were men and 6 were women; their average age was 61.2 years (range 50 to 71 years). Four patients had a history of mild hypertension. None of the patients had a family history of hypertrophic cardiomyopathy. Symptoms consisted of chest pain in 2 patients, exertional shortness of breath in 2 patients, and palpitation in 2 patients (Table 2). Two patients had histories of chronic hepatitis, while the others had no known risk factors for hepatitis C virus infection, such as a history of intravenous drug use or previous blood transfusions. Mildly elevated serum aminotransferase was measured in 6 patients. Two patients had tall R waves in lead V_5 of the surface electrocardiogram, and 2 patients showed giant negative T waves in leads V_4 or V_5. The two-dimensional and M-mode echocardiogram showed mild to moderate thickening of the interventricular septum and of the left ventricular posterior wall. Three patients showed asymmetric septal hypertrophy. The left ventricular end-diastolic pressure was increased in 5 patients. A pressure gradient within the left ventricle was measured in none. Six patients had ace of spade-shaped deformities of the left ventricle with a ratio of apical thickness to middle anterior free wall thickness > 1.3. None had angiographically visible coronary artery disease.

Histopathological studies showed mild to severe degrees of myocyte hypertrophy in the right or left ventricle, and mild to moderate fibrosis. Mild cellular infiltration was seen in 5 patients. Type 1b hepatitis C virus RNA was detected in the serum of 5 patients. Quantitative analysis of hepatitis C virus RNA by competitive nested polymerase chain reaction showed that the copy number in the serum was 5.5×10^3 to 8.6×10^6 genomes/ml. Hepatitis C virus RNA was found in the biopsy specimens of 5 patients. Biopsy specimens were analyzed for hepatitis C virus genomes in 3 of the 6 patients with apical hypertrophy, and were found positive for hepatitis C virus RNA in all 3. Analysis by fluorescent single-strand conformation polymorphism showed the presence of multiple clones in the sera of 4 patients with hypertrophic cardiomyopathy. Negative strands of hepatitis C virus RNA were found in the hearts of 2 patients.

Hepatitis C Virus Infection and Heart Diseases: A Multicenter Study in Japan

As a collaborative research project of the Committees for the Study Idiopathic Cardiomyopathy, under the auspices of the Japanese Ministry of Health and Welfare, a questionnaire was submitted to 19 Japanese medical institutions in 1997, and returned by 11 participants. The questionnaire inquired specifically about the prevalence of antibody against hepatitis C virus in patients with dilated and hypertrophic cardiomyopathy. The prevalence of antibody was also measured

	Case number								
	1	2	3	4	5	6	7	8	9
Age	64	50	56	65	60	64	71	69	52
Sex	M	F	M	F	F	F	F	M	F
Onset	Dyspnea	VT	VT	Dyspnea	SX (–)	AP	Syncope	Af	Dyspnea
AST (11–27 IU/L)	50	19	31	24	27	54	24	31	66
ALT (6–27 IU/L)	50	29	26	18	17	48	18	36	85
HCV RNA in serum	–	+	+	–	–	+	+	+	+
Type	–	1b	1b	–	–	1b	1b	1b	2a
Titer	–	4×10^6	8×10^4	–	–	1.3×10^5	2.4×10^5	8.6×10^5	5.5×10^3
ND									
HCV RNA in the heart									
(+) strand	+	+	ND	ND	ND	+	+	ND	+
(–) strand	–	–	ND	ND	ND	+	–	ND	+

Table 2
Clinical profiles of patients with hypertrophic cardiomyopathy with positive anti-hepatitis C virus antibody (AST = aspartate aminotransferase; ALT = alanine aminotransferase; ND = not done).

Tabelle 2
Klinische Befunde bei Patienten mit hypertrophischer Kardiomyopathie und nachgewiesenen Hepatitis-C-Antikörpern (AST = Aspartat aminotransferase; ALT = Alaninaminotransferase; *Autopsie; ND = nicht durchgeführt

among all patients seeking care in 5 academic hospitals. Clinical diagnosis, electrocardiographic and echocardiographic findings were detailed in patients with positive anti-hepatitis C virus antibody.

