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Global alert and response network for hepatitis C virus-derived heart diseases: A call to action

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Summary Hepatitis C virus (HCV) is the cause of many different forms of heart disease worldwide, and yet few cardiologists are aware of it as an etiology of heart disease, or its treatment. The burden of HCV-derived heart diseases is global, with a higher prevalence in Asia, Africa, and low- and middle-income countries. Our study showed that in more than 10% of Japanese patients, their cardiomyopathies are associated with HCV infection. More recently, we found in the USA that up to 15% of patients with heart failure with myocarditis have associated HCV infection. In contrast, in China 79% of patients with hepatocellular cancer and 37% of hepatitis C patients have heart disease, as detected by measuring a proven and sensitive biomarker of heart disease, NT-proBNP. In Pakistan, 17% of hepatitis C patients have heart diseases, as measured by this metric.

Based on these data, 3% of 6.6 billion (198 million) persons worldwide are infected with HCV, and 17—37% (34—73 million) persons are suffering from HCV-derived heart diseases. These figures may be comparable to the number of patients with hepatitis C. HCV infection causes only hepatitis in some patients, only heart diseases in some patients, and both hepatitis and heart diseases in other patients.

A global network is required to establish methods to detect heart diseases caused by infectious agents. Other goals for the network are the expansion of preventive and therapeutic programs in underprivileged countries.

Introduction

Heart failure is rapidly evolving to be a worldwide epidemic. Although most of the adverse outcomes related to cardiovascular diseases have been improving, the only exception is heart failure. As survival for acute cardiac catastrophic events such as myocardial infarction and sudden deaths improves, more patients suffer from heart failure. There are 23 million people with heart failure in the world, 5 million in the United States, and 550

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thousand new cases there in 2003 [1]. In western countries, the prevalence of ischemic heart failure is 24–83% (average 64%, $n = 37,791$) [2] in patients with mild to moderate heart failure who were enrolled in 21 clinical trials. In Japan, ischemic heart failure is less frequent in those with NYHA class II to III, and was the etiology in only 29% of 741 patients who were enrolled in 3 clinical trials [3–5]. In contrast, dilated cardiomyopathy is more frequent at 63%, and is the major cause of heart failure. In patients with severe heart failure who were candidates for heart transplantation, about one-half had ischemic heart failure and one-half had dilated cardiomyopathy in Western countries, while these etiologies were 6% and 80%, respectively, in Japan [6]. Therefore, dilated cardiomyopathy is the major cause of severe heart failure in Japan.

New classification of cardiomyopathies

In 1968, the World Health Organization (WHO) defined cardiomyopathy as a condition with different and frequently unknown etiologies in which the dominant feature is cardiomegaly and cardiac failure; excluded are myocardial dysfunction due to vascular disease, coronary artery disease, and systemic or pulmonary vascular disease. Initially, a useful distinction was made between secondary cardiomyopathies, in which the heart muscle disease was associated with a known single cause, systemic disease or syndrome, and primary cardiomyopathy, in which the heart muscle disease was of unknown etiology. In 1980, the WHO, jointly with the International Society and Federation of Cardiology, chose to limit the term cardiomyopathy to heart muscle disease of unknown etiology. The updated WHO definition in 1995 was ''diseases of myocardium associated with cardiac dysfunction'' and included for the first time newly recognized arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) and primary restrictive cardiomyopathy [7].

In 2006, the AHA expert consensus panel proposed the definition: Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of a generalized systemic disorder, often leading to cardiovascular death or progressive heart failure-related disability. Cardiomyopathies were divided into two major groups based on predominant organ involvement. Primary cardiomyopathies (genetic, nongenetic, acquired) are those solely or predominantly confined to heart muscle and are relatively few in number. Secondary cardiomyopathies show pathological myocardial involvement as part of a large number and variety of generalized systemic (multiorgan) disorders. The panel recommended that cardiomyopathies can be most effectively classified as primary: genetic; mixed (genetic and nongenetic), acquired; and secondary [8].

Recently, the European Society of Cardiology working group on myocardial and pericardial diseases defined a cardiomyopathy as a myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular diseases, and congenital heart disease sufficient to cause the observed myocardial abnormality. Cardiomyopathies were grouped into specific morphological and functional phenotypes; each phenotype was then sub-classified into familial and non-familial forms [9].

