



EDITORIAL

Cardiopulmonary complications in chronic liver disease

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Received: 2005-08-05 Accepted: 2005-08-25

Abstract

Patients with cirrhosis and portal hypertension exhibit characteristic cardiovascular and pulmonary hemodynamic changes. A vasodilatory state and a hyperdynamic circulation affecting the cardiac and pulmonary functions dominate the circulation. The recently defined cirrhotic cardiomyopathy may affect systolic and diastolic functions, and imply electromechanical abnormalities. In addition, the baroreceptor function and regulation of the circulatory homeostasis is impaired. Pulmonary dysfunction involves diffusing abnormalities with the development of the hepatopulmonary syndrome and portopulmonary hypertension in some patients. Recent research has focused on the assertion that the hemodynamic and neurohumoral dysregulation are of major importance for the development of the cardiovascular and pulmonary complications in cirrhosis. This aspect is important to take into account in the management of these patients.

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Key words: Cirrhosis; Portal hypertension; Cardiomyopathy; Hemodynamics; Vasoactive substances; Baroreceptors; Hepatopulmonary syndrome; Portopulmonary hypertension; Autonomic dysfunction

Møller S, Henriksen JH. Cardiopulmonary complications in chronic liver disease. *World J Gastroenterol* 2006; 12(4): 526-538

<http://www.wjgnet.com/1007-9327/12/526.asp>

INTRODUCTION

The clinical picture of patients with cirrhosis is dominated by the classical complications to portal hypertension, such as ascites, bleeding from esophageal varices, and encephalopathy. In addition, a considerable number of patients show signs of peripheral vasodilatation with

palmar erythema and reddish skin, raised and bounding pulse, and a low systemic blood pressure indicating a hyperdynamic circulation^[1]. The hyperdynamic syndrome comprises an increased heart rate, cardiac output, and plasma volume, and a reduced systemic vascular resistance and arterial blood pressure^[2-6]. The typical circulatory changes in patients with cirrhosis are summarized in Table 1. Increased cardiac output in cirrhosis was described more than 50 years ago^[7] and a hyperdynamic, hyporeactive circulation is today a well-characterized element in the clinical appearance of these patients^[8]. In addition, patients with cirrhosis develop complications from a variety of organs including the heart, lungs, and kidneys, and other organ systems. Besides the hepatorenal syndrome, this has led to the introduction of new clinical entities, such as cirrhotic cardiomyopathy and the hepatopulmonary syndrome.

Among the mechanisms involved in the peripheral arterial vasodilatation in cirrhosis, intensive research has focused on the presence of arteriovenous communications, increased blood volume, and potent vasodilating systems such as the NO and endothelin (ET) systems^[9-14]. Activation of a number of neurohumoral homeostatic system, like the renin-angiotensin-aldosterone systems (RAAS), the sympathetic nervous system (SNS), and the hypothalamic/neuropituitary release of vasopressin also seem to play a pivotal role in the circulatory dysfunction in cirrhosis^[15-18].

This review will focus on the pathophysiological aspects of the systemic circulatory abnormalities in cirrhosis with emphasis on cardiac and pulmonary dysfunctions.

SYSTEMIC CIRCULATION IN CIRRHOSIS

The cardiac output is primarily determined by the venous return, heart rate, and myocardial contractility, all of which are controlled by the autonomic nervous system. Among the mechanisms that may raise the cardiac output are increased sympathetic nervous activity, vasodilatation (low systemic vascular resistance), increased blood volume, and the presence of arterio-venous communications. It is noteworthy that the majority of these physiological changes are present in cirrhosis and may more or less contribute to raise cardiac output^[1,19]. In the early stages of compensated cirrhosis, the presence of a hyperdynamic circulation is often not apparent. But with the progression of the liver disease, there is an overall association between the severity of cirrhosis and the degree of hyperdynamic circulation. Investigations on circulatory changes and reactivity from the upright to the supine position, and vice versa, suggest that the patients are mostly hyperdynamic in the supine position^[20,21]. On the other hand, the pressor systems are relatively deactivated in the supine position and

Table 1 Circulatory changes in patients with 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 ↓

Heart

Left atrial volume ↑
 Left ventricular volume →(↓)
 Right atrial volume→↑↓
 Right ventricular volume →↑↓
 Right atrial pressure →↑
 Right ventricular end-diastolic pressure →
 Pulmonary artery pressure →↑
 Pulmonary capillary wedge pressure →
 Left ventricular end-diastolic pressure →

Pulmonary circulation

Pulmonary blood flow ↑
 Pulmonary vascular resistance ↓(↑)

Renal circulation

Renal blood flow ↓
 Renal vascular resistance ↑

Cerebral circulation

Cerebral blood flow ↓ →

Cutaneous and skeletal muscle circulation

Cutaneous blood flow →↑
 Skeletal muscular blood flow →↑

↑ Increase, → No change, ↓ Decrease.

it is well documented that sodium-water excretion is higher in the supine position than in the upright position^[22].

Pathophysiology of arterial vasodilatation

Peripheral vasodilatation in cirrhosis may be brought about either by overproduction of circulating vasodilators, or by vasodilators of intestinal or systemic origin, or by vasodilators that escape degradation in the diseased liver or bypass the liver through portosystemic collaterals^[19]. A predominantly splanchnic vasodilatation precedes renal sodium and water retention and plasma volume expansion, which correlates with activated counter regulatory vasoconstrictor systems^[6,19]. In 1988, Schrier *et al* proposed the “*peripheral arterial vasodilation hypothesis*”^[23]. According to this theory, primary splanchnic arteriolar vasodilatation leads to the reduction of the overall systemic vascular resistance, to avoid arterial underfilling with low arterial blood pressure. A reduced effective blood volume, which is that part of the blood volume where baroreceptors are located, leads to the activation of vasoconstrictor systems and secondary sodium-water retention^[6,23-25]. Thus, most of the hemodynamic changes seen in cirrhosis can be explained by this theory, as shown in Figure 1.