The presence of hepatitis C virus antibody was found in 74 of 697 patients (10.6%) with hypertrophic cardiomyopathy (mean age, 57.7 years) and in 42 of 663 patients (6.3%) with dilated cardiomyopathy (mean age, 56.5 years). In contrast, the prevalence of positive hepatitis C virus antibody among volunteer blood donors of 50 to 59 years of age was 2.4% [12]. Hypertrophic and dilated cardiomyopathies were both associated with significantly higher prevalences of positive antibodies than was measured among blood donors. In addition, positive hepatitis C virus antibody was more prevalent in patients with hypertrophic cardiomyopathy than in those with dilated cardiomyopathy.

Positive hepatitis C virus antibody was detected in 650 of 11,967 patients (5.4%) seeking care at 5 university hospitals, a significantly higher prevalence than in volunteer blood donors. Of the cardiac abnormalities observed in these patients with positive hepatitis C virus antibody, arrhythmias were the most frequent (21.5%). Electrocardiographic abnormalities were found in 130 of 349 patients tested (62.8%), most often in the form of arrhythmias or conduction disturbances. Echocardiographic examination suggested that hepatitis C virus infection was associated with left ventricular hypertrophy in over one half of the patients, ventricular dilatation in 40%, and decreased left ventricular systolic function in 34%.

This survey found a high prevalence of hepatitis C virus antibody in patients with hypertrophic and dilated cardiomyopathy, supporting previous results pointing to the importance of hepatitis C virus infection in the pathogenesis of cardiomyopathies. Interestingly, the prevalence of positive anti-hepatitis C virus antibody was higher in hypertrophic than in dilated cardiomyopathy. The study also suggests that several cardiac abnormalities other than cardiomyopathic disorders (e. g., arrhythmias) may result from hepatitis C virus infection, which may be a risk factor for such conditions (hypertension, myocardial infarction, etc.), although further study is necessary to confirm these associations.

Hepatitis C Virus Genomes from Formalin-Fixed Paraffin Sections of the Hearts

A collaborative multicenter study was performed under the chairman of the WHF Council on Cardiomyopathies, Dr. Maisch, to test reproducibility of detection of viral genomes using such as enteroviruses, adenovirus, cytomegalovirus and hepatitis C virus in formalin-fixed tissues. In this study, autopsy and biopsy materials were analyzed blindly. We found hepatitis C virus genomes in 2 out of 11 hearts (18%) with dilated cardiomyopathy and myocarditis from patients of Italy, and 4 out of 11 hearts (36%) from USA. Two hearts were from patients with myocarditis, and other 2 hearts were from patients with arrhythmogenic right ventricular cardiomyopathy or dysplasia (ARVC or ARVD). The results suggest that hepatitis C virus may be a causal agent of arrhythmogenic right ventricular cardiomyopathy as well as myocarditis and cardiomyopathies. As the detection of hepatitis C virus genomes in formalin-fixed sections seems less sensitive than frozen sections, hepatitis C virus infection may be a more frequent cause of myocardial injury than this incidence.

We have recently examined the detection of hepatitis C virus genomes from formalin-fixed paraffin sections of autopsied hearts from patients with myocarditis, and patients with dilated or hypertrophic cardiomyopathy which had been collected over many years in collaboration with Dr. Yutani at National Cardiovascular Center and with Dr. Kawai at Juntendo University. Among 106 hearts examined, β-actin gene as a house-keeping gene was amplified in 61 hearts (57.5%), confirming the feasibility of genomic analysis by PCR of paraffin-embedded tissues stored for many years. Among 61 hearts with a positive β-actin gene, hepatitis C virus RNAs were detected in 13 hearts (21%), and positive strands were found in 11 hearts (18%) and negative strands were seen in 4 patients (7%). Among 12 hearts with myocarditis, positive and negative strands were found in 2 and 2 hearts, respectively, and in total in 4 (33%). In the hearts with dilated cardiomyopathy, positive strands were found in 3 hearts (11.5%), and negative strands in 1 of these 3 hearts. In the hearts with hypertrophic cardiomyopathy, positive strands were detected in 6 hearts (26%), and negative strands in 1of these 6 hearts.

