

Splanchnic and systemic hemodynamic derangement in decompensated cirrhosis

Søren Møller MD DMSc¹, Flemming Bendtsen MD DMSc², Jens H Henriksen MD DMSc¹

S Møller, F Bendtsen, JH Henriksen. Splanchnic and systemic hemodynamic derangement in decompensated cirrhosis. *Can J Gastroenterol* 2001;15(2):94-106. Patients with cirrhosis and portal hypertension exhibit characteristic hemodynamic changes with hyperkinetic systemic circulation, abnormal distribution of blood volume and neurohumoral dysregulation. Their plasma and noncentral blood volumes are increased. Splanchnic vasodilation is of pathogenic significance to the low systemic vascular resistance and abnormal volume distribution of blood, which are important elements in the development of the concomitant cardiac dysfunction, recently termed 'cirrhotic cardiomyopathy'. Systolic and diastolic functions are impaired with direct relation to the degree of liver dysfunction. Significant pathophysiological mechanisms are reduced beta-adrenergic receptor signal transduction, defective cardiac excitation-contraction coupling and conductance abnormalities. Vasodilators such as nitric oxide and calcitonin gene-related peptide are among the candidates in vasodilation and increased arterial compliance. Reflex-induced, enhanced sympathetic nervous system activity, activation of the renin-angiotensin aldosterone system, and elevated circulation vasopressin and endothelin-1 are implicated in hemodynamic counter-regulation in cirrhosis. Recent research has focused on the assertion that the hemodynamic and neurohumoral abnormalities in cirrhosis are part of a general cardiovascular dysfunction, influencing the course of the disease with the reduction of organ function, with sodium and water retention as the outcome. These aspects are relevant to therapy.

Key Words: Cirrhosis; Hemodynamic derangement

Perturbations hémodynamiques périphériques et splanchniques secondaires à une cirrhose décompensée

RÉSUMÉ : Les patients atteints de cirrhose et d'hypertension portale présentent des changements hémodynamiques caractéristiques accompagnés d'une circulation générale hypercinétique, d'une répartition anormale du volume sanguin et d'un dérèglement neurohormonal. Il y a augmentation des volumes plasmatique et sanguin non central. La vasodilatation splanchnique a des répercussions pathogènes sur la résistance vasculaire périphérique inférieure et la répartition anormale du volume sanguin; ces perturbations jouent un rôle important dans l'apparition d'un dysfonctionnement cardiaque concomitant, désigné depuis peu sous « myocardiopathie cirrhotique ». On observe un dysfonctionnement systolique et diastolique en relation directe avec le degré de dysfonctionnement du foie. Parmi les principaux mécanismes physiopathologiques, mentionnons la diminution de la transduction des signaux par les récepteurs bêta-adrénergiques, le couplage vicieux excitation-contraction et les anomalies de la conduction. Les vasodilatateurs comme l'oxyde nitrique et le peptide lié au gène de la calcitonine figurent parmi les facteurs de vasodilatation et d'accroissement de la compliance artérielle. L'augmentation réflexe de l'activité du système nerveux sympathique, l'activation du système rénine-angiotensine-aldostérone ainsi que l'élévation de la vasopressine et de l'endothéline-1 dans la circulation interviennent toutes dans la contre-régulation hémodynamique dans les cas de cirrhose. La recherche porte, depuis peu, sur l'assertion selon laquelle les anomalies hémodynamiques et neurohormonales observées dans la cirrhose font partie d'un dysfonctionnement cardiovasculaire généralisé qui a une incidence sur l'évolution de la maladie, se traduisant par un dysfonctionnement organique et subséquent par une rétention hydro-sodée. Ce sont là des éléments importants à considérer dans le traitement.

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Departments of ¹Clinical Physiology and ²Medical Gastroenterology, Hvidovre Hospital, Copenhagen, University of Copenhagen, Copenhagen, Denmark

Correspondence and reprints: Dr Jens H Henriksen, Department of Clinical Physiology, Room 239, Hvidovre Hospital, Copenhagen, Denmark DK-2650. Telephone +45-3632-2203, fax +45-3632-3750, e-mail jens.h.henriksen@hh.hosp.dk

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Over the past decade, it has become apparent that the abnormal distribution of blood flow and volume is important for the development of circulatory derangement and renal dysfunction with sodium and water retention in patients with cirrhosis (1-5). Besides the presence of portal hypertension, these patients typically present with hyperdynamic systemic circulation with increased heart rate, cardiac output, splanchnic inflow and plasma volume, and low overall vascular resistance (6-9). The balance between vasodilating and vasoconstricting forces is abnormal, especially in decompensated patients, and endothelium-derived substances such as nitric oxide and endothelins seem important in circulatory derangement (8,10-13). In addition, recent evidence showed increased circulating levels of highly potent vasodilators such as calcitonin gene-related peptide (CGRP) and adrenomedullin (14-18). Moreover, the neurohumoral homeostatic systems such as the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS) and nonosmotic release of vasopressin are highly activated in most patients with advanced liver disease, especially with fluid retention, probably as a compensatory reaction (19-21).

In cirrhosis, arterial blood pressure has a characteristic circadian rhythm with almost normal values at night and low arterial blood pressure during the day (22,23). In addition to changes in vascular resistance that are mainly located in small arteries and arterioles, the tonus of larger arteries may also be modulated (21,24,25). Lastly, experimental and clinical evidence suggest that cardiac dysfunction is present even in the absence of alcoholic cardiomyopathy, and a latent cardiac insufficiency is most likely involved in the circulatory disturbances of advanced cirrhosis (26-29).

The objective of the present review is to outline basic elements of the circulatory changes in cirrhosis to provide an update of recent investigations on circulatory dysfunction, neurohumoral control of hemodynamics and the distribution of blood volume. Special attention is paid to biodynamics and bioactive substances that may have a potential effect on vasodilation and neuroendocrine regulation in compensating the severe circulatory dysfunction in chronic liver disease.

