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TOPIC HIGHLIGHT

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Hagen-Poiseuille's law: The link between cirrhosis, liver stiffness, portal hypertension and hepatic decompensation

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Abstract

The onset of hepatic decompensation in cirrhosis heralds an accelerated downhill course with poor outcome. The sole predictor of this decompensation in cirrhosis is increased hepatic vein to portal vein gradient hepatic venous pressure gradient (HVPG). Surrogate markers of liver function or hepatic reserve appear to be less relevant. The hepatic sinusoids become less elastic and more rigid as liver fibrosis and cirrhosis progress. We propose that the Hagen-Poiseuille's law, which applies to rigid, but not elastic vessels, determines the pressure-flow characteristics in the sinusoids. In the rigid cirrhotic liver, HVPG rises dramatically with any change in net surface area or radius, r^4 of the vasculature that follows surgical resection. This review relates liver stiffness to the risk of decompensation in patients with cirrhosis. The liver has a unique dual blood supply comprising a low pressure portal vein and high pressure hepatic artery. We compare the complexity of autoregulation in the normal elastic liver with that in the rigid cirrhotic liver. Therapeutic modalities to reduce portal pressure may reduce the risk of hepatic decompensation and improve outcomes in cirrhosis.

Key words: Portal hypertension; Liver stiffness; Hagen-Poiseuille's law

Core tip: Unlike the elastic normal liver, hepatic sinusoidal vessels become progressively more rigid with advancing cirrhosis and thus subject to Hagen-Poiseuille's law. Thereafter, pressure gradient is inversely proportional to the fourth power of vessel radius, r^4. Surgical resection reduces liver volume and thus net diameter of sinusoids, without reducing hepatic blood inflow. The net reduction in r, at the same flow rates increases pressure gradient by a factor r^4 and likely accounts for the poor outcomes in patients with cirrhosis and established portal hypertension. Reducing hepatic venous pressure gradient reduction

as part of the management of cirrhosis may reduce the risk of decompensation.

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INTRODUCTION

Functional hepatic reserve and liver regenerative potential

The normal healthy liver has a large functional redundancy or reserve (FHR)[1,2] and a significant regenerative potential (RP)[3] that allows it to withstand major damage and injury. Thus, over 75 percent of an adult liver, in which surrogate markers of FHR such as bilirubin and hepatic indocyanine green clearance are normal, can be resected without risk of liver failure. As cirrhosis advances these markers become less predictive of post resection decompensation[4].

Cirrhosis occupies a broad, complex, dynamic pathologic spectrum, with two distinct stages, both with different prognostic implications. There is the compensated stage, with a median survival of 12 years and the decompensated (variceal bleeding, hepatic encephalopathy and ascites) with a median survival of only two years[5].

In the cirrhotic patient, the hepatic venous pressure gradient, hepatic venous pressure gradient (HVPG) stands alone, in multiple logistic regression analysis, as the only independent variable predictive of post resection decompensation[6-12]. This pivotal role of HVPG is unexplained.

Increased HVPG also influences the regenerative potential of the cirrhotic liver. In the presence of increased HVPG, resection is associated with the differential expression of genes associated with apoptosis, rather than regeneration[13]. Several explanations have been proposed. The repeated cell divisions that underlie the process of cirrhosis may have led to senescence and telomere shortening and reduced the regenerative potential RP of the cirrhotic liver[14]. DNA damage checkpoint activation could also reduce the RP of the cirrhotic liver[15,16].

In this review, we propose that in contrast to the elastic vessel walls in the normal liver, cirrhotic sinusoids are rigid and therefore subject to the Hagen-Poiseuille's law. Thus, we argue that progression from the well compensated to the decompensated stage is merely a function of loss of elasticity. For any change in net sinusoidal surface area or radius r that follows surgical resection, sinusoidal pressure gradient rises dramatically by a factor equal to the fourth power of the radius, r^4, if blood flow is held constant. The resulting shearing forces can induce endothelial damage at high HVPG.

AUTOREGULATION OF BLOOD FLOW IN THE NORMAL AND CIRRHOTIC LIVER

The ability to maintain adequate blood flow, in the face of changes in the inflow perfusion pressure and consistent with metabolic demands is termed "autoregulation". This phenomenon, first described, for the kidneys, has since been demonstrated in several other organs[17] and classically involves active changes in the caliber of the inflow arterioles.

AUTOREGULATION: NORMAL *VS* CIRRHOTIC LIVER

The microvasculature of the liver is unique in that the blood supply is dual. Approximately 80 percent originates from the portal venous system at low pressure around 15 mmHg. The rest, around 20 percent derives from the hepatic artery, at considerably higher pressures that peak around 120 mmHg, in the terminal hepatic arteriole. The combined systems perfuse the hepatic sinusoids at pressures around 3-6 mmHg.

The portal venous system in the normal liver is a passive vascular bed. Active portal venous autoregulation has not been observed in the dog[18]. A myogenic response has been described in arterial resistance vessels that control blood flow in the liver.

Evidence for effective autoregulation in the normal pig liver is illustrated by the fact that a 62 percent resection increases portal venous pressure from 6.1 mmHg to just 8.2 mmHg, in spite of the significantly reduced net surface area or radius of the perfused sinusoids in the liver remnant. A 50% reduction in the radius of a rigid tube would be expected to increase the pressure gradient 16-fold at constant flow rate. After 75 percent resection, portal venous pressure merely doubles to 12 mmHg, suggesting a compensatory increase in r, likely related to autoregulation. It is only after more than 90 percent of the liver is resected that a major rise in sinusoidal pressure occurs. The rise in pressure leads to a marked increase in sinusoidal diameter and concomitant histological liver damage[19].

