Is Hepatitis C Virus a Cause of Idiopathic Dilated Cardiomyopathy? A Systematic Review of Literature

Francisco José Farias Borges dos Reis[1], Tiago Almeida de Sousa[2], Manoela S. Oliveira[2], Ney Dantas[3], Martha Silveira[4], Maria Ignês Freitas Melro Braghiroly[2] and Raymundo Paraná[5]

[1]Post-graduate Course in Medicine and Public Health Federal University of Bahia, Medical School, Physician of the Professor Edgar Santos General Hospital Cardiology Service (HUPES) - Federal University of Bahia; [2]Medical student of the Bahia Federal University of Bahia, Medical School; [3]Physician of the Professor Edgar Santos General Hospital Cardiology Service (HUPES) - Federal University of Bahia; [4]Librarian and MS underway in the Information Sciences Institute – Federal University of Bahia; [5]Professor of Medicine, Gastro-Hepatology unit, Federal University of Bahia (UFBA); Salvador, BA, Brazil

Recent studies have suggested that some patients with idiopathic dilated cardiomyopathy (IDC) are also afflicted with insidious forms of viral myocarditis. Participation of hepatitis C virus (HCV) in this process has been postulated. The objective of this study was to evaluate a possible association between hepatitis C virus and idiopathic dilated cardiomyopathy. Systematic review of the literature using electronic databases (MEDLINE, EMBASES, LILACS and COCHRANE) for the period from 1995 to 2005, limited to papers published in English, Spanish and Portuguese. Sixty-two papers were found, of which six were in accordance with the proposed methodology. After selection, the articles were classified by quality of data and number of variables studied. Most of the patients were male adults from 31 and 75 years old, who had ischemic cardiopathy excluded as etiology of the dilated cardiomyopathy. A significant association between dilated cardiomyopathy and hepatitis C virus was found in only two papers, both from Japan and by the same author. Most of the papers received low classifications, as they did not fulfill the systematization criteria.

Key Words: Idiopathic dilated cardiomyopathy, hepatitis C virus, systematic review.

Idiopathic dilated cardiomyopathy (IDC) is a syndrome characterized by univentricular or biventricular dilatation with contractile dysfunction, symptoms of congestive heart failure (CHF) and risk of early death [1,2]. This is a controversial clinical condition, and its diagnosis is performed by exclusion of other causes of cardiomyopathy. There have been few studies on IDC as a cause of CHF in Brazil, although it is an important cause of this syndrome in developed countries, affecting about 25% of all CHF patients [3].

Several etiological factors have been reported to be involved in IDC pathogenesis, including genetic factors, viral myocarditis, other cytotoxic injuries to the myocardium, immunological alterations and metabolic disturbances [3,4]. Recently, it has been suggested that some patients with IDC are also afflicted with insidious forms of viral myocarditis, through chronic inflammation mechanisms and self-immunity [5,6]. Evidence of viral participation is based on serology and/or the finding of viral DNA in the myocardium, demonstrated through PCR (polymerase chain reaction) techniques [7-9]. The physiopathology involves complex processes characterized by three distinct phases: infection of myocytes, toxin production and immunologically-mediated cytotoxicity [10], changing the entire heart anatomical and functional structure, leading to activation of an adaptive mechanism known as heart remodeling, which involves heart dilation and ventricular dysfunction in patients with CHF [11].

Recently, some studies have proposed that hepatitis C virus (HCV) generates a tissue lesion mechanism similar to that caused by enterovirus and Coxsackie-B-virus, which is common in cases of myocarditis [12]. HCV is the main cause of chronic hepatitis in western countries; this virus is currently the main motive for hepatic failure and liver transplants in developed countries [13]. It belongs to the *Flaviviridae* family [14] and its genome is composed of a single-strand RNA. At least six genotypes are known, with more than 50 subtypes [15]. Over 80% of the infected patients will develop chronic disease and 20% of them will progress to liver cirrhosis [16].

It is estimated that approximately two million people in Brazil and over 170 million worldwide are HCV carriers [17,18]. In the state of Bahia, in northeast Brazil, around 1.5% of the population is infected with HCV [19]. Users of injected drugs, patients who have had blood or by-products transfusions, especially those who received blood transfusions before the 1990s, chronic renal disease patients, healthcare professionals and individuals who have had piercing or tattooing are at risk for acquiring HCV infection [20].

