ANNALS of Hepatology

MODULE ?

Vol. 10 Suppl.1, 2011: S6-S14

# Pathophysiological basis of albumin use in cirrhosis

Vicente Arroyo,* Javier Fernandez*

* Liver Unit, Institut de Malalties Digestives i Metaboliques (IMDiM),
Hospital Clínic and Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS);
University of Barcelona and Centro de Investigación Biomédica en
Red en el Área temática de Enfermedades Hepáticas y Digestivas (CIBERehd); Barcelona, Spain.

**ABSTRACT**

During the course of cirrhosis, a progressive reduction of splanchnic vascular resistance takes place in parallel with a deterioration of cardiac function manifested by the disappearance of the hyperdynamic circulation due to a fall in cardiac output. This compromises arterial pressure and determines a homeostatic activation of endogenous vasoconstrictor systems. Cirrhotic patients are prone to developing renal vasoconstriction, decreased renal perfusion and renal failure in response to insults that impairs the effective arterial blood volume such as severe bacterial infections or other clinical events that produce hypovolemia. Although circulatory dysfunction in cirrhosis predominantly affects the kidney, it has also effects on other organs and systems: brain edema and encephalopathy, increased portal pressure and decreased intestinal motility. Albumin infusion is effective in the prevention of circulatory dysfunction after therapeutic paracentesis or acute bacterial infections and in in the treatment of hepatorenal syndrome. This effectiveness may be related to the dual effect of albumin on the cardio-circulatory function, the increase in the cardiac output and in the systemic vascular resistance. The administration of intravenous albumin not only expands the plasma volume and increases cardiac preload and cardiac output but also induces arterial vasoconstriction at the level of splanchnic microcirculation. Moreover, albumin is a powerful antioxidant as well as plays a crucial role in the transport of physiologic substances and disposal of toxic substances. Impairment of albumin function is one of the most characteristic traits of cirrhosis. Administration of exogenous albumin could be beneficial because of its positive effects on microcirculation.

**Key words.** Splanchnic microcirculation. Paracentesis. Bacterial infection. Liver failure.

## USE OF HUMAN ALBUMIN IN CIRRHOSIS

For decades, intravenous administration of human albumin has been one of the treatments most frequently used in patients with decompensate liver cirrhosis. Initially, its main indication was for the management of tense ascites, as it was considered that hypoalbuminemia was a key factor in the genesis of this disorder. Moreover, it is well known that plasma-volume expansion enhances the effect of furosemide and spironolactone. Currently, the main indication of albumin is in the treatment and prevention of severe circulatory dysfunction and hepatorenal syndrome usually appearing in cirrhotic patients with bacterial infections, particularly spontaneous bacterial peritonitis and the prevention of the circulatory dysfunction associated to therapeutic paracentesis.[1]

Albumin is a protein of 585 aminoacids and 66 kDa of molecular weight that hardly crosses the majority of capillaries. Albumin remains in the bloodstream and primarily contributes to the plasma oncotic pressure. Therefore, albumin inhibits the output of fluid from the intravascular compartment to the interstitial tissue and promotes its reabsorption from the interstitial space. The hepatic microcirculation is composed of special capillaries with large pores and high permeability, called the

**Correspondence and reprint request:** Dr. Vicente Arroyo
Director del Centro de Investigación Biomédica Esther Koplowitz
Hospital Clínic de Barcelona
C/ Villarroel No. 170. 08036 Barcelona, Spain
Tel: +34 9322-71724, Fax: +34 9331-29403
E-mail: varroyo@clinic.ub.es

*Manuscript received: December 16, 2010.*
*Manuscript accepted: December 16, 2010.*

sinusoids. The hepatic sinusoids are freely permeable to albumin and other high molecular weight proteins, such as fibrinogen. Albumin is synthesized by the liver cells, passes into circulation via the sinusoids and remains in the bloodstream for about 21 days.[2]

Albumin plays a crucial role in the transport of substances resulting from cellular catabolism from their place of production to the excretory organs, mainly the liver and kidney. Albumin also participates in the transport and disposal of toxic substances that accumulate in the course of acute and chronic pathological conditions, such as sepsis, cancer, kidney failure and diabetes. Finally, albumin also takes part in transporting hormones and drugs to target cells.[3-6] The presence of hypoalbuminemia, therefore, can limit the body's ability to eliminate toxic substances, to transport substances with essential physiological effects and it can alter drug pharmacokinetics. Albumin also has an important antioxidant capacity. Given the high concentration of albumin in blood, this protein is the body's most powerful extracellular antioxidant mechanism.[7] Albumin is able to bind free radicals and, once oxidized, is rapidly removed from circulation. Free radicals affect cell function, since they have harmful effects on cell membranes and intracellular organelles. It is, therefore, not surprising that oxidative stress has important effects on the function of many organs and systems, including the antibacterial capacity of granulocytes and macrophages,[8] and on microcirculation homeostasis.[9]

Hypoalbuminemia is one of the most characteristic traits of chronic liver failure. Traditionally hypoalbuminemia was considered to play an important role in the pathophysiology of ascites. Portal hypertension and decreased plasma oncotic pressure would induce an altered Starling balance in the hepatic and splanchnic microcirculation favoring the escape of fluid into the peritoneal cavity. Intravenous administration of albumin was previously used to correct this process. Subsequent investigations, however, showed that the formation of ascites is a process linked to a decrease in splanchnic vascular resistance and not to hypoalbuminemia.[10] Splanchnic arterial vasodilation produces two different types of processes.