Circulating vasodilators

In recent years, research has focused especially on vasodilating substances, such as NO, calcitonin gene-related peptide (CGRP), and adrenomedullin, but other vasodilators substances, like natriuretic peptides, tumor necrosis factor alpha, interleukins, substance P, ETs, and endocannabinoids,

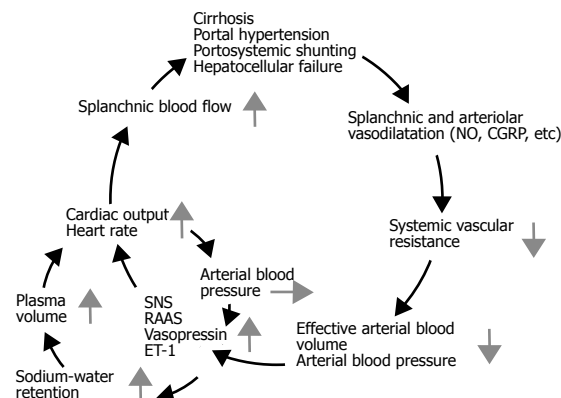


Figure 1 Pathophysiology of the splanchnic and peripheral arteriolar vasodilation and systemic hemodynamic changes in cirrhosis. Endogenous vasodilators may escape hepatic degradation, owing to portosystemic shunting and/or hepatocellular damage, and induce vasodilatation preferentially in the splanchnic vascular area. Reduced systemic and splanchnic vascular resistance leads to a reduced effective arterial blood volume, and hence to activation of vasoconstrictor systems. The hemodynamic and clinical consequences are increases in cardiac output, heart rate, and plasma volume and decreased renal blood flow, low arterial blood pressure, and fluid and water retention. The development of the hyperdynamic circulation may increase portal inflow and further aggravate the portal pressure in a vicious cycle. SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system; ET-1, endothelin-1.

have also been implicated^[12,26-32].

NO is synthesized in the vascular endothelium from L-arginine by NO synthase (NOS)^[33], of which three isoforms have been identified: inducible NOS (iNOS), constitutive endothelial NOS (ecNOS), and neuronal NOS (ncNOS)^[12,34]. In portal hypertension, there seems to be a diminished release of NO from sinusoidal endothelial cells in the cirrhotic liver^[34,35] whereas, in the systemic circulation, there is evidence of increased eNOS upregulation, which is probably related to shear stress^[26,33,36]. Exhaled air from cirrhotic patients contains higher NO levels than that of controls and correlates with the severity of disease and degree of hyperdynamic circulation; in animal models and cirrhotic patients, blockade of NO formation significantly increases arterial blood pressure and decreases plasma volume and sodium retention^[37-40]. Taken together, there is a growing body of evidence that the systemic NO production is increased and precedes the development of the hyperdynamic circulation in cirrhosis, thereby playing a major role in the arteriolar and splanchnic vasodilatation and vascular hyporeactivity^[12,41]. In addition, vascular endothelial growth factor (VEGF) seems to stimulate angiogenesis and the development of portosystemic collaterals, and recently blockade of the VEGF receptor-2 has been shown to inhibit this process^[42]. In spite of the experimental nature of the study, this principle may have some therapeutic implications in the treatment of portal hypertension.

CGRP, a 37-amino-acid neuropeptide with a neurotransmitter function, is on a molar basis the most powerful vasodilating peptide known^[43]. It is elevated in cirrhosis, especially in those patients with ascites and the hepatorenal syndrome^[43,44] and correlates to hemodynamic markers of vasodilatation and central hypovolaemia, such as cardiac output, systemic vascular resistance, arterial compliance, and central blood volume^[27,45-47]. Adrenomedullin is a vasodilating peptide with a sequence

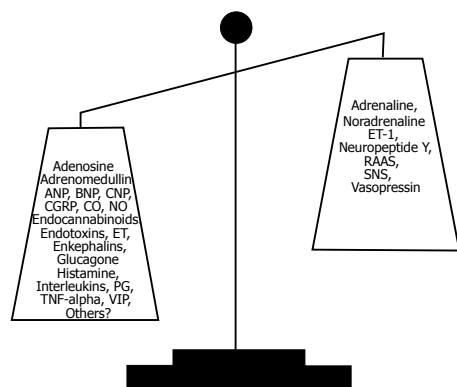


Figure 2 Imbalance between vasoconstricting and vasodilating forces. ANP, atrial natriuretic peptide; BNP and CNP: B- and C-type natriuretic peptides; CGRP, calcitonin gene-related peptide; ET, endothelin; TNF- α , tumor necrosis factor α ; VIP, vasoactive intestinal polypeptide; RAAS, The renin-angiotensin-aldosterone system; SNS, The sympathetic nervous system.

similarity to CGRP, it is primarily released from the adrenal medulla and induces relaxation of smooth muscle cells^[48]. The circulating levels of adrenomedullin seem to be higher in decompensated patients with cirrhosis and correlate with pressor substances, such as endothelin, renin, vasopressin, and catecholamines^[29,49,50].

In addition to a surplus of vasodilators, resistance to pressor hormones may play a role in the pathogenesis of vasodilatation, as patients with cirrhosis are hyporesponsive to the pressor effects of such potent vasopressors as noradrenaline, angiotensin II, and vasopressin^[51-53]. This may be brought about by a change in receptor affinity, a decrease in the numbers of receptors, and a variety of post-receptor defects^[54,55]. Helmy *et al* have reported hyporesponsiveness to angiotensin II and endothelin-1, chiefly because of enhanced NO generation^[41,56]. Thus, the excess of vasodilators combined with an inadequate hemodynamic response to vasoconstrictors may explain the vasodilatory state and vascular hyporeactivity in cirrhosis.

