Hemodynamic alterations in cirrhosis and portal hypertension

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Portal hypertension (PHT) is associated with hemodynamic changes in intrahepatic, systemic, and portosystemic collateral circulation. Increased intrahepatic resistance and hyperdynamic circulatory alterations with expansion of collateral circulation play a central role in the pathogenesis of PHT. PHT is also characterized by changes in vascular structure, termed vascular remodeling, which is an adaptive response of the vessel wall that occurs in response to chronic changes in the environment such as shear stress. Angiogenesis, the formation of new blood vessels, also occurs with PHT related in particular to the expansion of portosystemic collateral circulation. The complementary processes of vasoreactivity, vascular remodeling, and angiogenesis represent important targets for the treatment of portal hypertension. Systemic and splanchnic vasodilation can induce hyperdynamic circulation which is related with multi-organ failure such as hepatorenal syndrome and cirrhotic cardiomyopathy.

**Keywords:** Portal hypertension; Hyperdynamic circulation; Hepatic stellate cell; Endothelial cell; Intra hepatic vascular resistance

**INTRODUCTION**

Cirrhosis has been considered to be silent and static. However, we have recently recognized that cirrhosis is actually a tumultuous and dynamic disease. Cirrhosis is the final result of hepatic fibrosis and is reversible in the middle stages of development between fibrogenesis and fibrolysis. This disease leads to hemodynamic disorders that can have widespread impacts in the body according to the severity of the cirrhosis. Hemodynamic alterations including portal hypertension and hyperdynamic circulation are the main cause of morbidity and mortality in patients with cirrhosis.\(^1,3\) The pathophysiologic process of portal hypertension consists of three components: intrahepatic circulation, systemic (splanchnic) circulation, and collateral circulation. Additionally, continuous abnormalities in systemic circulation induce hyperdynamic circulation.\(^4,5\)

Portal pressure is due to intrahepatic resistance and portal blood flow, and is defined as a function of flow and resistance across the hepatic vasculature (pressure = flow/resistance). Development of portal hypertension can be influenced by changes in resistance and flow in the hepatic vasculature. Increased resistance of portal blood flow in cirrhotic liver induces portal venous dilatation and congestion of portal venous flow, leading to elevated portal pressure. Subsequently, portosystemic collaterals develop to counterbalance the increased resistance in portal blood flow, and induce an increase in venous return to heart which results in increased portal venous inflow. This hyperdynamic splanchnic circulation contributes to the maintenance and aggravation of portal hypertension.\(^4\) Increased intrahepatic resistance results from both vasoconstriction and fibrosis. Vasoconstriction is a reversible and dynamic condition which contributes up to 25% of increased resistance (Fig. 1).\(^5,7\)

Vasoreactivity such as vasoconstriction in hepatic circulation and vasodilation in systemic circulation plays a major role in pathophysiology of portal hypertension.\(^8\) Recently, vascular structural changes including vascular remodeling and angio-
dys-
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tory
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concepts
oidal
components
stellate
hepatic
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intrahepatic
contractility
hepatic
endothelin-1
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contribute
to
increased
vascular
defects
cirrhosis.
Furthermore,
alterations
in
increased
vascular
resistance
sinusoidal
vascular
remodeling
of
endothelial
cells
with
increased
vascular
defects
termed
"sinusoidal
vascular
remodeling".
The
characteristics
of
sinusoidal
remodeling
are
distinct
from
process
of
fibrosis,
collagen
deposition
of
HSC. 
In
this
process,
HSC
motility
and
migration
is
absolutely
required
to
promote
enhanced
coverage
of
HSCs
around
a
SECs-lined
sinusoid.
While
Transforming
growth
factor-β
(TGF-β)
is
largely
recognized
for
its
contribution
to
HSC-based
collagen
deposition,
there
is
significant
crosstalk
between
TGF-β
and
PDGF
involved
in
HSCs
motility.
Indeed,
these
signals
may
converge
at
the
level
of
a-actin
tyrosine
kinase. 
A
number
of
signaling
pathways
mediate
HSC
recruitment
to
vessels
in
vascular
remodeling
and
angiogenesis
including
PDGF,
TGF-β,
angiopoietins,
and
NO.
Platelet
derived
growth
factor
(PDGF)
is
probably
the
most
critical
factor
in
the
recruitment
of
pericytes
to
cirrhosis
that
likely
contribute
to
changes
in
sinusoidal
structure.
Indeed,
recent
studies
have
identified
a
number
of
alterations
in
SEC
phenotypes.
Figure 2. Pathogenesis of hyperdynamic circulation in cirrhosis and portal hypertension.

