Biol Res 31: 291-304 (1998)

The kidney in chronic liver disease: circulatory abnormalities, renal sodium handling and role of natriuretic peptides*

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Patients with chronic liver disease (Läennec's cirrhosis) present sodium chloride retention, leading to fluid accumulation within the extracellular space (edema) and specially in the abdomen (ascites). This article reviews the pathogenesis of the hemodynamic abnormalities observed in these patients, particularly the hypothesis of "primary arterial vasodilation", with an increased nitric oxide production by endothelial cells playing a major role in the pathogenesis of vasodilation. Since excessive renal sodium reabsorption precedes ascites formation, two hypotheses are analyzed with respect to the handling of renal sodium in chronic liver disease: the underfilling and overflow theories. Furthermore, the role of natriuretic peptides is reviewed, the increment in atrial natriuretic peptide observed in well compensated cirrhotic patients being considered as a compensatory response to volume expansion, although with renal resistance to this peptide in early stages of the disease. This review ends with an integrated explanation of the circulatory disturbances, renal sodium retention and renal resistance to atrial natriuretic peptide resulting in the sodium and water abnormalities observed in chronic liver disease.

Key terms: *ascites, chronic liver disease, circulatory abnormalities, edema, Läennec's cirrhosis, natriuretic peptides, nitric oxide, renal sodium handling*

INTRODUCTION

Patients with chronic liver disease (CLD) or Läennec's cirrhosis manifest a remarkable capacity for sodium chloride retention; indeed, they frequently excrete urine that is virtually free of sodium. Extracellular fluid accumulates excessively and eventually becomes manifest as clinically detectable ascites and edema. Cirrhotic patients, unable to excrete sodium, continue to gain weight as long as dietary sodium intake exceeds the maximal urinary sodium excretion. If access to sodium is not curtailed, the slow retention of this ion may lead to the accumulation of a vast amount of fluid in the extracellular space and specially in the abdomen (ascites).

The purpose of the present review is to summarize our understanding of the hemodynamic abnormalities observed in patients with CLD, and the pathophysiology of edema and ascites formation, with particular emphasis in the mechanisms acting in early phases of the disease.

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* This paper is gratefully dedicated to Dr Héctor Croxatto, a very generous man, a master of Physiology, a successful researcher and a great professor.

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Finally, we discuss the effects of atrial natriuretic factor on sodium and water handling in this condition.

CIRCULATORY ABNORMALITIES

Overview.

Patients and experimental animals with CLD exhibit hemodynamic changes characterized by increased cardiac output and heart rate, systemic vasodilatation, and reduced arterial blood pressure (BP) and peripheral resistance (50, 82). This "hyperkinetic circulation" is associated with increased total plasma and blood volume, but with an abnormal distribution of blood volume and remarkable neurohumoral regulation abnormalities. These circulatory changes are, in general, related to the severity of liver failure and greater in patients with fluid retention than in those without it.

The "central blood volume" includes the volume in heart cavities, lungs and central arterial tree, and can be determined as the product of the central circulation time, measured with the indicator dilution technique, and the cardiac output. Measuring the size of the "central" vascular compartment in cirrhosis is important because: a) it allows us to understand whether the hyperdynamic circulation is secondary to an elevation of the preload or a decrement of the afterload; b) volume-receptors and baro-receptors are located in this anatomical area and significantly influence sodium and water homeostasis. Interestingly, the "central" blood volume is substantially reduced in advanced cirrhotic patients, the lowest values having been observed in patients with tense ascites and very reduced systemic vascular resistance (44). However, the non-central blood volume –splanchnic area and the rest of peripheral circulation– is expanded in these patients (44).

In chronic liver disease, there is a very delicate balance between vasodilator and vasoconstrictor forces, that can be easily disturbed. In decompensated stages, vasoconstrictor systems (plasma renin-angiotensin, sympathetic nervous activity) are activated and the serum concentration of angiotensin II, norepinephrine, vasopressin and endothelin are elevated. Some of these agents seem to mediate the avid renal sodium retention typically observed during the development of the disease (see below). However, curiously, these changes run in parallel with an intense vasodilation observed in several (but no all) vascular trees.

Vasodilation in CLD with an increased blood flow has been described in several vascular areas, including splanchnic system, skin and muscles, with opening of arteriovenous shunts, and it directly correlates with the degree of central hypovolemia: the greater the vasodilatation, the greater the central hypovolemia (45). Moreover, the central blood volume correlates negatively with the portal venous pressure: the greater the portal congestion, the lower the central blood volume (44, 45). There is a simultaneous reduction in renal blood flow with intense renal vasoconstriction in patients with severe liver disease (31).