Vascular territories with vasoconstriction

Although cardiac output is increased, thus reflecting substantial vasodilatation, it may cover perfusions from vascular beds that are hyperperfused, normoperfused, and hypoperfused. The kidney in cirrhosis is a vascular region where vasoconstriction prevails and plays a pivotal role in the development of hepatic nephropathy with a decreased renal blood flow and glomerular filtration rate, increased sodium reabsorption, and decreased free water excretion^[6,57]. Liver dysfunction, central hypovolaemia, arterial hypotension, and neurohumoral activation with renal vasoconstriction seem to be of major importance. Recent results suggest that a decrease in the cardiac output in the face of severe vasodilatation and activation of the RAAS is an important determinant of the hepatorenal syndrome^[58]. Splanchnic vasodilatation and central hypovolaemia activate the SNS, the RAAS, the endothelin system, and increased release of vasopressin^[17,18]. The imbalance between vasoconstricting and vasodilating forces is illustrated in Figure 2. Secondary hyperaldosteronism and increased tubular sensitivity to aldosterone increase sodium reabsorption in the distal nephron, whereas SNS

stimulates sodium reabsorption in proximal tubules, the loop of Henle, and distal tubules^[59]. Angiotensin II mainly acts on the efferent arteriole and a low dose of an ACE-inhibitor may induce a significant reduction in glomerular filtration and a further reduction in sodium excretion, even in the absence of a change in arterial blood pressure. 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. Because of the arterial vasodilatation, the renal perfusion pressure is low and critically dependent on counter regulatory systems. For these reasons, blockers of these systems by ACE-inhibitors (captopril), angiotensin II antagonists (Losartan), β -adrenergic blockers, and V1 vasopressin antagonist may decrease further the renal blood flow^[60,61]. The hepatorenal syndrome denotes a functional and reversible impairment of renal function with a poor prognosis in patients with severe cirrhosis. Treatment is directed towards improving liver function, arterial hypotension, and central hypovolaemia, and reducing renal vasoconstriction for instance with the combined use of splanchnic vasoconstrictors such as terlipressin and plasma expanders like human albumin^[62].

Distribution of volumes and flow

Blood and plasma volumes are increased in patients with advanced cirrhosis^[25,63], and the distribution of blood in the different vascular beds is abnormal and relates to the severity of the disease^[64]. 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^[65-67]. The effective arterial blood volume is decreased with relation to the systemic circulatory derangement. Moreover, the central circulation time (i.e. central blood volume relative to CO) is substantially reduced and has a significant relation to poorer survival in advanced cirrhosis^[68,69].

During volume expansion, most cirrhotic patients respond with a further reduction in systemic vascular resistance rather than an increase in arterial blood pressure^[70,71]. Volume expansion by head-out water immersion provides, in principle, the same volume changes by central relocation as in healthy subjects^[70]. However, especially in decompensated cirrhosis, there may be a further decrease in the arterial blood pressure, owing to the unloading of baroreceptors, and renal salt-water excretion is prolonged and incomplete. The infusion of hyperosmotic solutions or albumin in cirrhosis results initially in a shift of fluid from the interstitial space into the plasma volume, with an expansion of the latter^[63,71]. Albumin infusion is important in the prevention of postparacentesis circulating dysfunction^[72]. When considering volume expansion in terms of the severity of the disease, certain differences become clear. Irrespective of severity, volume expansion produces a rise in stroke volume and cardiac output. Whereas in early cirrhosis there is a proportional expansion of the central and non-central parts of the blood volume, in late cirrhosis expansion is mainly confined to the non-central part, with a proportionally smaller increase in cardiac output, probably because of cardiac dysfunction (cirrhotic

cardiomyopathy) and abnormal vascular compliance^[71,73].

The increased plasma volume in cirrhosis should be considered secondary to the activation of neurohumoral mechanisms consequent on arterial vasodilatation, low arterial blood pressure, and reduced central and arterial blood volume. However, a non-volume-dependent activation of the SNS through hepatic reflexes, owing to portal hypertension, may occur. This has been documented in animal experiments and there are indications of such a reflex in men^[74]. Although the relative importance of non-volume-dependent sympathetic activation and volume/arterial pressure-dependent activation of SNS and other neurohumoral systems has not been finally established, the latter is probably far the most important.

CARDIAC DYSFUNCTION IN CIRRHOSIS

The hyperdynamic circulation in cirrhosis comprises increased cardiac output and work^[5,75]. In other circumstances, this would cause cardiac failure, but because of the decreased afterload as reflected by reduced systemic vascular resistance and increased arterial compliance, a left ventricular failure may be latent in cirrhosis^[75,76]. Cardiac failure may become manifest under strain or treatment with vasoconstrictors. This type of cardiac dysfunction has been termed as cirrhotic cardiomyopathy and includes impaired cardiac contractility with a systolic dysfunction, diastolic dysfunction, and electromechanical abnormalities with a prolonged *Q-T* interval^[77]. Various electrophysiological mechanisms for the conductance abnormalities and impaired cardiac contractility have been put forward, including reduced beta-adrenoceptor density, post-receptor signal defects, abnormal excitation-contraction coupling, and molecular abnormalities^[73].

Systolic dysfunction

At rest, when the systemic vascular resistance (afterload) against which the heart works is reduced, cardiac pressures are almost normal and may thereby mask an underlying ventricular dysfunction. Cardiac failure, therefore, becomes manifest only under conditions of hemodynamic stress. Thus, after the exercise, the left ventricular end-diastolic pressure increases, but the expected increase in cardiac stroke index and left ventricular ejection fraction (LVEF) are absent or subnormal, which indicates inadequate ventricular reserve response to a rise in ventricular filling pressure^[78,79]. A vasoconstrictor-induced increase in left ventricular afterload by 30% results in an increase in pulmonary capillary wedged pressure about double, without any change in the cardiac output^[80]. A similar pattern is seen after the insertion of transjugular intrahepatic portosystemic shunt (TIPS), but the increased cardiac pressures tend to normalize with time^[81-83]. A failure to increase cardiac output, despite an increased ventricular filling pressure, indicates that normalization of the afterload impairs cardiac performance and unmasks left ventricular dysfunction^[80]. Similar effects are seen after infusion of plasma expanders. Infusion of a plasma protein solution, however, increases cardiac output, as well as the right atrial pressure, pulmonary arterial pressure, and pulmonary capillary wedged pressure, whereas infusion of

packed red blood cells may not change these variables^[84].

