ARTÍCULO ESPECIAL

Cardiovascular abnormalities in special conditions of advanced cirrhosis. The circulatory adaptative changes to specific therapeutic procedures for the management of refractory ascites

M. Pozzi*, L. Ratti*, E. Redaelli*, C. Guidi* and G. Mancia**

**Centro Interuniversitario di Fisiologia Clinica e Ipertensione. Milano. Italy.

ABSTRACT
Advanced liver disease is characterized by decreased arterial blood pressure and peripheral vascular resistances, increased cardiac output and heart rate in the setting of a hyperdynamic circulatory pattern favoured by total blood volume expansion, circulatory overload and overactivity of the endogenous vasoactive systems. Reduced heart responses to stressful conditions such as changes in loading conditions of the heart in presence of further deterioration of liver function such as refractory ascites, hepatorenal syndrome, spontaneous bacterial peritonitis and bleeding esophageal varices have been recently identified and the knowledge of the cirrhotic cardiomyopathy syndrome has gained the dignity of a new clinical entity. Facing the availability of therapeutic interventions (paracentesis, transjugular intrahepatic portosystemic shunt, peritoneovenous shunt, orthotopic liver transplantation) currently employed to manage the life-threatening complications of the most advanced phases of cirrhotic disease, the knowledge of their impact on cardiovascular function is of paramount relevance.

INTRODUCTION
The syndrome of cirrhotic cardiomyopathy, first recognized in 1969 but mistakenly presumed to reflect latent alcoholic cardiomyopathy in patients with alcoholic cirrhosis, is now recognized to occur in all forms of cirrhosis, alcoholic and non-alcoholic, and thus is associated with cirrhosis per se. The hallmark of the syndrome is normal or increased ventricular contractility at rest, but depressed responsiveness to stimuli. In the past decade, many studies have demonstrated the clinical significance of this syndrome, from cardiac decompensation after surgery, cardiovascular procedures, therapeutic interventions targeted to manage the decompensated phase of cirrhosis and liver transplantation. Recent studies indicate that cirrhotic cardiomyopathy plays a key pathogenic role in hepatorenal syndrome. Indeed the past decade has seen an explosion of interest and awareness of this syndrome.

HEPATORENAL SYNDROME: CIRCULATORY CHANGES
Hepatorenal syndrome is one of the major complications of cirrhosis. As reported by Ginès et al., its annual incidence in patients with ascites is approximately 8%. The development of the hepatorenal syndrome entails a poor prognosis despite the progress in the therapeutic approaches elicited by the better knowledge of pathogenesis. As evidenced by Llach et al., parameters of renal function along with those related to cardiovascular derangement and activation of neurohumoral systems in decompensated cirrhosis are of paramount prognostic relevance. Since the beginning of the 1990’s many studies have shown the major role of nitric oxide in the pathogenesis of circulatory dysfunction in cirrhosis. It has been shown that arterial vasodilation involves mainly the splanchnic circulation with vasoconstriction being mainly expressed at the level of the muscles, the brain and the kidneys. Since vasodilation of the splanchnic arterial bed is linked to portal hypertension and nitric oxide is overexpressed in this vascular district, an interdependence between hepatorenal syndrome, circulatory derangement and liver cirrhosis has been clearly established. Renal dysfunction in cirrhotic patients follows a progressive course: it starts with abnormalities in renal sodium handling initially unrelated with overactivity of the renin-angiotensin-aldosterone and the

Correspondence: Dr. M. Pozzi.
Clinica Medica. Ospedale San Gerardo dei Tintori.
Via Donizetti, 106. 20052 Monza. Milano. Italy.
Correo electrónico: epa_monza@libero.it
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that blockade of renal vasodilating prostaglandins, and possibly nitric oxide, counteracting the systemic and renal effects of endogenous vasoconstrictors. Increasing plasma levels of these neurohormones with progression of disease, usually in the ascitic stage, lead to reduction of glomerular filtration rate because of a fall in renal perfusion due to renal vasostenosis. A marked increase in the plasma concentration of endothelins has been observed, but the pathogenic role of these vasoconstrictors in the development of the hepatorenal syndrome has been questioned. Nevertheless, renal function impairment could be the consequence of an imbalance between the overactivity of the systemic vasoconstrictor systems and local renal production of vasodilators. The evidence produced by many studies of the Barcelona group and by Laffi et al. that blockade of renal vasodilating prostaglandins by administration of nonsteroidal anti-inflammatory drugs is followed by deterioration of renal function supports this hypothesis. Renal ability to excrete free water is also markedly reduced at this stage, and most patients present dilutional hyponatraemia, which is mainly determined by the non-osmotic release of adiuretic hormone: this leads to a progressive further expansion of the total blood volume up to the full-blown expression of the hyperdynamic circulation. The marked increase in the activity of the renin-angiotensin-aldosterone and sympathetic nervous system further increase the dynamic component of intrarenal resistance and thus portal pressure. It is well known that studies performed by Fernández-Seara and Llovet et al. that patients with cirrhosis and ascites without hepatorenal syndrome show a typical circulatory pattern of increased total plasma volume, cardiac index and heart rate, along with reduced peripheral vascular resistance and arterial pressure. But in the latest stages of cirrhosis, when the hepatorenal syndrome develops, the mechanisms of further derangement of cardiovascular function become even more complex because a decreased cardiac function is involved too. Indeed, hemodynamic studies performed by Tristani and Cohó and Lebègue have shown that cardiac impairment, and in particular a reduction in cardiac output, plays a key role in further circulatory derangement characterising the hepatorenal syndrome. A significant number of patients with hepatorenal syndrome exhibit arterial hypotension, reduced cardiac output, low right atrial pressure and wedged pulmonary pressures with a tendency for peripheral vascular resistance to be slightly higher than in ascitic subjects without hepatorenal syndrome. The surprisingly relatively increased peripheral vascular resistance can be explained as a response to the extreme counterregulatory activation of the endogenous vasoconstrictors, in the absence of which a dramatic fall of peripheral resistance would be expected. It is thus likely that all the factors involved in the pathogenesis of cirrhotic cardiomyopathy merge dramatically at this latest stages of disease unmasking impaired heart contractility previously elicitably only after strain. Therefore, circumstances requiring further increase in cardiac work, such as bacterial infections, or any other precipitating conditions leading to hepatorenal syndrome, such as digestive hemorrhage, unveil cirrhotic cardiomyopathy.

