Cardiovascular Manifestations of Hepatitis C Virus

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KEYWORDS

• Hepatitis C virus • Carotid atherosclerosis • Coronary artery disease
• Cardiovascular mortality • Stroke • Peripheral artery disease

KEY POINTS

- Hepatitis C virus (HCV) infection is a prevalent condition associated with numerous extrahepatic manifestations, including cardiovascular manifestations.
- Epidemiologic studies have found that HCV is associated with cardiovascular mortality.
- HCV is also associated with carotid atherosclerosis, an increased risk of cerebrovascular events, coronary heart disease, and acute coronary events.
- Sustained virological response with interferon-based regimens is associated with reduced cardiovascular events, although this must be validated with newer direct-acting antivirals.
- The association between HCV and cardiovascular events may have significant economic and public health implications if cardiovascular risk prevention becomes a validated indication for therapy.

INTRODUCTION

Approximately 1% of the world's population, or 71 million people, are infected with the hepatitis C virus (HCV).[1] HCV is a major cause of chronic liver disease, culminating in cirrhosis, hepatocellular carcinoma, and increased hepatic-related mortality.[2] However, in addition to hepatic manifestations of HCV, multiple cohort longitudinal studies have underlined the important morbidity of extrahepatic manifestations of HCV.[3] The

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spectrum of extrahepatic manifestations of HCV is wide, ranging from cryoglobulinemia to neurologic manifestations but among the more intriguing associations that has been unraveled in the past decades is the association with metabolic alterations and with increased cardiovascular diseases.[3]

HCV, in particular genotype 3, induces steatosis, morphologically similar to that found in other causes of steatosis but with differing pathogenic mechanisms and prognostic implications.[4,5] In addition, the relationship between insulin resistance and HCV is equally complex with an increased risk of insulin resistance in HCV patients.[5] However, despite seemingly a more metabolic profile in HCV subjects, HCV infection is associated with reduced cholesterol serum levels or a more protective lipid profile,[6] further confusing the association between HCV and cardiovascular risk factors.

In recent years, the association between HCV infection and cardiovascular disease has been further examined in several epidemiologic studies. Due to the high prevalence of both cardiovascular disease and HCV, evidence connecting the 2 has occasionally been challenging to tease out. This article discusses the epidemiologic evidence and potential mechanisms linking the 2 and the impact of antiviral therapy on cardiovascular disease (Fig. 1).