The LVEF, i.e. the stroke volume relative to the left ventricular end-diastolic volume, is an often used measure of systolic function even though it is still very much influenced by preload and afterload. It has been reported to be normal at rest in some studies^[78,85-90] and reduced in one study in a subgroup of patients with ascites^[91]. The maximum aerobic exercise capacity and maximum heart rate are lower in the majority of patients with cirrhosis^[79,85,92]. After exercise, LVEF increases significantly less in cirrhotic patients than in controls^[79,92,93]. The reduced functional capacity may be attributed to a combination of blunted heart rate response to exercise, reduced myocardial reserve, and profound skeletal muscle wasting with impaired oxygen extraction^[85,94]. Normalization of the low systemic vascular resistance by vasoconstrictors results in an increase in the left atrial and left ventricular filling pressures^[75,80]. Therefore, attempts to normalize the reduced cardiac afterload seem to unmask a latent ventricular dysfunction which appears to be resistant to inotropic drugs^[77,80]. The expanded blood volume in advanced cirrhosis contributes to a persistent increase in cardiac output, which may overload the heart, with impaired cardiac contractility as the outcome^[20,86,95]. In patients with advanced cirrhosis and severe vasodilatation, activation of the RAAS, and impaired renal function, a reduced systolic function (a decrease in cardiac output) seems to be a major determinant for the development of the hepatorenal syndrome^[58].

Diastolic dysfunction

A diastolic dysfunction implies changes in myocardial properties that affect left ventricle acceptance of a sufficient volume during the diastole, despite normal filling pressures; the increased stiffness of the myocardial wall will thus result in impaired filling of the left ventricle^[96]. This increases the transmitral pressure gradient and the atrial contribution to ventricular filling in order to normalize the left ventricular diastolic volume. Determinants of a diastolic dysfunction include impaired left ventricular diastolic filling, in spite of high stroke volume. In the Doppler-echocardiogram, the E-wave reflects the early rapid transmitral flow and the A-wave the late atrial contribution to filling. Indications of diastolic dysfunction are a decreased E/A ratio and delayed early diastolic transmitral filling with prolonged deceleration and isovolumetric relaxation times^[97], as shown in Figure 3. In cirrhosis, the morphological basis of cirrhotic cardiomyopathy seems to be cardiac hypertrophy, patchy fibrosis, and subendothelial edema^[77,93]. In a number of studies, A-wave and E-wave velocities and deceleration times are much increased and the E/A-ratio is decreased in cirrhotic patients, especially in those with ascites^[91,97]. Recent studies of ventricular diastolic filling in cirrhosis support the presence of a subclinical myocardial disease with diastolic dysfunction, which, in ascitic patients, is improved after paracentesis and aggravated after TIPS^[82,88,91,97]. In these decompensated patients, paracentesis seems to ameliorate diastolic, but not systolic, function^[91]. Liver transplantation has recently been shown to revert cardiac alterations, including diastolic

dysfunction^[93]. It has been proposed that a diastolic dysfunction precedes systolic dysfunction in early heart disease and that antialdosterone treatment improves cardiac function. Pozzi *et al* recently demonstrated that antialdosterone treatment with K-canrenoate in cirrhosis ameliorated cardiac structure and function, but had almost no effects on systolic and diastolic functions^[98]. It is also possible that antialdosterone treatment may have beneficial effects on catecholamine-induced cardiac fibrosis, as described in heart failure^[99].

The clinical significance of diastolic dysfunction and the importance in cirrhotic cardiomyopathy have been questioned, as overt cardiac failure is not prominent in cirrhosis. However, there are several reports of unexpected death from heart failure following liver transplantation^[100], surgical portocaval shunts and TIPS^[81]. These procedures involve a rapid increase in cardiac preload. In a less compliant heart, the diastolic dysfunction could be enough to cause pulmonary edema and heart failure. This is consistent with the findings of Huonker *et al*^[82], who reported an increase in pulmonary artery pressure, pre-load, and diastolic dysfunction after TIPS. Diastolic dysfunction could thus account for part of the cardiac dysfunction in cirrhotic cardiomyopathy.

Electromechanical abnormalities

The sympathetic nervous activity influences the heart rate and electromechanical coupling by several mechanisms: noradrenaline binding to beta-receptors, receptor-mediated G protein interaction, and consequently stimulation of adenylcyclase, activation of cAMP-dependent phosphokinase A, and channel phosphorylation. Several receptor and post-receptor defects have been described in cirrhosis with reduced beta-receptor density and sensitivity^[101], and altered G protein and calcium channel functions^[102]. All these defects may explain both impaired chronotropic responses and electromechanical uncoupling. This coupling between the cardiac contractions and the arterial system is of major importance to the amount of work performed by the left ventricular myocardium, and thereby, of the strain on the heart^[85]. The ascending aorta and aortic arc are the most compliant systemic arteries in the body. The ability to contain the entire stroke volume without excessive deflection in the arterial systolic pressure profile is of crucial importance, especially in patients with a large CO and stroke volume. On the other hand, too compliant a central arterial system will be unable to perform a timely and prompt delivery of blood to the different parts of the body, but may delay the flow to important areas of the vascular bed. Thus, the heart and central arterial tree work together in an essential coordination of the oscillating blood flow. This is especially important when vascular beds with highly different hemodynamic resistances are connected to the central arterial system, as in chronic liver disease.

