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Expert Review of Cardiovascular Therapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierk20

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To cite this article: Mohammad Haykal, Akira Matsumori, Ahmed Saleh, Moatez Fayez, Hany Negm, Mohammad Shalaby & Samar Bassuony (2021) Diagnosis and treatment of HCV heart diseases, Expert Review of Cardiovascular Therapy, 19:6, 493-499, DOI: 10.1080/14779072.2021.1917383

To link to this article: https://doi.org/10.1080/14779072.2021.1917383

Published online: 02 Jun 2021.

EXPERT REVIEW OF CARDIOVASCULAR THERAPY
2021, VOL. 19, NO. 6, 493–499
https://doi.org/10.1080/14779072.2021.1917383

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REVIEW

Diagnosis and treatment of HCV heart diseases

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ABSTRACT

Introduction: Hepatitis C virus (HCV) infection is an important cause of a variety of otherwise unexplained heart diseases and myocardial injury. A high prevalence of HCV infection has been noted in patients with hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia/cardiomyopathy and myocarditis. Various arrhythmias, conduction disturbances and QT prolongation were also associated with HCV infection. A possible role of HCV infection in the pathogenesis of diabetes and atherosclerosis, and the role of immunogenetics of HCV cardiomyopathies is discussed. Recent studies suggest that mononuclear cells may be the major target of HCV, and clinical applications to test this new hypothesis are discussed.

Areas covered: In this review, we will evaluate the evidence that HCV causes various cardiovascular diseases, and discuss on the pathogenesis of these disorders.

Expert opinion: HCV is the cause of many different forms of heart disease worldwide, but their existence has not been recognized by most of cardiologists. The recognition and diagnosis are indispensable for the early treatment of these diseases. The diverse clinical manifestation of HCV infection and the presence of multiple extrahepatic disease syndromes could be explained by a new hypothesis that the target of HCV is leukocytes.

ARTICLE HISTORY
Received 8 January 2021
Accepted 12 April 2021

KEYWORDS
Arrhythmias; atherosclerosis; cardiomyopathy; hepatitis C virus; inflammation; immunity; leukocytes; myocarditis; pericarditis; therapy

1. Introduction

Hepatitis C virus (HCV) infection is an important cause of a variety of otherwise unexplained heart diseases and myocardial injury. A high prevalence of HCV infection has been noted in patients with hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia/cardiomyopathy and myocarditis. Various arrhythmias, conduction disturbances and QT prolongation were also associated with HCV infection. A possible role of HCV infection in the pathogenesis of atherosclerosis and carotid arterial remodeling, the role of immunogenetics in the pathogenesis of HCV cardiomyopathies, and therapeutic trials of HCV heart diseases will be discussed. Recent studies suggest that mononuclear cells may be the major target of HCV, and clinical applications to test this new hypothesis are discussed. In this review, we will evaluate the evidence that HCV causes various cardiovascular diseases, and discuss on the pathogenesis of these disorders.

2. Hepatitis C virus

HCV is a cause of both acute and chronic hepatitis, which may be mild illness lasting a few weeks or it can be more severe and serious, lifelong illness and end finally with liver cancer. About 71 million people have chronic HCV infection around the world. No effective vaccine is available against HCV although research in this area is ongoing.

3. Cardiotropism of HCV

HCV is blamed for unexplained heart diseases and myocardial injury particularly in chronic active hepatitis C [1]. In Japan, one of the collaborative research projects of the committee for the study of idiopathic cardiomyopathy found that 74 of 697 patients (10.6%) with hypertrophic cardiomyopathy had HCV antibody which were also present in 42 of 663 patients (6.3%) with dilated cardiomyopathy and in 650 of 11,967 patients (5.4%) seeking care in 5 academic hospitals. Other cardiac abnormalities, specifically arrhythmias, were present in these patients which suggest that HCV infection may be an important cause of unexplained heart diseases [2]. It is important to recall that HCV infection is significantly noted in patients with hypertrophic cardiomyopathy, dilated cardiomyopathy and myocarditis. Figure 1 shows the various cardiac effects of HCV [3]. The pathogenesis of HCV-induced cardiomyopathy is still not well understood [4].

Impaired cardiac function in liver cirrhosis was first found in patients with alcoholic liver disease and thus the toxic effects of ethanol was thought to be the cause. Impaired systolic and

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Article Highlights

- HCV is the cause of many different forms of heart disease worldwide, but their existence has not been recognized by most of cardiologists.
- HCV may cause hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia/cardiomyopathy and myocarditis, and may also cause various arrhythmias, conduction disturbances and QT prolongation.
- HCV infection may cause diabetes and atherosclerosis which are important risk factors of cardiovascular diseases.
- Immunogenetics play important role in the pathogenesis of HCV cardiomyopathies.
- The diverse clinical manifestation of HCV infection and the presence of multiple extrahepatic disease syndromes may be explained by a new hypothesis that the target of HCV is leukocytes.

diastolic functions were also demonstrated in post-viral cirrhosis. Increased left ventricular wall thickness in the pre-cirrhotic stage indicates the role of HCV in this structural abnormality which may be a co-factor for cardiac structural and functional abnormalities found in the more advanced stages of cirrhosis when portal hypertension develops and causes deleterious effects on systemic hemodynamics [5].