On the one hand, it induces a strong increase in the volume of blood flowing through the splanchnic circulation at high pressure, thus favoring the escape of fluid into the peritoneal cavity. On the other hand, it causes an effective arterial hypovolemia, the activation of systems that stimulate renal reabsorption of sodium and water (the renin-angiotensin-aldosterone system, sympathetic nervous system and antidiuretic hormone system) and fluid retention, which accumulates in the peritoneal cavity thus perpetuating the formation of ascites.[10,11]

The use of albumin in cirrhosis was reinforced after the reintroduction of therapeutic paracentesis. If performed without plasma volume expansion, this treatment is associated with persistent circulatory dysfunction in 75% of patients, as well as with kidney failure in approximately 15-20%. Moreover, it may shorten survival.[12,13] Plasma volume expansion with albumin decreases the incidence of post-paracentesis circulatory dysfunction from 75 to 15% approximately.[13,14]

The effectiveness of albumin in the prevention of post-paracentesis circulatory dysfunction encouraged researchers to test other potential indications, and this leads to new indications on the use of albumin into the management of decompensated cirrhosis. First, it was demonstrated that albumin infusion at the time of diagnosis of the infection reduces the incidence of type 1 hepatorenal syndrome and hospital mortality by more than 60% in patients with spontaneous bacterial peritonitis.[15] Secondly, the combination of albumin and vasoconstrictors is able to reverse the circulatory dysfunction and renal failure in patients with type 1 hepatorenal syndrome.[1,11,16-18]

Investigations are currently being carried out on large series of patients in Spain and Italy in search of a new indication. They are trying to demonstrate that the continuous improvement in circulatory dysfunction in cirrhosis, by weekly or fortnightly administration of albumin, reduces the incidence of other complications of cirrhosis, such us hepatic encephalopathy, gastrointestinal bleeding and bacterial infections.

## SPONTANEOUS CIRCULATORY DYSFUNCTION IN CIRRHOSIS

Traditionally, the circulatory dysfunction in decompensated cirrhosis was considered to be secondary to arterial vasodilation[10] (Figure 1). It was later demonstrated that this vasodilation occurs in the splanchnic area, and there is evidence that it could be related to a massive release of vasodilators as a result of portal hypertension. Numerous studies have shown that nitric oxide might be of significance.[19,20] However, the most widespread theory is that the mechanism is probably multifactorial, and that other vasodilators, such as prostaglandins,[21] subs-

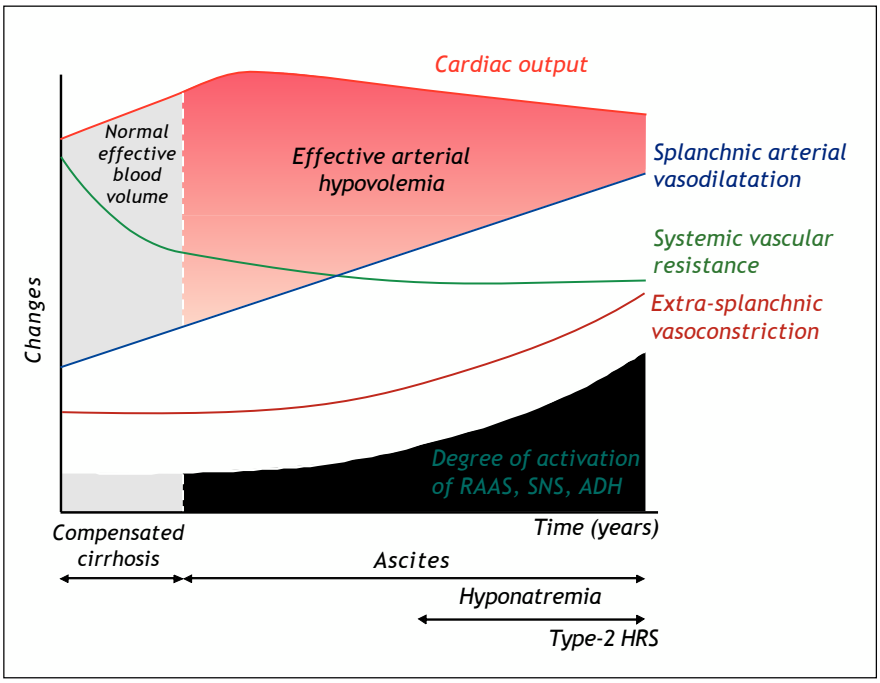


***Figure 1.*** *Periferal arterial vasodilatation hypotesis of renal dysfunction in cirrhosis. The main mechanism is a progressive reduction in splanchnic vascular resistance due to arterial vasodilatation. Initially this is compensated by a increase in cardiac output. However, subsequently there is an impairment in cardiac function and decrease in cardiac output that contributes to the decrease in effective arterial blood volume.* ***RAAS:*** *Renin-angiotensin-aldosterone system.* ***SNS:*** *Sympathetic nervous system.* ***ADH:*** *Antidiuretic hormone.*

tance P,[22] carbon monoxide,[23] calcitonin gene related peptide[24] and endocannabinoids[25] might also be involved.