Received on 18 January 2006; revised 10 June 2006.
Address for correspondence: Dr. Francisco José Farias Borges do Reis. Rua Quintino de Carvalho, nº 113, Aptº 301, Jardim Apipema Zip code: 40155-280. Salvador, Bahia, Brazil. E-mail: fbreis@cardiol.br. Phone: 71 3332-5870 / 8876-5870.

The Brazilian Journal of Infectious Diseases 2006;10(3):199-202.

The hypothesis that other tissue sites are the target of infection and active HCV replication, leading to associated diseases and also serving as immunological sanctuaries for this virus, has generated an active search for viral RNA in several organs and systems. The first paper that examined the presence of viral RNA in the myocardium of patients with dilated cardiomyopathy (DCM) was published in 1995 in Japan [12]. Though the authors presented evidence of HCV participation, other authors have indicated that it is not involved. Consequently, the role of HCV in IDC pathogenesis remains controversial.

We evaluated a possible association between hepatitis C virus and idiopathic dilated cardiomyopathy, based on published reports.

A Systematic Review of Literature

A systematic review of the literature was made using the main electronic databases of medical literature (MEDLINE, LILACS, EMBASE and THE COCHRANE LIBRARY), since the use of a single source does not reveal the sensitivity and precision of the research and is not thorough enough [21,22].

The following inclusion criteria were observed in the selection process: prevalence cross-sectional studies and/or case studies of HCV infection in patients with confirmed IDC diagnosis. Review papers, as well as those not written in English, Spanish or Portuguese, were not included. The following exclusion criteria were also considered: history of ischemic cardiopathy suspected by clinical history of typical thoracic pain, previous coronary event, myocardial cintilography and/or angiographic study; previous or current diagnosis of systemic arterial hypertension stages II or III, according to the classification proposed by the VI Joint International Committee; history of neoplasia and patients submitted to chemotherapy and/or with positive serology for Chagas' disease.

The consultation of the four databases was made with the following keywords and search strategies: (Myocardial Diseases OR cardiomyopath* OR myocardit*) and (Hepatitis C OR VHC OR HCV).

The articles were qualified according to criteria proposed by Figueiredo & Tavares-Neto (2001), depending on the amount of information in each article, based on a previously elaborated questionnaire: class A= 100% of the variables; class B= from 91% to 99% of the variables; class C= 50% or fewer of the variables; class D: from 51% to 70% of the variables; class E= from 71% to 90% of the variables [22].

The information contained in each article was systematized according to the following topics (1) Study identification: author(s), journal, publication year, country of origin; (2) Type of study: non-random cross-sectional prevalence, case-control, cohort; divided into comparison groups or not; (3) Characteristics of patients: gender, age, casuistic, affected by Diabetes mellitus or not, history of alcoholism, history of ischemic cardiopathy or not, neoplasia or chemotherapeutic treatment, diagnosis of systemic arterial hypertension or positive serology for Chagas' disease.

Data were stored and processed, using the Statistical Package for the Social Sciences (SPSS Chicago, IL, version 9.0, 1998).

Results

Sixty-two papers were found in the electronic databases (22 EMBASE; 40 PUBMED; 0 LILACS; 0 COCHRANE), but only six articles fulfilled the selection criteria. These studies involved from 62 to 245 patients and were published from 1995 to 2005 (Table 1).

Most of the papers divided the patients into two large groups: with or without dilated cardiomyopathy; most also excluded ischemic cardiopathy (ICP) as a cause of cardiomyopathy. Only one paper looked for IDC in a cohort study involving patients with confirmed HCV infection [23]; in all other studies the investigation process occurred inversely. Most were defined as transversal studies; though there were also prospective follow-up studies of HCV-infected patients (Table 1).

The age of the patients involved in the studies ranged from 31 to 75 years; most were males. Only one study was made using hearts of previously-autopsied patients [24] (Tables 1 and 2).

Only three articles attempted to exclude all possible causes for dilated cardiomyopathy [23,25,26], thus corroborating its idiopathic etiology. However, most papers at least excluded ischemic cardiomyopathy as an etiology, except for the study of Matsumori et al. in autopsied patients [24].