**SPONTANEOUS BACTERIAL PERITONITIS: CIRCULATORY CHANGES**

Spontaneous bacterial peritonitis is an infection of ascites that occurs in the absence of a contiguous source of infection (e.g., gastrointestinal perforation, abscess). In initial series published in the 1970’s, when this clinical condition was first described, the mortality associated with an episode of spontaneous bacterial peritonitis exceeded 80%. Improved knowledge of pathophysiology and accordingly amelioration of therapeutic approach in the last years have reduced the mortality rate to 20-30%, as reported in recent prospective studies with well defined diagnostic criteria (Rimola et al.11, Navasa et al.12 and Llovet et al.13). Still, mortality after a single episode of spontaneous bacterial peritonitis remains significant. Bacterial translocation, the phenomenon by which viable microorganisms from the gut lumen migrate to mesenteric lymphnodes and other extraintestinal sites, has been postulated as one of the main mechanisms involved in the pathogenesis of spontaneous bacterial peritonitis. Hemodynamic instability, progressive renal and hepatic failure, and hepatic encephalopathy are the clinical hallmarks of most patients dying from spontaneous bacterial peritonitis. Navasa et al.12 suggested that impaired renal function evolving in either type 1 or type 2 hepatorenal syndrome is favored by a further deterioration of the background hyperdynamic circulation of cirrhosis promoted by cytokines. It has been proposed that this hampered circulatory dysfunction might be the consequence of an accentuation of arterial vasodilation: nevertheless, an impairment of cardiac function could arise via reduced ventricular contractility by a cytokine-mediated septic cardiomyopathy. A recent study by Ruiz del Árbol et al.14 investigated the changes in systemic, renal and hepatic hemodynamics in cirrhotic patients with spontaneous bacterial peritonitis providing evidences that the cardiac dysfunction observed in this condition is a manifestation of cirrhotic cardiomyopathy. They studied 23 patients with spontaneous bacterial peritonitis by means of assessment of neurohumoral variables, plasma and ascitic fluid concentration of tumor necrosis factor-alfa (TNF-α), invasive hemodynamic variables (which included measurement of cardiopulmonary pressures, cardiac output and portal pressure gradient), systemic inflammatory response before and after cefotaxime administration. Eight patients developed renal failure, whereas the remaining did not. In the renal failure group cardiac output was lower, whereas peripheral vascular resistance, portal pressure gradient and degree of neurohumoral overactivity significantly higher. Mean arterial blood pressure was also lower in the patients with renal failure.
terial pressure, heart rate and cardiopulmonary pressures did not differ within groups. In the whole series there was a significant inverse correlation between plasma and ascites concentration of TNF-α and the baseline values of cardiac output. Plasma and ascites TNF-α levels were significantly higher in patients with renal failure. During treatment cardiac output significantly decreased and portal pressure gradient increased in the renal failure group, with no changes in systemic vascular resistance, heart rate and cardiopulmonary pressures as compared to baseline values in either group. Six out of 8 patients who developed renal failure died.

This study underscores the complex nature of the circulatory dysfunction associated with renal failure in spontaneous bacterial peritonitis. In particular at the end of treatment, cardiac output was 32% lower and systemic vascular resistance 31% higher in the renal failure group, as compared to the group without renal failure, suggesting that circulatory dysfunction and renal failure in spontaneous bacterial peritonitis is related to a decrease in cardiac output. Systemic vascular resistance is also a major factor: the slightly increased values observed as compared with subjects without renal failure should be expected to be even greater due to the extreme activation of the counterregulatory neurohumoral systems, suggesting impaired pressor response. The reduced cardiac output seems to be in line with the evidences of impaired cardiac reserve in patients with cirrhosis and hyperdynamic circulation. A reduction in cardiac output, in the absence of a significant increase in cardiopulmonary pressures, is consistent with a decreased venous return to the heart. The unchanged heart rate, facing the differences in mean arterial pressure and sympathetic nervous activity along with unchanged right atrial and pulmonary wedged pressures between groups, suggests a reduced stroke volume and impairment of cardiovascular reflexes.

