World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i42.15499

World J Gastroenterol 2014 November 14; 20(42): 15499-15517
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (11): Cirrhosis

Extrahepatic complications to cirrhosis and portal hypertension: Haemodynamic and homeostatic aspects

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Received: October 30, 2013 Revised: March 6, 2014
Accepted: June 20, 2014
Published online: November 14, 2014

Abstract

In addition to complications relating to the liver, patients with cirrhosis and portal hypertension develop extrahepatic functional disturbances of multiple organ systems. This can be considered a multiple organ failure that involves the heart, lungs, kidneys, the immune systems, and other organ systems. Progressive fibrosis of the liver and subsequent metabolic impairment leads to a systemic and splanchnic arteriolar vasodilatation. This affects both the haemodynamic and functional homeostasis of many organs and largely determines the course of the disease. With the progression of the disease, the circulation becomes hyperdynamic with cardiac, pulmonary as well as renal consequences for dysfunction and reduced survival. Infections and a changed cardiac function known as cirrhotic cardiomyopathy may be involved in further aggravation of other complications such as renal failure precipitating the hepatorenal syndrome. Patients with end-stage liver disease and related complications as for example the hepatopulmonary syndrome can only radically be treated by liver transplantation. As a bridge to this treatment, knowledge on the mechanisms of the pathophysiology of complications is essential for the choice of vasoactive drugs, antibiotics, drugs with specific effects on fibrogenesis and inflammation, and drugs that target specific receptors.

Key words: Fibrogenesis; Splanchnic haemodynamics; Inflammation; Bacterial translocation; Infections; Systemic circulation; Cirrhotic cardiomyopathy; Hepatopulmonary syndrome; Portopulmonary hypertension; Hepatorenal syndrome; Ascites

Core tip: Patients with cirrhosis develop extrahepatic functional disturbances as a multiple organ failure that involves the heart, lungs, kidneys, the immune systems, and other organ systems. Fibrosis of the liver leads to a systemic vasodilatation that affects both the homeostasis of many organ systems. The circulation becomes hyperdynamic, which is often further aggravated by infections. Changes in organ function involve the heart as a cirrhotic cardiomyopathy, the kidneys such as the hepatorenal syndrome and the lungs with development of a hepatopulmonary syndrome. Liver transplantation is often the only radical treatment and as a bridge to this treatment, knowledge on the mechanisms of the pathophysiology of complications is essential.

Møller S, Henriksen JH, Bendtsen F. Extrahepatic complications to cirrhosis and portal hypertension: Haemodynamic and homeostatic aspects. *World J Gastroenterol* 2014; 20(42): 15499-15517 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i42/15499.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i42.15499

INTRODUCTION

Patients with chronic liver failure typically present with symptoms relating to the diseased liver. In particular patients with cirrhosis show clinical, biochemical, and pathophysiological signs of structural and functional changes. Among these are alterations of the synthetic, excretory, and metabolic capacity, immunologic and regulatory function of hepatocytes, Kupffer cells, sinusoidal endothelial cells (SEC), biliary cells, and hepatic stellate cells (HSC). Impaired synthetic capacity of the hepatocytes leads to coagulopathy and to low circulating albumin level and often to jaundice related to compromised excretion of bilirubin and defects in conjugation[1]. When cirrhosis progresses the amount of fibrosis increases with development of regeneration nodules in the liver, which lead to portal hypertension[2]. Activation of the HSC by bioactive substances contributes to the elevated portal pressure[3]. One of the most important complications with relations to portal hypertension is bleeding from gastro-esophageal varices[4]. The combination of impaired hepatic degradation and porto-systemic shunting of vasodilators leads to a splanchnic and arterial vasodilatation with reduced splanchnic vascular resistance[5-7]. Over time a hyperdynamic, multi-organ failure syndrome develops with increased cardiac output and heart rate and decreased central blood volume[8-11]. Together with portal hypertension this leads to formation and perpetuation of ascites[12]. The hyperdynamic syndrome affects a variety of organ functions such as the lungs with development of the hepatopulmonary syndrome (HPS) and the heart with upcome of a cardiovascular dysfunction, including cirrhotic cardiomyopathy[13]. Due to the systemic and splanchnic vasodilatation, vasoactive systems like the sympatho-adrenergic, renin-angiotension-aldosterone, and the vasopressin system become activated[14]. This mediates vasoconstriction within the kidney with increased risk of development of hepatorenal syndrome (HRS)[15,16]. Translocation of bacteria from the gut to lymph nodes leads to complicating infections in relation to variceal bleeding and infected ascitic fluid as spontaneous bacterial peritonitis (SBP)[17,18]. Impaired phagocytic activity in cells belonging to the reticulo-endothelial system such as the Kuppfer cells may facilitate infections, which further aggravates the circulatory dysfunction[19,20].

During the last decade it has become clear that chronic liver failure is not only limited to a decreased liver function, but also involves impairment of most other organs in the body as part of a multi-organ syndrome particularly relating to haemodynamic and homoeostatic disturbances. This review imparts to highlight contemporary mechanisms of extrahepatic haemodynamic complications to chronic liver failure in patients with cirrhosis and portal hypertension.

PATHOPHYSIOLOGY OF THE LIVER

Structural and functional changes in cirrhosis

The microscopic human liver architecture is arranged in lobules with cords of liver cells radiated to a central vein. The portal tract consists of a triad containing a portal vein branch, a hepatic arteriole, and a bile duct[1]. Thus, the liver lobule is quantitatively formed by hepatocytes and cholangiocytes. In addition to these two primary epithelial cell populations the liver hosts SEC, Kupffer cells, and HSC, see Figure 1[21-23].

The hepatocytes accounts for approximately 80% of the total liver cell mass[24]. The hepatocytes have essential physiological functions, such as regulation of carbohydrate and lipid metabolism, clearance and inactivation of drugs, ethanol, toxins and various hormones and vasoactive substances. A very important function of the hepatocytes is the synthesis of plasma proteins, including albumin, C-reactive protein, fibrinogen, complement, and coagulation factors. In patients with acute and chronic liver injury hepatocyte apoptosis plays a major role for the impaired metabolic function[25]. When the liver is exposed for toxic substances such as drugs, alcohol, and hepatitis B or C virus, fibrogenesis increases and initiates the cirrhotic process with development of regeneration nodules with impairment of hepatocyte function[26,27]. The impaired metabolic function results in compromised degradation of various vasoactive substances, which is particularly important for the understanding of the systemic and splanchnic haemodynamic changes[28]. Atrial natriuretic peptide is cleared in the liver with extraction ratios of 22%-75%[29]. The hepatic extraction of glucagon has been determined by infusion studies and ranges 10%-20% and hepatic extraction ratios of adrenaline and noradrenaline are very high and ranges 63% to 67%[28]. Renin, angiotensin Ⅱ, substance P, vasopressin, and aldosterone are other important other bioactive substances with haemodynamic implications that are degraded in the liver[28].

Kupffer cells are liver macrophages and constitute 80% of all tissue macrophages of the reticuloendothelial system on the body and about 15% of the liver cells[24]. The Kupffer cells are important for the immune function of the liver and act as antigen presenting cells of bacteria, endotoxins, liopolysaccharide (LPS) and other antigens together with natural killer (NK) cells[30,31]. In addition, the Kupffer cells play an important role in the expression of proinflammatory cytokines such as tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1) and IL-6[32]. Furthermore, they play important roles in clearance of endotoxins, and in the defence of microbial infections and contribute to the production of the vasodilator nitric oxide[33].