In addition to the abnormal function of the calcium channels, Ward *et al*^[103] have shown a decrease in K⁺ currents in ventricular cardiomyocytes from cirrhotic rats, which prolong the *Q-T* interval. A prolonged *Q-T* interval is often present in chronic liver disease, potentially leading to ventricular arrhythmias and sudden cardiac

death^[75,77,104]. Bernardi *et al* have reported a prolonged *Q-T* interval, which is significantly related to the severity of the liver disease, plasma noradrenaline, and survival^[105]. A reversal of the *Q-T* interval seems to occur with improved liver function, for instance, after orthotopic liver transplantation^[106]. Results from our group indicate that the frequency adjusted *Q-Tc* becomes partly normalized after oral β -blocker treatment^[107]. The prolonged *Q-T* interval in cirrhosis should be considered as an element in the cirrhotic cardiomyopathy and may be of potential use in identifying patients at risk^[77]. Pathophysiological and clinical research is needed to assess the prognostic and therapeutic significance of the prolonged *Q-Tc* interval in chronic liver disease.

It can be concluded that there is evidence of a cirrhotic cardiomyopathy in cirrhosis that appears to be unmasked by procedures that stress the heart, such as pharmacological vasoconstriction, exercise, and by such portosystemic shunt procedures as insertion of TIPS. Future studies should be directed against an operable definition of cirrhotic cardiomyopathy, a delineation of the clinical importance, and potential treatment regimens. Until then, we still do not know how or if cirrhotic cardiomyopathy should be treated specifically.

CARDIOVASCULAR REGULATION IN CIRRHOSIS

Autonomic dysfunction

Evidence of autonomic defects in patients with cirrhosis has emerged from hemodynamic responses to standard cardiovascular reflex tests, such as Valsalva ratio, heart rate variability, and isometric exercise^[87,108-111]. Most studies of these issues have found a high prevalence of autonomic dysfunction in cirrhosis with associations to liver dysfunction and survival^[111,112]. The results of Mohamed *et al* suggest that the autonomic dysfunction is temporary, arises as a consequence of liver dysfunction, and may be reversible after liver transplantation^[106]. Whereas most studies have focused on the defects in the SNS, recent papers have emphasized the importance of a vagal impairment for sodium and fluid retention^[108,110,112]. Sympathetic responses to dynamic exercise seem to be normal in patients with cirrhosis, but those to isometric exercise are clearly impaired^[113,114]. Similarly, blood pressure responses to orthostasis are impaired, probably because of a blunted baroreflex function^[87,115,116]. Abnormal cardiovascular responses to pharmacological stimulations with angiotensin II, noradrenaline, and vasopressin in terms of impaired responses in blood flow and blood pressure have also been reported in cirrhosis^[117-119]. Dillon *et al*^[112] have described the correction of autonomic dysfunction in cirrhosis by captopril, which indicates that vagal dysfunction in cirrhosis is partly caused by neuromodulation by angiotensin II. Involvement of the RAAS is also supported by the data from La Villa *et al*, who recently reported that canrenone, an aldosterone antagonist, normalized cardiac responses to postural changes in compensated cirrhotic patients^[116].

At present the pathophysiological basis of the autonomic dysfunction is unknown, but it could be within the central nervous system through damage to

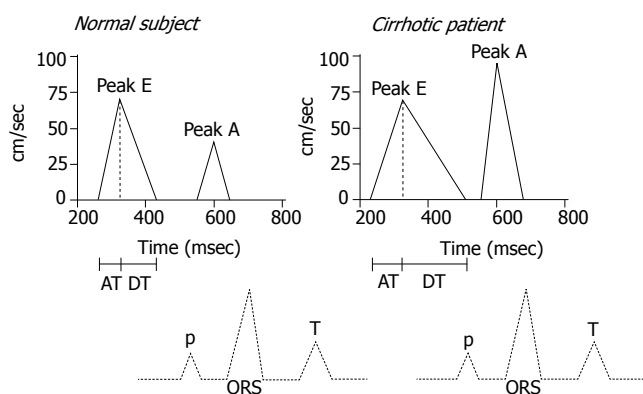


Figure 3 Diagram of the transmitral Doppler flow signal in the healthy state and in a patient with cirrhosis. The Doppler flow profile reflects the early filling of the ventricle (Peak E) and the late atrial contribution to its filling (Peak A). A decrease in the E/A ratio and prolonged acceleration time (AT) and deceleration time (DT) indicate diastolic dysfunction, as illustrated in the right panel. The broken lines are the time-related electrocardiogram.

the peripheral nerves or changes in neurotransmission in terms of a post-receptor defect which could explain the vascular hyporeactivity (Figure 4). From the amount of data available, a multifactorial etiology to the hyporesponsiveness in cirrhosis seems most likely.

Vascular hyporeactivity and arterial compliance in cirrhosis

The hyporeactivity of the vascular system in chronic liver disease is probably a result of a differential balance between vasoconstricting and vasodilating forces in different vascular areas (Figure 2). Generally, however, the vascular system in cirrhosis is very flexible as reflected by an overall increased vascular and arterial compliance^[120-122]. The systemic arterial compliance, defined as an increase in intra-arterial volume relative to an increase in transmural arterial blood pressure, is especially increased in patients with decompensated cirrhosis^[46]. This is because of the changes in the arterial wall, as well as dynamic changes, and is closely associated with the circulatory and homeostatic derangement^[47,122]. Therefore, the changes in arterial mechanics are partly reversible. The arteriolar tone adjusts the level of blood pressure and may thereby also affect large artery compliance. In fact, arterial compliance depends on the properties of arterial intrinsic elastic and smooth muscle, whereas arteriolar tone should result more from the balance between vasoconstrictors and vasodilators. The increased arterial compliance is directly related to the severity of liver disease and to the circulating vasodilator, CGRP, but is inversely related to circulating adrenaline, and unrelated to indicators of potent vasoconstrictor systems (SNS and ET-1)^[47,123]. In addition, other operative elements in the abnormal arterial compliance are blood volume abnormalities, hypoxia, and abnormalities in the C-type natriuretic peptide (CNP), but not to arterial natriuretic peptide. Arterial compliance is not affected by β -adrenergic blockade, but terlipressin almost normalizes it^[124]. Arterial compliance is an important determinant of the coupling between the heart and the arterial system, and of the dynamics