Peripheral arterial vasodilation hypothesis. Role of nitric oxide.

It has been proposed that "primary arterial vasodilation" is of pathogenic importance in the development of these circulatory and neurohumoral abnormalities. We shall briefly review the basis of this hypothesis and particularly the role of nitric oxide (NO) in its pathogenesis.

Since 1965, it has been known that the responsiveness to endogenous vasoconstrictor agents is impaired in cirrhosis (4). Numerous experimental and clinical studies have confirmed resistance to the vascular effects of angiotensin II, norepinephrine, serotonin and vasopressin in cirrhotic animals.

Various vasodilator agents have been proposed to explain these changes: glucagon, prostaglandins, kinins, endotoxins and –in recent years– natriuretic peptides, NO and calcitonin gene-related peptide (CGRP). Among these, vasodilator prostaglandins have a relevant role in maintaining renal hemodynamics, and

sodium and water excretion in decompensated CLD. Current research has failed to find one, major and specific bioactive substance; however, recent data strongly support the hypothesis that increased NO production is a major factor and perhaps a final common pathway that explains the peripheral vasodilation observed in this disease.

The endothelium-derived relaxing factor was discovered in 1980 (36). This potent vasodilator substance was later identified as NO, a simple molecule, synthesized from L-arginine by a family of enzymes named nitric oxide synthases (NOS).

Three major NOS isoenzymes produce NO. The **endothelial NOS** (eNOS) is predominantly membrane bound, is activated by mechanisms that result in calcium mobilization, produces continually small amounts (nmol range) of NO and has a role in the physiological control of BP (46). **Inducible NOS** (iNOS) is expressed in vessel walls and phagocytic cells in response to endotoxins and cytokines, and synthesizes NO in larger quantities (mmol range). Inducible NOS contributes markedly to the excessive vascular NO production and resulting hypotension observed in septic shock (67). Finally, the **neuronal NOS** (nNOS), may contribute to the central control of BP by depressing the sympathetic outflow (16).

In normal kidneys, eNOS has been found in glomeruli, vasculature, macula densa, collecting duct and inner medullary thin limb (75); while iNOS occurs in vascular smooth muscle, juxtaglomerular apparatus, proximal and collecting ducts cells (75).

Nitric oxide –acting as a messenger molecule– mediates vascular relaxation, inhibits platelet aggregation and adhesion to endothelium, and modulates leukocyte chemotaxis and adhesion. Many of these effects are mediated by activation of soluble guanylate cyclase after NO binding to its heme iron resulting in increased levels of 3',5'-cyclic guanosine monophosphate (cGMP). This substance is the common second-messenger of several agonists (nitrates, natriuretic peptides, enterotoxins) that activate different forms of guanylate cyclase (2). In various types of vascular tissues studied *in vitro*, vascular relaxation induced by nitrate esters is preceded by an increase in cGMP; moreover, in intact cells, guanylate cyclase activation occurs at very low concentration of nitrate esters (2).

Nitric oxide in cirrhosis.

In 1991, Vallance and Moncada (94) proposed that NO could be involved in the vasodilatation observed in CLD. Several studies –but not all– have shown that this hypothesis may be correct and that NO is produced in excess by the vasculature of cirrhotic patients and experimental animals.

Nitric oxide seems to play a very important role in the pathogenesis of arterial hypotension observed in animal models of portal hypertension (53), CCl_4-induced cirrhosis (20, 21, 70, 71, 99) and in cirrhotic patients (18, 86).

In portal hypertensive rats (53), the intravenous administration of Nω-nitro-L-arginine (NNA) –the specific competitive inhibitor of NO synthesis– significantly increases mean arterial blood pressure (MBP) and systemic vascular resistance. In addition, it induces a decrease in plasma volume and extracellular sodium space.

Aortic rings of cirrhotic rats show reduced vascular reactivity to angiotensin II (20) or to phenylephrine (99), and this hyporesponsiveness is reversed with endothelium denudation (20, 99) or NOS inhibition with NNA, but not with indomethacin, a cyclo-oxygenase inhibitor (20).