Rombola et al. also described acute pericarditis associated in patients with HCV infection. The most common viruses which may cause cardiac diseases during hepatitis are HBV and HCV, followed by cytomegalovirus, and Epstein-Barr virus [6]. Bertuccio et al. described a clinical case had unusual combination of acute HCV hepatitis and pericarditis in a young person who completely cured from the pericarditis but developed chronic HCV which may indicate that HCV was the cause of pericarditis [7]. Matsumori et al. found that HCV patients frequently associated with arrhythmia and arrythmogenic right ventricular dysplasia/cardiomyopathy which may lead to sudden cardiac death and this indicates that HCV is a cause of arrhythmias, and the use of anti-HCV treatment could potentially reduce sudden death in these patients [8].

Human immunodeficiency virus (HIV) and HCV infections both independently prolong QT interval. Co-infection with HCV increases the incidence of significant QT prolongation in HIV patients and predispose to torsade de pointes form of ventricular tachycardia [9]. HCV also leads to inflammatory LV aneurysms that may be the cause of idiopathic ventricular arrhythmias [10]. The most frequent alterations in electrocardiogram are

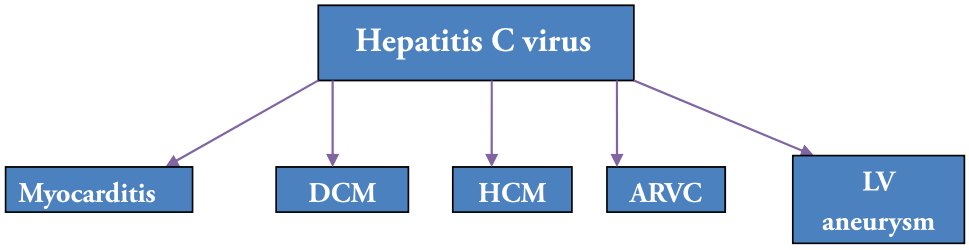

Figure 1. Various cardiac manifestations of HCV.
DCM: Dilated cardiomyopathy; HCM: Hypertrophic cardiomyopathy; ARVC: Arrhythmogenic right ventricular cardiomyopathy; LV: Left ventricle.

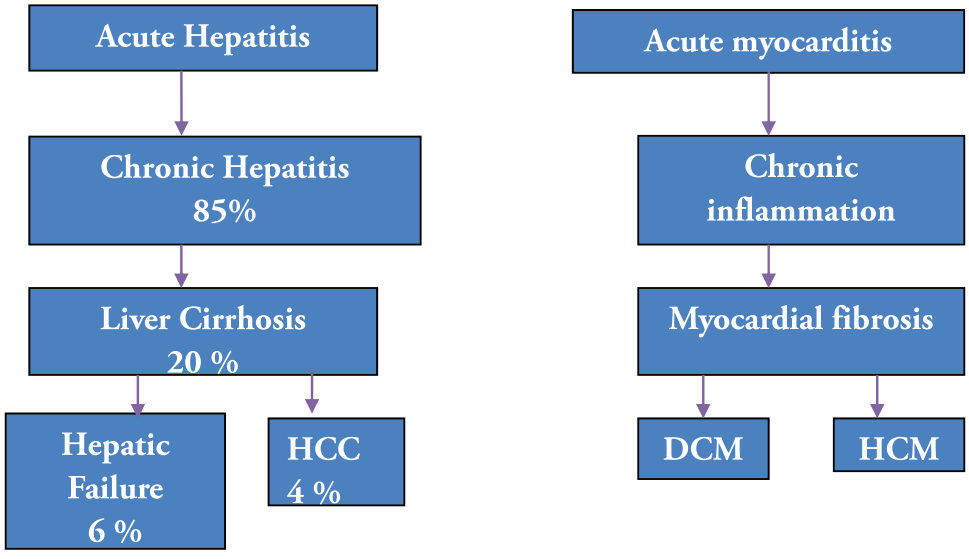

Figure 2. Sequences of cardiological events after viral invasion of the heart by HCV [8].
HCC: Hepatocellular carcinoma. DCM:-Dilated cardiomyopathy. HCM: Hypertrophic cardiomyopathy

conduction disturbances, axis deviations and arrhythmias. The incidence of cardiac manifestations develop during acute viral hepatitis is high, but with benign evolution [6].