However, common features are observed in sepsis, in which TNF-α notably plays a major role. As in septic cardiomyopathy, emerging evidence suggests that this and other cytokines, as interleukin 1β, depress myocardial contractility in cirrhosis via nitric oxide-dependent and independent pathways. It is thus conceivable that the observed contractile impairment in spontaneous bacterial peritonitis is a combination of septic and cirrhotic cardiomyopathy. Indeed, cardiac dysfunction in sepsis and cirrhosis bears remarkable similarities. Both conditions share hyperdynamic circulation and ventricular hypertrophy. Unfortunately this study did not include an evaluation of diastolic function and thus a definite conclusion, but only a strong suspect on the contribution of impaired relaxation of the left ventricle and thus of diastolic dysfunction to the complex cardiovascular disturbance in this subset of patients, cannot be drawn.

A recently published study performed by Fernández et al. assessed systemic and hepatic hemodynamics in a consecutive series of cirrhotic patients with spontaneous bacterial peritonitis, in whom ceftriaxone administration was coupled with albumin infusion. The authors found that treatment with third generation cephalosporins and albumin prevents circulatory and renal dysfunction in these patients. They also observed an increase in right atrial pressure, pulmonary arterial pressure and capillary pulmonary pressure, and a marked deactivation of the renin-angiotensin system. These data are consistent with a sustained expansion of the central blood volume. In this study these findings were associated with an improvement in cardiac function, as manifested by an increase in left ventricle systolic volume and stroke work index, which explains why the cardiac index was maintained despite a significant decrease in heart rate. However, this does not explain the significant increase in mean arterial pressure observed in the study which was mainly related to an increase in systemic vascular resistance. The improvement in the peripheral circulation observed in these patients was remarkable considering that the significant increase in systemic vascular resistance occurred in the setting of an intensive deactivation of the renin-angiotensin system. At variance with the observations of Ruiz-del Arbol el al. therapeutic plasma expansion with albumin, as proposed by Fernández et al., protects from hypovolemia. Differences in hemodynamic changes between the 2 studies could not be attributed to differences in infection resolution, but rather to the administration of albumin. In the study by Fernández et al., the authors did not observe significant changes in portal pressure and hepatic blood flow.

**LIVER TRANSPLANTATION AND CARDIAC DYSFUNCTION**

Liver transplantation can be considered as the ultimate therapeutic option for cirrhotic patients with complications of disease not otherwise amenable. However, transplantation constitutes a major physical stress for the cardiovascular system during both the trans-operative and the post-operative period. Myers and Lee have recently reviewed this topic, underlying the relevance of preoperatively assessment of cardiovascular function in cirrhotic transplant candidates: indeed, overt left ventricular failure has emerged as a significant cause of peri-operative morbidity and mortality in the liver transplant recipient. Donnovan et al. have preoperatively investigated by 2-dimensional and dobutamine stress echocardiography cirrhotic patients with end-stage disease before liver transplantation. They reported a 56% incidence of acute pulmonary edema during the early post-operative period. Intra-operatively cardiac output may either decrease because of reduced preload (third-space losses, acute anemia leading to hypovolemia, clamping devices on major veins reducing venous return) or impaired myocardial contractility (volume overload after aggressive fluid replacement strategy). 7-21% of postoperative deaths after liver transplantation are linked to heart failure. Nasraway el al. reported evidence for early post-operative myocardial depression and Spanier et al. identified heart failure as an independent predictor of mortality after liver transplantation. This finding may have therapeutic implications, such as the use of prophylactic inotropic agents in the peri-operative period. However, the role of interventions aimed at preserving ventricular compliance and reducing the post-operative increase in systemic vascular resistance is not proven. During the pre-operative period, optimization of right ventricular function is of great importance. This may be achieved by the use of inotropic agents, such as dobutamine, which improves myocardial contractility and vascular compliance, or by the administration of vasodilators, such as nitroglycerin, which reduces ventricular afterload. A recent study showed that the use of nitroglycerin during the pre-operative period reduces the incidence of peri-operative cardiovascular events in patients with cirrhosis and hepatopulmonary syndrome. In conclusion, the management of cardiovascular dysfunction in cirrhotic patients is a complex issue that requires a multidisciplinary approach involving specialists in cardiology, hepatology and anesthesiology. Further research is needed to identify effective strategies to prevent and treat cardiovascular complications in this high-risk population.
the trans-operative stress, cardiac performance may be hampered post-operatively as a consequence of changes in
the cardiovascular system. The progressive normalization
of the hyperdynamic circulatory state after the remo-
val of the cirrhotic liver and secondary to the increase in
peripheral vascular resistance and normalization of mean
arterial pressure may contribute to the occurrence of heart
failure because of sudden increase in afterload. Sampath-
kumar et al.23, in a retrospective analysis of over 700 cirr-
hotic patients undergoing liver transplantation at the
Mayo Clinic, have described myocardial dysfunction af-
after liver transplantation: they have observed a reversible
form of dilated cardiomyopathy during the early post-
transplant phase, with clinical manifestation of acute pul-
monary edema and respiratory failure. Echocardiography
revealed dilatation of all cardiac chambers and marked
reduction of the ejection fraction. All patients subse-
sequently showed resolution of their cardiac dysfunction
with ejection fraction gradually increasing to a median of
50%, without recurrent heart failure within the following
follow up period of 15 months after transplantation.
Cardiovascular system alterations during the post-trans-
plant period remains a controversial issue. Navasa et al.26
support the contention that most of the neurohumoral and
hemodynamic changes characterizing advanced liver di-
sease are rapidly abolished after the transplant. However,
Henderson27 suggested a residual hyperdynamic circula-
tory pattern in transplanted patients. Acosta et al.27, on the
contrary, claimed that cirrhotic patients presented normal
cardiac performance during either the pre- and post-trans-
plant period, casting doubts on the existence of cirrhotic
cardiomyopathy. Nevertheless, in a following study by
the same group28 they described after liver transplantation
an increase in percentage of patients with abnormal eje-
tion fraction. They postulated a role for increased afterlo-
ad on one side, due to the reversion of the hemodynamic
alterations characteristic of cirrhosis, and for the effects
of immunosuppression with cyclosporine. The most rele-
vant finding of their study was a decreased diastolic func-
tion after liver transplantation possibly linked to immuno-
suppressive therapy and/or high dose steroids that could
induce an increase in cardiac wall thickening and abnor-
mal left ventricular filling in the heart of organ recipient.
After transplant González et al.29 have shown the reversi-
bility of QT prolongation, one of the electrophysiological
abnormalities in the scenario of the cirrhotic cardiomyo-
pathic disease.