HEPATOSPLANCHNIC CIRCULATION IN CIRRHOSIS

It is beyond the scope of the present article to review in detail the profound circulatory disturbances in the hepatosplanchnic system of cirrhosis (7,30). At the microvascular level, there is a reduction in the hepatic vascular cross-sectional area, 'capillarisation' of the sinusoidal lining with reduced wall porosity, and in addition, occurrence of basement membrane. Other characteristic features include collagenization of the space of Disse, activation of fat-storing cells, swelling of hepatocytes and blocking of blood flow at the level of central veins and smaller hepatic veins, owing to fibrosis and the occurrence of nodules (31-37). The activation of contractile elements in the fat-storing cells may play a particular role. These cells are controlled by numerous regulatory systems, including those for glucagon, nitric oxide,

endothelin, cytokines and prostaglandins (11,38-42). It is important to note that recent experiments have indicated that splanchnic and hepatic nitric oxide synthase activity is decreased in experimental cirrhosis, and that transfection of the nitric oxide synthase gene reduces portal pressure substantially (43,44). In contrast, increased synthesis of nitric oxide has been substantiated through measurements of elevated nitric oxide in plasma, and exhaled air and increased nitric oxide synthase activity in monocytes (39,45,46). Fibrogenetic mechanisms and regulators of the hepatic microvasculature are the subject of intensive research. Moreover, intrahepatic shunts located in fibrous tissue seem to be under the control of several vasoactive substances. This leaves a picture of a more dynamic and functionally disturbed hepatic perfusion that may potentially be modulated by vasoactive drugs (47). As the cirrhosis progresses, perfusion through the hepatic artery increases and the overall hepatic blood flow may decrease, not change or increase (48); however, it should be kept in mind that, in patients with portal hypertension, a substantial part of the mesenteric circulation passes through portosystemic collaterals, and the extrahepatic collateral circulation with increased mesenteric inflow amounts to several litres per minute (7,30,48). In addition, there may be portopulmonary collaterals and mesenteric arteriolar dilations (49). A number of vasoactive candidates, such as glucagon, vasoactive intestinal polypeptide and nitric oxide, may increase mesenteric perfusion (30,50). Somatostatin, terlipressin and vasopressin may in part reverse the hyperkinetic splanchnic circulation that suggests a role for regulatory peptides (51,52). In addition, recent investigations have focused on the role of endothelins in abnormal hemodynamic hepatic or sinusoidal resistance (40,41,53-55). Thus, a substantial part of the reduction in the overall systemic vascular resistance is probably located in the splanchnic system (40). Because blood flow in this vascular territory is high, small mesenteric arteries, in addition to arterioles, may contribute to the vascular resistance.

Collateral blood flow through the azygos vein, as determined by the constant infusion thermodilution technique or Doppler ultrasonography, is important because it drains the esophageal varices (56). A high azygos blood flow is associated with an increased risk of variceal bleeding (57).

SYSTEMIC CIRCULATION IN CIRRHOSIS

Overall vascular resistance is decreased in patients with cirrhosis. However, a closer look at the individual organs and tissues shows areas of hypoperfusion, normal perfusion and hyperperfusion, which indicate vascular beds with a high resistance, for example in the kidneys, and a low resistance, for example, in the splanchnic system (58). Advances in modern technology permitting the assessment of regional perfusion have made it clear that the circulation in most of the vascular territories is disturbed (Table 1).

Background of vascular hyporeactivity: The pathogenesis of hyporeactivity of the vascular system in chronic liver disease is under debate (Figure 1). Experimental and clinical observations favour the presence of a surplus of circulating

TABLE 1
Hemodynamics of different vascular beds in cirrhosis

Hepatic and splanchnic circulation	
Hepatic blood flow may decrease, not change or rarely increase	
Hepatic venous pressure gradient may increase	
Postsinusoidal resistance may increase	
Systemic circulation	
Plasma volume may increase	
Total blood volume may increase	
Noncentral blood volume may increase	
Central and arterial blood volume may decrease or not change	
Cardiac output may increase	
Arterial blood pressure may decrease or rarely not change	
Heart rate may increase	
Systemic vascular resistance may decrease	
Cutaneous and skeletal muscle circulation	
Skeletal muscular blood flow may increase, not change or rarely decrease	
Cutaneous blood flow may increase or not change	
Renal circulation	
Renal blood flow may decrease	
Glomerular filtration rate may decrease or not change	
Pulmonary circulation	
Pulmonary blood flow may increase	
Pulmonary vascular resistance may decrease or rarely not change	
Renal vascular resistance may increase	

vasodilators either escaping hepatic degradation or bypassing the liver through portosystemic shunting (5,50,59,60). Combined with a potential resistance to pressor substances, this conceivably leads to a peripheral and splanchnic vasodilation with reduced systemic vascular resistance and abnormal distribution of the circulating blood volume (49,61,62). Vasodilation and activation of counter-regulatory mechanisms are probably closely related to the general circulatory dysfunction. Previous studies have shown impaired reaction to circulatory challenges, such as pressor stimuli, changes in body position and exercise (63-68). The pathophysiological basis for a reduction in systemic vascular resistance and the reduced responsiveness may be associated with an inability of the vessels to respond to constrictors, with the presence of vasodilators or with both (69). Animal studies have demonstrated decreased pressor reactivity to potent vasoconstrictors such as catecholamines (70,71). A decrease in either alpha-adrenergic receptor sensitivity or postreceptor responsiveness may explain the reduced responsiveness (58,69,72). It has been known for several years that patients with cirrhosis are resistant to the pressor effect of noradrenaline, angiotensin II and vasopressin (63,70,73,74). There may be a shift in the pressor concentration giving 50% effect, as well as a reduction in the maximal effect of the vasopressor. This may result from a change in receptor affinity, a decrease in the number of receptors and a variety of postreceptor defects. Most likely all of these mechanisms are implicated in cirrhosis. Thus, Gerbes et al (75) showed that leukocytes from patients with cirrhosis have a decreased number of beta-adrenoceptors, and Ma and Lee (76) showed that the cardiac dysfunction in experimental cirrhosis is in part due to the

