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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (10): Alcoholic liver disease

Peculiar characteristics of portal-hepatic hemodynamics of alcoholic cirrhosis

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Abstract

Alcohol-related cirrhosis is a consequence of heavy and prolonged drinking. Similarly to patients with cirrhosis of other etiologies, patients with alcoholic cirrhosis develop portal hypertension and the hepatic, splanchnic and systemic hemodynamic alterations that follow. However, in alcoholic cirrhosis, some specific features can be observed. Compared to viral cirrhosis, in alcohol-related cirrhosis sinusoidal pressure is generally higher, hepatic venous pressure gradient reflects portal pressure better, the portal flow perfusing the liver is reduced despite an increase in liver weight, the prevalence of reversal portal blood flow is higher, a patent paraumbilical vein is a more common finding and signs of hyperdynamic circulations, such as an increased cardiac output and decreased systemic vascular resistance, are more pronounced. Moreover, alcohol consumption can acutely increase portal pressure and portal-collateral blood flow. Alcoholic cardiomyopathy, another pathological consequence of prolonged alcohol misuse, may contribute to the hemodynamic changes occurring in alcohol-related cirrhosis. The aim of this review was to assess the portal-hepatic changes that occur in alcohol-related cirrhosis, focusing on the differences observed in comparison with patients with viral cirrhosis. The knowledge of the specific characteristics of this pathological condition can be helpful in the management of portal hypertension and its complications in patients with alcohol-related cirrhosis.

Key words: Alcohol-related cirrhosis; Portal hypertension; Splanchnic flow; Hyperdynamic circulatory syndrome; Alcohol-related cardiomyopathy

Core tip: Patients with alcoholic cirrhosis develop portal hypertension and hemodynamics alterations similarly to patients with cirrhosis of other etiologies, but some specific features can be observed. Compared to viral cirrhosis, sinusoidal pressure is generally higher, hepatic venous pressure gradient reflects portal pressure better, the portal flow perfusing the liver is reduced despite an increase in liver weight, the prevalence of reversal portal blood flow is higher, a patent paraumbilical vein is a more common finding and signs of hyperdynamic circulations, such as an increased cardiac output and decreased systemic vascular resistance, are more pronounced.

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INTRODUCTION

Alcoholic liver disease is a consequence of heavy and prolonged drinking that can progress from hepatic steatosis through to steatohepatitis, liver fibrosis and

eventually cirrhosis. The molecular pathogenesis is a multifactorial process involving alcohol metabolism and secondary mechanisms such as oxidative stress, endotoxin, cytokines and immune regulators[1]. Similarly to patients with cirrhosis of other etiologies, patients with alcoholic cirrhosis are prone to develop portal hypertension. Several studies show that only one third of patients with alcoholic cirrhosis are hospitalized before decompensation, and in the first year after discharge they have a 6% risk of developing variceal bleeding, a 4% risk of developing hepatic encephalopathy and a 20% risk of developing ascites[2]. The main factor leading to decompensation of alcohol-related cirrhosis is the persistence of regular alcohol consumption.

The aim of this review is to assess the portal-hepatic changes that occur in alcohol-related cirrhosis, focusing on the differences observed in comparison with patients with viral cirrhosis.

PORTAL-HEPATIC HEMODYNAMICS

In cirrhosis, portal pressure increases because of enhanced resistance to portal outflow[3-5] and an increase in splanchnic blood flow[6,7]. Several vasoactive systems and molecules activated in portal hypertension, first of all nitric oxide (NO)[8,9], determine a marked splanchnic vasodilatation, which is responsible for the increased splanchnic blood flow and the onset of hyperdynamic circulation. This is characterized by increased cardiac output and heart rate, splanchnic arterial vasodilatation and reduced arterial blood pressure[10-13]. Central blood volume is reduced, because of its displacement to splanchnic circulation, resulting into a central hypovolemia[14]. These events lead to a secondary and massive activation of counter-regulatory systems, mainly the renin-angiotensin-aldosterone system and the sympathetic nervous system[15,16]. However, in cirrhosis, the presence of autonomic dysfunction causes a reduced sensitivity to vasoconstrictors in the systemic and splanchnic vessels that contributes to the splanchnic vasodilatation and hyperdynamic circulation caused by NO and other vasodilating systems[17-20].