It is thus clear that there is need for thorough investiga-
tions to assess the effects of liver transplantation on the
cardiovascular status in cirrhotic patients, even if some
studies have evidenced the unpredictable, albeit often re-
versible, nature of this disorder. Meanwhile, accurate as-
essment of cardiovascular function before liver trans-
plantation is deemed to be necessary. Recent reports
indicated the role of dobutamine stress echocardiogra-
phy30,31 or myocardial perfusion scintigraphy32 before
transplant, but further and more conclusive studies are
obviously awaited. This because dobutamine stress echo-
cardiography might be a rather insensitive test: actually
this drug increases myocardial oxygen consumption
mainly by increasing myocardial contractility without re-
levant increases in afterload; that is the major challenge
faced by the heart in the post-transplantation setting.
No specific therapy can be advocated for this condition,
and thus management is largely empirical, mostly based
on the current management of non-cirrhotic causes of car-
diomyopathy. The use of dobutamine is unlikely to be ef-
flective due to the specific inotropic effect of this drug tar-
geted on β-receptors, which are notably desensitized in
cirrhotic cardiomyopathy.

THE IMPACT OF TREATMENT OF ASCITES ON
CARDIOVASCULAR FUNCTION. PARACENTESIS.
TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC
SHUNT (TIPS), LE VEEN SHUNT

Brief summary on management of ascites

A «stepped-care» algorithm in the management of ascites
in cirrhosis consists of the progressive implementation of
the therapeutic measures currently available, including
bed rest and low-sodium diet along with increasing doses
of diuretics. In this subset of patients, as well as in those
presenting tense ascites, para-
centesis and other procedures should be considered.

However, cardiac alterations are more frequently encoun-
tered in cirrhotic patients with ascites: moreover, a me-
chanical hindrance can further impair heart function when
tense ascites develops. The main reasons are that: a) these
patients experience more advanced hemodynamic and
neurohumoral alterations than pre-ascitic cirrhotics, and
b) the presence of ascites per se may cause increased in-
trathoracic pressure and bulging of the diaphragm, which
could mechanically interfere with the physiologic cardiac
movements during contraction and relaxation. Patients
with cirrhosis and ascites may need large volume or total paracentesis or may become candidates for TIPS or porto-collar shunting (Le Veen shunt, Denver shunt) if ascites becomes “refractory”. All these procedures may require further cardiac and haemodynamic adaptation. An increasing number of investigations in the last few years have focused their attention on the development of cardiac abnormalities in these patients, and the term “cardiorenal syndrome” has been proposed to include the different structural and functional alterations observed. Symptoms of cardiac impairment at rest may not be apparent even in these patients with far advanced liver failure; however, under physiological, pharmacological or “procedural” stress, the ventricular systolic function may give inadequate response. Therefore it has been suggested that special caution should be used when procedures that may cause acute changes in systemic hemodynamic are applied in these patients.

Paracentesis

A great deal of information has been obtained in the last years indicating that therapeutic paracentesis is a safe, rapid and effective therapy for ascites in cirrhosis, and it is currently considered the treatment of choice for tense or grade 3 ascites, provided plasma expansion is warranted to prevent the systemic circulatory disturbance that may follow if this measure is not applied. Despite no differences in long term mortality between cirrhotic patients with massive ascites treated with high dose diuretics and large-volume or total paracentesis, many studies have clearly indicated that paracentesis, followed by diuretics as maintenance therapy, can be considered the treatment of choice. This is based on the evidence that: a) the incidence of renal functional impairment and hepatic encephalopathy is significantly greater in diuretic-treated patients; b) ascites resolution, and accordingly relief of symptoms, is faster in paracentesis-treated subjects, and c) hospital stay is shorter after paracentesis with a better cost-effectiveness profile, despite the relatively high cost of albumin.