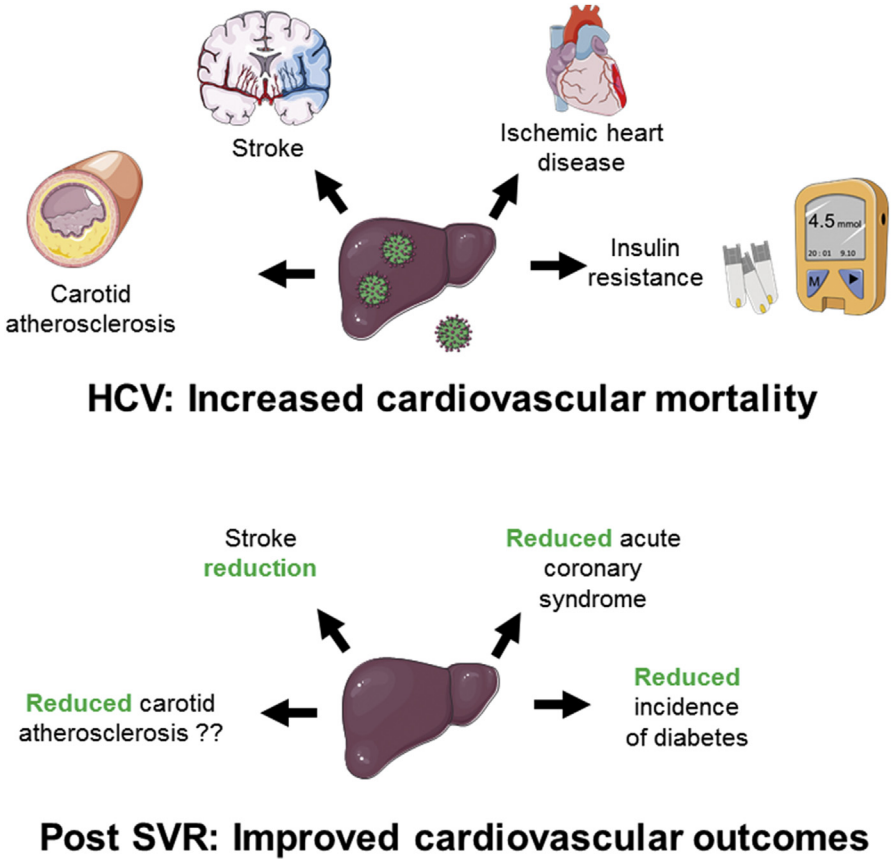

Fig. 1. Spectrum of the current understanding of cardiovascular manifestations of HCV infection before (*top panel*) and after (*bottom panel*) sustained virological response (SVR). (*Courtesy of* Servier Medical Art, Suresnes, France [www.servier.fr].)

HEPATITIS C VIRUS AND CARDIOVASCULAR MORTALITY

When dealing with the interaction between HCV and cardiovascular disease, the most pressing question remains whether HCV infection is associated with increased cardiovascular mortality. Surprisingly, a limited number of studies have attempted to answer this question and the results are somewhat contradictory. A retrospective cohort of more than 10,000 HCV-positive blood donors noted an increase in cardiovascular mortality in the HCV-positive group (hazard ratio [HR] 2.2, 95% CI 1.41–3.46).[7] An Asian cohort of more than 1000 HCV-positive individuals, the Risk Elevation of Viral Load Elevation and Associated Liver Disease/Cancer in HCV (REVEAL-HCV) study based in Taiwan, similarly found an increased risk of mortality for extrahepatic disease, when compared with HCV-negative individuals and, in particular, a higher risk of death from circulatory disease (HR 2.77, 95% CI 1.49–5.15).[2] In contrast, an Australian cohort of nearly 30,000 opioid substitution therapy recipients did not find increased cardiovascular mortality in HCV-positive individuals, although it may be argued that the population examined was different in this case to the other studies.[8] A systematic review and meta-analysis of these 3 studies nonetheless found a significant association between cardiovascular mortality and HCV infection (odds ratio [OR], 1.65; 95% CI 1.07 to 2.56, $P = .02$), although the investigators noted significant heterogeneity in the studies, suggesting that additional confounders or factors are yet to be identified in the link between HCV infection and cardiovascular mortality.[9] Similarly, in dialysis subjects a systematic review of 14 observational studies also identified an increased risk of cardiovascular mortality in HCV-positive individuals compared with HCV-negative controls (risk ratio 1.26, 95% CI 1.10–1.45).[10]

HEPATITIS C VIRUS AND SPECIFIC CARDIOVASCULAR DISEASE MANIFESTATIONS

Hepatitis C Virus Infection and Carotid Atherosclerosis

Japanese investigators were the first to identify a link between HCV infection and carotid atherosclerosis.[11–14] For instance, a cross-sectional study of 4784 individuals, including 2.2% positive for HCV, found that HCV seropositivity was associated with an increased risk of carotid-artery plaque (odds ratio [OR] 1.92, 95% CI 1.56–2.38, $P = .002$) and carotid intima-media thickening (IMT; OR 2.85, 95% CI 2.28–3.57, $P<.0001$).[12] These findings were confirmed in another Japanese study finding that HCV, but not hepatitis B virus infection, was associated with increased pulse wave velocity, a measure of arterial stiffness, in 7514 subjects.[13] More recently, the association between carotid atherosclerosis and HCV infection has also been reported in non-Asian populations. A prospective study in Italy by Petta and colleagues[15] in 174 consecutive genotype 1 HCV subjects found that HCV subjects had significantly more carotid atherosclerotic plaques and increased IMT when compared with controls. In addition, degree of liver fibrosis and more advanced age were independently associated with carotid plaques in multivariable regression.[15] Similarly, a cross-sectional Egyptian study in 329 HCV-positive subjects, found increased IMT in HCV-infected subjects when compared with individuals never infected with HCV using multivariable regression.[16] Finally, a large study based in Taiwan, including 7641 HCV-positive subjects and more than 30,000 controls based on health insurance claims data, found that that the excess risk of peripheral arterial disease development in HCV-infected subjects is 1.43-fold higher (95% CI 1.23–1.67) compared with non-HCV subjects.[17]