Identification of HCV in patients with IDC was performed in most studies through RT-PCR (reverse trancription PCR) in myocardium samples obtained from heart biopsies or *post mortem* exams [12,24-26]. However, Grumbach [27] and Dalekos et al. [23] only examined sera samples. Only Fujioka [25] and Kühl et al. [26] looked for RNA and DNA of viruses other than HCV in the myocardium as a cause of IDC.

In the evaluation of the quality of the papers: two articles were classified as "C" (71% to 90% of the variables), three as "D" (51% to 70% of the variables) and one as "E" (50% or less of the previously-defined variables) (Table 3). A significant relation between dilated cardiomyopathy and HCV was found in only two studies ($p = 0.039$ and 0.0047, respectively) [12,24].

Discussion

Physiopathogenesis of virus-induced dilated cardiomyopathy can include a latent phase in which most patients remain asymptomatic; however, sustained activation of the immune system causes continuous tissue destruction, necrosis or myocyte apoptosis. This tissue is replaced by fibroblasts, with progressive worsening of ventricular function and consequent CHF symptoms. Lack of knowledge concerning this causal factor leads to frequent diagnosis of idiopathic dilated cardiomyopathy; however, advances in viral-detection methods have made chronic virus infection an etiological possibility.

Table 1. Papers consulted, number of patients, subgroups and types of study

Authors	Patients	Subgroups*	Type of study
Matsumori et al., 1995 [12]	76	2 groups: 36 with DCM and 40 with CAD	Case-control
Dalekos et al., 1998 [23]	157	2 groups: 102 with HCV and 55 with IDC	Transversal study Prospective cohort study
Matsumori et al., 2000 [24]	106	5 groups: 50 with DCM, 42 with HCM, 14 with Myocarditis, 35 with ICP and 20 with NCD	Case-control
Fujioka et al., 2000 [25]	62	2 groups: 26 with IDC and 36 with NCD	Case-control
Kühl et al., 2005 [26]	245	Without Groups: 245 with IDC	Transversal study
Grumbach et al., 1998 [27]	122	3 groups: 61 with DCM, 12 with Myocarditis and 49 with CAD	Case-control

* DMC – Dilated Cardiomyopathy; IDC – Idiopathic Dilated Cardiomyopathy; CAD – Coronary Arterial Disease; HCV – Hepatitis C Virus; HCM – Hypertrophic Cardiomyopathy; IPC – Ischemic Cardiopathy; NCD – Non-Cardiac Diseases.

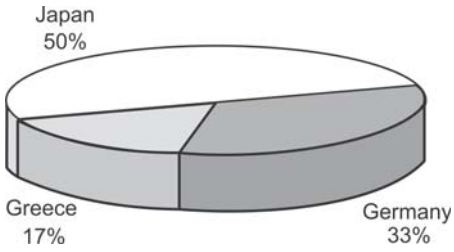
Table 2. Gender, average age and hospitalization time

References	Average age (years)	Male N(%) Female N(%)
Matsumori et al., 1995 [12]	46.5 ± 15.8	49 (64.4%) / 27 (35.6%)
Dalekos et al., 1998 [23]	53.5	94 (59.8%) / 63 (40.2%)
Matsumori et al., 2000 [24]	49.9 ± 18.7	71 (66.9%) / 35 (33.1%)
Fujioka et al., 2000 [25]	48 ± 15	48 (77.4%) / 14 (22.6%)
Kühl et al., 2005 [26]	52	178 (72.6%) / 67 (27.4%)
Grumbach et al., 1998 [27]	48 ± 14	89 (72.9%) / 34 (27.1%)

Table 3. Quality of the selected articles (scale of A (best) to E (worst)

References	Class
Matsumori et al., 1995 [12]	D
Dalekos et al., 1998 [23]	C
Matsumori et al., 2000 [24]	E
Fujioka et al., 2000 [25]	C
Kühl et al., 2005 [26]	D
Grumbach et al., 1998 [27]	D

Figure 1. Country origin of the studies



Enterovirus and coxsackie-B3 and B4-virus were the most widely related to myocarditis that progressed to dilated cardiomyopathy [28]. However, a recent study, based on endocardial biopsy of individuals with left ventricular systolic dysfunction, detected a high prevalence of the cardiac parvovirus B19 viral genome, revealing a strong association between this viral agent and IDC [29]. There was also a high prevalence of multiple viral infections in patients who had viral genome in the endocardial biopsy, suggesting that this association may play a key role in IDC pathogenesis [29].