Indeed, after the first classic studies performed by Quintero et al., Ginès et al. and Tito et al. of the Barcelona group examining the effects of either large-volume or single total paracentesis as compared to diuretics in the clinical management of tense-refractory ascites, it became clear that therapeutic plasma expansion with albumin after paracentesis prevents the hemodynamic derangement that may ensue after the unequivocal early beneficial circulatory effects. Several hemodynamic investigations have carefully examined the circulatory and neurohumoral effects of either large volume or total paracentesis and allowed to identify 2 distinct phases: the first, or early phase (during and within the first 12 h after the drainage of ascitic fluid), is characterized by an overall circulatory improvement, whereas the second, or late phase, can be characterized by a deterioration of circulatory and neurohumoral parameters that may become particularly critical in absence of therapeutic plasma expansion when the volume of ascites drained is more than 5 l. Guazzi et al., Simon et al., Panos et al. and Pozzi et al. examined the hemodynamic adaptive changes to ascites removal by paracentesis (approximately 10 l) in cirrhotic patients with either tense or refractory ascites. In particular, the studies performed by the last 2 authors provided detailed information also on the time-course of the changes of the hemodynamic and neurohumoral variables already during the procedure. Briefly, the main circulatory and neurohumoral effects of large volume or total paracentesis can be summarized as follows. The early effects consist of a reduction of right atrial pressure, pulmonary capillary wedge pressure, mean arterial pressure, systemic vascular resistance, plasma renin, aldosterone, norepinephrine, intraabdominal pressure, intrathoracic pressure, and an increase in stroke index, left ventricular diastolic and systolic volumes, cardiac index and atrial natriuretic peptide concentration. All these changes denote improved cardiac performances and possibly increased venous return due to the fall in intraabdominal and intrathoracic pressures, ultimately translating in increased cardiac transmural pressures. The late effects are characterized by a reduction of cardiac output to baseline values, a further decrease of systemic vascular resistance and a marked activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, which can reach values higher than pre-paracentesis levels. Thus the first phase is characterized by an expansion of the intravascular volume and the second by a progressive reduction of the effective intravascular volume. Many studies have provided evidence that the expansion of the intravascular volume by means of albumin administration at a dose of 6-8 g/l of ascites drained (and to a lesser extent by synthetic plasma expanders) prevents the occurrence of impairment in intravascular volume following ascites drainage by paracentesis. A latter study by Pozzi et al. corroborated the notion of the protective role of therapeutic plasma expansion after paracentesis on hemodynamic stability by demonstrating the sympathoinhibitory effects of paracentesis followed by albumin administration, at least in the short term, as evidenced by the reduction of the sympathetic nerve traffic at the muscle district by means of intraneural recordings along with the other neurohumoral variables. Luca et al. further confirmed the beneficial effects of intravenous albumin infusion on the hemodynamic and humoral changes after total paracentesis. A group of cirrhotic patients with tense ascites was randomized to receive albumin infusion or not at the end of the procedure. In untreated patients cardiac index, femoral blood flow and pulmonary capillary pressure reduced, along with a significant increase in neurohumoral variables and reduction of atrial natriuretic peptide. Portal pressure gradient and portocollateral flow reduced in both groups returning to baseline thereafter. Other numerous studies have extensively evaluated the protective role on intravascular volume changes induced by paracentesis followed by infusion of synthetic plasma expanders, notably less expensive than human al-