Although the association between coronary atherosclerosis and HCV has been validated in a wide variety of clinical settings, some conflicting studies have not identified this association. For instance, in the United States, a cross-sectional study based in HCV–human immunodeficiency virus (HIV) coinfected and HCV-monoinfected

subjects from the Women's Interagency HIV Study found that HCV infection was associated with increased IMT and presence of carotid plaques in univariable analysis but not in multivariable analysis when adjusted for other factors.[18] Despite a few negative studies displaying the lack of association, a systematic review has recently clarified that HCV infection was associated with carotid atherosclerotic plaques (pooled OR 2.27, 95% CI 1.76–2.94, $P<.001$) without significant heterogeneity between studies.[9] In addition, when pooling 7 case-control studies, this systematic review identified increased IMT in HCV subjects albeit in the presence of significant heterogeneity.[9]

Hepatitis C Virus Infection and Cerebrovascular Events

In light of the significant association between HCV infection and carotid atherosclerotic plaques, it would be expected that this would lead to an increased number of cerebrovascular events in HCV-positive subjects. For instance, in a community-based prospective cohort study, Lee and colleagues[19] found that during 382,011 person-years of follow-up the cumulative risk of cerebrovascular deaths was 1.0% and 2.7% for HCV-negative and HCV-positive, respectively ($P<.001$). This result was confirmed in multivariable cox regression and, interestingly, an association with HCV RNA levels was noted, although no significant association between HCV genotype and cerebrovascular death was identified.[19] Conversely, Younossi and colleagues[20] assessed the relationship between HCV and cardiovascular risk factors and outcomes using the US National Health and Nutrition Examination Surveys (NHANES), and they found that, although HCV infection was independently associated with certain cardiovascular outcomes, it was not associated with stroke. The systematic review cited previously nevertheless confirmed that HCV infection was associated with cerebrovascular events (pooled OR 1.35, 95% CI 1.00–1.82, $P = .05$), although the significance threshold was barely met.[9] Of note, although the bulk of the data linking HCV and cerebrovascular events relate to ischemic events, some data suggest that HCV may also be linked to increased risk of intracerebral hemorrhage.[21]

Hepatitis C Virus Infection and Coronary Artery Disease

In an Italian cohort of subjects with coronary artery disease (CAD) and controls, HCV seropositivity was found to be associated with the presence of CAD (OR 3.2, 95% CI 1.1–9.2, $P<.05$) even after adjustment for confounding risk factors.[22] Although this study was a case-control study and, therefore, potentially biased, the investigators noted increased proportions of HCV-positive subjects with increasing number of coronary vessels affected ranging from 4.5% for 1-vessel disease to 8.4% for 3-vessel disease ($P<.05$).[22] These results were later confirmed in a national, observational United States cohort of more than 82,000 HCV-infected veterans and nearly 90,000 uninfected controls in which HCV infection was associated, in multivariable analysis, with a higher risk of CAD (HR 1.25, 95% CI 1.20–1.30).[23] Yet another retrospective cohort study, at the University of Arkansas in the United States, compared 8251 HCV-positive individuals with 14,799 HCV-negative subjects and found an increased incidence of CAD events compared with controls (4.9% vs 3.2%, $P<.001$).[24] In the HCV cohort, subjects with detectable HCV RNA had a significantly higher incidence of CAD events compared with subjects who had no detectable RNA (5.9% vs 4.7%, $P = .04$), further reinforcing the association between CAD and HCV infection. Recent data from the HIV-HCV coinfection literature also underline this association. For instance, a study found that when comparing men with or without HIV and HCV infection, HCV infection was significantly associated with a higher prevalence of coronary artery calcium (prevalence ratio 1.29, 95% CI 1.02–1.63) and, although HCV infection and HIV infection were independently associated with the

finding of any plaque, there was no evidence of a synergistic effect due to HIV-HCV coinfection.[25] In addition, a retrospective study in HIV-HCV coinfected subjects found that coinfected subjects had a greater incidence of cardiovascular disease events and/or death than HIV-monoinfected individuals (4% vs 1.2%, $P = .004$), further underlining the importance of a holistic, non–liver-centric approach to HCV monoinfected and HIV-HCV coinfected subjects.[26]