Other reports of HCV prevalence in patients with IDC reported from 0% [23,25] to 16.6% [12]. However, in this latter paper, Matsumori does not exclude all possible etiologies of dilated cardiomyopathy, so they cannot be considered as idiopathic. This reduces the validity of his data for the corroboration of this association.

All of the studies that found significant associations between IDC and HCV were from Japan, although no agreement was observed even among these Japanese reports; consequently, this subject is still controversial.

Only the studies of Dalekos, Fujioka and Kühl et al. [23,25,26] used the term "idiopathic" and methodologically excluded all possible etiologies of dilated cardiomyopathy. This makes the data scientifically more reliable by ruling out any significant association between HCV and IDC. In examining the evidence for other viruses in the myocardium, both Fujioka et al. [25] and Kühl et al. [26] found significant associations, for enteroviruses (Coxsackie-B-virus) and Parvovirus B19, respectively.

The average affected patient age was similar among the studies; a predominance of male patients was also observed, probably due to the higher prevalence of male patients in these studies or to the higher exposition to risk factors for hepatitis C observed in this gender.

Many Japanese papers emphasized an association between hypertrophic cardiomyopathy (HCM) and HCV infection. Among these, only one was not published by Matsumori et al. [30]. One of them examined the possibility of there being various molecular mechanisms for the development of HCV-induced dilated and hypertrophic cardiomyopathy [24].

Among the articles selected for the systematic review, three of them were performed in Japan [12,24,25] and three in Europe [23,26,27]; some of them are cited many times in several international studies (Figure 1). Most of the articles received low classifications, based on the evaluation criteria of Figueiredo and Tavares-Neto, 2001 [31], demonstrating that these papers did not fulfill the systematization criteria. Consequently, conclusions concerning this association are limited.

After examining the published data, we consider that a possible association between hepatitis C virus and the development of dilated cardiomyopathy has not been sufficiently investigated. Further investigations with suitable methodology, such as longitudinal studies of HCV infected patients and case-control studies involving a large number of patients, are required. The formation of the study groups should observe possible confounding variables, since dilated cardiomyopathy is a chronic cardiopathy that requires successive hospitalizations and exposes the patient to parenteral risk and HCV-nosocomial transmission.