Among 13 patients with positive hepatitis C virus, the oldest sample was obtained in 1979, 7 hearts were autopsied between 1980 and 1989, and 5 hearts were au-

topsied since 1990, confirming that hepatitis C virus RNA can be amplified from paraffin-embedded cardiac specimens preserved for several years.

Pathogenesis of Cardiomyopathy by Hepatitis C Virus

The hepatitis C virus is a single-stranded RNA virus which frequently causes chronic liver disease. Since the cloning and expression of its genome many different hepatitis C virus-sequences have been reported from all over the world. These genomes are classified into 6 genotypes, which show variable degrees of homology in different regions of the genome. The highest homology is found in the 5'-non-coding region, whereas the nucleotide sequence of the N-terminus of the putative envelope protein, the so-called hypervariable region I, is extremely variable. In the blood of a given patient infected with the hepatitis C virus, a population of closely related mutants, termed quasispecies, is observed. Fluorescent single-stranded conformation polymorphism analysis is a new method to detect point mutation in nucleic acids useful to detect the heterogeneity of a viral population in patients with hepatitis C virus infection without having to sequence a large number of hepatitis C virus clones. Host factors such as age, gender, major histocompatibility complex and immunocompetence, as well as viral factors such as virus titer and genotype, have been shown to be important factors influencing the clinical outcome. In addition, the heterogeneity and complexity of the patient's virus population may be a predictor of therapeutic response to interferon. In our study, multiple clones were identified in the sera of our patients. These results suggest that specific clones with high affinity for the heart develop and cause cardiomyopathy.

The most remarkable feature of hepatitis C virus is the risk of persistent infection and progression to chronic disease. Persistent infection occurs in over 50% of patients with hepatitis C virus infection and may lead to chronic active hepatitis, cirrhosis and hepatocellular carcinoma. As adults myocytes may not replicate, the growth stimuli provided by hepatitis C virus infection may cause hypertrophic cardiomyopathy.

The presentation of viral myocarditis is variable. When myocardial necrosis occurs diffusely, congestive heart failure develops under the clinical diagnosis of dilated cardiomyopathy. If myocardial lesions are localized, ventricular aneurysm occurs. When complicated with arrhythmia, myocarditis may present as arrhythmogenic right ventricular dysplasia [8]. When myocardial necrosis is localized at the subendocardial region, restrictive cardiomyopathy may develop. It has not been proven yet that hypertrophic cardiomyopathy may be a sequel of viral myocarditis, but in fact asymmetrical septal hypertrophy is sometimes seen in patients with myocarditis [3]. Thus, hepatitis C virus infection may cause various forms of cardiomyopathy.

The reason why the apical part of the left ventricle develops hypertrophy is unknown. Viral myocarditis has been demonstrated to occur in various forms. When myocardial lesions are localized, ventricular aneurysms occur in animals with picornavirus infection such as coxsackievirus or encephalomyocarditis virus [2, 5–7, 11]. As hepatitis C virus may develop hypertrophy of myocytes, it is possible that apical hypertrophy may develop when hepatitis C virus is localized at the apical part of the left ventricle. The other possibility is that hypertrophy of the ventricle may be different depending on host factors such as the major histocompatibility complex, because it has been shown that the major histocompatibility complex influences the clinical manifestations and outcome of hepatitis C virus hepatitis. Further studies are necessary to clarify the mechanism of localization of hypertrophy caused by hepatitis C virus infection. However, the present study suggests that hepatitis C virus infection is an important cause of the apical and other forms of the disease.

Treatment Trial of Myocardial Injury Induced by Hepatitis C Virus by Interferon

We examined the effect of interferon on myocardial injury associated with active hepatitis C with collaboration with Drs. Oyake and Shimada at Shimane University. As TL-201-SPECT was a more sensitive method to detect myocardial injury induced by hepatitis C virus than electrocardiography or echocardiography, we used Tl-SPECT scores to evaluate the effect of interferon on myocardial injury. SPECT scores improved in 8 patients (53%) out of 15 patients in whom interferon therapy was completed. Circulating hepatitis C virus disappeared after interferon therapy in all 11 patients with improvement or no change, but hepatitis C virus genomes persisted in the blood in 2 aggravated patients. Although this study is preliminary, interferon therapy appears as a promising treatment for myocardial diseases caused by hepatitis C virus infection.

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