Some studies did not find a relationship between HCV and CAD. For instance, a retrospective cohort study among general practices in the United Kingdom, including 4809 HCV subjects and 71,668 matched controls with a median follow-up of 3.2 years, did not find a significant difference in the rates of myocardial infarction between HCV-positive and HCV-negative subjects (1.02 vs 0.92 events per 1000 person-years, $P = .7$).[27] Nevertheless, a systematic review of the available literature confirmed that the risk of an HCV-positive person to develop coronary atherosclerosis is about triple the risk in uninfected persons (OR 3.06, 95% CI 1.99–4.72),[28] whereas another systematic review found that HCV infection was associated with increased cardiovascular events (OR 1.20, 95% CI 1.03–1.40, $P = .02$).[9]

HEPATITIS C VIRUS INFECTION AND INSULIN RESISTANCE

Insulin resistance and/or type 2 diabetes is a known cardiovascular risk factor linked to cardiovascular morbidity and mortality. Although the evidence is complex and has been reviewed elsewhere,[5,29] multiple lines of evidence converge to suggest that there is a link between HCV and insulin resistance that may, in susceptible patients, lead to type 2 diabetes.

The epidemiologic evidence linking HCV to type 2 diabetes is multifaceted and complex to interpret because it is derived from retrospective and prospective clinical data often not collected primarily to assess for the effect of insulin resistance. A systematic review pooling 34 studies and a total of more than 300,000 subjects analyzed the risk of type 2 diabetes in subjects with HCV and found an OR of approximately 1.7 for type 2 diabetes in HCV patients (adjusted OR 1.68, 95% CI 1.15–2.20 for retrospective studies for instance).[30] This was later confirmed in another systematic review pooling 35 observational studies with a pooled OR of 1.7 for type 2 diabetes in HCV subjects compared with uninfected controls and a pooled OR of 1.9 when comparing to hepatitis-B infected controls.[31] In a longitudinal study of more than 1000 adults, HCV-positive patients at high risk of developing diabetes based on metabolic risk factors were 11 times more likely to develop diabetes than HCV-negative individuals, although this effect was not found in subjects at low risk of developing diabetes,[32] suggesting that HCV increases the risk of diabetes especially in predisposed individuals. Despite the clear epidemiologic link between HCV and insulin resistance, it remains unclear whether the magnitude of the increased cardiovascular risk in HCV patients is linked to the presence of insulin resistance, although type 2 diabetes is clearly associated with cerebrovascular events in HCV subjects, especially when the prevalence of type 2 diabetes is greater than 10%.[9]

IMPACT OF HEPATITIS C VIRUS SUSTAINED VIROLOGICAL RESPONSE ON CARDIOVASCULAR DISEASE

In the past years, direct-acting antivirals (DAAs) have revolutionized the management of HCV infection by achieving high rates of sustained virological response (SVR) with low rates of side effects and ever-shortening therapy duration. However, due to high costs, the effect of these therapies on hepatic but also extrahepatic and, in particular, cardiovascular, outcomes has been scrutinised.[33] For instance, in a