About one-half of hypertrophic cardiomyopathy occurs familially, and one-half of those patients are associated with gene mutations. However, many cases of non-familial hypertrophic cardiomyopathy are not associated with gene mutations. Also, some of the cases of dilated cardiomyopathy have the same gene mutations of hypertrophic cardiomyopathy. Although myocarditis is believed to be the major cause of dilated cardiomyopathy, myocarditis is often associated with hypertrophic cardiomyopathy which is caused by a viral infection such as hepatitis C virus [10–13], or by cardiac sarcoidosis as discussed below [14]. Therefore, one etiology is not consistent with one phenotype of cardiomyopathy. Because the therapy should be based on the etiology, we propose a new classification of cardiomyopathies as shown in Table 1. For example, when compared with the WHO classification, dilated cardiomyopathy is classified into infectious, genetic, and so forth for etiology, left or right ventricle for anatomy, and systolic dysfunction for physiology. Hypertrophic cardiomyopathy with obstruction is classified into genetic, infectious etc for etiology, septal hypertrophy for anatomy, and diastolic failure for physiology.

Global burden of cardiomyopathies: incidence and prevalence

There are few epidemiologic data of myocarditis. We conducted nationwide epidemiological surveys

Table 1 A new classification of cardiomyopathies.

I. Etiological classification	A. Genetic B. Infectious C. Nutritional D. Unknown
II. Anatomical (structural) classification	A. Dilated a. LV b. RV B. Hypertrophic a. Septum b. Diffuse c. Free wall d. Apex
III. Physiological (mechanical) classification	A. Systolic failure/dysfunction B. Diastolic failure/dysfunction C. Both D. Normal
IV. Electrical classification	A. Ion channel disorders B. Conduction system disease C. Others

Comparison of classifications of cardiomyopathies

WHO/ISFC classification	Proposed classification
DCM (with viral infection)	I B, II A a, III A
DCM (with gene mutation)	IA, II A a, III A
HCM (with gene mutation outflow obstruction)	I A, II B a, III B
Apical HCM (with unknown cause)	I D, II B d, III B
Apical HCM (with HCV infection)	I B, II B d, III B
ARVC/D (with gene mutation)	IA, II A b, III B
ARVC/D (with HCV infection)	I B, II A b, III B
Long QT syndrome	I A, IV A

of cardiomyopathies in Japan [14—16]. Disorders surveyed included idiopathic dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), ARVC/D, mitochondrial disease, Fabry's disease of the heart, and prolonged Q-T interval syndrome. We estimated that 17,700 persons had dilated cardiomyopathy (14 per 100,000), 21,900 had hypertrophic cardiomyopathy, 300 had restrictive cardiomyopathy, 520 had ARVD, 640 had mitochondrial disease, 150 had Fabry's disease of the heart, and 1000 had prolonged Q-T interval syndrome. The prevalence of both dilated cardiomyopathy and hypertrophic cardiomyopathy was higher in men than women: the men-to-women ratios were 2.6 and 2.3 for dilated cardiomyopathy and hypertrophic cardiomyopathy, respectively. Detailed data on patients with dilated cardiomyopathy or hypertrophic cardiomyopathy were collected by a follow-up survey. In one year, more patients with dilated cardiomyopathy (5.6%) died than with hypertrophic cardiomyopathy (2.8%): congestive heart failure and arrhythmias were the leading causes of death for dilated cardiomyopathy and hypertrophic cardiomyopathy, respectively.

Among patients with dilated cardiomyopathy ($n = 506$) and hypertrophic cardiomyopathy ($n = 330$) who had myocardial biopsies, significant mononuclear cell infiltrations were seen in 24% with dilated cardiomyopathy and 15% with hypertrophic cardiomyopathy suggesting the presence of inflammation/myocarditis in these patients. Cardiac troponin T was increased in 3% of dilated cardiomyopathy and 9% of hypertrophic cardiomyopathy patients. Hepatitis B antibody was detected in 8.6% of dilated cardiomyopathy and 14.6% of hypertrophic cardiomyopathy patients. Hepatitis C antibody was present in 6.7% of dilated cardiomyopathy and 9.5% of hypertrophic cardiomyopathy patients. These data suggested that hepatitis B and C virus may cause myocarditis and cardiomyopathies.