CO, cardiac output; eNOS, endothelial nitric oxide synthetase; NO, nitric oxide; HO, heme oxygenase; CM, carbon monoxide; TNF-α, tumor necrosis factor-α; RAA, renin-angiotensin-aldosterone; SNS, sympathetic nerve system; ADH, anti-diuretic hormone; VEGF, vascular endothelial growth factor; HE, hepatic encephalopathy; CCM, cirrhotic cardiomyopathy; HRS, hepatoportal syndrome; HPS, hepatopulmonary syndrome.

Systemic and splanchic circulation

Vasoregulatory imbalances in the splanchic circulation

In contrast to diminished intrahepatic bioavailability of NO, splanchic (and systemic) circulation shows a relative excess in regional NO generation. This increased production is largely endothelium-dependent, and is thought to be evidence of eNOS activation in splanchic endothelium. Some studies have shown that eNOS activation by the angiogenic growth factor, vascular endothelial growth factor (VEGF), may be a primary factor in initial eNOS activation which demonstrates interesting links between vasodilatation angiogenesis and vascular remodeling. Bacterial translocation during cirrhosis increases tumor necrosis factor-α (TNF-α) production which can also induce the increase of systemic NO production. Therefore, increased NO production in systemic and splanchic circulation contributes to decreased systemic vascular resistance and resultant hyperdynamic circulation. This in turn results in sodium retention and ascites mediated by a reduction of effective circulating volume, stimulation of sympathetic system, an activation of the renin-angiotensin-aldosterone system, and an increase of anti-diuretic hormone release (Fig. 2).

Vascular remodeling of systemic vessels in portal hypertension

Vascular remodeling is a long-term adaptive response to chronic changes in blood flow. Chronic increases in flow with dilation of the vascular channel are implicated in endothelial-based signals that mediate restructuring of the vessel, thereby allowing for chronic increases in vessel diameter and capacity for high volume flow. This change has been demonstrated in peripheral vessels including experimental models of portal hypertension which may be related to activation of eNOS.

Collateral circulation

Vasoregulatory imbalances in collateral circulation

The development of portosystemic shunts and collateral circulation such as esophageal and hemorrhoidal collateral vessels is a compensatory response to decompress the portal circulation and hypertension, but unfortunately contributes to significant morbidity and mortality. Vasodilation of pre-existing collateral vessels results in increased collateral blood flow and volume. The mechanism of collateral vessel regulation still remains unclear. The control of collateral circulation could be a key in managing complications of portal hypertension, therefore, experimental studies are performed.

Angiogenesis and vascular remodeling in collateral circulation

In addition to vasodilatation, the collateral circulatory bed develops through angiogenesis. Angiogenesis occurs through the proliferation of endothelial and smooth muscle cells in addition to vasculogenesis. Vasculogenesis refers to the recruitment of endothelial progenitor cells for the de novo synthesis of vessels. Angiogenesis and vasculogenesis are also influenced by NO and highly dependent on VEGF as the growth factor exerting pleiotropic effects to promote new vessel formation. Indeed, VEGF promotes vasodilation, vascular remodeling, and angiogenesis in part through NO-dependent or independent mechanisms. In animal models, neutralizing antibodies inhibited portosystemic shunting by blocking VEGF receptor 2, which further highlights the importance of VEGF and NO for increased portosystemic collateralization in portal hypertension. In addition, multi-kinase inhibitors such as sorafenib result not only in decreases of portosystemic shunts and improvement of portal hypertension but also inactivation of HSCs. This is under active investigation, however, more studies are needed for clinical application.
Hyperdynamic circulation

The hyperdynamic circulation is characterized by increased cardiac output and heart rate, and decreased systemic vascular resistance with low arterial blood pressure in cirrhotic patients.\textsuperscript{40-43} These hemodynamic alterations are initiated by systemic and splanchnic vasodilatation, and eventually lead to abnormalities of the cardiovascular system and several regional vascular beds including ones involved in hepatic, splanchnic, renal, pulmonary, skeletal muscle and cerebral circulation.\textsuperscript{5}