HSC are located in the space of Disse and they are in close contact with hepatocytes and SEC, Figure 1. They are rich of vitamin A, which relates to their function as hepatic storage of retinyl esters[34]. The HSCs are furthermore actively involved in fibrogenesis and metabolism. They are involved in matrix degradation and tissue inhibitor of metalloproteinase-1 (TIMP-1) has been shown to be a survival factor for HSC, and inhibition of the actions of TIMP-1 may be a target for antifibrogenic treat-

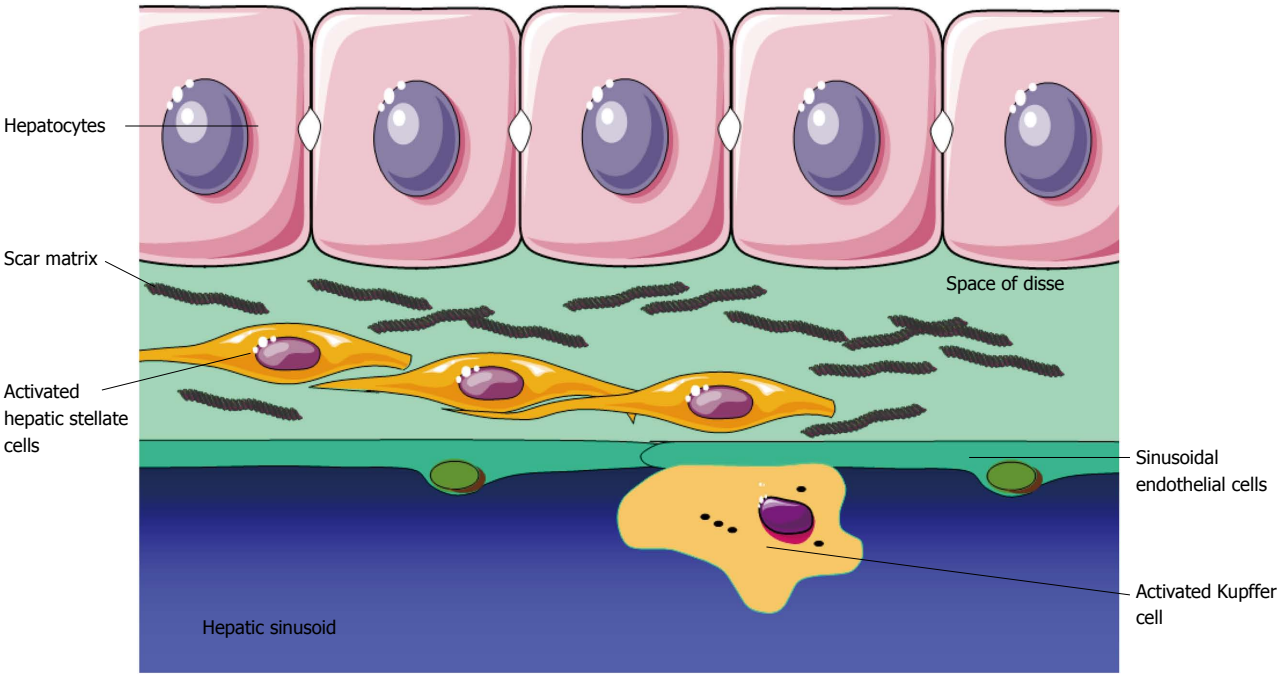

Figure 1 Fibrogenesis after liver injury. Hepatic stellate cells are activated into myofibroblasts that deposit scar matrix in the Space of Disse.

ment[35,36]. HSC has important contractile properties with relation to the development of portal hypertension[37]. Thus, vasoactive agents, such as endothelin-1 (ET-1), angiotensin-2, and trombin induces contraction[35,37]. From this point of view the contraction of HSC constitutes a reversible and dynamic component of the increase in the hepatic flow and regulation of the portal pressure[3]. This function is intimately associated with a counter regulation by nitric oxide and carbon monoxide, which induce relaxation of HSC and thereby ultimately reduces portal pressure[35,36]. The SECs possess highly specialised physiological functions as they serve as a source of several bioactive substances[38]. The cells are involved in regulation and production of proinflammatory cytokines and haemodynamically important vasoactive peptides and substances, including nitric oxide, ETs, prostanoids, and prostaglandins[39,40].

It can be concluded, that various cell types of the liver are deeply involved in the haemodynamic changes and extrahepatic complications. Thus, impaired hepatocyte degradation of vasoactive substances, production of vasodilators in the HSC and SEC, and impaired immune and clearance function of Kuppfer cells inducing production of proinflammatory cytokines and substances are of importance for the development of portal hypertension and directly involved in the pathophysiology of extrahepatic hemodynamic complications. Increased portal pressure leads to portosystemic shunts, and thereby increases the amount of vasodilators and other compounds that bypass the liver metabolism and degradation.

Fibrogenesis

The histological hallmark of chronic liver failure is development and perpetuation of fibrosis in the liver. Sustained fibrogenesis leads to cirrhosis, which is characterized by distortion of the liver parenchyma and reduction of vascular architecture. The fibrogenetic process is like a wound-healing response to injuries and a balance between formation and degradation of fibrotic tissue[35]. This process can be activated by injuries caused by for example viral hepatitis, alcohol intake, and autoimmune disorders. These stimuli primarily activate HSC into myofibroblasts-like cells with contractile, proliferative, and fibrogenic capacities and it is the primary cell type responsible for deposition of extracellular matrix in the liver[34]. The HSCs are located in the subendothelial space between the hepatocytes, Kupffer cells, and SECs so they mutually interact through numerous cellular processes extending across the space of Disse, see Figure 1[37]. Paracrine and autocrine activation of HSCs by tumour growth factor-β1, which is considered the most potent fibrogenic cytokine, initiates the fibrotic process in the liver[35]. In addition, the HSCs cover various physiological functions, including activation of the immune response, secretion of cytokines, and angiogenesis[34]. The activation of the HSC into myofibroblasts consists of an initiation phase and a perpetuation, followed by a resolution phase. Resolution of fibrosis refers to sequences of events such as apoptosis, senescence, or quiescence[27]. The inflammatory response plays an important role in fibrogenesis since inflammation always precedes fibrosis and immune activation induces fibrosis by bacterial LPSs[41]. Kupffer cells also activate HSC by increased NF-κB activity and secretion of pro-inflammatory cytokines, including TNF-α and monocyte chemoattractant protein[22,42]. Finally, NK cells have an anti-fibrotic effect by killing activated HSC. The contractile HSC contributes to the regulation of the sinusoidal blood flow and to

angiogenesis in the cirrhotic liver[37]. Thereby, the HSCs contribute to regulate intrahepatic blood flow and portal pressure. Together with SECs that excert a paracrine effect through nitric oxide synthesis, the HSC represent an important dynamic component of the sinusoidal haemodynamic resistance in cirrhosis.

It can be concluded that the HSCs are the major fibrogenetic cells type in the injured liver and its numerous functions have disclosed important targets for effective antifibrotic therapies[36,43].

REGULATION OF SPLANCHNIC AND HEPATIC BLOOD FLOW

Homeostasis of the hepatic blood flow is essential since the liver plays a major role in the clearance of waste products, drugs, and hormones. The liver receives 25% of the total resting cardiac output through the the hepatic artery and portal vein, the latter being responsible for 75% of the total hepatic blood flow[44]. The hepatic blood flow equals the ratio of the hepatic venous pressure gradient and post-sinusoidal resistance. In case of portal hypertension, a substantial portal systemic collateral circulation develops together with an increased mesenterial inflow[45]. The hepatic blood flow can be measured by the indocyanine green clearance (ICG) method applying the Fick-principle by measurements of ICG-concentrations in the liver vein and in a peripheral artery[46].

To maintain metabolic homeostasis, the hepatic blood flow must be adjustable to full fill changing metabolic demands. For example increased regional oxygen consumption is followed by proportional increased blood flow to the splanchnic area[44]. However, the liver *per se* is not able to control the portal inflow and it is the splanchnic organs that drain into the portal vein that primarily determine changes in portal venous blood flow. Therefore, different regulatory mechanisms are essential to maintain haemodynamic and metabolic homeostasis.