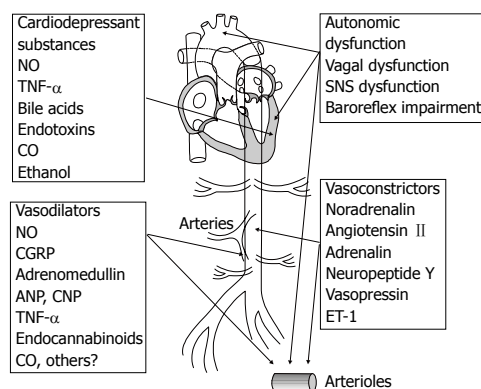


Figure 4 Vascular hyporeactivity in cirrhosis may originate in the central nervous system, the autonomic nervous system, from local mediators, or within the smooth muscle cell/heart muscle cell. An autonomic dysfunction may act at cardiac, arterial, and arteriolar levels. Vasodilators and vasoconstrictors may act variably at cardiac, arterial, and arteriolar levels. At the smooth cellular (arteriolar) level, hyporeactivity may be caused by increased concentrations of vasodilators (NO, nitric oxide; CGRP, calcitonin gene-related peptide; ANP, atrial natriuretic peptide; TNF- α , tumor necrosis factor- α ; endocannabinoids; CO: carbon monoxide) and/or decreased sensitivity to vasoconstrictors (ET-1: endothelin-1).

of intravascular volume relocation^[125]. An element in the elevated arterial compliance in advanced cirrhosis is the reduced arterial blood volume and blood pressure^[47].

Recent data suggest that the hyperdynamic circulation is mainly caused by circulatory alterations in the splanchnic area^[67]. Thus, arteriolar vasodilatation is a more localized event, whereas the increased arterial compliance is more general^[47]. Arterial compliance may therefore be an integral variable for vascular responsiveness, together with the systemic vascular resistance. Changed dynamic and static function of the arterial tree may contribute to the abnormal reactions of volume and baroreceptors, and have implications for the abnormal circulatory regulation, and potentially for therapy with vasoactive drugs. These aspects are, however, a topic for further research. In conclusion, arterial compliance is elevated in advanced cirrhosis. Besides a relation to age, body size, gender, and the level of the arterial blood pressure, arterial compliance is directly related to the severity of cirrhosis and the hyperdynamic circulatory derangement.

Baroreceptor function and homeostasis of arterial blood pressure in cirrhosis

The arterial vasodilatation contributes to the displacement of the central blood volume towards peripheral and splanchnic vascular regions, resulting in central and arterial hypovolaemia and activated counter regulatory mechanisms^[65,71,126]. The pronounced vasodilatation and the fall in arterial blood pressure elicit reduced baroreflex activity and diminished central signaling from the cardioinhibitory center and results primarily in SNS-mediated vasoconstriction of resistance vessels^[127]. The normal response to upright posture is a fall in arterial, central venous, and pulse pressures and there is a close relation between the decline in pulse pressure on the one hand and the rising heart rate and declining splanchnic blood flow on the other, which suggests that arterial baroreceptors initiate an increase in heart rate and

splanchnic vasoconstriction^[127]. Whether this pattern is disturbed in cirrhosis is unclear at present. Some studies have shown that a reduction in thoracic blood volume increases the sensitivity of the arterial baroreflex^[127,128]. A resetting of the baroreceptors is still discussed in human conditions in relation to wall tension of the fibroelastic tissues in the vessels and stretch-induced activation of the sodium-potassium channels^[127]. As mentioned above, autonomic dysfunction is well-established in cirrhosis^[112,114,129], and impaired baroreceptor reflex sensitivity has been suggested^[121,115,130]. The baroreceptor function is influenced by hypoxia^[131,132] which is often seen in cirrhosis and in particular in those patients with the hepatopulmonary syndrome^[133,134].

Baroreceptor sensitivity in the small subset of cirrhotic patients with arterial hypertension has not been investigated, but it is very likely that the co-existence of two different conditions of baroreceptor function involved may affect the cardiovascular regulation^[135]. Future studies should seek to reveal the direction of this possible baroreceptor dysfunction in this specific group of patients.

Blood pressure regulation

Potent vasodilators such as NO, CGRP, histamine, bradykinin, and serotonin have been implicated in the regulation of the blood pressure in chronic liver disease^[1]. A significant inverse relation of the potent vasodilator, adrenomedullin, to arterial blood pressure and ET suggests that these two vasoactive systems play a role in blood pressure regulation in cirrhosis. NOS blockade causes higher arterial blood pressure in cirrhotic rats. Inhibition of the endocannabinoid CB1 receptor raises arterial blood pressure in experimental cirrhosis, and anandamide from the monocytes of cirrhotic rats may contribute to the arterial hypotension observed^[132,136]. However, the significance of blood pressure dysregulation in human cirrhosis awaits further studies.

The arterial blood pressure is kept low below normal, depending on the state of the disease, as a circulatory compromise between the vasodilating and counter regulatory vasoconstricting forces affecting both vascular resistance and compliance. The arterial blood pressure possesses a circadian variation. Twenty-four-hour determinations in cirrhotic patients show that during the day, the systolic, diastolic, and mean arterial blood pressures are substantially reduced, whereas at night, the values are unexpectedly normal^[14]. In cirrhosis, the drop from day time to night-time and the rise from night-time to daytime show lower values than in controls. It is known from several diseases, such as uraemia and different types of heart failure, that the circulation of patients classified as "nondippers" is abnormally regulated. The combination of normal blood pressure and increased heart rate at night suggests abnormal regulation of the circulation in cirrhosis. Prolonged rest in the supine position (as during sleep) may lessen the abnormal distribution of the blood volume and improve the ability to maintain a normal "sleeping" arterial blood pressure, only at the cost of an increased heart rate and CO. The upright position further aggravates central hypovolaemia, and normal arterial blood pressure cannot be maintained, even when the heart rate and CO

are increased^[20,21,137]. The negative correlation of the arterial blood pressure to the Child score during the day and at night confirms that the hemodynamic derangement is related to the severity of the liver disease^[69]. The low arterial blood pressure, the abnormal distribution of the circulating medium and diurnal variation in arterial blood pressure, and the marked activation of neurohumoral systems contribute to the abnormal homeostatic regulation in patients with cirrhosis.