In alcoholic cirrhosis, portal vein pressure is influenced by the consumption of alcohol: Klein *et al*[21] showed that after one year of abstinence, portal vein pressure and the size of esophageal varices almost halved. Resuming oral alcohol intake significantly increased portal pressure and portal-collateral blood flow, worsening the portal hypertensive syndrome[21]. In patients with alcohol-induced cirrhosis, besides the chronic effects on the liver tissue and hemodynamics, ethanol can acutely increase portal pressure and portal-collateral blood flow. The increase in hepatic venous pressure gradient is maximum at 15 min and remains significant at 45 min after oral ethanol intake[22]. Hepatocyte swelling, a characteristic of alcoholic liver disease observed after the acute administration of alcohol[23-25], may determine an acute increase in intrahepatic resistance and, in turn, increased portal pressure.

Specific-features of alcohol-related cirrhosis are listed in Table 1.

Some studies have reported a higher portal pressure in patients with alcoholic cirrhosis compared with patients with viral cirrhosis at the same stage[26-28]. However, this finding may also relate to the methods used to determine portal pressure (vide infra).

In a study conducted by our group[29] the portal flow perfusing the liver per gram of liver tissue was lower in patients with alcoholic cirrhosis compared with patients with viral cirrhosis. On the other hand, despite a similar degree of severity of the disease, liver weight was higher in alcoholic cirrhosis. These findings suggest a more marked sinusoidal distortion and consequent higher sinusoidal resistance in alcoholic cirrhosis. Indeed, patients with alcohol-related liver disease show a marked reduction in relative sinusoidal area compared to patients with non-alcoholic cirrhosis. Moreover, only in patients with alcohol-related cirrhosis and markedly reduced sinusoidal area, portal pressure correlated inversely with sinusoidal area; this was not the case in patients with non-alcoholic liver disease[30]. These data are supported by another study in which portal venous tissue blood flow was evaluated in cirrhosis of different etiologies by Computerized Tomography[31]. In alcohol-related cirrhosis, portal venous and total hepatic tissue blood flow were significantly lower compared to hepatitis C virus (HCV)-related cirrhosis[31].

Reversal blood flow is a negative prognostic index in patients with liver cirrhosis. It is generally associated with the transit of blood from the portal vein to extrahepatic shunts or with the onset of ascites[32,33]. Hepatofugal flow is a characteristic feature of alcoholic cirrhosis, while it is not commonly observed in viral cirrhosis[33]. In patients with alcohol-related cirrhosis, reversal portal blood flow correlates with a more severe degree of hepatic failure[33-36]. The reason why reversal blood flow has a higher prevalence in alcoholic liver cirrhosis may relate, at least to some extent, to the association between alcohol-related etiology and portal-systemic shunts and pericentral fibrosis[33].

In patients with portal hypertension, portal-systemic collaterals develop as a consequence of the increased resistance to flow[37,38]. A patent paraumbilical vein is a common portal-systemic collateral in cirrhosis and its prevalence is significantly higher in patients with alcohol-related cirrhosis compared to those with viral cirrhosis[29,39]. Moreover, Le Moine *et al*[26] found that the prevalence of variceal bleeding was higher in patients with alcoholic cirrhosis compared to those with viral cirrhosis.

Also the severity of hyperdynamic syndrome seems to vary between patients with cirrhosis of different etiologies. A study including patients with both alcoholic and HCV-related cirrhosis showed that splanchnic arterial vasodilatation is more marked in the alcoholic group. As expected, in both groups cardiac output was higher and systemic vascular resistance lower compared to healthy volunteers, but the pathological modifications were more

Table 1 Portal-hepatic hemodynamics in alcohol-related and viral cirrhosis

	Alcohol-related cirrhosis	Viral cirrhosis
Increase in intrahepatic resistance	Increase in sinusoidal and postsinusoidal resistance	Increase also in presinusoidal resistance
Portal pressure	Higher increase in sinusoidal pressure	Lower increase in sinusoidal pressure
Hepatic venous pressure gradient	Accurately reflects portal pressure	Less accurately reflects portal pressure
Portal perfusion of the liver per gram of tissue in end-stage liver disease	Higher reduction	Lower reduction
Reversal portal blood flow	More common	Rare
Patent paraumbilical vein	More common	Less common
Hyperdynamic circulation	More pronounced	Less pronounced

pronounced in the alcoholic group. Moreover, the hepatic congestion index measured by ultrasound was increased only in alcoholic patients with cirrhosis and ascites[40].