References

1. Coughlin S.S., Neaton J.D., Sengupta A., Kuller L.H. Predictors of mortality from idiopathic dilated cardiomyopathy in 356,222 men screened for the Multiple Risk Factor Intervention Trial. Am J Epidemiol **1994**;139(2):166-72.
2. Dec G.W., Fuster V. Idiopathic dilated cardiomyopathy. N Eng J Med **1994**;331(23):1564-75.
3. Adams K.F.J., Zannad F. Clinical definition and epidemiology of advanced heart failure. Am Heart J **1998**;135:S204-S15.
4. Leiden J.M. The genetics of dilated cardiomyopathy – emerging clues to the puzzle. N Engl J Med **1997**;337(15):1080-1.
5. Pauschinger M., Bowles N.E., Fuentes-Garcia F.J., et al. Detection of adenoviral genome in myocardium of adult patients left ventricular dysfunction. Circulation **1999**;99(10):1348-54.
6. Pauschinger M., Doerner A., Kühl U., et al. Enteroviral RNA replication in the myocardium of patients with left ventricular dysfunction and clinically suspected myocarditis. Circulation **1999**;99(7):889-95.
7. Feldman A.M., Mcnamara D. Myocarditis. N Engl J Med **2000**;343(19):1388-98.
8. Jin O., Sole M.J., Butany J.W., et al. Detection of enterovirus RNA in myocardial biopsies from patients with myocarditis and dilated cardiomyopathy using gene amplification by polymerase chain reaction. Circulation **1990**;82:8-16.
9. Kandolf R., Ameis D., Kirschener P., et al. In situ detection of enteroviral genomes in myocardial cells by nucleic acid hybridization: an approach to the diagnosis of viral heart disease. Proc Acad Sci USA **1987**;84(17):6272-6.
10. Liu P., Mason J.W. Advances in the understanding of myocarditis. Circulation **2001**;104(9):1076-82.
11. Ono K., Matsumori A., Shioi T., et al. Cytokine gene expression after myocardial infarction in rat heart: possible implication in left ventricular remodeling. Circulation **1998**;98(2):149-56.
12. Matsumori A., Matoba Y., Sasayama S. Dilated cardiomyopathy associated with hepatitis C virus infection. Circulation **1995**;92(9):2519-25.
13. Lauer G.M., Walker B.D. Hepatitis C virus infection. N Engl J Med **2001**;345(1):41-52.
14. Okuda M., Li K., Beard M.R., et al. Mitrochondrial injury, oxidative stress and antioxidant gene expression are induced by hepatitis C virus core protein. Gastroenterology **2002**;122(2):366-75.
15. Liang T.J., Reherman B., Seeff L.B., Hoofnagle J.H. Pathogenesis, natural history, treatment and prevention of hepatitis C NIH conference. Ann Intern Med **2000**;132(4):296-305.
16. Conry-Cantilena C., Vanraden M., Gibble J., et al. Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. N Engl J Med **1996**;334(26):1691-6.
17. Brandão A.B.M., Fuchs S.C., Silva M.A.A., Emer L.F. Diagnóstico da hepatite C na prática médica: revisão de literatura. Pan Am J Public Health **2001**;9(3):161-8.
18. EASL International Consensus Conference on Hepatitis C. Paris, 26-28, February 1999. Consensus statement. European Association for the Study of the Liver. J Hepatol **1999**;30:956-61.
19. Paraná R., Vitvitski L., Berby F., et al. HCV infection in northeastern Brazil: unexpected high prevalence of genotype 3a and absence of African genotypes. Arq. Gastroenterol **2000**;37(4):213-6.
20. Hajjar L.A., Rosa T.T., Veiga J.P.R. Manifestações extra-hepáticas da hepatite C. Brasília Médica **1999**;36(3):96-105.
21. Jadad A.R., Moher D., Klassen T.P. Guides for reading and interpreting systematic reviews: II. How did the authors find the studies and assess their quality? Arch Pediatr Adolesc Med **1998**;152(8):812-7.
22. Mckibbon K.A., Walker-Dikes C.J. Beyond ACP Journal Club: how to harness MEDLINE to solve clinical problems. ACP J Club **1994**;120(2):A10-A2.
23. Dalekos G.N., Achenbach K., Christodoulou D., et al. Idiopathic dilated cardiomyopathy: lack of association with hepatitis C virus infection. Heart **1998**;80(3):270-5.
24. Matsumori A., Yutani C., Ikeda Y., et al. Hepatitis C virus from the hearts of patients with myocarditis and cardiomyopathy. Lab Invest **2000**;80(7):1137-42.
25. Fujioka S., Kitaura Y., Ukimura A., et al. Evaluation of viral infection in the myocardium of patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol **2000**;36(6):1920-6.
26. Kühl U., Pauschinger M., Noutsias M., et al. High prevalence of viral genomes and multiple viral infections in the myocardium of adults with "idiopathic" left ventricular dysfunction. Circulation **2005**;111:887-93.
27. Grumbach I.M., Heermann K., Figulla H.R. Low prevalence of hepatitis C virus antibodies and RNA in patients with myocarditis and dilated cardiomyopathy. Cardiology **1998**;90(2):75-8.
28. Bowles N.E., Richardson P.J., Olsen E.G., Archard L.C. Detection of Coxsackie-B-virus-specific RNA sequences in myocardial biopsy samples from patients with myocarditis and dilated cardiomyopathy. Lancet **1986**;1(8490):1120-3.
29. Tschope C., Bock C.-T., Kasner M., et al. High prevalence of cardiac parvovirus B19 infection in patients with isolated left ventricular diastolic dysfunction. Circulation **2005**;111(7):879-86.
30. Teragaki M., Nishiguchi S., Takeuchi K., et al. Prevalence of hepatitis C virus infection among patients with hypertrophic cardiomyopathy. Heart Vessels **2003**;18(4):167-70.
31. Figueiredo G.C., Tavares J.N. Estruturação de um banco de dados para análise secundária de informações em relatos ou série de casos. Rev Bras Ortoped **2001**;36(11/12):407-11.