Previous reports of findings that arterial hypertension does not occur together with cirrhosis of the liver are not true in an absolute sense. However, the prevalence of arterial hypertension in cirrhotic patients is substantially reduced, especially in advanced cirrhosis^[135]. As hypertensive patients are often effectively treated with diuretics, calcium channel antagonists, beta-blockers, ACE-inhibitors, etc., and some of these drugs are also applied in the treatment of cirrhosis and portal hypertension, the natural history and prevalence of cirrhosis in patients with arterial hypertension, arterial hypertension in patients with cirrhosis, and the interrelationship of these two diseases may be difficult to study today in prospective and untreated cases. Nevertheless, such studies are relevant, since there are many unsolved questions.

PULMONARY DYSFUNCTION IN CIRRHOSIS

Patients with cirrhosis often complain of dyspnea and platypnea, and arterial oxygenation is often impaired with orthodeoxia^[138,139]. The etiology of abnormal lung function and ventilation in cirrhosis may be multifarious and is often a combination of the presence of cardiac dysfunction, heavy smoking, and chronic obstructive lung disease which is common in patients with alcoholic cirrhosis^[140]. In addition, lung function and oxygenation can be affected by edema and tense ascites, which are ameliorated after diuretic treatment and paracentesis^[141]. But independent of smoking status, patients with cirrhosis have a compromised lung function with a reduced transfer factor and ventilation/perfusion abnormalities^[45,134,140,142] and arterial hypoxemia is seen in 30%-70% of patients with chronic liver disease, depending on the severity^[143,144]. Various pathophysiological factors may be involved in the reduced diffusing capacity, including an abnormal ventilation/perfusion ratio (V_A/Q), the presence of arterial venous shunts, and changes in the alveolar-arterial membrane (Figure 5).

Hepatopulmonary syndrome

The reduced diffusion capacity (transfer factor) has been related to the increased amount of blood in the lung capillaries^[145], but this does not seem to be the case, as there is a direct correlation between the amount of circulating red blood cells and flow in the lung capillaries and the diffusing capacity in normal physiology^[146]. To support this concept, we have earlier described direct relations between the diffusing capacity and the cardiac output and central blood volume in cirrhosis (Figure 5)^[45].

Pulmonary vascular resistance is most often decreased in cirrhosis^[147] and in a substantial number of patients there seem to be areas with a high perfusion rate in relation to alveolar ventilation^[45,140]. Besides the abnormal ventilation/

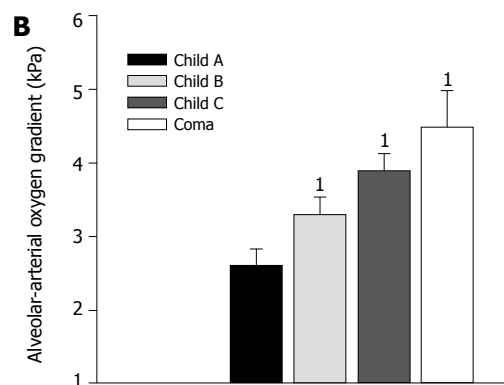
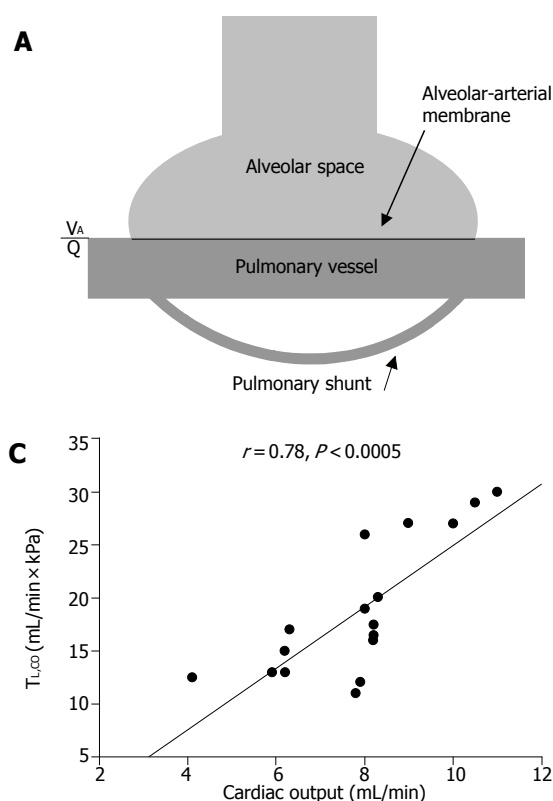


Figure 5 Panel A. Lung diffusion and blood oxygenation depend on the diffusion properties of the alveolar-arterial membrane, the degree of arterial-venous shunting through pulmonary shunts, and the degree of ventilation-perfusion inequality (V_A/Q). **Panel B.** The alveolar-arterial oxygen gradient increases with the severity of liver disease e.g. graduated according to the Child-Turcotte classification with the highest values in patients with hepatic coma. ¹denotes significant difference from Child class A patients (from Ref. [143]). **Panel C.** In cirrhosis, the diffusing capacity bears a direct relation to the increased cardiac output and to the central blood volume (not shown). Data from Ref. [45].

perfusion ratio and the presence of regular pulmonary arteriovenous shunts, intrapulmonary vascular dilatations have also been described^[134,140,147,148]. The condition with reduced transfer factor, abnormal ventilation/perfusion ratio or shunts, low arterial oxygen saturation, and pulmonary vasodilatation and hyperdynamics is termed as the hepatopulmonary syndrome^[134,149,150]. Pulmonary angiography of these patients has revealed two types of patterns with a spongiform appearance of the vessels and small arteriovenous communications^[134]. Fallon *et al.*^[151-153] have recently reported increased pulmonary vascular endothelial NOS and increased production of cholangiocyte endothelin-1 and increased expression of endothelin-B receptors. Experimental NO-dependent vasodilatation is supported by clinical studies showing increased NO in the exhaled air of cirrhotic patients^[154,155]. A recent paper has shown increased carboxyhemoglobin levels that correlate with arterial oxygen tension and alveolar-arterial oxygen gradient in patients with the hepatopulmonary syndrome^[156].