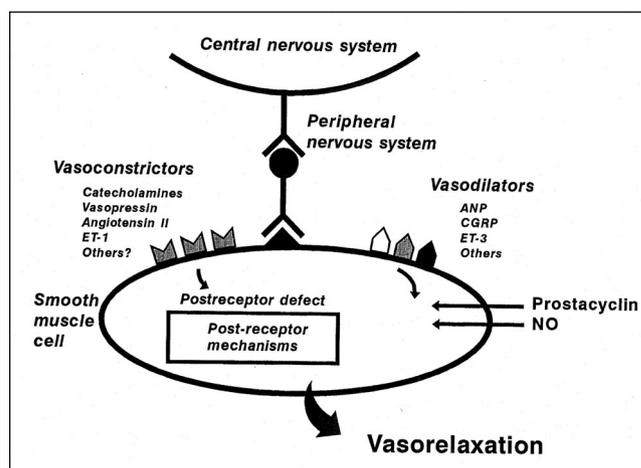


Figure 1) Causes of vascular hyporeactivity in cirrhosis may originate from the central autonomic nervous system, the peripheral autonomic nervous system or the smooth muscle cell. At the smooth muscle cellular level, hyporeactivity may be caused by increased concentrations of vasodilators (Table 2), decreased sensitivity to vasoconstrictors such as catecholamines, vasopressin, angiotensin II or endothelin (ET)-1 (down-regulation of receptors), or to a postreceptor defect in which nitric oxide (NO) could be implicated. ANP Atrial natriuretic peptide; CGRP Calcitonin gene-related peptide

combination of a receptor defect and postreceptor defects in the heart.

In recent years, research on vascular hyporeactivity in cirrhosis has primarily focused on nitric oxide, glucagon, CGRP, tumour necrosis factor-alpha (TNF- α) and adrenomedullin. Evidence of autonomic defects in patients with cirrhosis has emerged from various studies of hemodynamic response to standard cardiovascular reflex tests such as the Valsalva ratio, heart rate variability and isometric exercise (77-80). Most studies on these issues have found a high prevalence of autonomic dysfunction in cirrhosis, with associations with liver dysfunction and survival, including impaired autonomic response during tilting, despite adequate changes in catecholamines levels (81-84). These results point to a postreceptor defect as an explanation of the hyporeactive response in cirrhosis (85). Other studies suggest that the autonomic dysfunction is temporary, arising because of liver dysfunction and possibly reversible after liver transplantation (86). Whereas most studies have focused on defects in the SNS, recent papers have emphasized the importance of a vagal impairment for sodium and fluid retention (87,88). A sympathetic response to dynamic exercise seems to be normal in patients with cirrhosis, but the response to isometric exercise is clearly impaired (66,68,82,89). Similarly, blood pressure responses to orthostasis are impaired, probably because of a blunted baroreflex function (84,85,90,91). Abnormal cardiovascular responses to pharmacological stimulations with angiotensin II, noradrenaline and vasopressin, in terms of impaired responses in blood flow and blood pressure, have been reported (63,65). Dillon et al (92) reported that captopril corrected autonomic dysfunction, indicating that vagal dysfunction in cirrhosis is partly caused by a neuromodulation by angiotensin II. Thus, in ad-

dition to the presence of vasodilators and in spite of highly active vasoconstrictor systems, the sustained vasodilation is most likely related to changes in receptor affinity, downregulation of receptors and various postreceptor defects. Future research should reveal the pathophysiology of these complicated mechanisms.

Arterial blood pressure: The level of arterial blood pressure depends on the cardiac output and the systemic vascular resistance. The former is primarily determined by venous return, heart rate and myocardial contractility. The size of the systemic vascular resistance is determined by the tone of the smooth muscle cells in the small arteries and arterioles, which is then governed by complex local and central neurohumoral factors (93). The arterial blood pressure has a circadian rhythm, but is kept within its normal range by an arterial negative feedback baroreceptor reflex and other regulatory systems (94).

Arteriolar vasodilation may lead to the activation of counter-regulatory mechanisms with increased SNS and RAAS activity, increased nonosmotic release of vasopressin and probably release of endothelins (12,19-21,62,95). These systems may counter-regulate the systemic vasodilation and keep the otherwise very low arterial blood pressure in cirrhosis almost within the normal range. Whereas significant negative correlations of endothelin-1 (ET-1) to arterial blood pressure have been described in some patients with cirrhosis (96), other authors have been unable to show a prominent role of ET-1 in the homeostasis of arterial blood pressure (97,98). Thus, the role of endothelins in arterial hypotension of cirrhosis is unclear.

Several studies have shown that there is a relation between the degree of arterial hypotension in cirrhosis and the severity of hepatic dysfunction, signs of decompensation and survival (99,100).

Hitherto, arterial blood pressure in cirrhosis has been measured in patients who were awake and resting supine. Møller et al (22) reported the results of 24 h determinations in cirrhotic patients. During the day, the systolic, diastolic and mean arterial blood pressures were substantially reduced compared with those of controls, whereas at night, the values were unexpectedly normal.

The shifted and flat blood pressure-heart rate relation in patients with cirrhosis suggests that there is abnormal regulation of their circulation. The negative correlation of the arterial blood pressure during the day and at night to the Child-Turcotte score shows that hemodynamic dysregulation is related to the severity of the liver disease (22,23). Recently, Gentilini et al (101) reported that cirrhotic patients with arterial hypertension had no evidence of a hyperdynamic circulation. Although these patients showed impaired cardiovascular responses to tilting, they had a lower degree of renal impairment while standing, which could indicate a beneficial effect of increasing arterial blood pressure in patients with hepatic nephropathy.