Extrinsic regulatory mechanisms

The splanchnic blood flow increases normally after a meal[47]. The mechanisms are largely unknown but splanchnic blood vessels are richly innervated by sympathetic nerves from the prevertebral sympathetic ganglia and an increase in sympathetic nervous outflow is partly responsible for the initial increase in cardiac output together with mediators such as glucose and long-chain fatty acids[48]. The extrinsic neural control of intestinal blood flow is predominantly through sympathetic vasoconstriction mediated by alfa adrenoceptors. Sympathetic activity reduces intestinal blood flow by increasing the vascular resistance of the arterioles and veins, and this is among the major effects on beta-blocking agents on hepatic blood flow and portal pressure[4,14,49].

In normal conditions, the vascular compliance of the liver is sufficient to maintain pressure homeostasis, but in cirrhotic patients with increased systemic vascular compliance and reduced hepatic and portal compliance, the portal pressure and degree of porto-systemic shunting increases and thereby the risk of bleeding from oesophageal varices[4,50,51]. This risk is further increased following a meal that augment the hepatic inflow[52]. Inversely, changes in splanchnic haemodynamics may affect function of other organs and the existence of a hepatorenal reflex has been debated for years. Experimental and clinical studies have provided support for a direct link between the liver and the kidneys[53,54]. In human cirrhosis, reduced renal blood flow following an increase in portal pressure and a concurrent increase in renal venous ET-1 suport this assumption[55,56]. There are now both clinical and experimental evidence of a hepatic blood flow-dependent hepatorenal reflex and this is a primary pathophysiological mechanism for renal dysfunction in liver disease[57]. This reflex is activated by adenosine in the space of Mall and is regulated by hepatic blood flow[54] (Figure 2).

The liver receives blood from both the hepatic artery and the portal vein. From a homeostatic point of view this is unique, since it secures a constant blood flow to the liver through a hepatic arterial buffer system[58]. According to the hepatic arterial buffer hypothesis a reduction in portal blood flow will cause a local accumulation of adenosine not washed away from the space of Mall surrounding the hepatic arterial resistance vessels and this will lead to local vasodilatation[54,59]. The metabolic homeostatic mechanisms maintain constant oxygen delivery, whereas the myogenic homeostatic mechanisms maintain a constant intravascular pressure[60].

Local regulatory mechanisms

A number of hormones with vasoactive effects such as gastrin, vasoactive intestinal polypeptide, cholecystokinin, secretin, and glucagon are implicated in the fine-tuning of the splanchnic haemodynamics of the liver[11,61]. As previously mentioned, SECs and HSCs are intimately involved in the regulation of the sinusoidal blood flow and potent vasodilators such as nitric oxide, ET-1, and tromboxan-A2 play a role in the vasodilation/vasoconstriction balance and the dynamic component of the increase in portal pressure in cirrhosis[40,62-65].

In conclusion, several homeostatic mechanism are involved in maintaining blood flow and metabolism in the normal liver. During development of cirrhosis and portal hypertension these mechanisms may not be adequate to meet the requirements of the body and liver failure, metabolic insufficiency, and portal hypertension may develop.

ROLE OF INFLAMMATION, BACTERIAL TRANSLOCATION, AND INFECTION IN CIRRHOSIS

Patients with cirrhosis are more susceptible to bacterial infections and in particular SBP, urinary tract and pulmonary infections, and Clostridium difficile infections[66,67]. The reduced ability to effective clearance of bacteria primarily relates to impaired cellular immune function

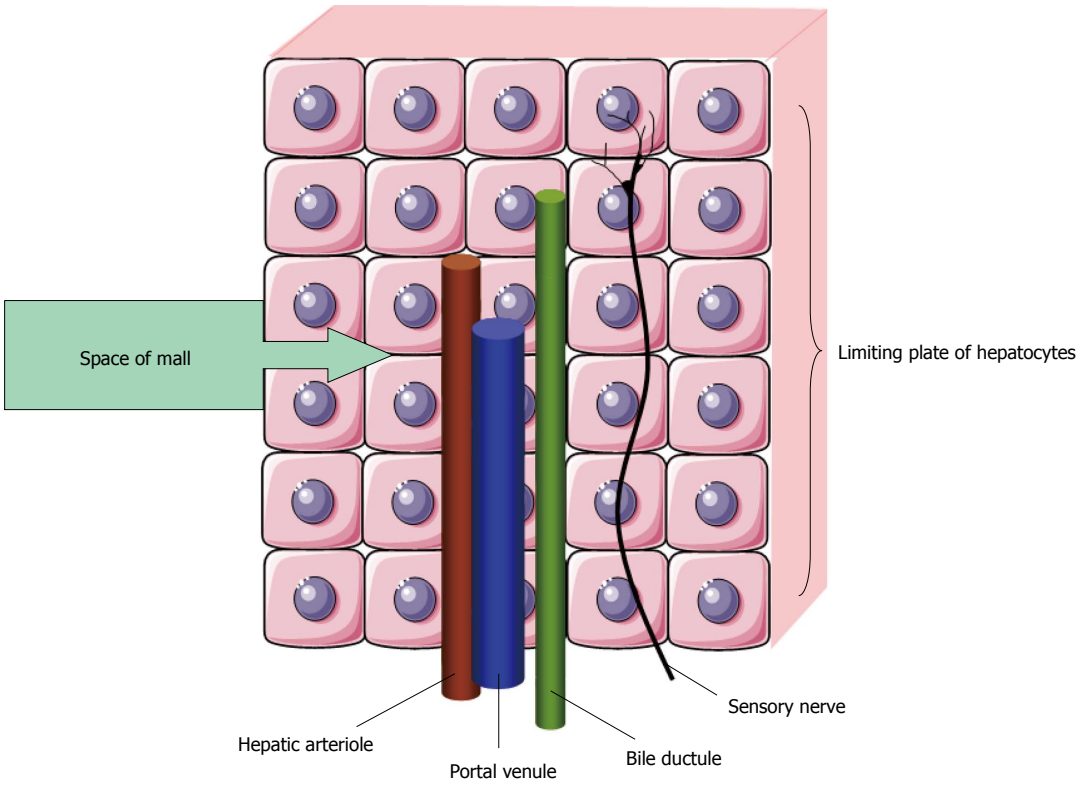

Figure 2 Space of Mall is a small space of fluid surrounding a hepatic arteriole, a portal venule and a bile ductule. Adenosine is secreted into the space of Mall. A reduction in portal blood flow increases adenosine levels and leads to hepatic arteriolar vasodilataion and activation of sensory nerves after[54].

of macrophages and monocytes, depressed neutrophil phagocytic and intracellular killing and deficiencies in the complement system[68-70]. Together with increased intestinal permeability and gut bacterial overgrowth this immune dysfunction facilitates transition of bacteria from the gastrointestinal tract to mesenterial lymph nodes, see Figure 3[18,70]. Bacterial translocation of especially Escherichia coli from the gut plays a significant role for the development of spontaneous infections, in particular SBP[71]. Presence of bacteria or bacterial products in splanchnic lymph nodes, ascitic fluid, or in the circulation significantly challenges the homeostatic haemodynamic balance and the hyperdynamic circulatory state. Bacterial translocation activates monocytes and lymphocytes and increase the circulating levels of pro-inflammatory cytokines such as TNF-α and IL-6 as a "cytokine storm" and subsequent activation of nitric oxide[18,72]. This inflammatory response further augments the circulatory dysfunction and aggravates the vasodilatory state[73]. Several surrogate markers of bacterial translocation has been proposed. Lipopolysaccharide binding protein is synthesised in the liver in response to bacteria and increased levels in cirrhotic patients correlate to the activation of different vasoactive systems, pro-inflammatory cytokines and nitric oxide[74]. Findings of bacterial DNA may reflect presence of bacterial components in body fluids and plasma, and preliminary studies have been promising[75], but the assessment is associated with significant technical challenges[76]. In patients with cirrhosis, infection of the ascitic fluid as in SBP is frequent, and it is an important risk factor for the development of circulatory and renal dysfunction[71,77,78]. Some patients may develop a systemic inflammatory response syndrome with fever, increased heart rate, respiratory failure and activated immune system[79] and sepsis in case of a confirmed bacterial etiology[73]. Severe bacterial infections and in particular SBP are main causes for the development of HRS as about 33% of patients with SBP develop HRS[80,81].