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bumin. These studies concluded that an impairment of circulatory parameters can occur in 60-70% of patients submitted to paracentesis without any therapeutic plasma expansion, in 30-40% of patients treated by paracentesis followed by infusion of synthetic plasma volume expanders (like dextran or polygeline), and in 18% of subjects treated with albumin infusion (8 g/l of ascites drained). Thus an inverse relationship between the incidence of hemodynamic derangement after paracentesis and the half-life of the plasma expander employed seems to exist. Ruiz del Árbol\(^{\text{59}}\) characterized the circulatory impairment that follows total paracentesis followed by synthetic plasma expander administration (dextran 70 infusion). Nearly 30% of patients developed “post-paracentesis circulatory dysfunction”, which is mainly caused by an accentuation of the arteriolar vasodilation already present in untreated cirrhotic patients with ascites. This is followed by a further increase in the homeostatic activation of the neurohumoral systems, which in turn brings about a further increase in intrathoracic vascular resistance. Ginès et al\(^{\text{80}}\) reported that the development of this syndrome is associated by a shorter probability of survival. Actually, no one study has addressed the issue of whether post-paracentesis circulatory dysfunction can be considered as a condition favored by pre-existing cirrhotic cardiomyopathy so far. A recently published study by Vila et al\(^{\text{44}}\) compared the hemodynamic changes after paracentesis in patients who did or did not develop post-paracentesis circulatory dysfunction. Patients with post-paracentesis circulatory dysfunction are those who show the greater reduction in mean arterial pressure and systemic vascular resistance after paracentesis. The cause of the reduced systemic vascular resistance appears an enhanced arteriolar vasodilation. Post-paracentesis hypovolemia stimulates the renin-aldosterone and sympathetic nervous system as a compensatory mechanism in order to maintain circulatory homeostasis. Plasma renin activity, aldosterone and norepinephrine are significantly increased in these patients after paracentesis and plasma renin activity increase closely correlates with the decrease of systemic vascular resistance. Again, one could speculate if cardiac dysfunction could be somehow involved in the pathogenesis of post-paracentesis hypovolemia; however, parameters of systolic function were not different in patients who did or did not develop this syndrome. No data are at present available on possible differences regarding left ventricle diastolic function impairment. In conclusion, the large body of evidence indicates that overall favorable circulatory effects follow paracentesis when therapeutic plasma expansion with albumin is warranted. If less than 5 l are drained, synthetic plasma expanders may be equally effective. Human albumin is necessary when larger volumes of ascites are drained. In the setting of truly refractory ascites of cirrhosis 4 potential therapeutic options are currently available. Repeated large volume paracentesis plus albumin infusion is the most widely employed therapeutic approach because of relatively low rate of complications and practical readiness as outpatient. Liver transplantation is the best option, when feasible, due to the low survival expectancy of patients with this condition. Peritoneous shunting is accompanied by high rate of complications and is becoming less frequently employed in many centers. TIPS, a non-surgical method of portal decompression functioning as a surgical side-to-side portacaval shunt, has gained widespread popularity that led to head to head comparisons with paracentesis. Transjugular intrahepatic portosystemic shunt (TIPS) Ascites develops as a direct consequence of portal hypertension. Sinosoidal and post-sinusoidal portal hypertension are mainly associated with the development of ascites. In such cases, the development of portal hypertension is associated with changes in systemic hemodynamics and renal sodium and water retention with accumulation of fluid in the peritoneal cavity. TIPS involves the creation of a low-resistance channel between the portal and hepatic veins which decompresses the portal vein ultimately reducing portal pressure. Thus, by this reduction, TIPS ameliorates a fundamental pathophysiologic abnormality in patients with refractory ascites. TIPS is the more recent treatment introduced for the management of portal hypertension and from a theoretical point of view it should correct the 2 main factors involved in ascites development: a) by reducing portal pressure it should decrease the degree of splanchic arterial vasodilation as well as ameliorate the arterial vascular underfilling, accordingly suppressing the endogenous vasoconstrictor systems, improving renal perfusion and thus restoring response to diuretics, and b) by decompressing the splanchic and hepatic microcirculation, it should decrease the production of lymph, both in the liver and splanchic organs, thus avoiding saturation of the capacity of this drainage system capable of a daily removal of up to 1.1 of fluids. Actually the more frequent indications for TIPS are bleeding esophageal varices not responding to endoscopic therapy and refractory ascites. Studies dealing with hemodynamic and cardiac changes after TIPS procedure mainly included patients selected as being in stable hemodynamic conditions and presumably without overt cardiovascular pathologies. Short-term hemodynamic changes after TIPS When a shunt is created between the hepatic and the portal vein (a kind of portacaval fistula), the high splanchic blood flow is delivered to the systemic circulation. Thus, within minutes of TIPS placement, the cardiac output rises and the systemic vascular resistance decreases. This is followed by both an increase in left-sided filling pressures (pulmonary capillary wedge pressure) as well as right atrial pressure. The decrease in systemic vascular resistance is a physiological response to accommodate the increase in cardiac output and should not be looked at as an impairment in systemic hemodynamics. The mean pul-
Monetary arterial pressure generally rises due to both increased pulmonary vascular resistance and pulmonary blood flow. The latter is directly due to increased return of blood flow from the portal bed to the systemic circulation due to TIPS itself, while the former is possibly related to both increased pulmonary venous hypertension and neurohumoral factors. In some cases frank heart failure with development of pulmonary edema has been noted. Those with pre-existing pulmonary hypertension are particularly prone to develop right-sided volume overload with increased ventricular end-diastolic volumes. Indeed, several studies performed by various authors (Azoulay et al17, Stanley et al18, Huonker et al19) have reported an aggravation of the hyperdynamic circulation. This observation has initially raised some doubts on the beneficial effects of this procedure in cirrhotic patients.

The increase in cardiac output after TIPS is mainly due to the increased cardiac refilling secondary to shunt opening. Merli et al20 measured the intrathoracic blood volume immediately after TIPS and an increase of this compartment was clearly evidenced. Moreover, the percent increase of intrathoracic volume directly correlated with the percent increase of cardiac output.