The frequency of the hepatopulmonary syndrome in patients with cirrhosis is not yet established. Different reports have given different frequencies of reduced arterial oxygen saturation in cirrhotic patients varying from about 10% to as high as 70%^[143,157,158].

The degree of gas exchange abnormalities, such as the oxygen tension and the alveolar-arterial oxygen gradient, correlates with the severity of liver disease (Figure 5). The diagnosis of the hepatopulmonary syndrome relies on the demonstration of arterial hypoxemia ($PaO_2 < 9.31$ kPa), an age-adjusted increased alveolar-arterial oxygen gradient (> 2.66 kPa) and intrapulmonary vasodilatation^[159,160]. According to the severity of deoxygenation, four stages have been proposed^[160]. A 100% oxygen shunt study with the

patient breathing 100% oxygen may discriminate between functional and anatomic shunts^[154]. Contrast-enhanced echocardiography is considered as the method of choice in the diagnosis of the hepatopulmonary syndrome^[161]. Agitated saline (microbubbles) is injected into a brachial vein and the bolus is shortly seen in the right heart chambers. A positive test for intrapulmonary vasodilatation occurs with delayed visualization of the microbubbles in the left heart chambers after more than three heart beats^[162]. Finally, a lung perfusion scan with the injection of macroaggregated albumin and estimation of the extra-pulmonary shunt fraction can be used^[148]. From counts over lungs and brain, the shunt fraction can be calculated and a value $> 6\%$ is considered positive with a sensitivity of 85%^[148,160].

No specific treatment, apart from long-term oxygen therapy, is available for the hepatopulmonary syndrome. It has been reversed by successful orthotopic liver transplantation in some patients^[144,163] and by insertion of a TIPS in others^[164]. TIPS insertion increases pulmonary artery pressure but cardiorespiratory complications are common and TIPS cannot be recommended for this indication at present^[165,166].

Portopulmonary hypertension

The association between portal hypertension and pulmonary artery hypertension is termed portopulmonary hypertension and is defined as a mean pulmonary artery pressure > 3.325 kPa and pulmonary vascular resistance > 120 dyn·s/cm⁵, and normal left atrial pressure (< 1.995 kPa)^[147]. It is seen infrequently in cirrhosis with an average prevalence from 1% to 4%^[167]. Symptoms are typically progressive and include fatigue, dyspnea, and edema^[134]. Systemic vascular resistance and cardiac output are not different from that of cirrhotic patients

without portopulmonary hypertension, whereas their arterial oxygenation is impaired^[168]. The histological appearance of pulmonary vessels is similar to that seen in primary pulmonary artery hypertension, and includes smooth muscle proliferation and hypertrophy^[160]. Local vasoconstrictor systems, like the endothelin system, may play a role and recently the administration of a mixed ET-antagonist has showed beneficial effects in portopulmonary hypertension^[169,170]. Treatment of portopulmonary hypertension is in general non-specific and palliative, and includes vasodilators, such as calcium channel blockers, nitrates, and prostacyclin^[160].

CONCLUSION

So far, a huge body of research has revealed that, in addition to portal and splanchnic complications to chronic liver disease, complications relating to the systemic and pulmonary circulation affect the prognosis of the patient as part of a multi-organ syndrome. Splanchnic vasodilatation in relation to portal hypertension is responsible for the hyperdynamic circulation and abnormal distribution of blood volume with a reduced "effective arterial blood volume" and activation of baroreceptor and volume-receptor reflexes as the outcome. The enhanced vasodilatation and counter regulatory over-activity of vasoconstrictor systems play major roles in the development of the multi-organ failure in cirrhosis with impaired function and perfusion of kidneys, lungs, brain, skin, and muscles. The function of the heart in cirrhosis is disturbed, with an increased cardiac output and heart rate. Left atrial and ventricular volumes tend to be slightly dilated, whereas the cardiac pressures are normal at rest. Cardiac performance and the systolic and diastolic functions are clearly impaired, in relation to the degree of liver dysfunction. The impaired cardiac contractility, termed cirrhotic cardiomyopathy, is different from that seen in alcoholic heart muscle disease. Reduced β -adrenergic receptor signal transduction and a defective cardiac excitation-contraction coupling are among the significant pathophysiological mechanisms. The cirrhotic heart is overloaded with a high-output failure and at the same time hyperdynamic and dysfunctional, and strain may unmask latent heart failure. In addition, the circulation and the function of a variety of organs are disturbed, including the lungs, kidneys, brain, and peripheral tissues. No specific treatment can be recommended and the only radical treatment option is liver transplantation. A considerable number of patients present with reduced pulmonary vascular resistance, impaired ventilation, and hypoxemia as part of a hepatopulmonary syndrome. A few patients develop portopulmonary hypertension with increased pulmonary vascular resistance.

Although there are still major unsolved questions that remain to be answered, the circulatory and neuroendocrine derangements play important roles in the clinical aggravation, hepatopulmonary dysfunction, and circulatory reactivity. This aspect is important to take into account in the clinical handling of the patient and the assessment of the prognosis.

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