PORTAL PRESSURE MEASUREMENT

Portal pressure is currently estimated by the measurement of the hepatic venous pressure gradient, which is the difference between wedged and free hepatic vein pressure, measured by hepatic vein catheterization[41-43]. The method measures indirectly the sinusoidal pressure, thus estimating portal pressure[44,45]. Therefore, it is not able to detect an increase in presinusoidal resistance. Indeed, it has been shown that the measurement of wedged hepatic vein pressure closely reflects portal pressure in patients with alcoholic cirrhosis, but it underestimates portal pressure in patients with nonalcoholic cirrhosis[46], probably because of a pre-sinusoidal component to the portal hypertension of viral cirrhosis[47]. The measurement of wedged hepatic venous pressures in alcohol-related cirrhosis provides a reliable estimate of the severity of portal hypertension, while hemodynamic evaluation of nonalcoholic cirrhosis should include direct portal vein pressure measurement in order to avoid underestimation of the portal-hepatic gradient[46,48].

The different anatomical changes of intrahepatic portal circulation in alcoholic and viral cirrhosis was confirmed by a meta-analysis of the agreement between wedge hepatic vein pressure and portal vein pressure in cirrhotic patients[49]. Wedged hepatic pressure measurement correlated well with direct portal pressure measurement and the agreement was sufficiently good to use this as a surrogate measurement[49-51]. However, the agreement between the two measurements was lower in HCV-related cirrhosis compared to alcohol-related cirrhosis[49]. The lack of a presinusoidal component to portal hypertension in alcoholic cirrhosis may explain why an inverse relationship between portal blood velocity and flow, and hepatic venous pressure gradient was reported only in a study of patients with alcoholic cirrhosis[52].

ALCOHOLIC CARDIOMYOPATHY

In patients with cirrhosis, progressive stages of cardiac disease have been documented. Cirrhotic cardiomyopathy is characterized by impaired cardiac contractility during preload and afterload, decreased β-adrenergic receptor function, post-receptor dysfunction, defective excitation-contraction coupling, conductance abnormalities[53] and decreased heart rate variability[54], regardless of the etiology of cirrhosis. Alcohol-related cardiomyopathy, one of the consequences of prolonged alcohol consumption, can occur in subjects both with and without cirrhosis[55,56]. While chronic (10-12 years) consumption of amounts of ethanol as low as 25 g/d in males and 12 g/d in females is associated with an increased risk of cirrhosis, > 90 g/d for at least 5 years seem to be needed for inducing changes in cardiac structure and function[2,57-60]. The pathogenesis of such dysfunction is probably related to cell death and modifications in myocyte homeostasis[61], including oxidative damage, deposition of triglycerides, impaired myofilament calcium sensitivity, altered protein synthesis and direct effect of acetaldehyde, a major product of alcohol metabolism[62]. The dysfunction of the autonomic nervous system which is typical of alcohol misusers also contributes to the cardiac alterations observed in this condition[63]. Alcoholic cardiomyopathy is characterized by left ventricular hypokinesis, left ventricular dilatation, tachyarrhythmias (transient atrial fibrillation), QT interval prolongation and sudden cardiac death[64-66]. Despite the different pathogenesis, the distinction with cirrhotic cardiomyopathy can be difficult, since some features, such as QT interval prolongation and autonomic dysfunction, are common. On the other hand, 4-chamber dilatation with normal or decreased left ventricular wall thickness is more commonly observed in alcohol-related cirrhosis[67,68], while cirrhotic cardiomyopathy is more often characterized by hypertrophy, at least in the early stages[69]. It is plausible that the cardiac dysfunction which characterizes alcohol-related cardiomyopathy may contribute to the hemodynamic changes occurring in alcohol-related cirrhosis.

CONCLUSION

Alcohol-related cirrhosis is characterized by some peculiar features of portal-hepatic hemodynamics, compared to cirrhosis of other etiologies. The knowledge of the specific characteristics of this condition may help in the management of portal hypertension and its complications in patients with alcohol-related cirrhosis.

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