Liver cirrhosis is characterized by a long course that lasts between 15 and 20 years. The natural history of this disease depends mainly on the occurrence and progression of single complications which are today more fully understood and therefore more treatable. More specifically, those complications involving hemodynamic mechanisms have been extensively studied in recent years. Indeed, the mechanisms involved in the occurrence of sodium positive balance and ascites, with or without renal dysfunction, have been clarified. It is now possible to distinguish between two different stages in the presence of hemodynamic modifications. In the first stage, an increasing accumulation of water and sodium may occur, leading to an increase in total plasma flow. Subsequently, there is a period of vascular instability and finally, the progressive appearance of typical signs of hyperdynamic circulation. During the second stage, cardiac function may be modified and consequently profoundly altered. The early administration of diuretics (antialdosterone) seems to be capable of modifying cardiac dysfunction, leading to a return towards a physiological status through a rapid increase in diuresis and natriuresis and a decrease in plasma volume.

Key words: Cardiac dysfunction; Hemodynamic derangement; Liver cirrhosis.

Introduction

Liver cirrhosis is a long process lasting between 15 and 20 years. Several modifications take place during the course of the disease, often due to compensatory mechanisms. Through an early diagnosis and the correct treatment of the complications due to cirrhosis, it is possible to prolong life. Indeed, the majority of clinical and pathogenetic studies are aimed at establishing whether hemodynamic alterations are involved in the most frequent complications, such as ascites, encountered in liver cirrhosis. Moreover, research is dedicated to a better understanding of the alterations in the neuroendocrine and autacoid systems, which are modified once chronic liver disease shows the morphological and clinical patterns of cirrhosis, generally in a progressive manner. Finally, knowledge about the production of physiological molecules capable of inducing diuresis and anti-diuresis is also imperative to better understand the underlying processes that take place during cirrhosis.

Hormonal alterations

The most important hormonal systems are represented by the major vasoactive systems: the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS). These systems are progressively activated. Generally, their modifications are directed at maintaining a balance for a relatively long period of time. In fact, any attempt to block or reduce the degree of activation of one system or another through pharmacological treatment normally leads to a worsening of systemic hemodynamics, renal function and/or hydroelectrolyte balance. Several studies performed during different stages of chronic liver disease have led to major insights into the importance of hemodynamic alterations.

In about 80% of cases ascites occurs 15 years after the first diagnosis and is considered the most important complication of cirrhosis, since in most patients its appearance marks the worsening of liver disease. Other phenomena of relevant importance also occur, including gastrointestinal bleeding, portosystemic encephalopathy, renal dysfunction and hepatocellular carcinoma. These are considered major complications, since they affect survival.
between the portal vein and the vena cava. Portal hypertension is generally classified as pre-hepatic, intra-hepatic or post-hepatic; an increased intra-hepatic resistance to portal blood flow is the main mechanism leading to portal hypertension in cirrhosis, although other causes of portal hypertension may supervene, especially portal or splenic vein thrombosis. In this case, thrombosis represents an additional complication that is not rare during cirrhosis.

Some progressive modifications in the liver tissue structure and organization are thought to be the main cause of portal hypertension. These include nodular regeneration with compression of the sub-lobular vein, as suggested some years ago by Popper and Hutterer, activation of hepatic stellate cells due to the increased availability of vasoconstricting agents, with deposition of collagen in the space of Disse, the so-called capillarization of the sinusoids, and splanchic dilation with progressive hyperemia of the splanchic area and an increased portal blood flow. The accumulation of blood in the splanchic area is sometimes compared to the physiological state of digestion. Alterations in the acute stages may precede the intracellular accumulation of fluid and cell swelling because of osmotic changes and ion channel modifications. Indeed, although there is no proof that demonstrates a definitive link between portal hypertension and the systemic circulation, the increased production of nitric oxide (NO) and other vasodilating substances is believed to be a determining factor.