Previous studies in the 1980s demonstrated that the 5-year survival rate for dilated cardiomyopathy was approximately 50%, but more recent studies into the 1990s reported better survival rates of 70—80%. Survival rates in our study (78.6% in newly

diagnosed patients and 75.7% in total patients) were similar to those in the studies conducted in the 1990s in which the proportion of asymptomatic patients was similar to our study [16]. Five variables, left ventricular dilatation, lower left ventricular ejection fraction, higher NYHA functional class, older age, and male sex were independently related to poor prognosis [17].

Role of viruses in the pathogenesis of cardiomyopathies

The myocardium is involved in a wide range of viral infections. In some cases, myocarditis may be the primary disorder; in others, it may occur as part of a systemic disease. Myocarditis is thought to be most commonly caused by enteroviruses, particularly coxsackievirus B. However, in many cases, when myocarditis has been diagnosed on the basis of clinical characteristics, no definite confirmation of viral origin is obtained, despite extensive laboratory investigations. The evidence is often only circumstantial, and a direct, conclusive proof of cardiac involvement is not available. However, accumulating evidence links viral myocarditis with the eventual development of dilated cardiomyopathy [18–20].

The clinical presentation of viral myocarditis is variable. When myocardial necrosis occurs diffusely, congestive heart failure develops and, later, dilated cardiomyopathy. If myocardial lesions are localized, a ventricular aneurysm may form. When complicated with arrhythmias, myocarditis presents as arrhythmogenic right ventricular cardiomyopathy (Fig. 1) [21]. When myocardial necrosis is localized to the subendocardium, restrictive cardiomyopathy may develop. While it has not been established that hypertrophic cardiomyopathy may be a complication of viral myocarditis, asymmetrical septal hypertrophy has, in fact, sometimes been observed in patients with myocarditis [22].

The myocardium may be the target of several types of viral infections. Recently, the importance of hepatitis C virus (HCV) has been noted in patients with hypertrophic cardiomyopathy, dilated cardiomyopathy, and myocarditis [10–13,23,24].

Phenotypes of HCV cardiomyopathies

In an initial study, we found HCV RNA by polymerase chain reaction in the hearts of 19% of patients with dilated cardiomyopathy [24]. Over a 10-year period, we identified 9.9% of patients with dilated cardiomyopathy had evidence of HCV infection, in contrast to only 2.5% of patients with ischemic heart disease. The main clinical manifestations at initial presentation were heart failure and cardiac arrhythmias. Positive and negative strands of HCV RNA were detected in the hearts of patients [23]. Because negative RNA molecules are intermediates in the replication of the HCV genome, we presume that HCV replicates in myocardial tissues.

During the same period, we identified 14.1% of patients with hypertrophic cardiomyopathy had evidence of HCV infection. None of these patients had a family history of hypertrophic cardiomyopathy. Apical hypertrophic cardiomyopathy was diagnosed in 8% of patients who had ace of spade-shaped deformities of the left ventricle. Histopathologic studies showed mild to severe degrees of myocyte hypertrophy in the right or left ventricle, mild to moderate fibrosis, and mild cellular infiltration. Positive and negative strands of hepatitis C virus RNA were found in the biopsied hearts of patients [25]. Teragaki and coworkers [26] recently found 18 of 80 Japanese patients with hypertrophic cardiomyopathy (22.5%) had positive HCV antibodies, a prevalence significantly higher than in controls.

Prolonged persistence of hepatitis C virus genomes in paraffin-embedded hearts

A multicenter study by the Scientific Council on Cardiomyopathies of the World Heart Federation (Bernhard Maisch, MD, Chairman) showed HCV genomes in 18% of patients with dilated cardiomyopathy and myocarditis from Italy, and in 36% from the United States, two from patients with myocarditis and two with ARVC [25], which suggests that HCV may cause ARVC.

In collaboration with the National Cardiovascular Center and Juntendo University, we have detected HCV RNA in paraffin sections of autopsied hearts from 26% of patients with hypertrophic cardiomyopathy, 12% of patients with dilated cardiomyopathy, and 33% of patients with myocarditis [13]. We also examined autopsied hearts from patients with dilated cardiomyopathy in a collaborative study with the University of Utah and found HCV RNA in 35% of hearts. The sequences of HCV genomes recovered from these hearts were highly homologous to the standard strain of HCV [25]. However, the rates of HCV genomes detection in the hearts of patients with cardiomyopathies varied widely among different regions of the world.