Two mechanisms have been invoked to explain the decreased systemic vascular resistance induced by TIPS: a) a decrease in the vasopressor system (catecholamines and renin-angiotensin-aldosterone) due to better cardiac filling, and b) an increased availability of vasodilator substances in the systemic circulation due to opening of the shunt. Studies on changes of vasodilator substances after TIPS have shown conflicting results (Merli et al21, Martinet et al22), while many studies reported a decrease in plasma concentration of endogenous vasconstrictors after TIPS (Jalan et al23, Salerno et al24). These early modifications induced by TIPS (right atrial pressure, pulmonary arterial pressure and pulmonary capillary wedge pressure increase) have been interpreted as a consequence of an initial inability of the filling capacity of the right ventricle to cope with the shunted blood volume. However, this phenomenon is rather transient, indicating that the heart is able to increase its work so as to cope to this stressful condition. In agreement with the above considerations, changes in echocardiographic parameters documenting cardiac modifications have been reported one month after TIPS. These include increased left ventricular systolic diameter, left ventricular systolic diameter and estimated pulmonary arterial pressure and reduced pre-ejection period and isovolumic relaxation time. All authors claim that a sufficient cardiac reserve is necessary to meet the demands of the post-TIPS short-term modifications.

Medium and long-term haemodynamic changes after TIPS

Some studies reported data about the modifications of haemodynamic status and cardiac function in cirrhotic patients 2 to 12 months after TIPS. Jalan et al23 showed that the cardiac index after TIPS returned to normal values after 2 months, suggesting an adaptation of the heart to handle the increased preload, despite persistently low peripheral vascular resistance. Merli et al20 observed that echocardiographic changes suggesting modifications in cardiac function were completely reversed in 11 patients with non alcoholic cirrhosis after 6-9 months, also suggesting a good adaptation of cardiac function to increased preload. In another series of 21 patients treated with TIPS, at 3 months, Lotterer et al24 showed that all cardiovascular and hemorural parameters had returned to baseline levels, except a slight persistent increase of carbon monoxide, which completely normalized when patients were re-evaluated one year later after TIPS placement.

A recent study by Salerno et al25 compared the effects of TIPS in 2 groups of patients: those with high plasma renin activity resting levels (> 4 ng/ml/h) identified as those with effective hypovolemia before TIPS, and those without hypovolemia (plasma renin activity < 4 ng/ml/h). A large majority of the «hypovolemic» patients had a more severe degree of liver dysfunction and TIPS performed for refractory ascites; all but one patients in the other group received TIPS for bleeding esophageal varices. Although patients with known cardiovascular disease were excluded from the study, echocardiographic parameters assessed before TIPS were more frequently altered in the «hypovolemic» patients (lower stroke volume and left ventricular volumes, reduced E/A ratio, suggesting the presence of diastolic dysfunction). The TIPS procedure induced exacerbation of the hyperkinetic circulation in both groups, as previously reported. In the «hypovolemic» patients, plasma renin activity decreased and atrial natriuretic factor increased, indicating redistribution of liquid compartments and improved filling of the central part of circulation. Moreover, in these patients, TIPS procedure improved cardiac performance as shown by an increased left ventricle end-diastolic volume and stroke volume, and a tendency of the E/A ratio to normalize. The ability to transiently increase the cardiac hemodynamic work (cardiac output and stroke volume) may represent a good prognostic index for «hypovolemic» patients treated with TIPS.

In conclusion, the role of TIPS in the management of refractory ascites is evolving. Refractory ascites can be mobilized in up to 90% of patients. However, the choice of the patients to be submitted seems to be a relevant issue because in those subjects with moderate liver dysfunction TIPS can frequently mobilize ascites and convert diuretic-resistant ascites to diuretic-sensitive, ameliorate liver function, nutritional status and probably quality of life. The same does not seem to be the case in subjects with more relevant liver dysfunction (Child C), who are notably more prone to develop hepatic encephalopathy and further deterioration of liver function after TIPS placement. Indeed hepatic encephalopathy is the most common complication of TIPS. More than 40% of patients develop post-TIPS hepatic encephalopathy. Although hepatic encephalopathy prior to TIPS is a predictor of post-TIPS encephalopathy, new onset or worsening of hepatic encephalopathy develops in approximately 30% of cases, most
of which responding to common treatment. Shunt dys-
function is another problem. It occurs in 40% of patients
treated without the so-called covered stents (those pre-
vventing intimal proliferation that leads to shunt obstruc-
tion) that since their recent introduction have actually re-
duced the occurrence of this problem.

The relevant issue of pre-TIPS assessment of cardiac
function and cardiac reserve must be underscored in order
to prevent, facing the evidences previously mentioned,
cardiac malfunction after the procedure. Finally, the ef-
ects of TIPS on survival, even in those patients with only
mild-to-moderate liver failure, remains to be clarified. At
present 4 large-scale randomised controlled trials of TIPS
versus serial large volume paracentesis have been publis-
shed. Three of these report better ascites control in the
TIPS group, with higher incidence of hepatic encephalo-
pathy, higher cost and no clear evidences on overall sur-
vival. The recently published trial by Salemo et al. re-
ports a survival advantage for TIPS-treated patients.
However, only one of these studies (Sanyal et al.) provi-
ded a specific cut-off of cardiac ejection fraction (> 50%)
for eligibility to enrolment. However, the ejection frac-
tion of patients with cirrhosis is usually greater than 60%.
Azoulay et al. have recently suggested that an ejection
fraction of greater than 60% may be more appropriate as
an inclusion criterion for entry in a TIPS study, since pa-
tients with an ejection fraction between 50% and 60%
may have a higher risk of post-TIPS heart failure secon-
dary to failure in handling the blood volume returned
from the splanchnic circulation immediately after TIPS
insertion. As the experience with TIPS continues, and the
level of sophistication of patient screening improves (e.
g., with the routine assessment of the ejection fraction at
enrolment) along with improvement of the technology of
the stent itself (polytetrafluoroethylene-covered stents),
the results of future trials may be better than those of past
trials.