The abnormal diurnal variation in arterial blood pressure and the immense activation of neurohumoral systems probably contribute to the abnormal regulation and distribution of

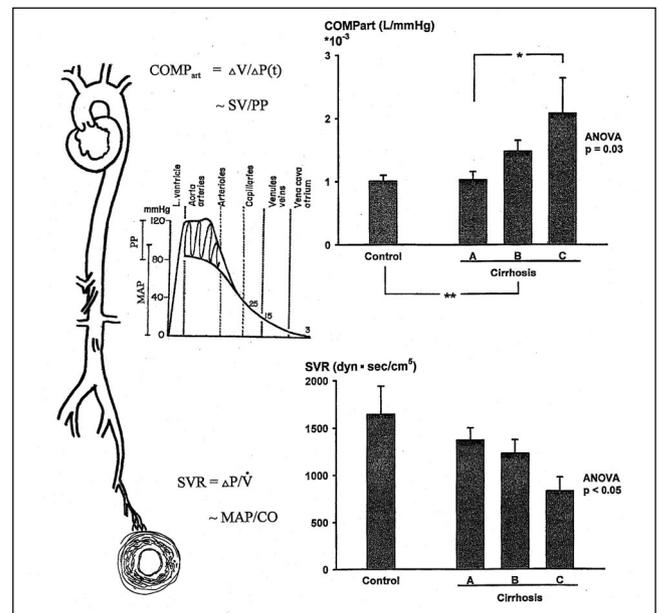


Figure 2 Arterial compliance ($COMP_{art}$) and systemic vascular resistance (SVR) are fundamental properties of large arteries and arterioles, respectively. $COMP_{art}$ is a change in arterial blood volume relative to a change in transmural pressure ($\Delta V/\Delta P(t)$). An index of $COMP_{art}$ is stroke volume relative to pulse pressure (SV/PP), where PP equals systolic minus diastolic arterial blood pressure. SVR is determined as mean pressure difference from the arterial tree to the right atrium relative to volume flow ($\Delta P/V$). An index of SVR is mean arterial blood pressure relative to cardiac output (MAP/CO). $COMP_{art}$ and SVR are shown for patients with cirrhosis ($n=31$), stratified in Child-Turcotte classes A, B and C groups, and in control subjects ($n=10$). Substantial changes with high compliance and low vascular resistance exist in patients with advanced cirrhosis as elements of their circulatory dysfunction. Data were analyzed by using one way ANOVA. * $P<0.05$; ** $P<0.01$. Data from reference 103

the circulating medium, and to sodium and fluid retention in patients with cirrhosis (102).

The properties of the arterial wall may be important in relation to the circulatory and homeostatic derangement in these patients. Thus, changed dynamic and static function of the arterial tree may contribute to the abnormal reactions of volume- and baroreceptors. Henriksen et al (103) recently reported elevated values of arterial compliance (stroke volume relative to pulse pressure) in patients with cirrhosis. The increased arterial compliance was directly related to the severity of the disease and to the circulating vasodilator peptide, CGRP, but inversely related to the level of the arterial blood pressure (103). A change in arterial compliance may indicate static changes in the composition of the arterial wall (ie, the relation between elastic and collagen fibres and accumulation of disease-related deposits) or dynamic changes caused by alterations in smooth muscular tone (Figure 2). Arterial compliance may be an integral variable for vascular responsiveness, together with the systemic vascular resistance, and dynamic and static properties of the arterial tree may have implications for the abnormal circulatory regulation, and potentially for therapy with vasoactive drugs. These aspects are, however, a topic for further research.

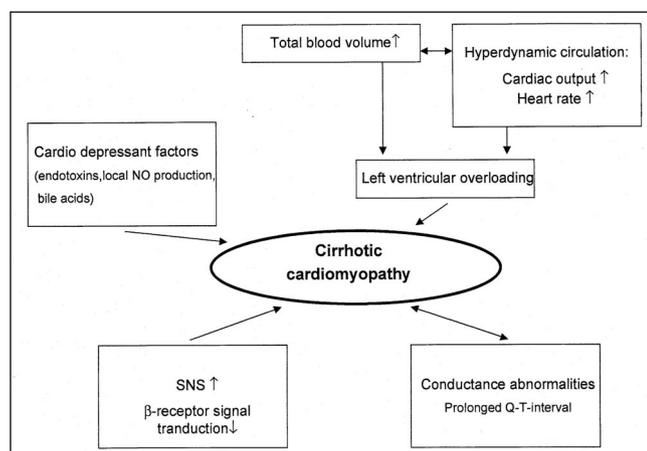


Figure 3) Potential pathophysiological components involved in the development of cirrhotic cardiomyopathy. NO Nitric oxide; SNS Sympathetic nervous system

Cardiac dysfunction: In patients with advanced cirrhosis, cardiac output is increased, leading to a hyperdynamic circulatory state (9). The increase in cardiac output is primarily a consequence of the increase in heart rate, but the stroke volume may also increase in some patients (101,104). The hyperdynamic circulation with the persistent increase in cardiac output and the associated expansion of the blood volume may result in prolonged overloading of the heart with impaired cardiac contractility as the outcome. Although determinations of heart volumes in cirrhosis have shown somewhat divergent results, findings of relatively increased volumes support the assumption of impaired loading of the heart. Thus, both normal heart volumes, and increased left atrial and left ventricular end-diastolic volumes have been reported in cirrhosis (27,101,105-108). Møller et al (109) used a magnetic resonance imaging technique and showed that the right ventricular systolic and diastolic volumes decreased, and that the left ventricular systolic and diastolic volumes slightly increased. Other studies have confirmed that left ventricular failure may be especially latent because of the decreased systemic vascular resistance and thereby a reduced afterload (106,109). Cardiac dysfunction may manifest under strain or treatment with vasoconstrictors such as angiotensin II, which increases the afterload and left atrial pressure, and thereby unmasks a left ventricular failure (68,76,110-112). Recently, impaired left ventricular diastolic filling has been reported in cirrhosis, which also supports the presence of a subclinical myocardial disease with diastolic dysfunction (27). Portal decompression with a transjugular intrahepatic portosystemic shunt (TIPS) is associated with an initial increase in cardiac output, and left atrial and ventricular volumes, and a further decrease in systemic vascular resistance, but the values seem to return to baseline after about one year (108,113). The increased left atrial volume, pressure and total pulmonary resistance after TIPS probably also reflect a diastolic dysfunction of the hyperdynamic left ventricle in these patients (108). Patients with ascites have a more hyperdynamic heart, but, on the other hand, the presence of ascitic fluid may decrease the pre-

load, owing to increased intrathoracic pressure, and affect respiratory mechanics (100,114). Accordingly, paracentesis has been reported to increase the stroke volume and cardiac output (107,115-117).