The pathogenesis of HCV-induced cardiomyopathy remains to be clarified, but persistent myocarditis may lead to myocyte death [3]. The sequences of cardiological events resulting from viral invasion to the heart may be almost the same as those occurring due to viral invasion to the liver except for that cardiomyocytes does not undergo mitotic division so hypertrophic cardiomyopathy occurs in the heart instead of hepatocellular carcinomas in the liver. These sequences are illustrated in (Figure 2) [8].

Matsumori and colleagues studied the correlation between human leukocyte antigen and HCV infection and they concluded that immunological involvement of DPB1 gene may play a role in HCV-HCM development at the allelic manner level via polymorphic amino acids residues. Each clinical outcome of HCV infection had different HLA-mediated immune response explained by different risk alleles among HCV-related diseases including chronic liver diseases, asymptomatic carrier and HCV-DCM [8].

Despite the fact that the human major histocompatibility complex (MHC), which is located on the short arm of chromosome 6 and encodes for several protein products involved in immune function including complement, tumor necrosis factor (TNF) alpha, and the HLA complex, plays a role in the susceptibility to various diseases, no significant association was found between these markers and HCV-HCM [11]. In addition, HCV-DCM is more associated with alleles of the non-HLA genes than the HLA genes themselves, so HCV- DCM and HCV-HCM most likely develops due to different pathogenic mechanisms [11].

Studies also showed that some European workers with HCV had no cardiac diseases which means that HCV infection has different effects on the heart according to the human genetic background and geographic regions [2].

Increased intimal thickness of the carotid artery and the presence of plaques in it were found in HCV patients which means that HCV plays a role in the pathogenesis of carotid arterial remodeling [12].

4. HCV and diabetes mellitus as a risk of cardiovascular diseases

The role of chronic inflammation in the pathogenesis of type 2 diabetes mellitus (T2DM) is well recognized, as evidenced by the elevated levels of inflammatory cytokines, C-reactive protein and immunoglobulin free light chains in patients with T2DM [13,14]. Hepatic fibrosis, duration of HCV infection, and the presence of insulin resistance have been recognized as predisposing factors [15]. The new onset of T2DM in patients with chronic HCV infection predicts cirrhosis decompensation [16]. HCV infection can induce insulin resistance and cause diabetes [17,18]. The molecular mechanism remains to be clarified, but oxidative stress, cytokines, inhibition of insulin signaling, and reduced expression of glucose transporters may allbe part of the mechanism [19].

During infection, HCV proteins increase the release of proinflammatory cytokines, such as interleukin-6 and TNF-alpha, which then upregulate gluconeogenesis and enhance lipid accumulation in the liver [20–22].

Central adiposity related to T2DM and hepatic steatosis have been shown to be associated [23]. The decrease in HbA_{1c} level in patients with diabetes has been shown to improve hepatic fat content [24]. An improvement in HbA_{1c} levels with HCV eradication may also improve hepatic steatosis, which frequently accompanies HCV-related liver disease [20]. Patients with compensated HCV cirrhosis have higher rates of decompensation when they have diabetes and insulin resistance, and that insulin resistance was a predictor of overall mortality [25]. Thus, HCV eradication might prevent the development of decompensated cirrhosis not only by the elimination of the fibrotic and hepatotoxic effects of HCV, but also by reducing HbA_{1c} levels and improving insulin resistance in patients with T2DM.

5. HCV and atherosclerosis

Atherosclerosis is an inflammatory process and viral infections cause pro-inflammatory processes which may cause atherothrombosis. Elevated pro-inflammatory cytokines, such as TNF-alpha, inhibit insulin signaling, with dysregulation of glucose and lipid metabolism. This contributes to steatosis, increasing the risk to develop T2DM, which, in turn, favors the oxidative stress and perpetuates the chronic inflammation, accelerated liver fibrosis and impaired antiviral treatment efficacy [26]. Chronic HCV infection induces a proinflammatory state due to overexpression of cyclooxygenase-2, pro-inflammatory cytokines, increased oxidative stress, and immune stimulation, leading to endothelial dysfunction, atherosclerosis and finally, to cardiovascular disease [27]. HCV infection causes insulin resistance associated with endothelial dysfunction, persistent inflammation, and lipid imbalance that lead to atherosclerosis [28]. Measurement of the carotid intima-media thickness showed that patients with HCV infection had higher frequency of atherosclerotic changes [29].

HCV RNA has been demonstrated in the atherosclerotic plaques in carotid arteries suggesting the direct effect of HCV on atherosclerosis plaques formation by local inflammation [30]. The mechanisms by which the HCV is involved in atherosclerosis remains to be clarified. The direct and indirect effects of HCV, such as inflammation, lipid, and glucose metabolism alterations, may be related [31]. It is interesting that successful treatment of HCV infected patients showed a significant decrease of intima-media thickness [32].