Bacterial translocation may be affected by measures that ameliorate bacterial overgrowth, intestinal permeability, and immunity, Figure 3. Thus, anti-, pre,- and probiotics and drugs that reduce the gastro-intestinal transit time may be of benefit[82,83]. Beta-blockers may also reduce the gastrointestinal transit time and reduce bacterial overgrowth, and results of a recent metaanalysis suggest that beta-blockers may even prevent SBP[84].

In conclusion, bacterial infections are important complications in cirrhosis. The mechanisms are complex and bacterial translocation lead through activation of pro-inflammatory mediators to a homeostatic imbalance that may precipitate renal and circulatory failure and lead to a multiorgan failure syndrome.

SYSTEMIC CIRCULATION

The circulatory homeostasis is largely intact in patients with early cirrhosis and portal hypertension. But with the progression of the disease over the portal hypertensive, preascitic to the decompensated, portal hypertensive, ascitic stage, there is an overall direct relation between the

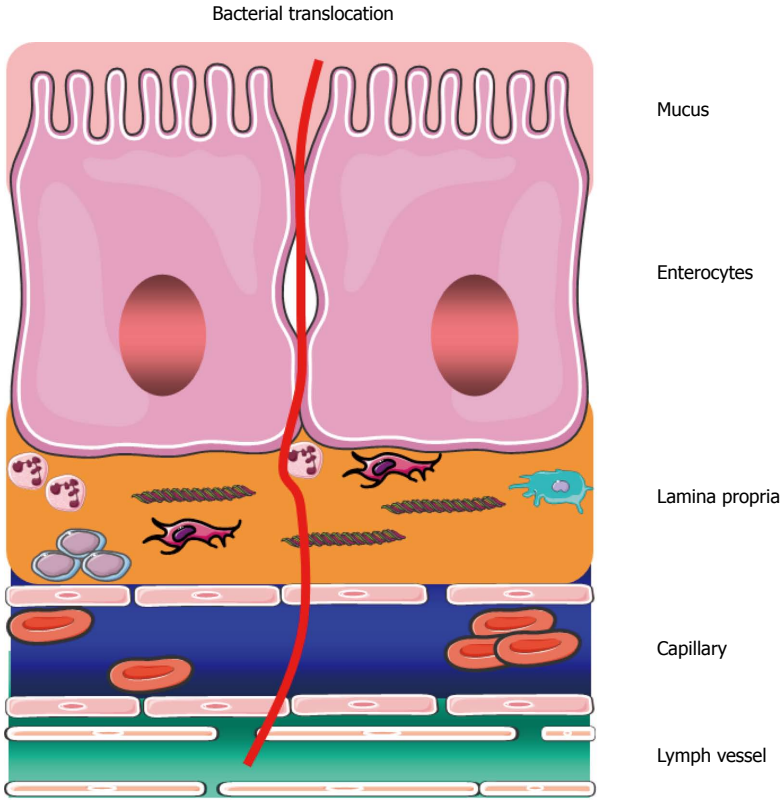

Figure 3 Illustration of bacterial translocation from the gastrointestinal lumen through the epithelial layers and capillaries to the lymphatic vessels.

Table 1 Vasodilating and vasoconstricting forces involved in disturbed haemodynamics in cirrhosis (Alphabetic order)

Vasodilator systems
Adenosine
Adrenomedullin
Atrial natriuretic peptide
Bradykinin
Brain natriuretic peptide
Calcitonin gene-related peptide
Carbon monoxide
Endocannabinoids
Endothelin-3
Endotoxin
Enkephalins
Glucagon
Histamine
Hydrogen sulphide
Interleukins
Natriuretic peptide of type C
Nitric oxide
Prostacyclin (PGI2)
Substance P
Tumour necrosis factor-α
Vasoactive intestinal polypeptide
Vasoconstrictor systems
Angiotensin Ⅱ
Adrenaline and noradrenaline
Endothelin-1
Neuropeptide Y
Renin-angiotensin-aldosterone system
Sympathetic nervous system
Vasopressin

severity of cirrhosis *e.g.*, reflected by the Child or MELD scores and the degree of hyperdynamic circulation[85-89].

The pathophysiological origin for a variety of extrahepatic complications is a splanchnic and systemic arteriolar vasodilatation that precedes renal sodium and water retention and plasma volume expansion[90]. According to the "peripheral arterial vasodilation hypothesis"[91], primary splanchnic arteriolar vasodilation leads to reduction of the overall systemic vascular resistance and in advanced disease, to avid arterial underfilling with low arterial blood pressure. A modification of this, "the forward theory of ascites formation" combines arterial underfilling with a forward increase in hepatosplanchnic capillary pressure and filtration with increased lymph formation[90]. A reduced effective blood volume, which is that part of the blood volume where volume and baroreceptors are located, leads to activation of vasoconstrictor systems and secondary sodium-water retention[90-93]. A number of potent intrinsic vasodilators are implicated in this and summarised in Table 1. Particular focus has been given to nitric oxide, calcitonin gene-related peptide, and adrenomedullin. Other substances with vasodilating properties which have been implicated are natriuretic peptides, TNF-α, IL-6, substance P, vascular endothelial growth factor, and cannabinoids[65,94-102]. The delicate homeostatic balance between primary vasodilatating and counterregulatory vasoconstriction is significantly deviated towards a sustained systemic vasodilatation, in spite of highly acti-

Table 2 Circulatory changes in specific vascular beds in cirrhosis

Systemic circulation
Plasma volume ↑
Total blood volume ↑
Non-central blood volume ↑
Central and arterial blood volume ↓ (→)
Cardiac output ↑
Arterial blood pressure ↓ (→)
Heart rate ↑
Systemic vascular resistance ↓
Arterial and total vascular compliance ↑
Heart
Left atrial volume ↑
Left ventricular volume → (↑)
Right atrial volume → ↑ ↓
Right ventricular volume → ↑ ↓
Right atrial pressure → ↑
Right ventricular end diastolic pressure →
Pulmonary artery pressure → ↑
Left ventricular end diastolic pressure →
Hepatic and splanchnic circulation
Hepatic blood flow ↓ → (↑)
Hepatic venous pressure gradient ↑
Postsinusoidal resistance ↑
Renal circulation
Renal blood flow ↓
Glomerular filtration rate ↓ →
Pulmonary circulation
Pulmonary blood flow ↑
Pulmonary vascular resistance ↓ (↑)[1]
Cutaneous and skeletal muscle circulation
Skeletal muscular blood flow ↑ → ↓
Cutaneous blood flow ↑ → ↓

[1]Portopulmonary syndrome. ↑ → ↓ denote: Increased, unchanged, or decreased, respectively. Parenthesis denotes less frequent changes.

Table 3 Characterization of cirrhotic cardiomyopathy

Definition
A cardiac dysfunction in patients with cirrhosis characterised by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease
Diagnostic criteria
Systolic dysfunction
Blunted increase in cardiac output with exercise, volume challenge or pharmacological stimuli
Resting EF < 55%
Diastolic dysfunction
E/A ratio < 1.0 (age-corrected)
Prolonged deceleration time (> 200 ms)
Prolonged isovolumetric relaxation time (> 80 ms)
Supportive criteria
Electrophysiological abnormalities
Abnormal chronotropic response
Electromechanical uncoupling/dyssynchrony
Prolonged Q-T interval
Enlarged left atrium
Increased myocardial mass
Increased BNP and pro-BNP
Increased troponin I

BNP: Brain natriuretic peptide; E/A: Early diastolic/atrial filling ratio; EF: Left ventricular ejection fraction.

vation of all vasoconstrictor systems. This is most likely related to a combination of changes in receptor affinity, down regulation of receptors and several post-receptor defects but future research should further disclose the pathophysiology[13,103].