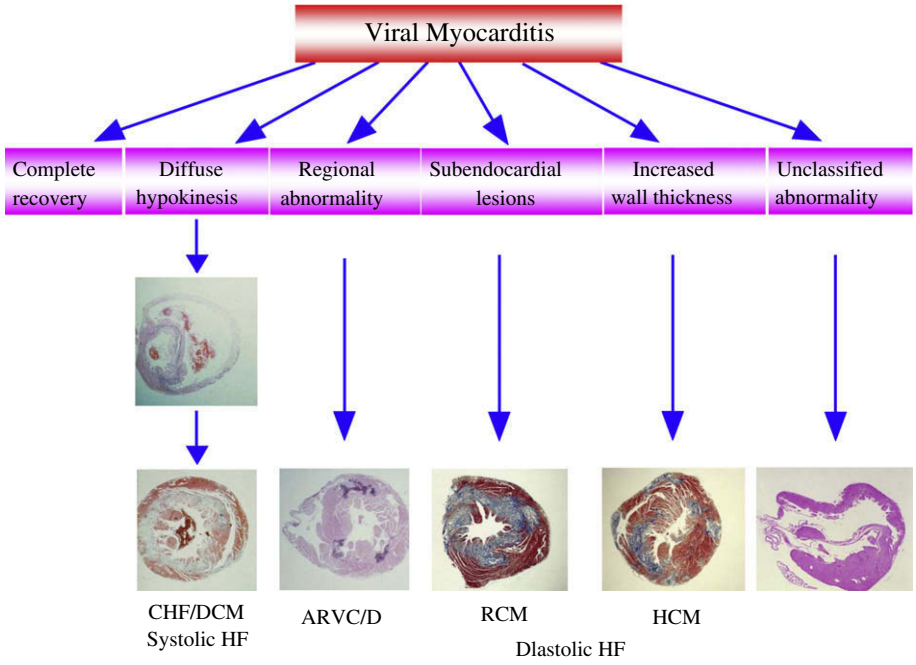

Figure 1 Viral myocarditis and its sequelae. Animal models of viral myocarditis show that similar lesions are developed in viral myocarditis as seen in dilated cardiomyopathy (DCM), arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC/D), restrictive cardiomyopathy (RCM) and hypertrophic cardiomyopathy (HCM). CHF: congestive heart failure, HF: heart failure.

For example, no HCV genome was detected in 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. We analyzed sera stored during the US Myocarditis Treatment Trial [27] of immunosuppression in patients with heart failure and myocarditis. Anti-HCV antibodies were identified in 4.4% of patients, including 5.9% of patients with biopsy-proven myocarditis. According to the US Centers for Disease Control, the prevalence of HCV infection in the general US population is 1.8% [28], thus 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 [29].

Genes responsible for development of different phenotypes of HCV cardiomyopathies

The major human 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-a, and the human leukocyte antigen (HLA) complex, the polymorphisms of which are often proposed as determinants for the susceptibility to various diseases. Recent studies of 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 allele distributions, using frequencies of phenotype in patients with hypertrophic or dilated cardiomyopathy.

We found that DPB1∗0401 and DPB1∗0901 were significantly associated with an increased risk of HCV-hypertrophic cardiomyopathy in the dominant model. The disparity in the gene-dose effect of two susceptible DPB1 alleles may be attributable to the difference between the susceptible and resistant residue-combination consisting of the DPb anchor pocket for antigenic peptide-binding. These results implied that the HLA-DP molecules with a specificity pocket appropriate for an HCV antigen(s) might confer the progressive process of hypertrophic cardiomyopathy in HCV-infected individuals [30].

To delineate the susceptibility locus, we also genotyped 44 polymorphic markers scattered

across the entire MHC region in patients with HCV-dilated cardiomyopathy and HCV-hypertrophic cardiomyopathy. We mapped HCV-dilated cardiomyopathy susceptibility to a non-HLA gene locus spanning from NFKBIL1 to MICA gene loci within the MHC class III-class I boundary region. Our results showed that HCV-dilated cardiomyopathy was more strongly associated with alleles of the non-HLA genes rather than HLA genes themselves. In addition, no significant association was found between the MHC markers and HCV-hypertrophic cardiomyopathy. This marked difference in the MHC-related disease susceptibility for HCV-associated cardiomyopathy strongly suggests that the development of HCV-dilated cardiomyopathy and HCV-hypertrophic cardiomyopathy is under the control of different pathogenic mechanisms [31].