HCV may also accelerate allograft vasculopathy after cardiac transplantation [33,34]. Further studies are necessary to detect the risk of transplant coronary artery disease in recipients of hearts from HCV positive donors [35].

6. Therapeutic trials of HCV myocarditis and cardiomyopathies

Matsumori and colleagues used interferon in the treatment of HCV induced dilated cardiomyopathy and striated myopathy guided by serial measurements of serum HCV RNA and cardiac troponin T, and found that most patients develop chronic inflammation of the heart and, later, dilated cardiomyopathy due to necrosis and loss of cardiomyocytes. Since

cardiomyocytes do not readily replicate, HCV infection may promote cardiomyocyte hypertrophy and leads to hypertrophic cardiomyopathy [4]. It was suggested that the use of the French pine tree bark extract (pycnogenol) may be beneficial for the treatment of myocarditis and cardiomyopathy based on the following mechanisms:

1. Pycnogenol inhibits NF-κB transcription factor.
2. Pycnogenol prevents expression of vascular cells adhesion molecules and intercellular adhesion molecules that are known to be potent co-stimulatory factors to the circulating T-cells that lead to release of many inflammatory mediators [36].
3. Pycnogenol inhibits secretion of TNF-alpha and IL-1beta [37].
4. Pycnogenol inhibits release of reactive oxygen species and nitric oxide from macrophages [38].
5. Pycnogenol inhibits HCV replication [39].

Activation of protein kinase C (PKC) inhibits both cardiac Na and Ca channels by phosphorylating specific sites in certain domains of channel subunits. It also degrades connexin 43, the major protein in myocardial gap junctions that plays an important role in cell to cell coupling and communication. Since there was a correlation of connexin 43 expression with ventricular LPs, it was thought that PKC-induced degradation of connexin 43 may be the cause of non-ischemic dilated cardiomyopathy through favoring the development of ventricular LPs [40]. Immunosuppressive agents may ameliorate inflammation in patients with HCV myocarditis in spite of viral persistence [41], and therapeutic strategies of the immunosuppressive treatment with antiviral agents would be reasonable.

7. A new concept of pathogenesis of HCV-induced diseases

Mononuclear cells was found to be a primary target of HCV infection where antibody against HCV-core antigen stained peripheral blood mononuclear cells (PBMC) in an immunohistochemical study, and the majority of positive staining was seen in CD68-positive macrophages. HCV-core antibody stained mostly mononuclear cells in different body organs as the liver, heart, kidney, and bone marrow, but not hepatocytes, myocytes, or globular cells. Positive staining was found in PBMC and mononuclear cells of various tissues by antibody against NS4 protein, which also supports that HCV replicates in mononuclear cells [42].

Thus, monocytes/macrophages are the major target of HCV, and these cells may cause inflammation in various organs (Figure 3).

Matsumori et al. showed that HCV infection frequently caused cardiac and renal abnormalities in patients. Various cardiomyopathies were found, but cardiac hypertrophy is the most common manifestation of cardiac abnormality, and left ventricular posterior wall hypertrophy was most frequent. Thus, HCV infection may be an important cause of hypertophic cardiomyopathy and dilated cardiomyopathy [43] (Figure 4). From the previous data, it was suggested that CD68 monocytes/macrophages are the major target of HCV, and that CD3-positive T cells or CD20-positive B-cells are not major targets. Thus, preparations targeting leukocytes infection might be used to treat HCV infection [44] . This could be tested by studying the effect of antiviral agents on mononuclear cells in vitro.

The diverse clinical biology of HCV and the presence of multiple extrahepatic disease syndromes could be explained by the effect of hematopoietic tissues – specifically monocytes in the bone marrow – on the virus via immune escape and viral modulation of host immune responses. The virus may also spread locally through the lymphatic system where it reaches the peripheral lymph nodes which may be the cause for infection of the immune cells prior to recirculation.

8. Cardiology and ultrasonography research unit (CURU) experience in the field of diagnosis and treatment of HCV heart diseases

Since 2007, CURU has valuable experience in the field of diagnosis and treatment of HCV heart diseases and published 5 different studies in this field which are summarized below.