### Hemodynamic alterations

According to Schrier et al., during the first stage of hemodynamic modification there is an expansion of the intravascular compartment. This phenomenon may be proven by the temporary decrease in plasma renin activity, which reflects a decreased activity of the RAAS. This period is generally thought to be very short, immediately followed by two different modifications: a) the progressive dilation of the arterial bed; b) a decrease in the effective arterial blood volume (EABV), that is the blood present in the major arterial vessels of the chest. As a result of this situation, the mean arterial pressure tends to decrease, while the cardiac output and heart rate are increased. In other words, prior to the onset of clinical signs of fluid accumulation, such as ascites, there are evident clinical signs of hyperdynamic circulation. The esophageal veins are enlarged and the opening of the portosystemic shunts is responsible for the deviation of about 80% of the blood which normally flows through the liver. At this point, the hepatic arterial blood flow increases and the splanchic circulation shows the first signs of hepatic escape of blood, with reversal of the portal flow and arteriovenous shunt formation. The opening of arteriovenous shunts may represent a compensatory phenomenon since they are present in several organs, such as the muscle, skin, lungs and the kidney, where they are located between the medulla and cortex. Since a significant part of portal blood flow is diverted to systemic circulation, ammonia and other dangerous molecules of intestinal origin may reach the brain, explaining the occurrence of hepatic encephalopathy.

The accumulation of blood in the splanchic compartment may parallel peripheral vasodilatory phenomena, and in this context the increased production of vasodilating substances, principally NO, seems to be the most important. In fact, any attempt to block NO synthase is followed by an increase in mean arterial pressure and an improvement in systemic circulation, both in animals and in man. The vasodilating effect in both the splanchic and peripheral areas may be due to an increased production, together with NO, of glucagon, prostaglandins, vasoactive intestinal peptide, with a decrease in central blood volume. A yet unexplained phenomenon is represented by the fact that there is a decrease in the peripheral vascular resistance in several areas, but not within the kidney. However, renal outer cortex hypoperfusion due to local arterial vasoconstriction is reversible, as demonstrated first by Epstein et al. At the same time, the opening of the arterial venous shunts within the kidney has been observed by Kew et al., Wilkinson et al. and our group.

Before the theory of Schrier et al., two other suggestive hypotheses were formulated to explain the pathogenesis of sodium retention and the occurrence of ascites in cirrhosis. According to the “underfilling” theory, the occurrence of ascites is mainly due to an increased intra- and post-sinusoidal portal pressure, with alterations of the Starling forces in the splanchic compartment, spillover of lymphatic fluid through the glissonian membrane and consequent hypovolemia that, in turn, forces the kidney to retain water and sodium. A positive sodium balance, however, may be observed before the onset of ascites and the circulating blood volume may be augmented rather than reduced, suggesting that sodium and water retention in cirrhosis with portal hypertension may occur prior to extra-circulatory fluid accumulation: the “overflow” theory was formulated on this basis.

The mechanism responsible for fluid accumulation and the increased circulating blood volume could be a neurogenic or hormonal link between the liver and kidney, explaining the so called “hepatorenal reflexes”. On the other hand, sodium receptors and baroreceptors capable
of signaling to the kidney have been found in the portal tract as demonstrated by a series of experimental research\textsuperscript{38}. For some aspects, this latter theory may explain the previously described initial increase in blood volume and the consequent decrease in plasma renin activity. In this setting, the infusion of saline leads to a very low natriuretic response, while renal plasma flow and glomerular filtration rate as well as central blood volume may be increased\textsuperscript{39,40}.

Another explanation proposed to explain abnormal “primary” sodium and water retention is the decrease in natriuretic factors; it, however, lacks any definitive proof\textsuperscript{36,41}. Practically, the theory of “peripheral arterial vasodilation”\textsuperscript{21} can be considered a more completed version of the “underfilling” theory, underlining the general increase in the capacitance of the vascular bed, with a consequent poor distribution of blood in different areas and a decrease in the EABV\textsuperscript{42,43}. In this light, the “underfilling” theory is still valid, explaining the abnormal stimulation of arterial baroreceptors in the central compartment, followed by the activation of the SNS. Then, in a brief time, it is possible to observe the activation of the RAAS, that parallels an increased production of arginine vasopressin, explaining the progressive tendency towards renal sodium and water retention, eventually followed by ascites formation.