Two recent findings have demonstrated that the mechanism of circulatory dysfunction in cirrhosis is much more complex than previously thought. Firstly, experimental studies in cirrhosis have demonstrated the existence of intense vascular neoformation in the liver and in the splanchnic area related to the presence of high levels of proangiogenic substances.[26,27] The total number of blood vessels is much higher in cirrhotic rats than in healthy animals. The decrease in vascular resistance in the splanchnic area would therefore result not only from arteriolar vasodilation but also from an increase in the concentration of blood vessels. Evidence that the use of drugs with antiangiogenic activity improves circulatory function confirms the importance of the latter mechanism.[28] Secondly, studies in patients with liver cirrhosis found that in parallel to the progressive reduction of splanchnic vascular resistance during the course of cirrhosis, there is also a progressive deterioration of cardiac function manifested by the disappearance of the hyperdynamic circulation due to a fall in cardiac output.[29,30] Spontaneous circulatory dysfunction in cirrhosis is therefore the result of a fall in splanchnic vascular resistance and decreased cardiac function, both of which progresses during the course of the disease. Several factors contribute to the deterioration of cardiac function. There may be a decrease in venous return; furthermore, there is evidence of a cirrhotic cardiomyopathy with diastolic dysfunction that may compromise the inotropic function. Finally, chronotropic heart function is severely impaired and patients do not increase heart rate, despite having an intense sympathetic nerve activity.[31,32]

One of the most significant aspects of the circulatory function in cirrhosis is its extreme sensitivity to events that produce arterial hypovolemia. This is manifested primarily by the development of renal failure. The administration of diuretics, therapeutic paracentesis without albumin[12,13] or severe bacterial infections[15,33] are associated with renal failure in approximately 15-30% of these patients. Under physiological conditions the regulation of blood pressure and effective arterial blood volume is carried out mainly in the splanchnic and renal vascular compartments. When an effective hypovolemia takes place, whether as a result of loss of volume or vasodilation, vasoconstriction systems become activated to maintain blood pressure by acting in these vascular territories.[34] In cirrhosis, the regulatory effect of blood pressure, however, occurs preferentially in the kidney, since the splanchnic vasculature is highly resistant to the effect of endogenous vasoconstrictors due to the massive release of vasodilator substances occurring in the vascular compartment.[19-25] It is also possible that newly formed vessels in the splanchnic area do not react with the required in-

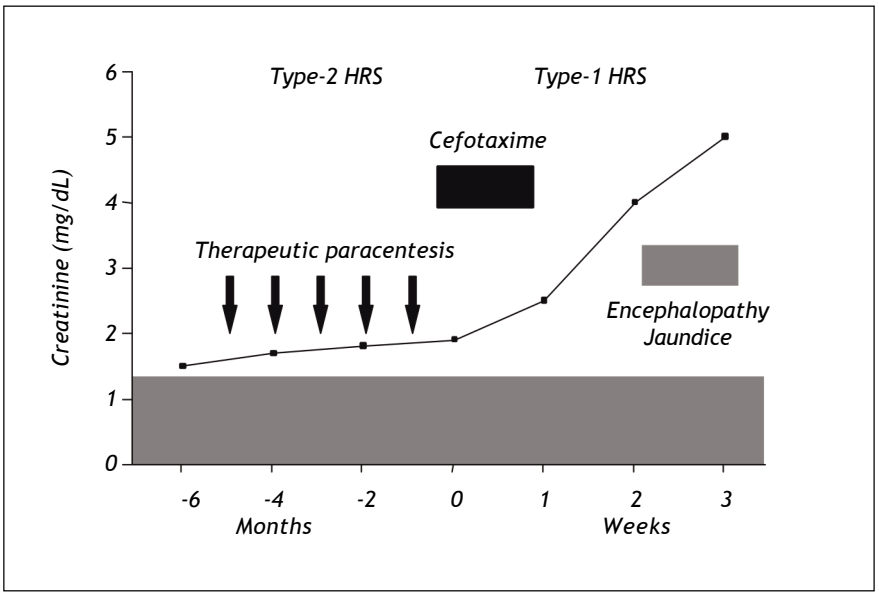


***Figure 2.*** *Clinical course of a patient with type-2 HRS and refractory ascites requiring frequent hospitalizations for repeated paracentesis that developed type-1 HRS following an episode or spontaneous bacterial peritonitis treated by cefotaxime. Type-1 HRS occurred despite rapid resolution of the infection. The patient also developed aggravation of liver failure and hepatic encephalopaty and died 3 weeks after the onset of the infection.*

tensity. Cirrhotic patients are therefore prone to developing renal vasoconstriction, decreased renal perfusion and renal failure in response to insults that compromise the effective arterial blood volume.[11]

