Pathophysiology of Portal Hypertension

Yasuko Iwakiri, PhD

KEYWORDS

• Hyperdynamic circulation • Fibrosis • Cirrhosis • Nitric oxide • Lymphatic system • Splenomegaly

KEY POINTS

- The primary cause of portal hypertension in liver cirrhosis is increased intrahepatic vascular resistance.
- A reduction of intrahepatic vascular resistance could ameliorate portal hypertension.
- Arterial vasodilatation in the splanchnic and systemic circulations worsens portal hypertension.

INTRODUCTION

Portal hypertension is a detrimental complication resulting from obstruction of portal blood flow, such as cirrhosis or portal vein thrombosis.[1,2] In liver cirrhosis, increased intrahepatic vascular resistance to the portal flow increases portal pressure and leads to portal hypertension (**Fig. 1**). Once portal hypertension develops, it influences extrahepatic vascular beds in the splanchnic and systemic circulations, causing collateral vessel formation and arterial vasodilation. This process helps to increase the blood flow into the portal vein, which exacerbates portal hypertension and eventually brings the hyperdynamic circulatory syndrome.[1,2] As a result, esophageal varices or ascites develops. This article discusses recent advances in understanding of factors that contribute to an increase in intrahepatic vascular resistance and an increase in blood flow in the splanchnic and systemic circulations, and the future directions of basic/clinical research in portal hypertension.

INTRAHEPATIC CIRCULATION

An Overview

The primary cause of portal hypertension in cirrhosis is an increase in intrahepatic vascular resistance. In cirrhosis, increased intrahepatic vascular resistance is a result

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Section of Digestive Diseases, Department of Internal Medicine, Yale University School of Medicine, 1080 LMP, 333 Cedar Street, New Haven, CT 06520, USA
E-mail address: yasuko.iwakiri@yale.edu

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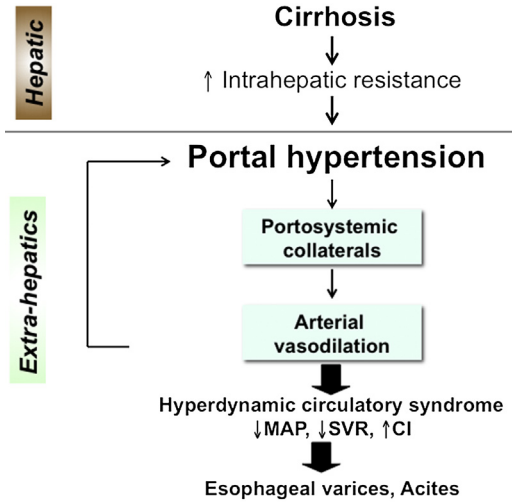

Fig. 1. Portal hypertension leads to the development of the hyperdynamic circulatory syndrome, characterized by decreased mean arterial pressure (MAP), decreased systemic vascular resistance (SVR), and increased cardiac index (CI).

of massive structural changes associated with fibrosis/cirrhosis and intrahepatic vasoconstriction.[2–4] It is reported that intrahepatic vasoconstriction accounts for at least 25% of increased intrahepatic vascular resistance.[5] Phenotypic changes in hepatic cells, such as hepatic stellate cells (HSCs) and liver sinusoidal endothelial cells (LSECs), are known to play pivotal roles in increased intrahepatic vascular resistance and have been studied intensively. This article summarizes important factors that increase intrahepatic vascular resistance in liver fibrosis/cirrhosis.

Endothelial cell dysfunction

LSECs are the first line of defense protecting the liver from injury,[2] and the cells exert diverse effects on liver functions including blood clearance, vascular tone, immunity, hepatocyte growth,[6] and angiogenesis/sinusoidal remodeling.[7,8] Therefore, LSEC dysfunction could lead to impaired vasomotor control (primarily vasoconstrictive), inflammation, fibrosis, and impaired liver regeneration,[1,9] all of which facilitate the development of liver cirrhosis and portal hypertension.

Decreased vasodilators Nitric oxide (NO) is likely the most potent vasodilator molecule known today. In cirrhotic livers, NO production/bioavailability is significantly diminished, which contributes to increased intrahepatic vascular resistance.[2,9–12] At least 2 mechanisms explain the decreased NO production. First, the NO synthesizing enzyme endothelial NO synthase (eNOS) is inhibited by negative regulators (such as caveolin-1), which are upregulated during cirrhosis; as a result, NO production decreases.[11] Details regarding eNOS regulation in liver cirrhosis can be found elsewhere.[2,12] Second, oxidative stress is increased in cirrhosis. LSECs receive oxidative stress in response to a wide variety of agents, such as bacterial endotoxins, viruses, drugs, and ethanol.[13–15] During cirrhosis, increased superoxide radicals spontaneously react with NO to form peroxynitrite ($ONOO^-$), an endogenous toxicant,[16] thereby decreasing NO's bioavailability as a vasodilator.[13] Antioxidant molecules such as vitamin C,[14] vitamin E,[17] superoxide dismutase,[15,18] and *N*-acetylcysteine[19]