In general, an increase in cardiac output can be attributed to an increase in venous return, heart rate, and myocardial contractility, all of which are controlled by the autonomic nervous system. Arteriolar dilatation, the presence of arteriovenous communications, expanded blood volume, and enhanced sympathetic nervous activity may further raise the cardiac output; most of these pathophysiological mechanisms may operate in advanced cirrhosis[6,11,14]. In early cirrhosis, the presence of a hyperdynamic circulation is often not apparent. But with the progression of the liver disease, there is an overall association to the degree of hyperdynamic circulation. Studies on circulatory changes with posture suggest that the patients are mostly hyperdynamic in the supine position[104-107]. Blood and plasma volumes are expanded in advanced cirrhosis but the distribution between central and non-central vascular areas is imbalanced[108-111]. Thus, by different techniques it has been established that the central and arterial blood volume is most often decreased, whereas the non-central blood volume, in particular the splanchnic blood volume is increased in animals and patients with cirrhosis[6,109,112,113]. The effective arterial blood volume and the central circulation time (*i.e.*, central blood volume relative to cardiac output) are substantially reduced and bear a significant relation to poorer survival in advanced cirrhosis[114]. The haemodynamic changes pertaining to specific vascular beds are shown in Table 2.

In the decompensated state, plasma volume expansion is a prevailing feature and should be considered secondary to the activation of neurohumoral mechanisms consequent on mainly splanchnic vasodilatation, low arterial blood pressure, and reduced central and arterial blood volume.

Evaluation of systemic haemodynamic changes in clinical practice is complex. Even patients with early cirrhosis may exhibit a hyperdynamic circulatory state and a few patients with decompensated cirrhosis with considerable fluid retention may present a relatively normal circulation[86]. Recently, it has become apparent that patients with advanced disease and refractory ascites may have a suppressed cardiac output[115,116]. Moreover, pharmacological treatment *e.g.*, with β-blockers may attenuate a hyperdynamic circulatory state[86,117,118]. However, on a whole, there is a direct relationship between the state of vasodilatation, the systemic circulatory derangement and the progression of the liver disease, development of complications and prognosis.

CHANGES IN CARDIAC FUNCTION

Subclinical impairment of the function of the cirrhotic heart has been known for 60 years[119]. However, it is only

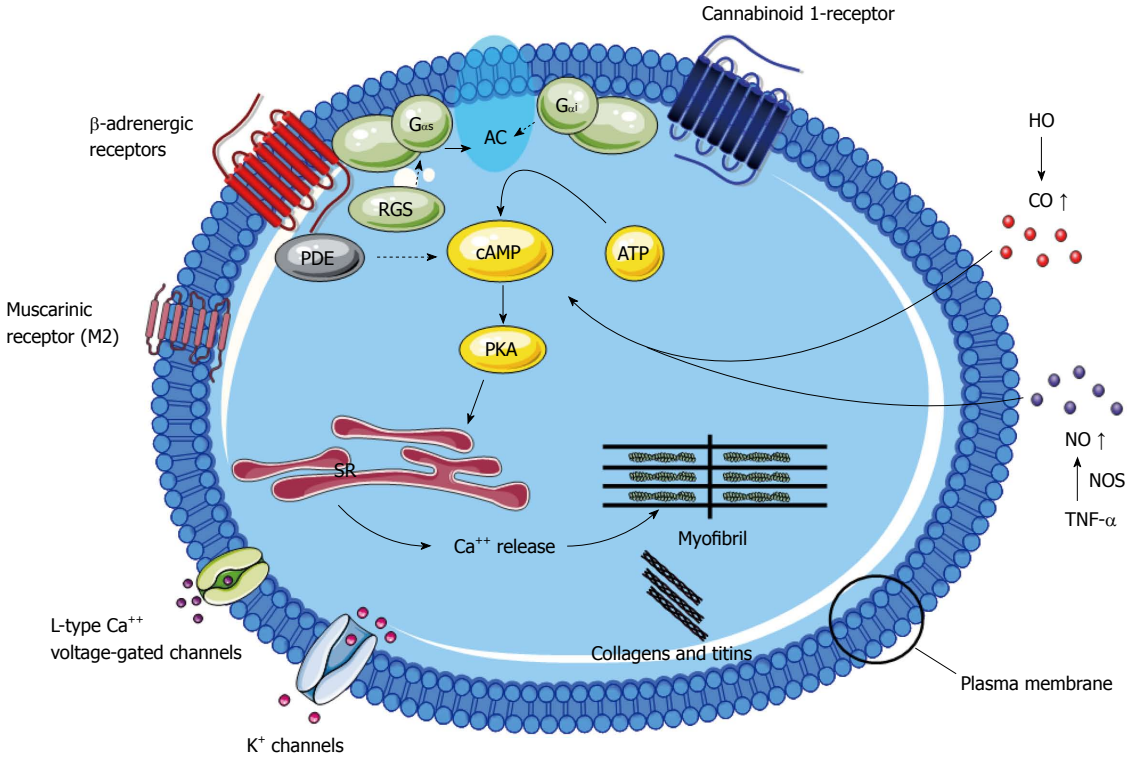

Figure 4 Mechanisms of cirrhotic cardiomyopathy. The figure reviews the most important mechanisms involved in cirrhotic cardiomyopathy: Desensitisation and downregulation of β-adrenergic receptors with decreased content of G-protein (Gαi: inhibitory G protein; Gαs: stimulatory G protein) and following impaired intracellular signalling; alterations in particular in M2 muscarinic receptors; upregulation of cannabinoid 1-receptor stimulation; altered plasma membrane cholesterol/phospholipid ratio; increased inhibitory effects of haemooxygenase (HO), carbon monoxide (CO), nitric oxide (NO), and tumour necrosis factor-α (TNF-α); reduced density of potassium channels; changed function and fluxes through L-type calcium channels; altered ratio and function of collagens and titins. Many post-receptor effects are mediated by adenylcyclase (AC) inhibition or stimulation. PKA: Protein kinase A.

recently that the reduced function of the heart has been associated with the development of various complications of cirrhosis. Results of experimental and clinical studies have shown impaired myocardial contractility as well as electrophysiological abnormalities in cirrhosis, which have crystalized the clinical entity cirrhotic cardiomyopathy[13,120,121]. This term denotes a chronic cardiac dysfunction, characterised by blunted contractile responsiveness to stress and altered diastolic relaxation with electrophysiological abnormalities, such as prolongation of the Q-T interval, all occurring in the absence of any other cardiac disease, Table 3[122,123]. This cardiac dysfunction may affect the prognosis of the patients and aggravate the course during invasive procedures such as surgery, insertion of a transjugular intrahepatic portosystemic shunt (TIPS), and liver transplantation[124-126]. The pathophysiological mechanisms include changes in the cardiomyocyte plasma membrane, attenuated function of the beta-adrenergic pathway, and greater activity of inhibitory systems[123,127]. Other studies have focused on negative inotropic effects of nitric oxide, nitration of cardiac proteins, carbon monoxide, endogenous cannabinoids, bile acids, and endotoxins[128,129]. The mechanisms of cirrhotic cardiomyopathy are summarised in Figure 4.

Systolic dysfunction

In patients with cirrhotic cardiomyopathy, cardiac failure may become manifest only under conditions of haemodynamic stress. Thus, the left ventricular end-diastolic pressure increases after exercise, but the expected increases in cardiac stroke index and left ventricular ejection fraction (LVEF) are absent or subnormal, which indicates an inadequate response of the ventricular reserve to a rise in filling pressure[130]. A vasoconstrictor-induced increase of 30% in the left ventricular afterload results in a doubling in pulmonary capillary wedged-pressure, with no change in cardiac output[131]. This response may be useful in diagnosing cirrhotic cardiomyopathy. A similar pattern is seen after insertion of TIPS, but the raised cardiac pressures tend to normalise with time[132,133]. Some of these patients (12%) may develop manifest cardiac failure in association with the TIPS insertion[134]. A failure to increase cardiac output, despite increased ventricular filling pressure, indicates that normalisation of the afterload impairs cardiac performance and unmasks left ventricular dysfunction[131].