Type-2 hepatorenal syndrome is the most extreme manifestation of the circulatory dysfunction that spontaneously develops in cirrhotic patients[11] Type 1 hepatorenal syndrome is probably a different process than type 2 (Figure 2). Although the pathophysiology is similar in both syndromes, a decreased peripheral resistance and cardiac function, circulatory dysfunction in type-1 hepatorenal syndrome is very fast, intense and frequently associated with failure in the function of other organs including the brain, adrenal glands, lungs, and coagulation. On the other hand it often occurs in close relationship to a precipitating factor, often an infection, a fact not common in type-2 hepatorenal syndrome.[11]

Although circulatory dysfunction in cirrhosis predominantly affects the kidney, it is also observed in other organs and systems (Figure 3). Sympathetic overactivity secondary to circulatory dysfunction decreases intestinal motility, induces intestinal bacterial overgrowth, and may promote bacterial translocation from the intestinal lumen into the systemic circulation, causing severe infections.[35] The intrahepatic portal circulation is also sensitive to the vasoconstrictor action of angiotensin-II, norepinephrine and antidiuretic hormone. The intense activation of these systems as a result of circulatory dysfunction may contribute to the high portal pressure that is observed in patients with advanced cirrhosis and ascites.[29,36,37] Hyponatremia secondary to the hypersecretion of antidiuretic hormone may induce brain edema and encephalopathy.[38] The use of diuretics for the treatment of ascites that responds poorly to these drugs (refractory or recurrent ascites) is associated to hepatic encephalopathy in 25% of cases.[39] Studies have shown the existence of a close relationship between renal blood flow and cerebral blood flow as well as between them and the degree of activation of endogenous vasoactive systems.[40] Patients with hepatorenal syndrome are those with a lower cerebral blood flow. The role of this cerebral hypoperfusion in the predisposition of hepatic encephalopathy in these patients is not known.[41,42]

Finally, recent studies have found that critically-ill patients with decompensated cirrhosis and bacterial infections present relative adrenal insufficiency with a frequency of 50-70%, with inappropriately low cortisol levels and poor response to cortocotropin.[43-45] Cortisol is essential for successful vascular response to endogenous vasoconstrictor systems. Relative adrenal insufficiency, therefore, could contribute to circulatory dysfunction in these patients. The impairment in multiorgan function associated to circulatory dysfunction in cirrhosis constitutes the rationale for the prolonged use of albumin in the long-term studies that are being developed in Spain and Italy.

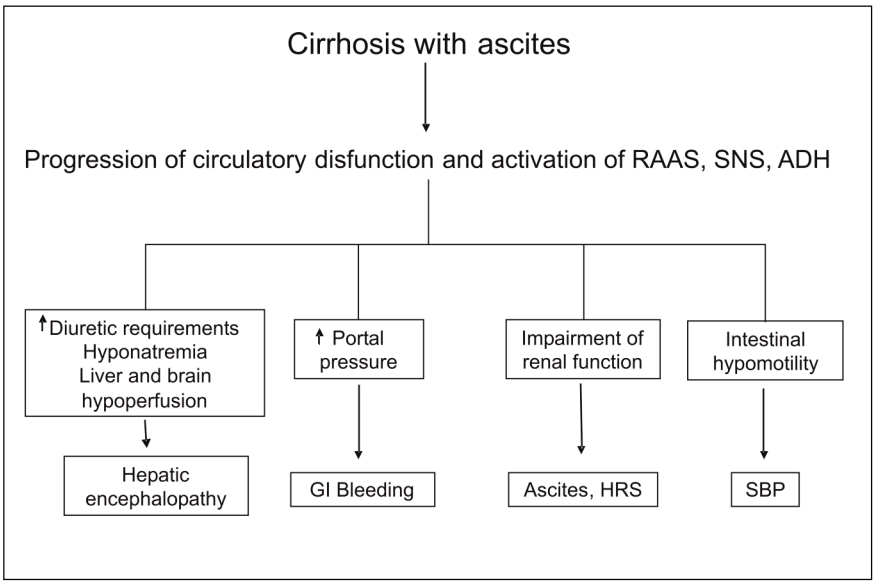


***Figure 3.*** *Potential contribution of systemic circulatory dysfunction on cirrhotic complications.*

## POST-PARACENTESIS CIRCULATORY DYSFUNCTION

It occurs in approximately 70% of patients treated with total paracentesis without administration of plasma expanders.[12,13] The incidence is very low when the volume of ascites removed is less than 5 L, but progressively increases in parallel to the volumen of paracentesis when the amount of fluid removed is above this limit.[14] The mechanism of circulatory dysfunction is dual. Patients develop a decrease in peripheral vascular resistance, indicating an arterial vasodilation. The site where this process occurs is unknown, although it is possible that it takes place in the splanchnic area. This disorder is accompanied by a reactive activation of endogenous vasoconstrictor systems with increased plasma renin activity and noradrenaline. Despite this sympathetic hyperactivity, the cardiac output and pulse rate do not increase, indicating that in addition to the decrease in systemic vascular resistance, inadequate cardiac response to vasodilation participates in the circulatory impairment.[46]