Alcoholic cardiomyopathy is well known in patients with alcoholic cirrhosis (118). However, experimental and clinical evidence show that, in cirrhosis, the heart is unable to modulate cardiac performance (26,119), which in some patients is reflected by elevated circulating cardiac troponin I (29). This has given rise to the introduction of the clinical entity, cirrhotic cardiomyopathy, which may be due to different pathophysiological mechanisms (Figure 3) (76,108,119). Thus, impaired cardiac contractility may be associated with the presence of high output heart failure and a persistent hyperdynamic circulation. Among other potential mechanisms are production of cardiodepressant substances such as endotoxins, nitric oxide and bile acids, decreased beta-adrenergic receptor function, and changes in the pre- or afterload, owing to the increased total blood volume (76,91,119). The implications of these findings, together with cardiac conductance abnormalities such as a prolonged Q-T interval (28,120), are that clinically important cardiac dysfunction may occur, thereby stressing the impact of latent heart failure in patients with cirrhosis.

Pulmonary circulation and hepatopulmonary syndrome: In cirrhosis, pulmonary vascular resistance is usually decreased (121,122). Analysis of pulmonary circulation may be obscured by the presence of cardiac dysfunction or by the fact that many patients with alcoholic cirrhosis are heavy smokers (121,122). However, independent of associated chronic obstructive lung disease, these patients often have compromised lung function with a reduced transfer factor and ventilation-perfusion abnormalities (123-126). High ventilation-perfusion ratios have been documented in some areas of the lungs in a substantial number of patients (123,127). In addition, there may be obvious pulmonary arteriovenous shunts, but the fraction of the cardiac output passing through regular shunts is relatively small, as shown by the near normal arterial oxygen saturation in most patients (121,126,128-130). The role of portopulmonary shunts has not been evaluated.

The reduced transfer factor has been related to an increased amount of blood in the lung capillaries (122,131). However, this seems to be a misconception because there is a direct relation between the amount of circulating red blood cells in the lung capillaries and the transfer factor in normal physiology and in other pathological conditions (Figure 4) (132). Moreover, a direct relation between the central and arterial blood volume on the one hand, and the transfer factor on the other, has recently been shown in patients with cirrhosis (126).

The triad of severe liver disease, gas exchange abnormalities and evidence of intrapulmonary vascular dilations has been termed the 'hepatopulmonary syndrome' (133,134). The etiology is unclear, but vasoactive substances such as nitric oxide and ET-1 have been implicated in its pathogenesis (135,136). In the advanced state, patients may exhibit pronounced hypoxemia and reduced aerobic capacity

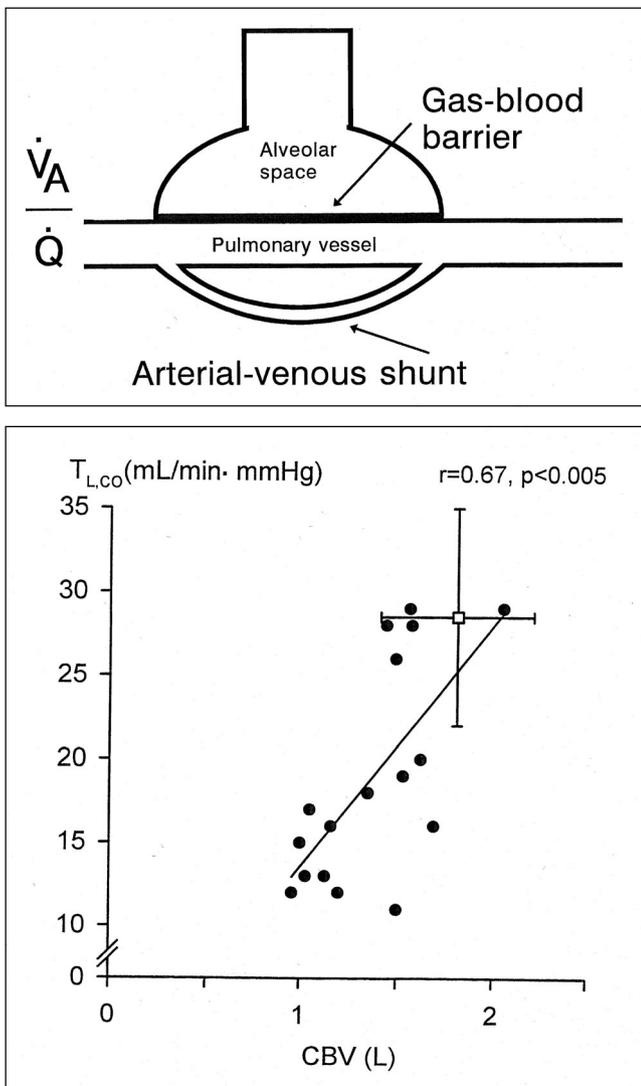


Figure 4) Top Lung diffusion depends on the diffusion properties of the blood-gas barrier, the degree of arterial-venous shunting and the degree of ventilation-perfusion inequality. **Bottom** The central and arterial blood volume (CBV) has been found to be low with a direct relation to the low diffusing capacity (transfer factor $T_{L,CO}$). Data from reference 126. \dot{Q} Flow; \dot{V}_A Alveolar ventilation

(112,137). The hepatopulmonary syndrome has been successfully reversed by orthotopic liver transplantation and TIPS (138-141). The frequency of hepatopulmonary syndrome in patients with chronic liver disease is uncertain, but it may be diagnosed accurately by the use of macroaggregated albumin lung perfusion scan, contrast echocardiography or both (142-144).