A decrease in the EABV is observed especially in advanced cirrhosis, even though the initial decrease in peripheral vascular resistance is provisionally compensated by an increase in circulating plasma volume\textsuperscript{21} which occurs in order to counteract the increased capacity of the vascular bed and the blunt stimulation of the arterial baroreceptors, with a reduced activation of the vasoconstricting mechanisms. In other words, the initial stages of decompensated cirrhosis are characterized by a reduction in peripheral vascular resistance and an increase in cardiac output, whereas plasma renin activity and plasma noradrenaline levels as well as sodium balance are normal\textsuperscript{21}. With the progression of the disease, the vasodilatory effect of NO and other molecules leads to a more severe hyperdynamic circulation, characterized by a further increase in cardiac output and circulating plasma volume, which, however, are not sufficient to restore mean arterial pressure or reduce the degree of activation of the main vasoconstricting systems. Indeed, the arterial baroreceptors are further activated, followed by an even greater activation of the SNS and RAAS. Clinical signs of water retention become evident, and ascites eventually becomes tense and less responsive to diuretic treatment. In some patients, especially those with alcoholic liver disease, hepatic albumin synthesis may also be depressed, leading to a more pronounced decrease in the plasma oncotic pressure. Therefore, the theory proposed by Schrier et al.\textsuperscript{21} seems to be the most important in explaining the steps leading to positive sodium balance. However, some points, such as primary sodium retention observed during cirrhosis in both animals\textsuperscript{31} and humans\textsuperscript{36}, remain unclear. It is thus reasonable to propose a combined hypothesis, represented by two different stages, which may more easily explain the entire course of sodium and water abnormalities in cirrhosis and the occurrence of the hepatorenal syndrome\textsuperscript{38-40,44}.

Finally, the nonosmotic secretion of arginine vasopressin plays a major role in determining water retention\textsuperscript{45,46} with hyponatremia, observed in about 15-30% of patients in some clinical studies\textsuperscript{47}.

### Cardiac dysfunction

As previously mentioned, the modifications in hemodynamics that occur during cirrhosis are represented by the development of hyperdynamic circulation. During the first stage it is possible to observe high blood volume and cardiac output, together with low systemic vascular resistance accompanied by abnormal sodium and water retention\textsuperscript{21}. During this period, hemodynamic derangement occurs only in the supine position, while in the upright position systemic hemodynamics tend to normalize\textsuperscript{3,4,48}. Such a response is opposite to the physiological one, since in healthy subjects assuming the standing position there are no appreciable changes in cardiac output or systemic vascular resistance. Anyway, the principal vasoconstricting systems (SNS and RAAS) seem to be immediately activated upon standing, in both normal and pathological conditions. In patients affected by liver cirrhosis without signs of decompensation, that is during the pre-ascitic period, renal sodium and water retention is evident only in the upright position\textsuperscript{3}.

In decompensated cirrhosis, on the other hand, sodium retention occurs in both the upright and supine positions. In a previous research\textsuperscript{49}, we observed that in patients with ascites and hyperdynamic circulation, the supine position is characterized by a higher than normal left ventricular ejection fraction and cardiac index and a lower left ventricular end-systolic volume index and systemic vascular resistance. Standing induced a decrease in the left ventricular end-diastolic volume index in both patients and control subjects. Healthy volunteers maintained cardiovascular homeostasis (as indicated by an unchanged cardiac index) by increasing the left ventricular ejection fraction and heart rate, thus reducing the left ventricular end-systolic volume index. In contrast, cirrhotic patients experienced a decrease in stroke volume index and cardiac
index, and an increase in systemic vascular resistance and arterial elastance, despite marked increments in the heart rate, plasma renin activity and plasma norepinephrine levels. Similar observations were also made in patients with decompensated cirrhosis, with some evident differences between normotensive and hypertensive patients, the latter being somewhat protected from hyperdynamic derangement for a long period of time.  

These phenomena may suggest an impairment in myocardial contractility in the presence of strong activation of the principal vasoconstricting systems, although such modifications were not evident in the supine position because of the reduced overload.  

The reason why cirrhotic patients with hyperdynamic circulation show normalization of the hemodynamic parameters while standing may be based on the increased sequestration of circulating blood in the splanchnic area, where portal hypertension with general dilatation is usually demonstrable. In this context, an increase in circulating blood volume appears as a compensatory phenomenon, especially in the upright position, probably due not only to a reduction in the pre-load, but also to an abnormal cardiac response to this reduction. The latter possibility is supported by the fact that the left ventricular ejection fraction and systemic vascular resistance decrease during standing only in cirrhotic patients when compared to control subjects.  