## CIRCULATORY DYSFUNCTION AFTER BACTERIAL INFECTION

Bacterial infections are one of the most important causes of circulatory dysfunction and renal failure in cirrhosis; approximately 30-40% of patients with severe infections develop renal failure.[33,47,48] In many cases, renal failure is reversible, disappearing after resolution of infection; in others, however, renal failure persists in spite of the resolution of infection. In most of these patients renal failure follows a rapidly progressive course (type 1 hepatorenal syndrome), and this is frequently associated to failure in the function of other organs. Finally, in other patients renal insufficiency remains stable after resolution of the infection (type 2 hepatorenal syndrome).[11,30,33] The infection that most often causes renal failure is spontaneous bacterial peritonitis, followed by symptomatic urinary tract infection (acute pyelonephritis) and cellulites.[47,48]

There are experimental studies showing that bacterial infections in cirrhotic rats are associated with a much stronger inflammatory response than in healthy animals.[49] Moreover, in cirrhotic patients with spontaneous bacterial peritonitis, it has been shown that patients who develop renal failure are those with a greater inflammatory response, as estimated by the concentration of leukocytes in ascitic fluid and cytokine levels in ascites and blood.[50]

Studies performed in patients with spontaneous bacterial peritonitis have shown that the development of type-1 hepatorenal syndrome occurs as a result of a dual mechanism. On the one hand, a rapid and intense decrease in vascular resistance that determines the activation of endogenous vasoconstrictor systems. On the other hand, a failure in heart function with decreased cardiac output. This latter process is due to both a deterioration inotropic and chronotropic function. Patients do not develop tachycardia despite circulatory dysfunction and increase in the activity of the sympathetic nervous system.[29]

## ROLE OF ALBUMIN IN LIVER FAILURE

Traditionally, the therapeutic role of albumin has been attributed solely to its oncotic properties. The use of albumin in the management of fluid retention and edema in diseases such as cirrhosis, nephrotic syndrome or protein-losing enteropathy is a clear example of this. However, the albumin molecule has many other functions that are important in physiology and pathophysiology. The albumin molecule has sites with high and low affinity for binding fatty acids and other hydrophobic substances[3-6,51] (Figure 4). Albumin, therefore, plays a major role in the transport of lipids and other hydrophobic molecules from their site of absorption or synthesis to peripheral tissues. Many drugs are transferred to the target organs through this process. Also many toxic substances from cellular catabolism are also transported to their excretory organs (liver and kidney) by binding to albumin. This phenomenon is especially relevant in diseases with high cellular catabolism (cancer, diabetes, sepsis). At the level of cis-34, the albumin molecule has a domain with ability to stabilize free-radicals, which gives a significant antioxidant capacity to the albumin molecule. Due to its high concentration in plasma and interstitial tissue, albumin is the most important antioxidant at extracellular level.[7] Finally there are other domains, particularly at the N-terminal, with the ability to bind metals which, if not removed, increase the oxidative stress.[51]

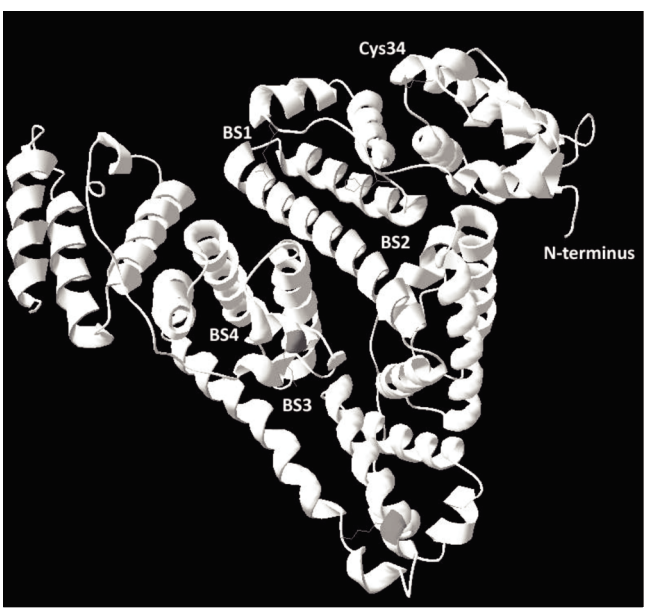


***Figure 4**. Molecular structure of albumin. BS Binding sites for fatty acids and other hydrophobic substances.*

Functional proteomic studies using electron spectroscopy techniques by magnetic resonance imaging (MRI) allow to assess many features of albumin function, including the binding capacity, the efficiency in the transport of hydrophobic molecules (absorption, binding and release in target organs) and in the detoxification of catabolic products (capacity of albumin to bind, transport and finally release toxic substances produced through metabolism), the assessment of the conformation of the molecule at the binding sites and the role of N-terminal chelation. Using these techniques it has been shown that albumin function in cirrhosis is deeply impaired.[51] The capacity of binding fatty acids and other hydrophobic molecules and the ability for transport and detoxification is virtually absent (less than 20% as compared to healthy individuals). The mechanism that determines this decline in albumin function in cirrhosis is not known. It may be a reversible process. Liver failure determines the accumulation of large amounts of hydrophobic molecules. Sepsis, which also alters the function of albumin, is a frequent event in cirrhosis. Finally, both infections and liver failure are associated with increased oxidative stress. All these processes would saturate the binding sites of albumin and decrease its detoxification and transport functions. Albumin dialysis (MARS® system) is intended to remove these substances so as to make endogenous albumin functional again. However, a second possibility is that certain ligands irreversibly alter the molecular characteristics of albumin. Although traditionally it has been suggested that damaged albumin is rapidly eliminated, degraded and replaced by new molecules, this fact is probably not operating in cirrhosis, a condition in which albumin synthesis is profoundly impaired.