Multiorgan circulatory failure in cirrhosis: Hyperdynamic circulation is found in the majority of patients with advanced cirrhosis. The circulation of the hepatosplanchnic bed, lungs, kidney, brain, muscle and skin is disturbed (48). Thus, intensive research on the hemodynamics and function of diverse organs has revealed that the hyperdynamic state in cirrhosis is a syndrome that affects multiple organs and can be described appropriately as a multiorgan circulatory failure (104,145). It is important to consider this aspect in the clinical

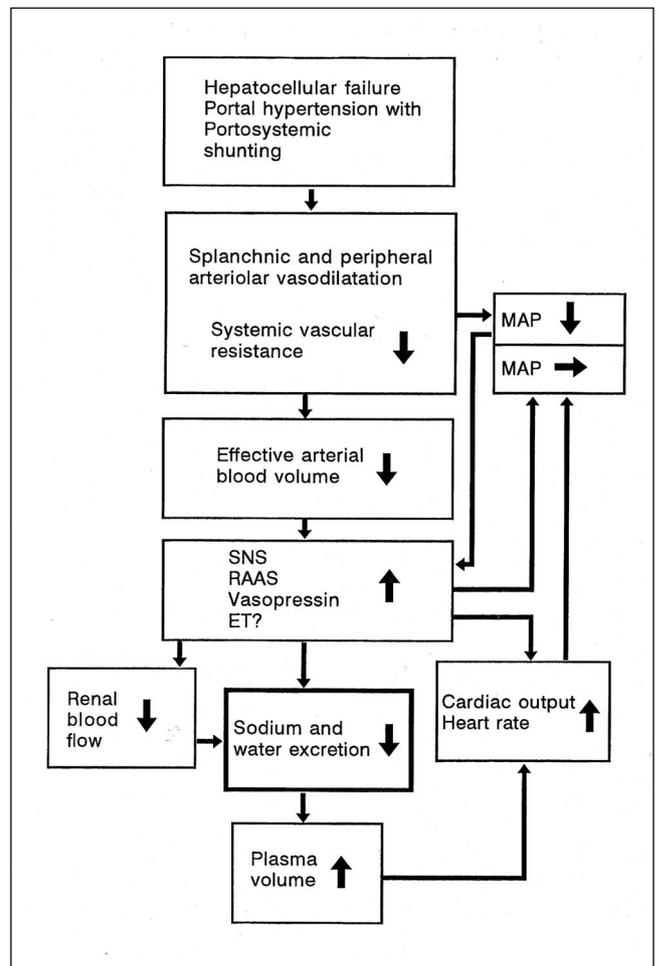


Figure 5) Pathophysiology of the splanchnic and peripheral arteriolar vasodilation and systemic hemodynamic changes in cirrhosis. A reduced systemic vascular resistance leads to a reduced effective arterial blood volume and hence activation of different vasoconstrictor systems. The hemodynamic and clinical consequences are increases in cardiac output, heart rate and plasma volume, and decreased renal blood flow, low or low to normal arterial blood pressure, and fluid and water retention. ET Endothelin; MAP Mean arterial blood pressure; RAAS Renin-angiotensin aldosterone system; SNS Sympathetic nervous system

handling of the patient and in the assessment of the prognosis (57). It can be concluded that patients with cirrhosis have an increased cardiac output with occurrence of hypo-, normo- and hyperperfused systemic vascular beds, but the exact distribution of the increased cardiac output among the different organs, tissues and types of vessels remains to be clarified. Most likely, the blood flow pattern will change with the progression of the disease from preportal hypertensive, to portal hypertensive preascitic, to portal hypertensive ascitic, to full-blown hepatorenal syndrome (HRS).

REGULATION OF SODIUM-WATER RETENTION
A decade ago, Schrier et al (146) proposed the peripheral arterial vasodilation hypothesis. According to this hypothesis, peripheral and splanchnic vasodilation may lead to a reduction in the systemic vascular resistance and arterial blood

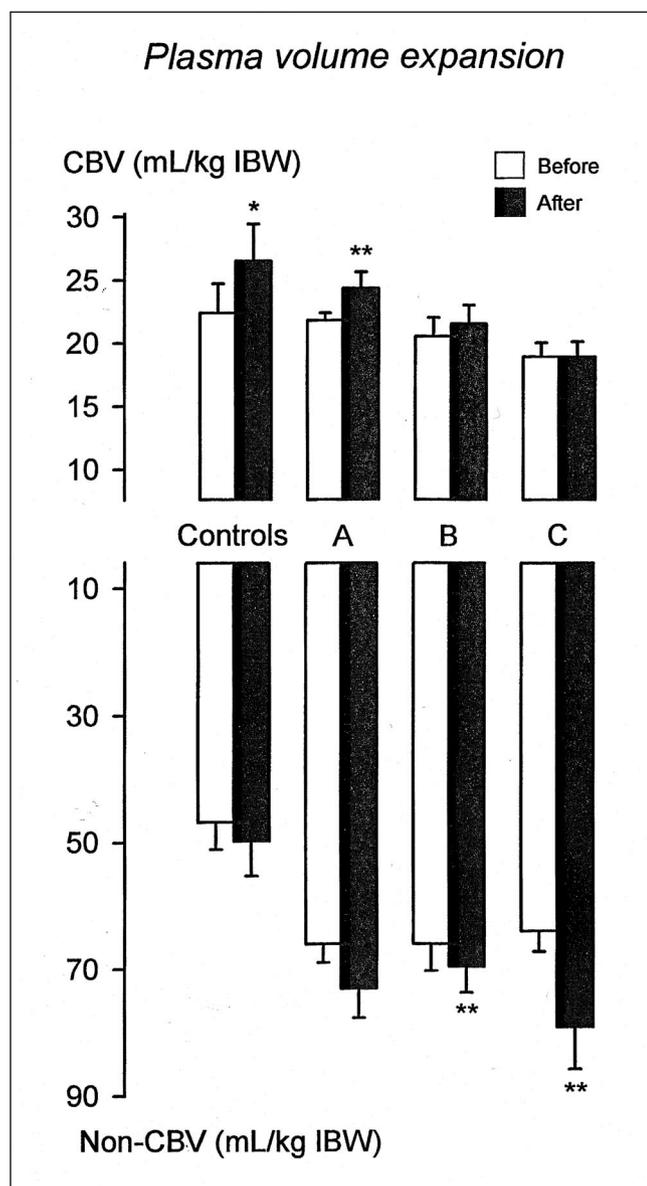


Figure 6 Central and arterial blood volume (CBV) and noncentral blood volume (Non-CBV) in patients with cirrhosis of different severity according to the Child-Turcotte classes A, B and C, and in control subjects before and after acute volume expansion. CBV is decreased in patients with advanced disease compared with patients with mild cirrhosis or control subjects, whereas the noncentral blood volume is expanded in patients with advanced disease. CBV can increase after acute volume expansion only in patients with mild disease and in controls. * $P < 0.05$; ** $P < 0.01$. Data from reference 173

pressure, which are primary events in the retention of sodium and water (Figure 5) (20,147). Over the past few years, nitric oxide, CGRP and adrenomedullin have attracted special interest as systemic and splanchnic vasodilators and are discussed.