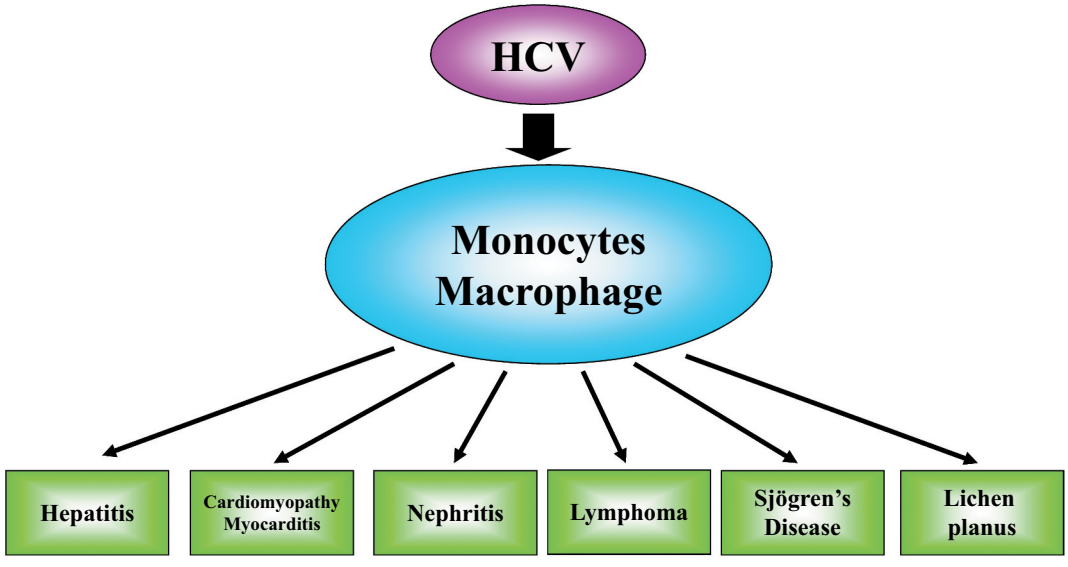

Figure 3. Primary target of HCV is leukocytes especially CD68 positive monocyte/macrophages, and these cells may cause inflammation in various organs.

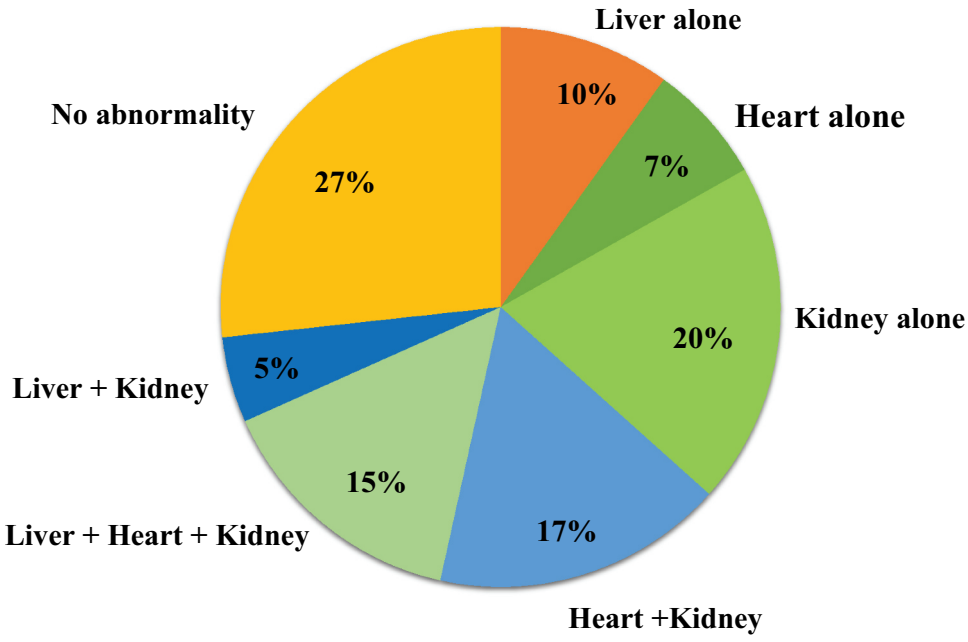

Figure 4. Incidence of abnormality of the liver, heart and kidney with HCV antibody positive people who visited a hospital. Abnormality of the kidney was most common, then the liver and heart followed.

In 2008, Haykal et al studied the effect of HCV infection on systolic and diastolic function of the left ventricle (LV), finding that patients with HCV infection had impaired systolic and diastolic functions of LV [45]. Haykal et al (2010) studied left atrial functions in HCV patients with and without cardiovascular risk, a study which showed significant statistical difference in LA excitation- contraction interval in HCV patients with or without cardiovascular risk factors when compared with normal controls. This finding might constitute an explanation for atrial arrhythmias frequently observed in HCV patients through creating reentry circuits [46]. In 2011, Saleh et al studied the cardiac involvement in HCV patients using tissue Doppler imaging and NT-proBNP. Their results showed that HCV group has shown significant statistical increase in A wave, deceleration time, highly significant decrease in tissue Doppler E_a and A_a, highly significant increased E/E_a ratio, significant decrease in E_a/A_a ratio and significant increase in SR_a. NT-proBNP levels showed highly significant increase and the best cutoff value of NT-proBNP to detect diastolic dysfunction in HCV group was 213 pg/ml. Significant correlation was detected between NT-proBNP level and tissue Doppler parameters. The best cutoff value of E/SR_e ratio to detect diastolic dysfunction in HCV group was 0.91, with 75% sensitivity and 100% specificity [47] . Haykal et al (2013) studied the role of anti-inflammatory treatment with cetirizine in patients presented with heart failure and had HCV infection and their study showed that myocardial function was substantially improved in patients who took cetirizine, and there was a significant decrease in LV average global strain, significant increase in LV ejection fraction [48].