The clinical consequences of impaired albumin function in liver failure are not known, but could be significant. The combination of hypoalbuminemia and functionally impaired endogenous albumin causes a profound alteration in the transport, metabolism and excretion of many endogenous and exogenous substances which, instead of being appropriately removed, will circulate as free compounds with the capacity to arbitrarily react. The pharmacokinetics and pharmacodynamics of many drugs and, therefore, effectiveness and side effects are severely affected. Finally, the existing oxidative stress caused by liver failure and other associated problems such as bacterial infections can not be corrected by the action of albumin. Increased oxidati-

ve stress can alter the microcirculation and cell function thus contributing to the multiple organ failure that characterizes many patients with liver failure.[52]

## EFFECT OF ALBUMIN IN THE CIRCULATORY DYSFUNCTION OF CIRRHOSIS

The administration of intravenous albumin in patients with cirrhosis and ascites not only expands the plasma volume and increases cardiac preload and cardiac output but also increases peripheral vascular resistance, suggesting that arterial vasoconstriction occurs (Figure 5). This effect is not observed with synthetic expanders.[53,54] The mechanism that determines the vasoconstrictor effect of albumin is not well studied. It may take place at the level of the microcirculation and be secondary to a decrease in nitric oxide release. Plasma levels of von Willebrand Factor, whose synthesis is parallel to that of nitric oxide, are decreased in patients receiving albumin but not in those receiving plasma expanders.[54] A decrease in the levels of oxidative stress in the microcirculation after administration of exogenous albumin functionally active is another possibility.

The effectiveness of albumin in the prevention of post-paracentesis circulatory dysfunction, in the prevention of circulatory dysfunction after acute bacterial infections bacterial or in the treatment of hepatorenal syndrome may be related to this dual effect of albumin on the cardio-circulatory function, the increase in the cardiac output and in the systemic vascular resistance.

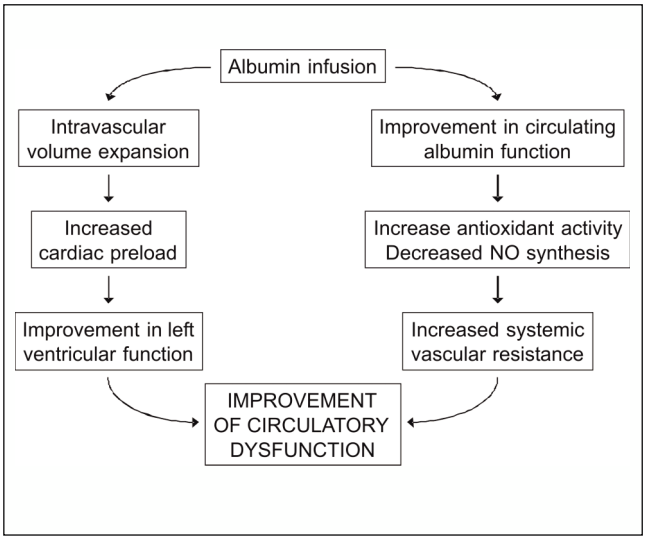


***Figure 5.*** *Mechanism of the effect of I.V. albumin on systemic hemodynamics in cirrhosis.*

## DISCLOSURE OF CONFLICT OF INTERESTS:

This article forms part of a supplement supported by an unrestricted grant from Grifols. The author received payment for the preparation of this article and attendance at the symposium in which it was presented.