Treatment of HCV cardiomyopathies

In patients with HCV hepatitis, the success of treatment can be measured by the biochemical and virologic 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 [32]. We used TL-201-SPECT imaging, 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 [32]. This preliminary study suggests that interferon is a promising treatment for myocardial disease caused by HCV. We have also reported beneficial treatment with interferon guided by serial measurement of serum HCV RNA and cardiac troponin T in a patient presenting with dilated cardiomyopathy and striated myopathy attributable to HCV infection [33].

Global alert and response network: hepatitis C virus-derived heart diseases

Scope of the problem

As discussed above, HCV is the cause of many different forms of heart disease worldwide, and yet few cardiologists are aware of it as an etiology of heart disease, or its treatment. HCV infection is seen globally, and is often undetected and therefore untreated. The burden of HCV-derived heart diseases is global, with a higher prevalence in Asia, Africa, and low-and middle-income countries. HCV-derived heart diseases are chronic, persistent, and devastating diseases.

The global prevalence of HCV carriers is estimated to average 3%, ranging from 0.1 to $\geqslant$10% among different countries. In Asia, the virus is highly prevalent in Mongolia, Vietnam, Myanmar, and China. In Africa, a high prevalence is present in central countries and in Egypt, and in South America, a high prevalence is observed in Brazil. The highest prevalence ($\geqslant$10%) has been recorded in Mongolia, Egypt, Tanzania, Guinea, and Cameroon. Therefore, HCV infection is an important and treatable health concern in developing countries in Asia, Africa, and South America [34].

Our study showed that in more than 10% of Japanese patients, their cardiomyopathies were associated with HCV infection. More recently, we found that up to 15% patients with heart failure with myocarditis in the USA have HCV infection. In contrast, 79% of patients with hepatocellular cancer and 37% of hepatitis C patients in China have heart disease, as detected by measuring a proven and sensitive biomarker of heart disease, NT-proBNP (Table 2) [35]. In Pakistan, 17% of hepatitis C patients have heart disease as measured by this biomarker (Figs. 2 and 3) [36]. Based on these data, 3% of 6.6 billion (198 million) persons worldwide are infected with HCV, and 17—37% (34—73 million) persons are suffering from HCV heart diseases. These figures may be comparable to the number of patients with hepatitis C.

HCV infection causes only hepatitis in some patients, only heart diseases in some patients, and both hepatitis and heart diseases in other patients. In addition, HCV infection is associated with enhanced atherosclerosis, and more than 20% of people with HCV infection have diabetes mellitus which is an important risk factor of cardiovascular disease [37].

Impact of treatment of HCV-derived heart disease

No proven strategy has been identified to reduce the numbers of patients living with, and dying from, cardiomyopathies and myocarditis due to infectious agents. Yet, the morbidity and mortality

Table 2 NT-proBNP in patients with hepatitis B and C in China.

Groups	*n*	NT-proBNP		
		>55 pg/mL (n)	>55 pg/mL (%)	mean ± SD (pg/mL)
Healthy controls	203	0	0.0	22.3 ± 12.0
HBV-infected	342	35	10.2[a]	51.2 ± 97.08[a]
HCV-infected	181	48	26.1[b,c]	358.0 ± 2548[b,c]

Data from Wang et al. [35].
[a] $p < 0.01$.
[b] $p < 0.0001$ vs. healthy controls.
[c] $p < 0.0001$ vs. HBV.

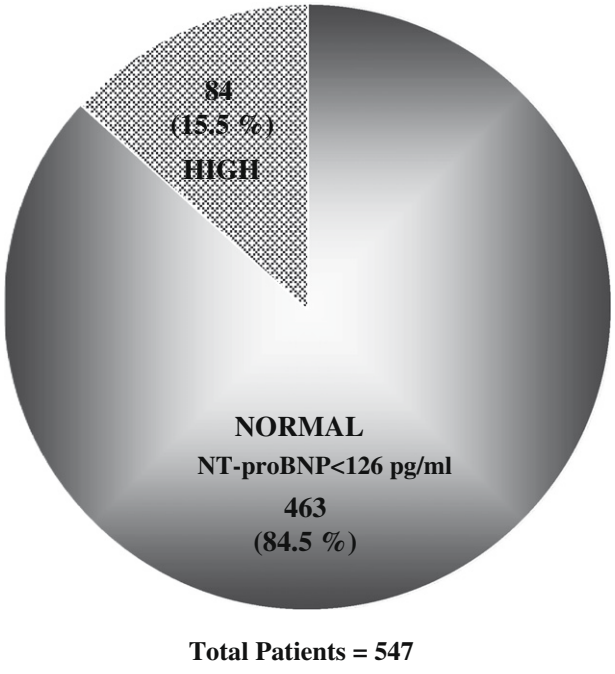

Figure 2 Circulating NT-ProBNP in patients with HCV infection in Pakistan. Data from Sheikh [36].