9. Expert Opinion

Hepatitis C virus (HCV) is a cause of both acute and chronic hepatitis, an illness which can be mild, lasting a few weeks, or much more serious lifelong illness possibly ending in liver cancer. Impaired cardiac function in liver cirrhosis was observed in patients with alcoholic liver disease, suggesting that the toxic effects of ethanol was the cause. However, impaired systolic and diastolic functions were also demonstrated in post-viral cirrhosis. Increased left ventricular wall thickness in the pre-cirrhotic stage indicates the role of HCV in this structural abnormality which may be a co-factor for cardiac structural and functional abnormalities observed in more advanced stages of cirrhosis when portal hypertension develops causing deleterious effects on systemic haemodynamics.

While HCV is the cause of various and different forms of heart disease worldwide, relatively few cardiologists are aware of it as an etiologic agent of heart disease nor its treatment. HCV causes various cardiomyopathies such as hypertrophic and dilated cardiomyopathies, arrhythmogenic right ventricular cardiomyopathy/dysplasia, myocarditis, arrhythmias, conduction disturbances and QT prolongation. Cardiac troponins I and T and N-terminal pro-B-type natriuretic peptide(NT-proBNP) are good biomarkers in diagnosing HCV heart disease in HCV positive patients.

Atherosclerosis involves an inflammatory process and as viral infections are common etiologic agents of inflammation, viral infections such as HCV may be involved in atherosclerosis and athero-thrombosis.

Immunogenetic factors may play a role in the development of different phenotypes of HCV heart diseases. Studies on human leukocyte antigen (HLA) demonstrated that immunological involvement of DPB1 (an HLA class II histocompatibility antigen) gene may play a role in HCV-related cardiomyopathies and development at the allelic manner level via polymorphic amino acids residues. Each clinical outcome of HCV infection had a different HLA-mediated immune response explained by different risk alleles among HCV-related diseases

including chronic liver diseases, asymptomatic carrier and HCV-cardiomyopathies.

It is to be noted, however, that HCV-related dilated cardiomyopathy is more associated with alleles of the non-HLA genes than the HLA genes themselves, indicating HCV-related dilated cardiomyopathy and hypertrophic cardiomyopathy develop primarily due to different pathogenic mechanisms. HCV infection has different effects on the heart according to the host genetics and geographic regions. HCV is located in infiltrating cells, mostly monocytes/macrophages in various organs, and this suggests that these cells are the major target of HCV.

The diverse clinical biology of HCV and the presence of multiple extrahepatic disease syndromes could be explained by the effect of hematopoietic tissues – specifically monocytes/macrophages in the bone marrow on the virus via immune escape and viral modulation of host immune responses. Because the virus can spread locally through the lymphatic system where it reaches the perihepatic lymph nodes, this may be a cause for infection of the peripheral immune cells prior to recirculation. It has been suggested that CD68 monocytes/macrophages are the major target of HCV, and that CD3-positive T cells or CD20-positive B-cells are not major targets. These findings suggest that pharmacologic preparations targeting leukocyte infection may be used to treat HCV.

There is a need for new trials of therapeutic agents against HCV infections (including HCV-induced heart diseases) based on the new hypothesis that the primary target of HCV infection is the mononuclear cell compartment. In this light, anti-inflammatory therapy by anti-histaminic agents and pycnogenol may be promising therapeutic agents.

Acknowledgments

We thank Dr. Steven Tracy for helpful comments.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Matsumori A, Matoba Y, Sasayama S. Dilated cardiomyopathy associated with hepatitis C virus infection. Circulation. 1995;92 (9):2519–2525.