### REFERENCES

1. European Association for the Study of the Liver, Ginès P, Angeli P, Lenz K, Møller S, Moore K, Moreau R, Merkel C, et al. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010; 53: 397-417.
2. Rothschild MA, Oratz M, Schreiber SS. Albumin metabolism. *Prog Liver Dis* 1972; 4: 19-29.
3. Fasano M, Curry S, Terreno E, Galliano M, Fanali G, Narciso P, Notari S, et al. The extraordinary ligand binding properties of human serum albumin. *IUBMB Life* 2005; 57: 787-96.
4. Varshney A, Sen P, Ahmad E, Rehan M, Subbarao N, Khan RH. Ligand binding strategies of human serum albumin: how can the cargo be utilized? *Chirality* 2010; 22: 77-87.
5. Quinlan GJ, Martin GS, Evans TW. Albumin: biochemical properties and therapeutic potential. *Hepatol* 2005; 41: 1211-9.
6. Oettl K, Stadlbauer V, Petter F, Greilberger J, Putz-Bankuti C, Hallstrom S, Lackner C, et al. Oxidative damage of albumin in advanced liver disease. *Biochim Biophys Act* 2008; 1782: 469-73.
7. Roche M, Rondeau P, Singh NR, Tarnus E, Bourdon E. The antioxidant properties of serum albumin. *FEBS Lett* 2008; 582: 1783-7.
8. Shawcross DL, Wright GA, Stadlbauer V, Hodges SJ, Davies NA, Wheeler-Jones C, Pitsillides AA, et al. Ammonia impairs neutrophil phagocytic function in liver disease. *Hepatol* 2008; 48: 1202-12.
9. Cicco G, Cicco S. The influence of oxygen supply, hemorheology and microcirculation in the heart and vascular systems. *Adv Exp Med Biol* 2010; 662: 33-9.
10. Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrosis. *Hepatol* 1998; 8: 1151-7.
11. Arroyo V, Fernández J, Ginés P. Pathogenesis and treatment of hepatorenal syndrome. *Semin Liver Dis* 2008; 28-81-95.
12. Ruiz del Arbol L, Monescillo A, Jimenez W, Garcia Plaza A, Arroyo V, Rodés J. Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. *Gastroenterol* 1997; 113: 579-86.
13. Ginès P, Titó L, Arroyo V, Planas R, Panés J, Viver J, Torres M, et al. Randomized comparative study of therapeutic paracentesis with and without albumin in cirrhosis. *Gastroenterol* 1988; 94: 1494-502.
14. Ginès A, Fernández-Esparrach G, Monescillo A, Vila C, Domènech E, Abecasis R, Angeli P, et al. Randomized trial comparing albumin, dextran 70 and polygeline in cirrhotic patients with ascites treated by paracentesis. *Gastroenterol* 1996; 114: 1002-10.
15. Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, Castells L, et al. Effect of intravenous albumin on

renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999; 341: 403-9.
16. Salerno F, Gerbes A, Gines P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome. *Gut* 2007; 56: 1310-8.
17. Ortega R, Ginès P, Uriz J, Cárdenas A, Calahorra B, De Las Heras D, Guevara M, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome; results of a prospective non-randomized study. *Hepatol* 2002; 36: 941-8.
18. Gluud LL, Christensen K, Christensen E, Krag A. Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome. *Hepatol* 2010; 51: 576-84.
19. Vallance P, Moncada S. Hyperdynamic circulation in cirrhosis: a role for nitric oxide? *Lancet* 1991; 337: 776-8.
20. Bomzon A, Blendis LM. The nitric oxide hypothesis and the hyperdynamic circulation in cirrhosis. *Hepatol* 1994; 20: 1343-50.
21. Bruix J, Bosch J, Kravetz D, Mastai R, Rodés J. Effects of prostaglandin inhibition on systemic and hepatic hemodynamics in patients with cirrhosis of the liver. *Gastroenterol* 1985; 88: 430-5.
22. Fernández-Rodriguez CM, Prieto J, Quiroga J, Zozoya JM, Andrade A, Núñez M, Sangro B, et al. Plasma levels of substance P in liver cirrhosis: relationship to the activation of vasopressor systems and urinary sodium excretion. *Hepatol* 1995; 21: 35-40.
23. De las Heras D, Fernández J, Ginès P, Cárdenas A, Ortega R, Navasa M, Barberá JA, et al. Increased carbon monoxide production in patients with cirrhosis with and without spontaneous bacterial peritonitis. *Hepatol* 2003; 38: 452-9.
24. Bendtsen F, Schifter S, Henriksen JH. Increased circulating calcitonin gene-related peptide (CGRP) in cirrhosis. *J Hepatol* 1991; 12: 118-23.
25. Caraceni P, Domenicali M, Giannone F, Bernardi M. The role of the endocannabinoid system in liver diseases. *Best Pract Res Clin Endocrinol Metab* 2009; 23: 65-77.
26. Fernández M, Semela D, Bruix J, Colle I, Pinzani M, Bosch J. Angiogenesis in liver disease. *J Hepatol* 2009; 50: 604-20.
27. Paternostro C, David E, Novo E, Parola M. Hypoxia, angiogenesis and liver fibrogenesis in the progression of chronic liver disease. *WJ Gastroenterol* 2010; 16: 281-8.
28. Mejias M, Garcia-Pras E, Tiani C, Miquel R, Bosch J, Fernandez M. Beneficial effects of sorafenib on splanchnic, intrahepatic, and portocollateral circulations in portal hypertensive and cirrhotic rats. *Hepatol* 2009; 49: 1245-5.
29. Ruiz-del-Arbol L, Urman J, Fernández J, González M, Navasa M, Monescillo A, Albillos A, et al. Systemic, renal and hepatic hemodynamics derangement in cirrhotic patients with spontaneous bacterial peritonitis. *Hepatology* 2003; 38: 1210-8.
30. Ruiz-del-Arbol L, Monescillo A, Arocena C, Valer P, Ginès P, Moreira V, Milicua JM, et al. Circulatory function and hepatorenal syndrome in cirrhosis. *Hepatol* 2005; 42: 439-47.
31. Møller S, Henriksen JH. Cirrhotic cardiomyopathy. *J Hepatol* 2010; 53: 179-90.
32. Alqahtani SA, Fouad TR, Lee SS. Cirrhotic cardiomyopathy. *Semin Liver Dis* 2008; 28: 59-69.
33. Follo A, Llovet JM, Navasa M, Planas R, Forns X, Francitorra A, Rimola A, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. *Hepatol* 1994; 20: 1495-501.
34. Saitoh T, Ogawa Y, Aoki K, Shibata S, Otsubo A, Kato J, Iwasaki K. Bell-shaped relationship between central blood volume and spontaneous baroreflex function. *Auton Neurosci* 2008; 143: 46-52.
35. Wiest R, Garcia-Tsao G. Bacterial translocation in cirrhosis. *Hepatol* 2005; 41: 422-33.
36. Gatta A, Bolognesi M, Merkel C. Vasoactive factors and hemodynamic mechanisms in the pathophysiology of portal hypertension in cirrhosis. *Mol Aspects Med* 2008; 29: 119-29.
37. Cichoz-Lach H, Celinski K, Slomka M, Kasztelan-Szczerbinska B. Pathophysiology of portal hypertension. *J Physiol Pharmacol* 2008; 59(Suppl. 2): 231-8.
38. Guevara M, Baccaro ME, Torre A, Gómez-Ansón B, Ríos J, Torres F, Rami L, et al. Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: a prospective study with time-dependent analisis. *Am J Gastroenterol* 2009; 104: 1382-9.
39. Arroyo V, Ginès P, Gerbes AL, Dudley FJ, Gentilini P, Laffi G, Reynolds TB, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *Hepatol* 1996; 23: 164-76.
40. Guevara M, Bru C, Ginès P, Fernández-Esparrach G, Sort P, Bataller R, Jiménez W, et al. Increased cerebrovascular resistance in cirrhotic patients with ascites. *Hepatol* 1998; 28: 39-44.
41. Ahl B, Weissenborn K, van den Hoff J, Fischer-Wasels D, Köstler H, Hecker H, Burchert W. Regional differences in cerebral blood flow and cerebral ammonia metabolism in patients with cirrhosis. *Hepatol* 2004; 40: 73-9.
42. Iversen P, Sørensen M, Bak LK, Waagepetersen HS, Vafaee MS, Borghammer P, Mouridsen K, et al. Low cerebral oxygen consumption and blood flow in patients with cirrhosis and an acute episode of hepatic encephalopathy. *Gastroenterol* 2009; 136: 863-71.
43. Tsai MH, Peng YS, Chen YC, Liu NJ, Ho YP, Fang JT, Lien JM, et al. Adrenal insufficiency in patients with cirrhosis, severe sepsis and septic shock. *Hepatol* 2006; 43: 673-81.
44. Marik PE, Gayowski T, Starzl TE. The hepatoadrenal syndrome: a common yet unrecognized clinical condition. *Crit Care Med* 2005; 33: 1254-59.
45. Fernández J, Escorsell A, Zabalza M, Felipe V, Navasa M, Mas A, Lacy AM, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: Effect of treatment with hydrocortisone on survival. *Hepatol* 2006; 44: 1288-95.
46. Luca A, García-Pagán JC, Bosch J, Feu F, Jiménez W, Ginés A, Fernández M, et al. Beneficial effects of intravenous albumin infusion on the hemodynamic and humoral changes after total paracentesis. *Hepatol* 1995; 22: 753-8.
47. Terra C, Guevara M, Torre A, Gilabert R, Fernández J, Martín-Llahí M, Baccaro ME, et al. Renal failure in patients with cirrhosis and sepsis unrelated to spontaneous bacterial peritonitis: value of MELD score. *Gastroenterol* 2005; 129: 1944-5.
48. Fasolato S, Angeli P, Dallagnese L, Maresio G, Zola E, Mazza E, Salines F, et al. A. Renal failure and bacterial infections in patients with cirrhosis: epidemiology and clinical feature. *Hepatol* 2007; 45: 223-9.
49. Ramírez MJ, Ibáñez A, Navasa M, Casals E, Morales-Ruiz M, Jiménez W, Arroyo V, et al. High-density lipoproteins reduce the effect of endotoxin on cytokine production and systemic hemodynamics in cirrhotic rats with ascites. *J Hepatol* 2004; 40: 424-30.
50. Navasa M, Follo A, Filella X, Jiménez W, Francitorra A, Planas R, Rimola A, et al. Tumor necrosis factor and interleu-

kin-6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. *Hepatol* 1998; 27: 1227-32.

51. Jalan R, Schnurr K, Mookerjee RP, Sen S, Cheshire L, Hodges S, Muravsky V, et al. Alterations in the functional capacity of albumin in patients with decompensated cirrhosis is associated with increased mortality. *Hepatol* 2009; 50: 555-64.
52. Arroyo V. Human serum albumin: not just a plasma volume expander. *Hepatol* 2009; 50: 355-7.
53. Fernández J, Navasa M, Garcia-Pagan JC, G-Abraldes J, Jiménez W, Bosch J, Arroyo V. Effect of intravenous albumin on systemic and hepatic hemodynamics and vasoactive neurohormonal systems in patients with cirrhosis and spontaneous bacterial peritonitis. *J Hepatol* 2004; 41: 384-90.
54. Fernández J, Monteagudo J, Bargallo X, Jiménez W, Bosch J, Arroyo V, Navasa M. A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. *Hepatol* 2005; 42: 627-34.