Clinical features and pathogenesis

Hyperdynamic circulation is clinically presents with tachycardia, hypotension, and bounding pulses. Although hyperdynamic circulation \textit{per se} is not distressing to the patient, this phenomenon is clinically relevant due to its propensity to aggravate or precipitate some of the complications associated with portal hypertension. Severity of hyperdynamic circulation correlates with advancing liver failure with patients with end-stage liver failure generally showing the greatest extent of peripheral vasodilatation and increased cardiac output.\textsuperscript{31-34} Thus, virtually all patients with decompensated cirrhosis show evidence of hyperdynamic circulation. However, the presence of portal hypertension, rather than liver failure, is essential for the development of hyperdynamic circulation. Since the gut and liver receive a third of the entire cardiac output, hyperdynamic circulation directly or indirectly contributes to two of the most troublesome complications of cirrhosis: ascites and variceal bleeding. In concert with the increased total cardiac output, mesenteric blood flow also increases.\textsuperscript{45,46} Moreover, studies in both humans and animal models of cirrhosis or portal hypertension confirm that mesenteric hyperemia is due not only to a passive increase in blood flow as part of the increased cardiac output, but also to mesenteric vasodilatation. In other words, the percentage of overall cardiac output perfusing the mesenteric organs also increases.\textsuperscript{42,43,45,46} Recently, bacterial infection has been recognized as a risk factor for precipitating variceal bleeding.\textsuperscript{47} The underlying mechanism of this curious observation remains unknown, but it has been suggested that humoral substances released during the course of sepsis, including endotoxins and cytokines such as TNF-α, intensify the hyperdynamic circulation and thus increase blood flow through varices. The exact pathogenic mechanisms leading to hyperdynamic circulation remain to be definitively determined. Several factors to date have been hypothesized to be involved, including humoral substances, central neural activation, tissue hypoxia, and hypervolemia.\textsuperscript{48}

Multi-organ involvement

Heart

Cirrhotic cardiomyopathy was first described in the late 1960s although it was mistakenly attributed to latent or subclinical alcoholic cardiomyopathy for many years.\textsuperscript{49-51} Despite an increased baseline cardiac output, cirrhotic patients have a suboptimal ventricular response to stress. These individuals show blunted systolic and diastolic contractile responses to stress in conjunction with evidence of ventricular hypertrophy or chamber dilatation, and electrophysiological abnormalities including prolonged QT intervals. The pathogenesis of this syndrome is multifactorial and includes diminished β-adrenergic receptor signal transduction,\textsuperscript{2,52-55} cardiomyocyte cellular plasma membrane dysfunction, and increased activity or levels of cardio-depressant substances such as cytokines, endogenous cannabinoids, and nitric oxide.\textsuperscript{5} Although cirrhotic cardiomyopathy is usually clinically mild or silent, overt heart failure can be precipitated by stress from liver transplantation or transjugular intrahepatic portosystemic shunt insertion. Recent studies suggest that the presence of cirrhotic cardiomyopathy may contribute to the pathogenesis of hepatorenal syndrome precipitated by spontaneous bacterial peritonitis,\textsuperscript{56} acute heart failure after insertion of transjugular intrahepatic portosystemic shunts,\textsuperscript{57,58} and increased cardiovascular-associated morbidity and mortality after liver transplantation.\textsuperscript{59}

The Kidney

Renal vasoconstriction is characteristic in kidney with splanchnic vasodilation and hyperdynamic circulation, and may be responsible for the development of hepatorenal syndrome. Renal vasoconstriction develops as a consequence of effective hypovolemia and ensuing neurohumoral activation.\textsuperscript{60} This provides the rationale for treating hepatorenal syndrome with albumin infusion and vasoconstrictors (terlipressin, norepinephrine, or midodrine).\textsuperscript{61}

The Lung and Brain

Vasodilatation in the lung leads to ventilation perfusion mismatch and even arterio-venous shunts in the pulmonary circulation; these result in hepato-pulmonary syndrome, characterized by marked hypoxemia.\textsuperscript{62,63} In some cases, this may evolve into the opposite situation with markedly increased pulmonary vascular resistance seen in portopulmonary hypertension.\textsuperscript{64} This is thought to develop through endothelial dysfunction and vascular remodeling of the pulmonary circulation.\textsuperscript{65} Changes in
cerebral blood flow and vascular reactivity associated with portal hypertension are considered to contribute and facilitate some of the brain abnormalities of hepatic encephalopathy.

CONCLUSIONS

Portal hypertension is associated with vascular alterations in intrahepatic and systemic circulation. Extensive research has improved our understanding of the pathogenic mechanisms underlying hemodynamic derangement, allowing the development of novel treatment modalities. Future studies should focus on pharmacologic and genetic approaches to modulate vascular biologic systems to ameliorate complications and symptoms relating to hemodynamic alterations in patients with cirrhosis and portal hypertension.

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