•• **First documentation of heart disease caused by HCV**

2. Matsumori A, Yutani C, Ikeda Y, et al. Hepatitis C virus from the hearts of patients with myocarditis and cardiomyopathy. Laboratory Investigation. 2000;80(7):1137–1142. .
3. Matsumori A. Hepatitis C virus and cardiomyopathy. Circ Res. 2005;9:144–147.
4. Omura T, Yoshiyama M, Hayashi T, et al. Core protein of hepatitis C virus induces cardiomyopathy. Circ Res. 2005;96:148–150.
5. Pozzi M, Redaelli E, Ratti L, et al. Time course diastolic dysfunction in different stages of chronic HCV related liver diseases. Minerva Gastroenterol Dietol. 2005.
6. Rombola F, Spinoso A, Bertuccio SN. Cardiac manifestations during viral acute hepatitis. Infez Med. 2006;14:29–32.
7. Bertuccio SN, Rombolà F, Bertuccio A, et al. HCV infection and pericarditis: an extrahepatic manifestation? Infez Med. 2005;1:42–44.
8. Matsumori A Cardiovascular effects of HCV. Scientific day in research institute of ophthalmology. December 4,2007; Cairo, Egypt.
9. Nordin C, Kohli A, Beca S, et al. Importance of hepatitis C co-infection in the development of QT prolongation in HIV-infected patients. J Electrocardiol. 2006;39:199–205.
10. Chimenti C, Calabrese F, Thiene G, et al. Inflammatory left ventricular microaneurysms as a cause of apparently idiopathic ventricular tachyarrhythmias. Circulation. 2001;104(2):168–173. .
11. Shichi D, Kikkawa EF, Ota M, et al., The haplotype block, NFKBIL1-ATP6V1G2-BAT1-MICB-MICA, within the class III-class I boundary region of the human major histocompatibility complex may control susceptibility to hepatitis C virus-associated dilated cardiomyopathy. Tissue Antigens. 66(3): 200–208. 2005.

• **Important publication suggesting that MHC may control susceptibility to HCV cardioimyopathy.**

12. Ishizaka N, Ishizaka Y, Takahashi E, et al., Association between hepatitis C virus seropositivity, carotid-artery plaque, and intima-media thickening. Lancet (London, England). 359(9301): 133–135. 2002.

• **Important publication supporting that HCV may cause atherosclerosis.**

13. Navarro-Gonzalez JF, Mora-Fernandez C, De Fuentes MM, et al. Inflammatory molecules and pathways in the pathogenesis of diabetic nephropathy. Nature Rev Nephrol. 2011;7(6):327–340. .
14. Matsumori A, Shimada T, Shimada M, et al. Immunoglobulin free light chains: an inflammatory biomarker of diabetes. Inflamm Res. 2020;69:715–718.

• **Important recent publication supporting a role of inflammation in diabetes**

15. Drazilova S, Gazda J, Janicko M, et al. Chronic hepatitis C association with diabetes mellitusand cardiovascular risk in the era of DAA therapy. Can J Gastroenterol Hepatol. 2018;2018:6150861.
16. Huang YW, Yang SS, Fu SC, et al. Increased risk of cirrhosis and its decompensation in chronic hepatitis C patients with new-onset diabetes: a nationwide cohort study. Hepatology. 2014;60(3):807–814. .
17. Shintani Y, Fujie H, Miyoshi H, et al. Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. Gastroenterology. 2004;126(3):840–848. .
18. Vanni E, Abate ML, Gentilcore E, et al. Sites and mechanisms of insulin resistance in nonobese, nondiabetic patients with chronic hepatitis C. Hepatology. 2009;50(3):697–706. .
19. Sheikh MY, Choi J, Qadri I, et al. Hepatitis C virus infection: molecular pathways to metabolic syndrome. Hepatology. 2008;47 (6):2127–2133. .
20. Bastard J-P, Maachi M, Van Nhieu JT, et al. Adipose tissue IL-6 content correlates with resistance to insulin activation of glucose uptake both in vivo and in vitro. J Clin Endocrinol Metab. 2002;87 (5):2084–2089. .
21. Nelson DR, Lim HL, Marousis CG, et al. Activation of tumor necrosis factor-alpha system in chronic hepatitis C virus infection. Dig Dis Sci. 1997;42:2487–2494.