**Peritoneovenous shunt**

In the early seventies Le Veen first devised and introdu-
ced the peritoneovenous shunt as a prosthetic system spe-
cifically designed to treat patients with refractory ascites.
It consists of a multiperforated plastic tube that connects
the intraabdominal cavity with the jugular vein (by sub-
cutaneous positioning under local anaesthesia) via a uni-
directional pressure-sensitive valve. The intravenous por-
tion of the tube is positioned up to the superior vena cava,
close to the right atrium. It is advisable to remove by pa-
recanesis most of the ascitic fluid from the peritoneal ca-
vity in order to avoid immediate passage of massive
quantity of ascitic fluid in the systemic circulation with
risk of acute cardiac overload.

After positioning, the shunt produces a sustained expan-
sion of the circulating blood volume by the intermittent
passage of ascitic fluid, through the pressure-sensitive
valve, into the systemic circulation. Most studies publis-
hed by the Toronto group showed that the shunt produces
an almost immediate rise in mean right atrial pressure and
increase in cardiac output, a decrease in peripheral vascu-
lar resistance, a marked but slow suppression of the plas-
ma levels of renin, catecholamines and antidiuretic hor-
none, a sustained and very rapid increase in atrial natriuretic peptide, urinary volume and sodium excretion,
ultimately improving the response to diuretics at smaller
dose as compared to that required pre-shunt and amelio-
ration of the nutritional status in the long term. All
these findings are consistent with the combined ef-
fects of increased right atrial pressure induced by volume
expansion leading to stimulation of atrial natriuretic pep-
tide secretion via atrial stretching. Therefore, it appeared
as a very rational therapeutic approach to refractory asci-
tes. However, in the long term the patients tend to remain
hypotensive with decreased peripheral vascular resistance
in presence of relative suppression of systemic and renal
sympathetic nervous system overactivity (reduced renal
norepinephrine production) and evidence of a still impai-
red renal sodium handling: this implies that factors other
than the renin-aldosterone system and the sympathetic
nervous system are involved in the control of sodium ex-
crution in cirrhotic patients with refractory ascites treated
with the Le Veen shunt.

The peritoneovenous Le Veen shunt caused initial enthu-
siasm and was initially advocated as the treatment of
choice for severe ascites and even hepatoportal syndrome.
However recent studies demonstrated a hospital mortality
of up to 30% and a one-year survival no better than 30%.
Moreover, up to 70% of the shunts are occluded within
the first post-operative year: this occurs as a consequence
of deposition of fibrin within the valve or around the ve-
nous portion of the catheter or even thrombosis of the su-
perior vena cava and infection of the shunt. It has been
proposed that other peritoneovenous prosthesis (Denver
shunt) or the insertion of a titanium tip at the venous ex-
tremity of the Le Veen shunt could reduce the incidence
of shunt occlusion, but these contentions have not been
corroborated by the results of randomised controlled trials
(Ginés et al. and Henrikse et al.). Moreover, peritoneal
fibrosis or even intestinal obstruction observed after shunt
positioning may hamper liver transplantation. Thus, poor
long-term patency, excessive rate of complications requi-
ing frequent hospitalisations and no survival advantage
compared to medical therapy in controlled trials have led
to virtual abandonment of this procedure in most hepato-
lology centres worldwide (Suzuki and Stanley, and Ginès
et al.1). In conclusion, it is well known that hemodynamic
and cardiac alterations are more frequent and relevant in asci-
tic cirrhotic patients. These patients are treated with large
volume paracentesis followed by the infusion of plasma
volume expanders and may become candidates for TIPS
or even liver transplantation. All these procedures may indu-
ce haemodynamic modifications and require cardiac adap-
tation. Paracentesis decreases the intrathoracic pressure, im-
proving venous return to the heart and therefore facilitates
cardiac function. Right atrial pressure and systemic pul-

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monary resistance decrease and cardiac index improve after this procedure. Systemic vascular resistance after paracentesis decreases. However, this physiological hemodynamic adaptive change to cope increased cardiac output in cirrhosis may not be pronounced in these patients developing post-paracentesis circulatory dysfunction. At present there are not sufficient information as to whether cardiac function is directly involved in the development of postparacentesis circulatory dysfunction.

After TIPS opening, a large amount of the splanchnic blood flow is delivered to the heart inducing an increase in preload in the short-term. TIPS induces a rapid cardiac adaptation to cope with the shunted blood volume. Echocardiographic changes however demonstrate a rapid cardiac adaptation increased pre-load resulting in increased cardiac output and stroke volume even in those patients who were "hypovolemic" and showed initial signs of diastolic dysfunction before TIPS.

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