Nitric oxide: In 1991, Vallance and Moncada (148) proposed that nitric oxide could be implicated in the peripheral vasodilation in cirrhosis and related to the hemodynamic abnormalities (149). Several human and animal studies have supported this concept (39,150-152), whereas others have been unable to do so (153-155). To support the hypothesis,

blockade of nitric oxide formation significantly improves the systemic hyperdynamic circulation by increasing arterial blood pressure and decreasing plasma volume and sodium retention (150,156-158). Moreover, infusion of the nitric oxide donor L-arginine aggravates the systemic vasodilation and hyperdynamic circulation of patients with cirrhosis (85,159). Fernando et al (154) reported that N-acetylcysteine prevented the development of the hyperdynamic circulation in portal vein-ligated rats, but no beneficial effects have been shown in humans. Thus, some studies have found that the hyperdynamic circulation is reversed by the blockade of the nitric oxide system, whereas other studies have concluded that the nitric oxide system can only be partially responsible for the vasodilation in cirrhosis. More clinical studies are needed to establish the precise role of nitric oxide in the hemodynamic alterations in cirrhosis and potential therapeutic aspects.

CGRP: CGRP is a peptide consisting of 37 amino acids and has neurotransmitter function in the nervous system (160). On a molar basis, it is the most powerful vasodilating peptide known (160). Circulating CGRP has been reported to be elevated in cirrhosis and to increase with the severity of the disease, with the highest reported concentrations in patients with ascites and HRS (14,15). Møller et al (126) reported that elevated plasma CGRP is directly correlated to cardiac output and negatively correlated to systemic vascular resistance. These findings were further substantiated in other patients, in whom a covariation of CGRP with central hemodynamics was found (161). Increased CGRP may also contribute to the abnormal distribution of the blood volume and the increased arterial compliance reported in these patients (16,152). The final definition of the role of CGRP in hemodynamic alterations in cirrhosis must await the development of specific antagonists.

Adrenomedullin: Adrenomedullin, a recently discovered vasodilating peptide consisting of 52 amino acids with a sequence similar to that of CGRP, is primarily released from the adrenal medulla and induces relaxation of smooth muscle cells (162,163). Injection of adrenomedullin into animals produces a pronounced vasorelaxation, probably owing to the release of nitric oxide, and brings about a decrease in systemic vascular resistance and arterial blood pressure (164,165). Increased circulating adrenomedullin concentrations have been reported in patients with such different circulatory disorders as cardiac, renal and hepatic failure (166). Various studies have shown increased circulating levels of adrenomedullin, which correlate with the degree of liver dysfunction (17,18,167). Plasma adrenomedullin is generally higher in patients with decompensated cirrhosis and correlates with pressor substances, such as endothelin, renin, aldosterone and catecholamines (17,18,168,169). In addition, adrenomedullin seems to be related to renal impairment in cirrhosis, as reflected by correlations to creatinine clearance and urinary sodium excretion (18,167). However, the potential role of this very potent vasodilating agent and its prohormones in the hyperdynamic circulation and abnormal volume distribution in cirrhosis needs further research (170).

REGULATION OF BLOOD VOLUMES

Systemic arteriolar vasodilation may lead to an abnormal distribution of the circulating medium with a decrease in the effective blood volume and to an expansion of the noncentral blood volume, including the splanchnic bed (61,62). In advanced decompensation with fluid retention and ascites, most investigators agree that the effective blood volume is decreased (1,171-173). At the portal hypertensive preascitic stage, there is some controversy, because dynamic indicator kinetic data show a decreased central and arterial blood volume, whereas a static gamma camera technique revealed increased values (61,173-175). There is also controversy about the activation of the powerful pressor and sodium- and water-retaining systems. Thus, Blendis (176) reported that up to one in four portal hypertensive preascitic patients has suppressed RAAS, SNS and vasopressin. Moreover, in most cases there seems to be a progressive increase from normal values to slightly increased values in preportal hypertensive patients, to a further increase in portal hypertensive preascitic patients, to highly increased values in ascitic patients and patients with HRS (177,178). Thus, it is possible that different mechanisms and different time scales apply in different patients and different etiologies of cirrhosis. This is an important topic for future research.

Recent research has indicated that patients with early cirrhosis are able to expand their central and arterial blood volume in response to plasma volume expansion (126,179). Conversely, patients with advanced cirrhosis are unable to expand this part of their blood volume (Figure 6). Both categories of patients, however, respond to plasma volume expansion with a further decrease in systemic vascular resistance without changes in the arterial blood pressure. These results are consistent with investigations on the change in central volume expansion when the patient moves from the upright to supine position (101,175).