22. Lecube A, Hernández C, Genescà J, et al. Proinflammatory cytokines, insulin resistance, and insulin secretion in chronic hepatitis C patients: a case-control study. Diabetes Care. 2006;29:1096–1110.
23. Mirza MS. Obesity, visceral fat, and NAFLD: querying the role of adipokines in the progression of nonalcoholic fatty liver disease. ISRN Gastroenterol. 2011;2011:592404.
24. Tang W, Xu Q, Hong T, et al. Comparative efficacy of anti-diabetic agents on nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized and non-randomized studies. Diabetes Metab Res Rev. 2016;32:200–216.
25. Calzadilla-Bertot L, Vilar-Gomez E, Torres- Gonzalez A, et al. Impaired glucose metabolism increases risk of hepatic decompensation and death in patients with compensated hepatitis C virus-related cirrhosis. Dig Liver Dis. 2016;48:283–290.
26. Lonardo A, Adinolfi LE, Petta S, et al. Hepatitis C and diabetes: the inevitable coincidence? Expert Rev Anti Infect Ther. 2009;7:293–308.
27. Babiker A, Jeudy J, Kligerman S, et al. Risk of cardiovascular disease due to chronic hepatitis c infection: a review. J Clin Transl Hepatol. 2017;5:343–362.
28. Targher G, Bertolini L, Padovani R, et al. Differences and similarities in early atherosclerosis between patients with non-alcoholic steatohepatitis and chronic hepatitis B and C. J Hepatol. 2007;46:1126–1132.
29. Mostafa A, Mohamed MK, Saeed M, et al. Hepatitis C infection and clearance: impact on atherosclerosis and cardiometabolic risk factors. Gut 2010;59:1135–1140.
30. Boddi M, Abbate R, Chellini B, et al. Hepatitis C virus RNA localization in human carotid plaques. J Clin Virol. 2010;47:72–75.
31. Adinolfi LE, Rinaldi L, Nevola R. Chronic hepatitis C, atherosclerosis and cardiovascular disease: what impact of direct-acting antiviral treatments? World J Gastroenterol. 2018;24:4617–4621.
32. Petta S, Adinolfi LE, Fracanzani AL, et al. Hepatitis C virus eradication by direct-acting antiviral agents improves carotid atherosclerosis in patients with severe liver fibrosis. J Hepatol. 2018;69:18–24.
33. Vassalle C, Maisini S, Bianchi F, et al. Evidence of association between hepatitis C virus seropositivity and coronary artery disease. Heart. 2004;90:565–566.
34. Haji SA, Starling RC, Avery RK, et al. Donor hepatitis C seropositivity is an independent risk factor for the development of accelerated coronary vasculopathy and predicts outcome after cardiac transplantation. J Heart Lung Transplant. 2004;23:277–283.
35. Marelli D, Bresson J, Laks H, et al. Hepatitis C-positive donors in heart transplantation. Am J Transplant. 2002;2:443–447, Heart Transplant Program, University of California, Los Angeles, USA
36. Peng Q, Wei Z. Lau BHS Pycnogenol inhibits tumor necrosis factor-α-induced nuclear factor kappa B activation and adhesion molecule expression in human vascular endothelial cells. Cell Mol Life Sci. 2000;57:834–841.
37. Cho KJ, Yun CH, Yoon DY, et al. Effect of bioflavonoids extracted from the bark of Pinus maritime on proinflammatory cytokine interleukin-1 production in lipopolysaccharide-stimulated RAW 2647. Toxicol Appl Pharmacol. 2000;168:64–71.
38. Bayeta E. Pycnogenol inhibits release of reactive oxygen species and NO from macrophages. Nutr Res. 2000;20:249–259.
39. Ezzikouri S, Nishimura T, Kohara M, et al. Inhibitory effects of Pycnogenol on hepatitis C virus replication. Antiviral Res. 2015;113:93–102.
40. Hiramatsu SH, Maruyama T, Ito H, et al. Influence of Interferon Therapy on signal-averaged and ambulatory electrocardiograms in patients with chronic active hepatitis. Int Heart J. 2005;46:1033–1040.
41. Frustaci A, Calabrese F, Chimenti C, et al. Lone hepatitis C virus myocarditis responsive to immunosuppressive therapy. Chest. 2002;122:1348–1356.
42. Matsumori A, Shimada M, Obata T. Leukocytes are the major target of hepatitis C virus infection: possible mechanism of multiorgan involvement including the heart. CVD Prevention and Control. 2010;5:51–58.
•• **Important publication supporting that leukocytes are the major target of HCV.**
43. Matsumori A, Otani M, Otani H, et al. Hepatirtis C virus infection as a cause of cardiomyopathies and nephritis. (abstract). Presented at International Congress of Cardiomyopathies and Heart failure, 2016, Kyoto, Japan.
44. Fueda Y, Kotera H, Matsumori A. Prevention of nutritional deficiencies in chronic hepatitis C patients. New virus removal treatment. ESPEN 2019. ESPEN19-LB–2137.
45. Haykal M, Negm H, Negm E, et al. Assessment of myocardial functions in Egyptian patients with hepatits C viral infection. Master thesis 2008; 111–112
46. Haykal M Assessment of left atrial functions in HCV patients with and without cardiovascular risk factors. Poster presentation. Cardioalex conference 2010.
47. Saleh A, Matsumori A, Negm H, et al. Assessment of cardiac involvement of hepatitis C virus; tissue Doppler imaging and NT pro BNP study. J Saudi Heart Assoc. 2011;23:217–223.
48. Haykal M, Matsumori A, Negm H. Anti-inflammatory treatment with cetirizine improves refractory heart failure in patients with hepatitis C virus- induced myocarditis. Can J Cardiol. 2014;30(10): S121.