Some years ago, cardiac abnormalities have been described in the presence of hemodynamic derangement. Such modifications were considered to be related to the toxic effects of alcohol on the heart. More recently, hemodynamic derangement, as well as myocardial alterations, have been described mainly in patients with post-viral cirrhosis. The observations were based on the discovery of systolic and diastolic dysfunction, electrophysiological abnormalities with prolonged QT interval and blunted ventricular response to different physiological stimuli. These particular modifications were observed in both cirrhotic rats and humans. The term “cirrhotic cardiomyopathy” was thus coined and is the one usually used in the literature. However, morphological alterations of myocardial tissue are usually absent. In the current review, we therefore prefer the term “cardiac dysfunction”.  

Several experimental studies have been performed in order to establish the pathogenetic mechanisms leading to cardiac dysfunction, especially in rats with experimental cirrhosis induced by bile duct ligation. Alterations of the autonomic receptors and their signal transduction pathways have been reported. If compared to control rats, bile duct ligation rats showed decreased β-adrenergic receptor density without any modifications in their binding affinity. Moreover, the isolated left ventricular papillary muscle from bile duct ligation rats showed an altered isoproterenol-stimulated contractility, suggesting a defective muscarinic function. Finally, membrane fluidity appeared significantly blunted or decreased with an increased cholesterol to phospholipids ratio. According to some suggestions, the decrease in the density and function of myocardial β-adrenergic receptors, together with the altered membrane composition, could be related to the hemodynamic alterations, while the inhibition of muscarinic function may be considered compensatory. Some circulating molecules may play a role in the myocardial dysfunction of cirrhosis as well. Indeed, the presence of circulating substances like tumor necrosis factor-alpha and other cytokines in blood may lead to an increase in NO synthase and hemo-oxygenase activity. Moreover, an increased release of NO, induced by vascular shear stress, may also stimulate hyperdynamic circulation. The role played by NO in inducing cirrhotic cardiac dysfunction was described some years ago following pre-incubation with the non-specific NO synthase inhibitor N(G)-monomethyl-L-arginine. Other investigators observed that the activity by β-adrenergic receptors could be blocked with the restoration of muscle contractility. Another study demonstrated that the use of the hemo-oxygenase antagonist zinc protoporphyrin provoked a reduction of the elevated cyclic guanosine monophosphate levels with a consequent improvement in myocardial contractility.  

From a clinical point of view, the myocardial dysfunction of cirrhotic subjects seems to represent a particular disorder during this disease. However, the morphological alterations necessary to define the term “cardiomyopathy” still seem to be lacking, at least in the first stage of liver cirrhosis. In fact, some authors distinguish the functional alterations occurring during pre-ascitic cirrhosis from those occurring during ascitic cirrhosis. In the first stage, patients are completely asymptomatic, although sometimes they complain of excessive fatigue. Moreover, an increase in brain natriuretic peptide has been reported; its plasma levels have been observed to be directly correlated with the degree of systolic dysfunction and septal thickness. Moreover, it is possible to observe an increase in ventricular mass, which becomes more evident with the progression of the disease, especially in decompensated cirrhosis. In fact, the electrophysiological and biochemical alterations demonstrated in experimental animals as well as in humans may be explained by the worsening of hemodynamic derangement. More specifically, myocardial modifications may appear an adaptation to the continuous expansion of the circulating blood volume. In fact, volume and cardiac overload is considered a con-
sequence of the continuous sodium and water retention, possibly combined with modifications in the neurohormonal systems which may have abnormal tropic effects on myocardial tissue\textsuperscript{70}. In this regard, however, available evidence indicates that cardiac dysfunction may be reversible after liver transplantation, confirming the functional nature of the disorder\textsuperscript{71,72}.

From a functional point of view, patients affected by non-alcoholic liver disease may show a decrease in stroke volume during tilting, together with a reduction in cardiac index and a significant increase in heart rate\textsuperscript{49}. Moreover, other authors described myocardial contractile dysfunction in patients with alcoholic and non-alcoholic cirrhosis demonstrated on the basis of the elongation of the pre-ejection period/left ventricular ejection ratio during both rest and after exercise\textsuperscript{60}. Other experiments demonstrated a sub-maximal increase in cardiac output after exercise in alcoholic and non-alcoholic cirrhotic subjects\textsuperscript{73,74} and an inverse relationship between the peak systolic pressure and systolic volume, again suggesting an impairment in myocardial function\textsuperscript{68,73,74}. Systolic dysfunction seems to be correlated with sympathetic dysfunction\textsuperscript{55,62}. The other aspect of functional cardiac activity revolves around diastolic dysfunction, which is demonstrated by a reduced arterial elastance ratio with dilation in the left atrium and an increase in the isovolumic relaxation time\textsuperscript{68,69,75}. These particular aspects are less evident, but may be important in determining a decrease in diastolic relaxation, correlated with calcium removal\textsuperscript{76}.