LVEF reflects systolic function, even though it is very much influenced by preload and afterload. It has been reported to be normal at rest in some studies and reduced in one study of a subgroup of patients with ascites[130,131,135]. After exercise, LVEF increases less in cirrhotic patients than in controls[130,136,137]. The reduced functional capacity may be attributed to a combination of blunted heart rate response to exercise, reduced myocardial reserve, and pro-

Table 4 Diagnostic criteria for the hepatopulmonary syndrome and portopulmonary hypertension

HPS	PoPH
Presence of liver disease	Presence of liver disease and portal hypertension
$P_{A-a}O_2$ > 15 mmHg (> 2 kPa)	Mean pulmonary arterial pressure > 25 mmHg
Positive contrast enhanced echocardiography[1]	Pulmonary vascular resistance > 240 dyn·s·cm^{-5} left atrial pressure < 15 mmHg

[1]Visualisation of microbubbles in the left heart chambers within three or more cardiac cycles implies definite intrapulmonary vascular dilatation. $P_{A-a}O_2$: Alveolar-arterial oxygen gradient; PoPH: Portopulmonary hypertension; HPS: Hepatopulmonary syndrome.

found skeletal muscle wasting with impaired oxygen extraction[138,139]. By modern techniques like tissue-Doppler and speckle tracking echocardiography, it is possible also to detect systolic and diastolic dysfunction at rest[140,141].

Diastolic dysfunction

The clinical significance of diastolic dysfunction and its importance in cirrhotic cardiomyopathy has been questioned, as overt cardiac failure is not a prominent feature of cirrhosis. However, there are several reports of unexpected death from heart failure following liver transplantation, surgical portocaval shunts, and TIPS[134,142]. These procedures involve a rapid increase in cardiac preload. In a less compliant heart, the diastolic dysfunction could be enough to cause pulmonary oedema and heart failure. This is consistent with the findings of an increase in pulmonary artery pressure, pre-load, and diastolic dysfunction after TIPS[132]. Diastolic dysfunction affecting left ventricular filling may progress to systolic dysfunction[123,143]. The pathological basis of the increased stiffness of the left ventricle seems to be cardiac hypertrophy, patchy fibrosis, and subendothelial oedema[131,136,144]. Decreased E/A ratio and delayed early diastolic transmitral filling with prolonged deceleration and isovolumetric relaxation times indicate diastolic dysfunction on the Doppler echocardiogram and corresponding characteristics on the tissue-Doppler and speckle tracking echocardiography[131,140,141,145].

Q-T interval prolongation

In cirrhotic patients, the Q-T interval is prolonged and significantly related to the severity of the liver disease, portal hypertension, portosystemic shunts, elevated brain type natriuretic peptide (BNP) and pro-BNP, elevated plasma noradrenaline, decreased heart rate variability, and reduced survival[122,124,146-149]. The prolongation of the Q-T interval is partly reversible after liver transplantation and beta-blocker treatment[146,150]. Recently, it has been documented that gastrointestinal bleeding further prolongs the Q-T interval in cirrhosis and independently predicts bleeding-induced mortality[151]. The prolonged Q-T interval in cirrhosis should be considered an element in the cirrhotic cardiomyopathy and may be of potential use in the stratification and identification of patients at risk[149,152].

Taken together, cirrhotic cardiomyopathy encompasses impaired contractility and diastolic relaxation, and electrophysiological abnormalities in particular prolonged Q-T interval. Independent of aetiology of cirrhosis, systolic dysfunction can be diagnosed at rest by for example tissue-Doppler imaging or demasked by physical or pharmacological stress. Diastolic dysfunction can be detected by echocardiography or tissue-Doppler imaging. Cirrhotic cardiomyopathy may aggravate complications such as gastro-intestinal bleeding and development of the HRS. Liver transplantation may revert the cardiac dysfunction but surgery and TIPS insertion may also aggravate the condition.

CHANGES IN PULMONARY FUNCTION

Pulmonary dysfunction involves diffusing abnormalities with development of the HPS and portopulmonary hypertension (PoPH) in some patients with cirrhosis. The circulatory and neuroendocrine derangements seem to play important roles in the hepatopulmonary dysfunction and these aspects should be taken into account in the management of diffusing and oxygenation-related complications of cirrhosis. Below are the two main entities HPS and PoPH shortly considered and the pathophysiological differences summarised in Table 4.

HPS

A condition with reduced diffusing capacity, abnormal ventilation/perfusion ratio and intrapulmonary vascular dilatations, and low arterial oxygen saturation in association with liver disease and absence of cardiopulmonary disease is termed HPS[153-156]. Arterial deoxygenation is reflected by a widened alveolar-arterial oxygen gradient ($P_{A-a}O_2$)[88,157]. The frequency of HPS in patients with cirrhosis is variably reported from 5%-50% according to the type of population with respect to aetiology, geography, etc [154,156,158-160]. The pathophysiological hallmark of HPS, is dilatations of capillaries near the alveolar areas, see Figure 5. Fallon *et al*[153] have recently reported increased pulmonary vascular endothelial nitric oxide synthase (NOS) and increased production of cholangiocyte ET-1 and increased expression of ET-B receptors[161,162]. Recently, pulmonary angiogenesis have been implemented in the development of this complicated pathophysiology[163].

From a practical point of view HPS is defined by arterial hypoxaemia [PaO_2 < 70 mmHg (or 9.3 kPa)], an age-adjusted increase in $P_{A-a}O_2$ > 15 mmHg (or 2.0 kPa) and presence of intrapulmonary vasodilatations[154,162]. A large proportion of patients with HPS present with insidious onset of dyspnea, platypnea (upon standing), orthodeoxia, clubbing, and cyanosis[164]. The diagnosis requires arterial blood gas measurements and calculation of $P_{A-a}O_2$, Contrast-enhanced echocardiography (CEE) is today considered the most sensitive test and method of choice in the diagnosis HPS[156], but also injection of macroaggregated

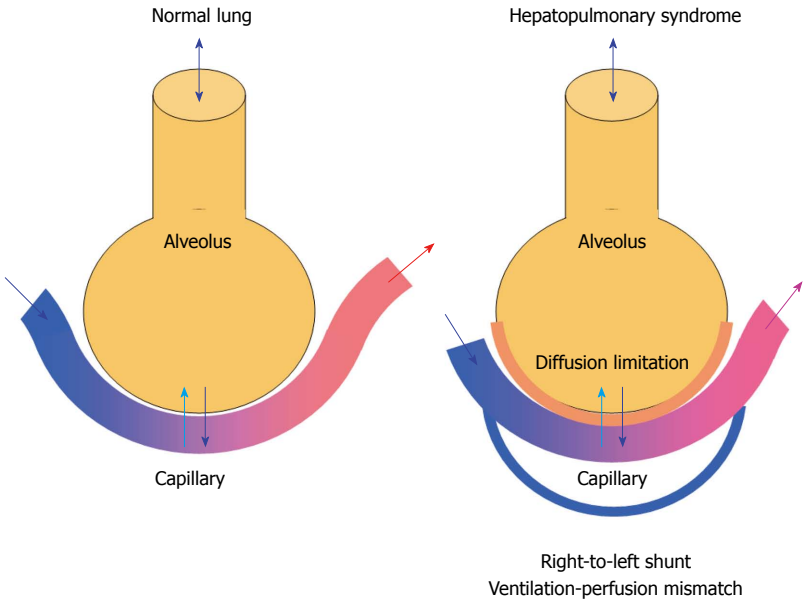

Figure 5 Gas exchange in the normal lung (left) and mechanism of hepatopulmonary syndrome (right). The hepatopulmonary syndrome comprises an increased alveolar-arterial oxygen gradient owing to diffusion limitations and development of intrapulmonary right-to-left shunts leading to arterial hypoxaemia.

albumin with estimated the extra-pulmonary shunt fraction > 6% indicates presence of HPS[165]. Currently, the following criteria for HPS are: (1) Presence of liver disease; (2) $P_{A\text{-}a}O_2 \geqslant 15$ mmHg (2.0 kPa); and (3) a positive CEE (Table 4).