retrospective cohort study of 3113 HCV-positive individuals, interferon-based therapy use was associated with a significant reduction of stroke in HCV subjects (HR 0.39, 95% CI 0.16–0.95, $P = .039$) after adjusting for known prognostic factors, suggesting a potential benefit for interferon-based therapy to reduce cardiovascular events in HCV.[34] Another Taiwanese study, including 1411 HCV diabetic subjects treated with pegylated interferon and ribavirin matched by propensity-score to the same number of controls, found that HCV therapy was associated with less ischemic strokes (HR 0.53, 95% CI 0.30–0.93) and reduced rates of acute coronary syndrome (HR 0.64, 95% CI 0.39–1.06) in the specific population of HCV-infected diabetics.[35] In a Scottish cohort of HCV subjects, SVR was also associated with reduced cardiovascular disease (adjusted HR, 0.70, $P = .001$).[36] Finally, a recent French study in 1323 HCV subjects with compensated cirrhosis followed up for a median of 58 months found that subjects who had achieved SVR had a lower risk of cardiovascular events (HR 0.42, 95% CI 0.25–0.69, $P = .001$) and major adverse cardiac events, although there was no association with viral genotype.[37] Therefore, although there is a clear lack of data for the effect of DAA-based therapy on cardiovascular events, the evidence for interferon-based therapy points toward reduced cardiovascular risk after achieving SVR. This might be an important public health consideration to address the current prevalent DAA reimbursement strategies that limit payment only for patients with advanced liver disease and disregarding metabolic and cardiovascular risk factors.

PATHOGENESIS OF HEPATITIS C VIRUS–INDUCED CARDIOVASCULAR INJURY

The potential association between HCV infection and cardiovascular risk raises the question of the mechanism underlying this association. Metabolic factors may play a role. The insulin resistance associated with HCV leads to hyperglycemia, endothelial dysfunction, and inflammation, all of which produce vessel damage and unstable plaques. A recent study showed an increased cardiac left ventricular mass in normotensive HCV-positive individuals, similar to hypertensive subjects.[38] In addition, the investigators noted a significant correlation between insulin resistance and left ventricular mass among HCV-infected subjects, and a strong relationship between HCV viral load and both left ventricular mass and insulin resistance.[38] The presence of HCV may also induce a chronic, systemic inflammatory state with effects in distant organs and tissues. The immune response to HCV induces the upregulation of proinflammatory cytokines and chemokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6 and IL8, and chemokine ligand 2 (CCL2), which are released in the bloodstream and may amplify and worsen the inflammatory lesions outside of the liver.[39–41] Maruyama and colleagues[42] performed a myocardial scintigraphy study of HCV-infected subjects and found that 87% had myocardial perfusion defects. Interestingly, these myocardial defects seemed to fluctuate and improve after successful HCV eradication with interferon-based therapy.[42] The proinflammatory, profibrogenic milieu that characterizes long-standing, severe liver damage may be more prone to systemic effects. Consistent with this suggestion, in genotype 1 HCV subjects, severe hepatic fibrosis (F3/F4 vs F1/F2) was independently associated with the development of carotid plaque, according to a study by Petta and colleagues,[15] even among subjects younger than 55 years old. Finally, a direct colonization of atherosclerotic lesions cannot be excluded, in keeping with the observation that cardiovascular damage may correlate with viral load.[41,42] A single report identified HCV RNA sequences within plaque tissue[43] but this has not been independently confirmed.

SUMMARY

Increasing epidemiologic evidence suggests that there is a link between cardiovascular disease and HCV infection (see **Fig. 1**). Earlier studies showed an association between surrogate markers of cardiovascular disease, such as IMT and HCV infection[44]; however, this was not confirmed in other studies.[16] Subsequently, HCV infection has been associated with cerebrovascular disease[19] and CAD.[45] Although imperfect, numerous studies suggest a link between HCV infection and increased cardiovascular mortality independently of other known risk factors.[2,7] Although, there seems to be converging evidence underlying a possible association between chronic HCV infection and cardiovascular events, such as carotid atherosclerosis, cerebrovascular events, CAD, and other cardiovascular manifestations, the evidence is complex and other studies have not found such an association.[46] Far from being a purely academic discussion, further well-conducted prospective trials are required to answer this question. If validated, the improvement of cardiovascular outcomes by curing HCV, especially in individuals at high-risk for cardiovascular events, could represent an important future indication for HCV therapy regardless of liver disease staging. This would, of course, have important economic and public health implications, and could become the predominant indication for HCV therapy in the near future.

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