Finally, according to Wong et al.\textsuperscript{68}, cardiac dysfunction may also be due to interstitial fibrosis, possibly responsible for myocardial exhaustion and diastolic dysfunction\textsuperscript{68,77}.

**Concluding observations**

Apparently, any complication described during the long course of liver cirrhosis is important, especially when it is capable of reducing the patient’s survival. There are several major complications\textsuperscript{1}. From a clinical point of view, however, all complications stem from portal hypertension, with the exception of hepatocellular carcinoma. The most commonly studied, as well as the most frequently occurring complication is ascites\textsuperscript{1}. Ascites seems to be the consequence of abnormal sodium and water retention, with an increase in circulating blood volume. During the non-ascitic period, increased retention of sodium and water ensure the normal filling of the arterial bed\textsuperscript{21}.

In the next stage, because of the increased levels of NO and the reduced reactivity of peripheral $\beta$-receptors, there is a progressive decrease in peripheral vascular resistance. This chronic condition may effectively explain the occurrence of cardiac dysfunction, which may become more severe, especially in patients with decompensated cirrhosis. In this latter stage, the most effective pathogenetic factor involved in sodium and water retention is represented by the “underfilling” theory. However, peripheral vasodilation is not generalized since there is evident proof of local vasoconstriction, for example in the kidneys and brain\textsuperscript{34,78,79}.

The principal mechanism responsible for the abnormal sodium and water retention is the decrease in EABV, which appears secondary to peripheral arterial vasodilation, although the means for the correct measurement of EABV are not currently available, nor is central blood volume always correctly measured. Approximate clinical measurements were carried out by some authors\textsuperscript{80} who measured the blood volume present in different chambers of the heart, the central arterial tree and the lungs. The same group reported a decreased central blood volume in patients with both compensated and decompensated cirrhosis in the supine position, in the presence of an increased circulating plasma volume\textsuperscript{81,82}. They later did not confirm the decrease in central blood volume in patients with decompensated cirrhosis, but did confirm an increased blood volume in the splanchnic area using a total body scintigraphic technique. In contrast with these reports, other authors\textsuperscript{83} described an increased central blood volume during compensated cirrhosis. In some aspects, both experiences confirm the uncertainties revolving around the role played by peripheral vasodilation and thus around the actual moment when EABV briefly increases and immediately afterwards, progressively decreases. In any case, the progressive accumulation of sodium and water, when massive, seems to lead to other consequences, principally represented by cardiac dysfunction, together with ascites formation. Cardiac dysfunction, however, is also present during the pre-ascitic stage, in which the basic therapeutic approach of administering an anti-aldosteronic may represent a worthy acquisition\textsuperscript{84}. In this case, an early light diuretic regimen seems particularly useful in determining a reduced rate of blood volume expansion and thus in preventing both portal hypertension and myocardial dysfunction.

**Riassunto**

La cirrosi epatica è caratterizzata da un lungo decorso, variabile fra i 15 ed i 20 anni. Dal punto di vista pratico la storia naturale di questa malattia dipende dal presentarsi di una o più complicazioni che oggi sono meglio conosciute e quindi più facilmente trattabili. Di tali complicazioni, quelle che si basano sulle alterazioni emodinamiche sono state di recente più intensamente studiate, coinvol-
gendo il bilancio sodico positivo, la presenza di ascite e un’eventuale sofferenza renale. Delle due fasi che si possono verificare in corso di cirrosi, la prima, in genere, comporta l’eccessiva ritenzione di sodio e di acqua con conseguente aumento del volume plasmatico totale, mentre la seconda fase, dopo un periodo di instabilità emodinamica, è contrassegnata dalla progressiva comparsa dei tipici segni della circolazione ierodinamica. Soprattutto in questa seconda fase la funzione cardiaca è più o meno profondamente modificata. La precoce somministrazione di diuretici, e di antialdosteronici in particolare, sembra capace di combattere la disfunzione cardiaca e portarla verso una normale funzionalità attraverso il rapido aumento della diuresi e della natriuresi con diminuzione significativa del volume plasmatico.

**Parole chiave:** Alterazioni emodinamiche; Cirrosi epatocellulare; Disfunzione cardiaca.

**References**