At present there is no effective medical therapy for HPS. Insertion of TIPS has been reported to be successful, but it may result in increased pulmonary pressures and is therefore not recommended[166,167]. Since HPS is reversible after liver transplantation, it has become an indication for urgent liver transplantation and the long-term outcome after LT in HPS is increasingly favorable[168,169].

Portopulmonary hypertension

PoPH is defined as a mean pulmonary artery pressure > 25 mmHg and pulmonary vascular resistance >240 dyn•s•cm^{-5}, and normal left atrial pressure (< 15 mmHg), see Table 4[154,170,171]. The histological appearance of pulmonary vessels is similar to that seen in primary pulmonary artery hypertension, and includes smooth muscle proliferation, hypertrophy, and fibrosis[154]. Various pathophysiological aspects seem to be involved in the development of portopulmonary hypertension, including vasoproliferation, genetics, and inflammation with increased pulmonary phagocytosis[154]. Of particular interest is the activation of potent local vasoconstrictor systems, like serotonin and the ET system. ET-1 is produced in the pulmonary endothelium and binding to ET_A and ET_B receptors on the pulmonary smooth muscle cells leads to vasoconstriction[172-175]. Symptoms are typically progressive and include fatigue, chest discomfort, exertional dyspnoea, oedema, and syncope[175,176]. The median survival in patients with PoPH is considered low, about six months[177] and lower than in patients with idiopathic pulmonary hypertension[171]. The diagnosis can be based on radiological, echocardiographic, lung functional, and haemodynamic findings. Pulmonary function tests often show reduced lung volumes, diffusing capacity, and forced vital capacities and widened $P_{A\text{-}a}O_2$[178]. For purposes of screening, Doppler-echocardiography can be used to estimate pulmonary pressures and right ventricular systolic pressure. Right ventricular systolic pressure thresholds from > 30 to > 50 mmHg as cutt-off limits are still discussed[156,179].

Different medical treatments that modify the circulation have been applied. These include prostacyclin analogs such as epoprosterol[180], ET receptor antagonists such as bosentan[180,181], and phosphodiesterase-5 inhibitors such as sildenafil[182]. The effects of these drugs are however modest. TIPS and liver transplantation are not treatment options of choice in these patients sice a mean pulmonary artery pressure > 35 mmHg is associated with increased mortality following liver transplantation[168,183,184].

In conclusion, a considerable number of cirrhotic patients present with changes in pulmonary vascular resistance, impaired ventilation, and hypoxaemia as part of HPS or PoPH. Although, the prevalence varies, the circulatory and neuroendocrine derangements seem to play important roles in the clinical aggravation, hepatopulmonary dysfunction, and circulatory reactivity of these entities. Therefore these pathophysiological aspects should be taken into account in the clinical management of the patient with cirrhosis and pulmonary dysfunction.

CHANGES IN RENAL FUNCTION

Acute kidney injury (AKI) is frequent in patients with cirrhosis and determines the prognosis in advanced cirrhosis. HRS denotes a functional and partly reversible impairment of renal function. HRS is precipitated by

Table 5 New diagnostic criteria for the hepatorenal syndrome from the International Ascites Club (2013)[192]

Cirrhosis with ascites
Serum creatinine > 133 μmol/L (1.5 mg/dL)
No improvement of serum creatinine (decrease to a level of < 133 μmol/L) after at least 2 d with diuretic withdrawal and volume expansion with albumin. 1 g/kg of body weight per day up to a maximum of 100 g/d
Absence of shock
No current treatment with nephrotoxic drugs
Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/d, or microhaematuria, (> 50 red blood cells per high power field) and /or a normal renal ultrasonography

factors that aggravate the effective hypovolaemia in decompensated cirrhosis, by lowering arterial pressure and cardiac output and enhance sympathetic nervous activity.

Acute kidney injury in cirrhosis

Acute renal failure is estimated to occur in approximately 20% of hospitalized patients with cirrhosis[185]. Several attempts have been made to achieve agreement on a more precise definition of AKI. AKI has been defined as an increase in serum creatinine ≥ 133 μmol/L (≥ 1.5 mg/dL) or an increase > 50%, but initiatives from the Acute Kidney Injury Network and others have defined AKI as an absolute increase in serum creatinine > 26.4 μmol/L (≥ 0.3 mg/dL) (or a 50% increase over 48 h)[186]. Differential diagnosis of AKI in cirrhosis is difficult as it ranges from pre-renal AKI (45%), intra-renal AKI including acute tubular necrosis and glomerulonephritis (32%), HRS (23%), and seldom post-renal AKI (< 1%).

HRS

Approximately 20% of the cirrhotic patients with ascites who are resistant to diuretics, progress to HRS[187]. HRS denotes a functional prerenal failure that is unresponsive to volume expansion in patients with chronic liver disease and ascites without significant morphological changes in renal histology, and with a largely normal tubular function (Table 5)[78,188]. The prognosis of patients with a full-blown HRS is poor ranging from days to weeks and liver transplantation is the only radical treatment for the HRS[187,189]. Two types of HRS have been defined depending on the rapidness and the extent of the renal failure[78,190,191]. Type-1 HRS is an acute form with a rapid decrease in renal function and renal failure as an independent predictive factor; type-2 HRS is a chronic form with a more stable renal dysfunction[191,192].

Pathophysiology of HRS

The major elements in the development of HRS are the diseased liver, the circulatory dysfunction with vasodilatation and lowering of the arterial blood pressure, the abnormal systemic neuro-humoral regulation with activation of the sympathetic nervous system which alters renal autoregulation, a cardiac dysfunction due to cirrhotic cardiomyopathy with a pre-terminal decline in cardiac output[40,193,194]. These aspects are summarised in Figure 6.

Low systemic vascular resistance, central hypovolaemia, reduced baroreflex sensitivity, and abnormal renal autoregulation play a pivotal role in the circulatory dysfunction[111,193,195]. In patients with increased sympathetic nervous activity, the autoregulation curve may be shifted towards the right side[193]. Because of this, even minor reductions in arterial blood pressure may be harmful to renal perfusion. Thus, the renal blood flow decreases with the advancement of the clinical stage of liver dysfunction[196] and in these patients low arterial pressure relates to survival[11,85,197]. Cirrhotic cardiomyopathy has been described as a condition with impaired contractile responsiveness to stress and altered diastolic relaxation[123]. With the progression of the disease, the reduction in the systemic vascular resistance becomes so severe that the hyperdynamic cirrhotic heart is unable further to increase the high cardiac output, which leads to an underfilling of the central vascular bed and effective central hypovolaemia[111,188,198]. There is now evidence from several studies of a relation between the terminal decline in cardiac output and the progression of the disease, development of HRS, and survival[115,116]. We have therefore recently hypothesized a cardiorenal interaction in patients with advanced cirrhosis and renal dysfunction that refers to a condition where cardiac dysfunction in cirrhosis is a major determinant of the course of patients who develop HRS[199] (Figure 7).

Bacterial translocation from the gut plays a significant role for spontaneous infections and the circulatory dysfunction characterised by aggravation of vasodilatation elicited by an inflammatory response with the production of proinflammatory cytokines such as TNF-α and IL-6 as a "cytokine storm"[72]. SBP is frequent in patients with cirrhosis and is an important risk factor for the development of circulatory dysfunction and HRS (Figure 3)[71,77,78].

The future in terms of therapy will probably attack different aspects in the pathophysiological process. A multi-target strategy should seek efficiently to counteract the arterial vasodilatation, central hypovolaemia, and arterial hypotension by administration of potent vasoconstrictors such as terlipressin combined with human serum albumin. Development of orally long-acting systemic vasoconstrictors should be encouraged. All patients with HRS including those who respond to terlipressin and albumin should be properly prioritized on the waiting list for liver transplantation.