Several studies have shown increased circulating vasopressin and activation of the SNS, RAAS and endothelin systems (Table 2) (12,19,95,178). The marked activation of these systems indicates a decreased effective plasma volume and emphasizes the importance of abnormal volume distribution. Substantial evidence supports the systemic vasodilation as a key feature in the activation of vasoconstrictive and sodium- and water-retaining systems. In addition, systemic hemodynamic alterations are important for the low renal blood flow (RBF) and renal dysfunction in cirrhosis (180-182). Decreased mean arterial blood pressure, especially in a more advanced stage of the disease, reduces the effective renal perfusion pressure (183). Activation of the RAAS may contribute to decreased renal perfusion, but the RAAS may also have more complex regulatory effects within the kidney (172,177,178,182). It has been shown that vasopressin does not change renal perfusion substantially (184). Noradrenaline, adrenaline and ET-1 may be important elements in the renal hypoperfusion and sodium-water retention in advanced cirrhosis (19,185). Local vasodilators, such as prostaglandins, most likely function to compensate, at least in part, the progressive renal vasoconstriction seen in advanced cir-

TABLE 2
Potential vasodilating and vasoconstricting substances or systems in arteriolar vasodilation and counter-regulation in cirrhosis

Vasodilators	
	Adenosine
	Adrenomedullin
	Atrial natriuretic peptide
	Calcitonin gene-related peptide
	Endothelin-3
	Endotoxin
	Enkephalins
	Glucagon
	Histamine
	C-type natriuretic peptide
	Nitric oxide
	Prostacyclin
	Substance P
	Tumour necrosis factor-alpha
	Vasoactive intestinal polypeptide
Vasoconstrictors	
	Adrenaline and noradrenaline
	Endothelin-1
	Renin-angiotensin aldosterone-system
	Sympathetic nervous system
	Vasopressin

rhosis (186-188). In decompensated patients, the normalization of arterial blood pressure may increase renal perfusion and improve renal function (189). Accordingly, a combination of prolonged administration of ornipressin and albumin infusion has recently been reported to reverse HRS (190). The concomitant effect of a number of drugs on systemic and splanchnic hemodynamics on the one hand, and renal perfusion and function on the other, has been reviewed elsewhere (189). A major problem in intensive diuretic treatment and treatment of portal hypertension is the adverse effects on the systemic hemodynamics, as deranged systemic hemodynamics, per se, may reduce renal function.

Treatment with alpha-adrenergic blocking agents, and potentially with ET-1 blockers, may reverse renal vasoconstriction, but their effect on arterial blood pressure may overrule beneficial local effects on the kidney (42,191).

HRS denotes a condition characterized by functional renal failure consequent on hepatic failure, most commonly of cirrhotic origin (180,181). No clinical or pathoanatomical signs of other known causes of renal failure are present. The clinical characteristics of the HRS are a very low urinary concentration of sodium (less than 10 mmol/L), high urine to plasma ratio of creatinine (more than 30), high urine specific gravity (greater than 1.010) and, infrequently, a few casts in the urine. HRS has been classified into two clinical types: type I HRS, characterized by a rapidly progressive reduction in renal function and type II HRS, where the onset of renal failure is slower (180). In general, HRS is characterized by a decrease in RBF and glomerular filtration rate (GFR), avid sodium water retention with formation of ascites, azotemia and sometimes oliguria. HRS may be considered to be a progressive, functional nephropathy, consequent

on circulatory and dysregulatory collapse. The renal perfusion pressure is decreased, not only because of the low arterial blood pressure in advanced cirrhosis, but also because of elevated renal venous pressure, especially in patients with tense ascites (32). The enhanced sympathetic nervous activity may alter the autoregulation curve of the kidney with a shift to the right. At an arterial perfusion pressure below about 70 mmHg, the relation between RBF and perfusion pressure becomes almost linear, whereas above this pressure RBF is more or less independent of changes in arterial blood pressure (32).

Patients with a high Child-Turcotte score, high portal pressure, avid sodium water-retention or HRS have the highest plasma levels of circulating catecholamines, and there are several indications that enhanced renal sympathetic nervous activity plays an important part in renal vasoconstriction and the development of HRS (19,178). The normal response to activation of renal sympathetic nerves is increased renin secretion, increased proximal tubular reabsorption of sodium and, when sympathetic activity intensifies, decreased RBF and GFR (192). The highly significant inverse relation between noradrenaline overflow or the noradrenaline concentration in the renal vein on the one hand and RBF on the other may illustrate this (193). In the early stage of nephropathy, the RBF is more decreased than the GFR (high filtration fraction), the GFR later decreases substantially and patients with full-blown HRS have a low filtration fraction, indicating preferential constriction of the afferent arteriole (32).

The hemodynamic changes in cirrhosis point toward renal hypoperfusion as being, at least initially, a physiological response to changes in the systemic circulation. It seems likely that increased SNS activity is a primary pathogenic factor, but other systems, such as the RAAS and endothelins, may also play a role (172,177,181,193). Accordingly, the increased activity of plasma renin correlated inversely with the RBF and GFR (180). However, angiotensin II mainly acts on the efferent arterioles. A low dose of an angiotensin-converting enzyme inhibitor induced a signifi-

cant reduction in the GFR and filtration fraction, and a further reduction in sodium excretion, even in the absence of a change in arterial blood pressure (32,180). This suggests that the integrity of the RAAS is important for the maintenance of renal function in cirrhotic patients and that RAAS overactivity does not solely contribute to the adverse renal vasoconstriction. Absence of or decreased activity in local renal vasodilator systems, such as the prostaglandins, may also play a role in the HRS (194). Recent results of infusion of terlipressin or ornipressin on renal function have shown beneficial effects, with an increased GFR in patients with HRS (190,195). Implantation of TIPS in patients with the HRS have also shown improvement in renal function, including a reduction in the activity of the RAAS (196-198).

CONCLUSIONS

Although the past decade has seen a considerable increase in our understanding of the abnormal hemodynamics and the neurohumoral dysregulation, it is still an enigma why patients with cirrhosis are vasodilated and overloaded but, from a functional point of view, hypovolemic. The mechanisms behind the abnormal distribution of the blood volume and the cardiovascular dysfunction need further investigation. The location and nature of the decreased splanchnic and systemic vascular resistance and increased arterial compliance are important.

Drugs for the treatment of portal hypertension are becoming increasingly available. However, further dysfunction of the systemic circulation may threaten the course of the disease. The predominant single factor that may affect renal function is further deterioration of the systemic circulation with reduced arterial blood pressure. The potential risk of reduction in renal function should, therefore, always be kept in mind when treating patients with cirrhosis. On the other hand, agonists and antagonists of the powerful systems implicated in the decompensated liver disease may give us important information about the pathogenesis of circulatory derangement and HRS, and hopefully lead to improvement in the treatment of cirrhosis.

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