are high. We can treat these diseases by anti-viral agents, and some patients with cardiomyopathies and heart failure may be cured. Thus, treating these persons much earlier in the disease process–because of the ability to identify and treat HCV infection–will reduce the burden of cardiomyopathies and heart failure in patients and reduce the costs of treatment of these complex and long-term diseases.

Impact of HCV on cardiac sudden death

Our epidemiological study showed that HCV infection was associated with severe arrhythmia for which patients consulted their physicians [38]. Recently, we have also demonstrated that HCV is highly associated (40%) with arrhythmogenic right ventricular dysplasia/cardiomyopathy in which cardiac sudden death occurs frequently due to fatal arrhythmia. Thus, HCV may be an important cause of arrhythmias. Therefore, anti-HCV treatment could potentially reduce sudden death in

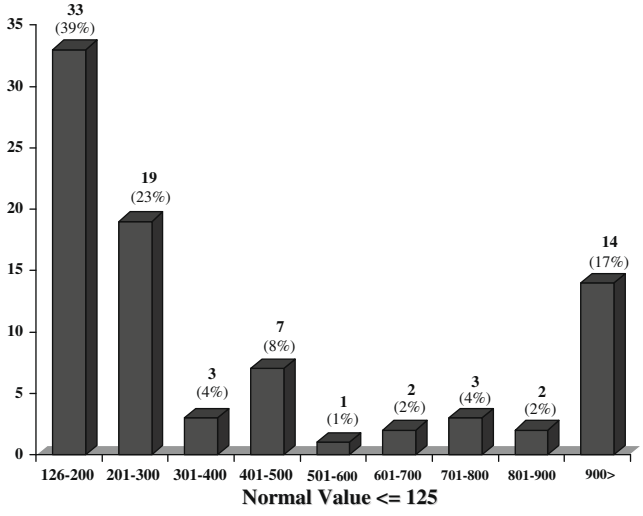

Figure 3 Prevalence of high NT-proBNP in patients with HCV infection in Pakistan. Data from Sheikh [36].

patients with arrhythmias associated with HCV infection.

Impact of HCV on vascular disease

There are several reports on the association of diabetes mellitus and HCV infection. Also, HCV infection has been reported as a risk factor of atherosclerosis [39,40]. Therefore, it is important to clarify the role of HCV infection as a risk factor of atherosclerosis and vascular diseases, especially in the geographic areas with a high prevalence of HCV infection. The anti-viral treatment may cure the diseases, and decrease the number of patients. Thus, the cost to treat these patients and, importantly, the burden of disease to the patients can be decreased.

Strategic opportunity: a call to action

A global network is required to establish methods to detect heart disease caused by infectious agents. Other goals for the network are the expansion of preventive and therapeutic programs in underprivileged countries. Model programs are underway, such as the ''Global Network on Myocarditis", which is working to develop standardized viral detection methods in cardiomyopathies and myocarditis. After establishment of these methods, training programs will be developed to teach the detection and treatment of patients, especially in underprivileged regions, and registry-based programs set-up to monitor cardiomyopathies and myocarditis due to infectious agents.

A similar program specifically for HCV-derived cardiovascular diseases is needed. This can be accomplished using two easy, inexpensive, and reliable measurements to clarify the presence of HCV-derived cardiovascular diseases. First, HCV antibody is measured. Second, in HCV antibody-positive persons, BNP or NT-proBNP, a proven sensitive biomarker of cardiovascular diseases, is measured. These tests require just a small amount of blood and they can be performed at any routine clinical laboratory in the world.

The second step of this program is to collect the detailed clinical information on the HCV antibody-positive patients with increased BNP/NT-proBNP values. Thereafter, a clinical treatment trial is needed.

This paper serves as a call to action to cardiologists and researchers around the world to participate in a Global Alert and Response Network of Hepatitis C Virus-derived Heart Diseases to define the scope of the problem and implement preventive and therapeutic programs. Treating HCV in these persons will reduce the burden of cardiomyopathies and heart failure and reduce the costs of treatment of these complex and long-term diseases.

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