CHANGES IN ADRENAL FUNCTION

Increased cortisol levels due to activation of the hypothalamus-pituitary-adrenal axis represent an important adaptive mechanism in critical illness, regulating inflammation and cardiovascular response to the sympathetic nervous system. Circulating cytokines, such as TNF-α and IL-6, might impair pituitary responsiveness leading to inadequate cortisol secretion[200,201]. This has been termed relative adrenal insufficiency (RAI), which is associated

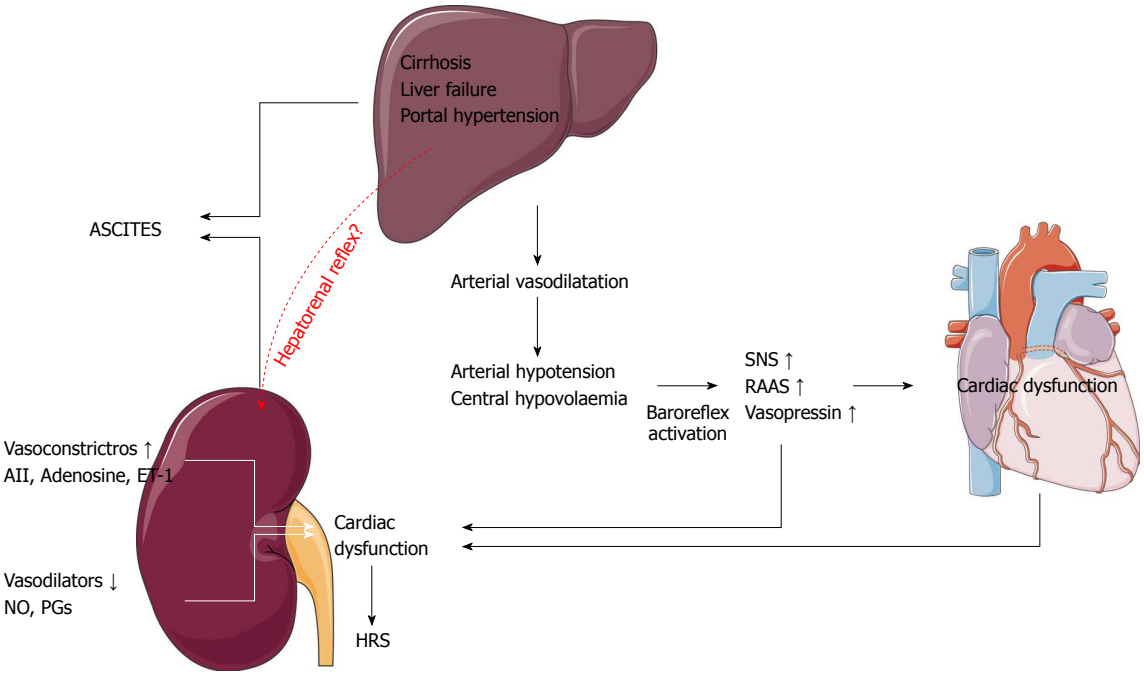

Figure 6 Pathophysiological mechanisms in the development of ascites and the hepatorenal syndrome. SNS: Sympathetic nervous system; RAAS: The renin-angiotensin-aldosterone system; AII: Angiotensin II; ET-1: Endothelin-1; NO: Nitric oxide; PGs: Prostaglandins.

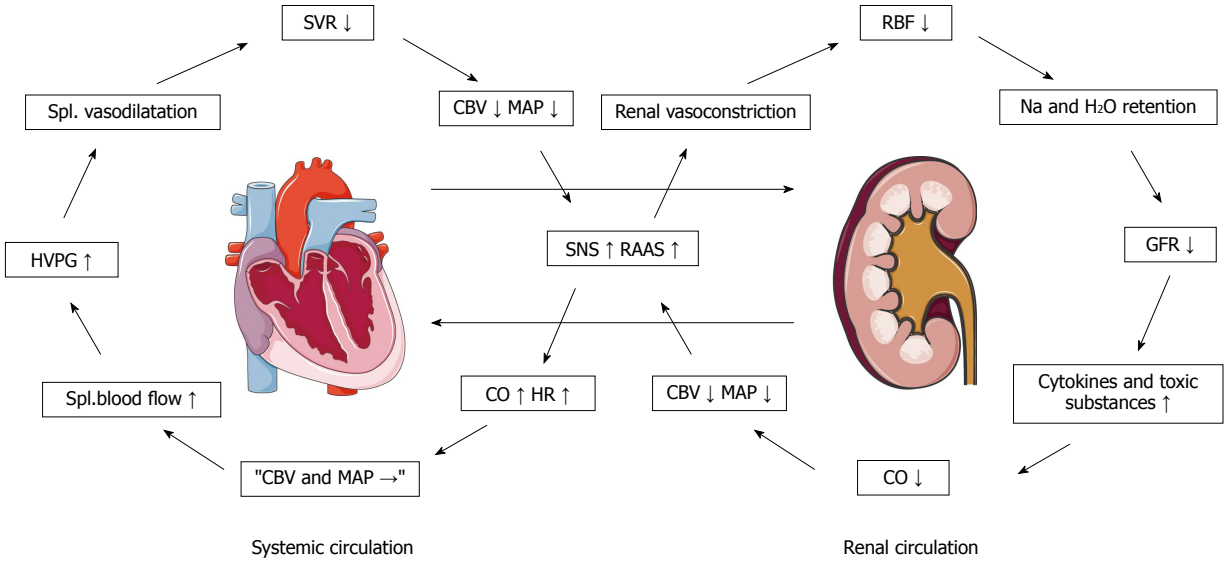

Figure 7 Pathophysiological proposal for the background of a cardiorenal syndrome in cirrhosis[194]. CBV: Central blood volume; CO: Cardiac output; GFR: Glomerular filtration rate; HR: Heart rate; HVPG: Hepatic venous pressure gradient; MAP: Mean arterial pressure; RAAS: Renin-angiotensin-aldosterone system; RBF: Renal blood flow; SNS: Sympathetic nervous system; SVR: Systemic vascular resistance.

with more pronounced hemodynamic instability, vasopressor dependency and increased mortality in critically ill patients[202,203].

In addition, RAI has been reported in cirrhosis as part of a hepato-adrenal syndrome with inhibition of ACTH and CRH due to high levels of pro-inflammatory cytokines[203,204]. Since patients with adrenal insufficiency may exhibit similar characteristics in terms of cardiac dysfunction, we recently hypothesized that adrenal insufficiency may contribute to cirrhotic cardiomyopathy and to precipitate HRS[200]. The relation between cardiac dysfunction and development of HRS should therefore be focus for treatment strategies that seek to improve cardiac function[116].

CONCLUDING SUMMARY

The recent years have considerably improved our knowledge on the mechanisms of disease processes in chronic liver disease. The cellular and humoral responses related

to the fibrogenesis, inflammation, and bacterial translocation have been shown to be highly involved in the development of portal, splanchnic, and systemic haemodynamic complications to chronic liver disease. These extra-hepatic complications comprise changes in numerous organ systems as a multi-organ failure syndrome. The arterial vasodilatation and the general increased vascular compliance are directly linked to the cardiac and circulatory changes and to pulmonary haemodynamics and function. In conditions such as HRS and PoPH a preferential reactive and counter-regulatory vasoconstriction is prevailing. The function of the heart in cirrhosis is disturbed, with a hyperdynamic circulation with increased cardiac output and heart rate. Cardiac performance and the systolic and diastolic functions are clearly impaired and may contribute to other complications such as HRS as part of a cardio-renal syndrome.

Knowledge on the mechanisms of development of complications is crucial with respect to choice of vasoactive drugs, drugs with specific effects on fibrogenesis and inflammation, and drugs that target specific receptors. Although major unsolved questions remain, the circulatory and humoral derangements play important roles in the clinical aggravation of renal complications, cardio-pulmonary dysfunction, and circulatory reactivity. This aspect is important to take into account in futures research programmes and in the clinical handling of the cirrhotic patient.

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P- Reviewer: Gupta S, Procopet B **S- Editor**: Qi Y **L- Editor**: A **E- Editor**: Ma S

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ISSN 1007-9327