Several compounds have been designated as potential candidates for liver autoregulation: acetylcholine, endothelium derived relaxing factor NO, carbon monoxide CO and hydrogen sulphide H_2S are possible vasodilators; the three isopeptides of endothelium constricting factor endothelin ET, ET-1, ET-2 and ET-3 are possible vasoconstrictors. The adenosine washout hypothesis suggests that adenosine might exert physiological control and that the hepatic arterioles dilate, when adenosine builds up in the space of Mall. The targets for the candidate compounds include hepatic stellate cells that have a peri-sinusoidal distribution and smooth muscle cells that are

located proximal or distal to the hepatic sinusoids.

It is highly significant that in the normal liver, hepatic arterial flow is not essential to maintain liver viability. Acute ligation of the hepatic artery has little impact on liver metabolism. By contrast, when the main portal trunk is ligated, sinusoidal flow is significantly reduced[20].

The normal liver has symmetric architecture allowing blood to flow in an orderly fashion from portal vein and hepatic artery radicals within the portal triads and across the sinusoids to the hepatic vein. By contrast, disorganized nodules disrupt the symmetrical, acinar structure in the cirrhotic liver[21].

Scant data are available on hepatic blood flow in the cirrhotic liver in man, but some are available in animals. In the CCl_4 cirrhotic rat model, total hepatic flow is significantly reduced[22]. This is due mainly to reduced flow in the low-pressure portal venous system. There is some compensation for this from an increased hepatic artery flow, which doubles its contribution from 20 percent in the normal liver to 40 percent in the well-compensated cirrhotic liver.

The contribution may be higher in the decompensated cirrhotic. The hepatic arterial supply becomes even more important for maintaining viability of the cirrhotic liver, especially as the HVPG increases.

PRESSURE GRADIENT IN THE NORMAL AND CIRRHOTIC LIVER

The Hagen-Poiseuille equation $\Delta P = 128\ \mu LQ/\pi r^4$ is a physical law in fluid dynamics, which governs the pressure gradient ΔP, in a fluid with a viscosity μ, flowing through a rigid cylindrical pipe of length L, and radius r, at volumetric flow rate Q. Thus, the pressure gradient ΔP is inversely related to r^4 and any change in radius will result in an exponential change in the pressure gradient.

The normal liver is elastic. The sinusoidal vessels are distensible and thus not directly subject to the Hagen-Poiseuille law. Passive increases in vessel radius at least partially accommodate for any increase in flow, buffering changes in the hepatic vein to portal vein pressure gradient.

By contrast, with advancing cirrhosis, there is progressive rigidity associated with reduction in the radius of the vessel walls, which exponentially increase the pressure gradient. Increased HVPG increase sinusoidal shear stress and can worsen liver ischemia.

Liver elasticity can be independently assessed using magnetic resonance elastography magnetic resonance elastography or elastography, and liver stiffness by Fibroscan[23]. Liver stiffness is an independent predictor of hepatocellular carcinoma (HCC) outcome[24]. A number of recent studies have shown that transient elastography correlates well with HVPG[12,25]. These tests may be more predictive of post resection outcomes[10]. Meta-analysis of studies of liver stiffness suggest an association with risk of decompensation, liver cancer and death in patients with chronic liver disease[26].

DRUGS THAT REDUCE PORTAL HYPERTENSION

Systemic therapy-sorafenib

Sorafenib is an oral multi-kinase inhibitor that inhibits cell proliferation and angiogenesis. It targets several tyrosine kinases such as Raf kinase, vascular endothelial growth factor receptor 2 and 3 as well as platelet derived growth factor receptor beta. It is the only drug currently approved for the treatment of HCC[27].

An interesting and potentially important observation from animal models is that sorafenib reduces developing and established portal hypertension[28-30]. Two recent studies in patients with cirrhosis and HCC have demonstrated a decrease in portal venous flow or pressure on sorafenib[31,32], with a trend towards better survival in those patients with reduced HVPG (20.5 mo *vs* 10.6 mo). Two of the four responders received concomitant beta-blockers.

The effect of sorafenib on portal venous flow and portal pressure in patients with cirrhosis and HCC deserves further study. Sorafenib might exert this protective effect through reduction of portal pressure.

In the pivotal trial of sorafenib in HCC[27], liver tumor arising within a background of hepatitis C virus (HCV) cirrhosis faired better than with chronic HBV or other chronic liver disorders. One possible explanation might be that unlike HBV related HCC that can arise in non-cirrhotic livers, HCV infected patients are almost invariably cirrhotic[33]. Improved survival in these patients might reflect an effect of sorafenib on portal pressure.

Since a trend towards improved survival was observed in HCC patients on sorafenib that had reductions in HVPG[32], a combination of sorafenib plus propranolol, nadolol or carvedilol, obeticholic acid or statins in HCC patients might prove useful in increasing patient survival or in reducing the risk of decompensation post resection or trans-arterial chemo-embolization.

CONCLUSION

Scarring and nodule formation in the cirrhotic liver reduces elasticity and increases stiffness. With increasing stiffness, the sinusoidal vessel walls become rigid. Hagen-Poiseuille's law governs pressure-flow characteristics in the cirrhotic liver. Thus, HVPG increases exponentially in cirrhosis with reduction in sinusoidal vessel well, but less so in the normal liver. The consequent shearing forces can lead to severe damage to endothelial cells. Trials correlating portal pressure reduction using drugs such as sorafenib, propranolol, nadolol or carvedilol, obeticholic acid and statins, with outcomes in patients with increased portal pressure or cirrhosis may be warranted.

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