Nω-nitro-L-arginine –infused in conscious, unrestricted cirrhotic and control rats (21)– resulted in a dose-related increase in BP in both groups. However, cirrhotic animals were more sensitive than controls to the pressor effect of the NOS inhibitor; *e.g.*, at the lowest dose of NNA, BP significantly rose in cirrhotic rats but not in controls (21). Aortic cGMP concentration –considered a good estimate of NOS/soluble guanylate cyclase pathway activity in the arterial wall (7)– was found markedly elevated in rats with ascites, and even earlier in the course of the disease (without ascites) when they begin to retain sodium (70). The vascular hyporesponsiveness to noradrenaline

–studied in the forearm circulation of cirrhotic patients– was reduced by the administration of NOS inhibitor, L-NMMA, further supporting the increased vascular synthesis of NO in these patients (18). Finally, Niederberger *et al* (71) administered for 7 days oral N-nitro-L-arginine methyl ester to CCl_4-induced cirrhotic rats with ascites. These animals normalized their high cGMP aortic concentration, reduced their elevated cardiac output, increased their MBP and reduced their elevated plasma renin activity and vasopressin concentrations. Moreover, at least in a preliminary study (61), one week of L-NAME treatment augmented urinary sodium and water excretion, and reduced ascites.

Nevertheless, not all studies have confirmed these results. Fernández *et al* (35), studying rats with portal hypertension induced by partial portal vein ligation and with biliary cirrhosis secondary to chronic bile-duct ligation, found that constitutive and inducible NOS activities were similar to those observed in sham-operated rats. Sogni *et al* (85), evaluating the response to L-NMMA in normal and chronic bile-duct ligated rats, found no difference in systemic and splanchnic hemodynamics. Differences between the model used to produce CLD or the study design (*in vitro vs in vivo*) may account for the variability in these results.

The protein expression of eNOS is increased in the aorta, mesenteric vessels (62) and also in renal arterioles (15) of CCl_4-induced cirrhotic rats with (62, 85) and without ascites (85). These findings keep in line with functional studies demonstrating that iv administration of acetylcholine –a vasodilator agent acting through eNOS– induces higher renal vasodilation in cirrhotic rats than in controls (37). In other words, kidneys from cirrhotic animals –under appropriate stimulation– release more NO than controls (37).

The role of the inducible NOS is less clear. Some groups (18) describe an increased expression of the enzyme in glomeruli of chronic bile-duct ligated rats. However, Weigert *et al* (99) –using Northern blot analysis– could not detect iNOS mRNA in the aortic rings of rats with CCl_4-induced hepatic cirrhosis, while Bosch-Marcé *et al* (15) reported no protein expression in renal tissue of CCl_4-induced cirrhotic rats. Moreover, Kanwar *et al* (47) reported a significant decrement of its activity in bile-duct ligated rats.

Methylene blue (MB) is a potent inhibitor of soluble guanylate cyclase, the target enzyme of NO mediated relaxation (2). Short term iv infusions of MB administered to patients with septic shock have been able to increase MBP, systemic resistance and improve left ventricular stroke work (73), but without sustained clinical improvement. Analogously, we (5) infused MB (1 mg/kg in 100 ml 0.9% NaCl in 10 min) to 4 healthy volunteers and 9 patients with decompensated hepatic cirrhosis, observing a significant increment in MBP in cirrhotic patients but not in controls. No changes were observed in cardiac output, central venous pressure and oxygen transport. Methylene blue was well tolerated and there was no change in methemoglobinemia. We (93) also administered MB to a group of CCl_4-induced cirrhotic rats, without ascites, determining their MBP and glomerular filtration rate (GFR). Cirrhotic animals had lower BP than controls, but BP did not change with the MB infusion; however, post infusion GFR was significantly higher in cirrhotic animals.

Our data, obtained in a pre-ascitic phase of CLD, are keeping in line with other experimental and clinical studies, showing that well compensated animals (96) and patients (100) show a significant reduction in renal vascular resistance with an increment in renal plasma flow and GFR. Moreover, in cirrhotic rats, this hyperfiltration coexists with an increased glomerular size (96) and it might be associated with a preferential dilation of the afferent arteriole.

Role of calcitonin gene-related peptide.

This is a newly discovered 37-aminoacid peptide that –as NO– belongs to the non-adrenergic, non-cholinergic neurotransmitter family. It exerts local paracrine regulatory functions, localizes in central and peripheral

nervous system, and is a very powerful vasodilator agent (66). Circulating levels of CGRP are high in cirrhosis and directly related to the severity of the disease; the fact that they become normal during liver transplantation suggests that this molecule may participate in the pathogenesis of vasodilation observed in this disease (43, 63).

RENAL SODIUM HANDLING IN CHRONIC LIVER DISEASE

The pathogenesis of the deranged sodium homeostasis of cirrhosis is complex and remains the subject of a continuing controversy. A least two hypothesis have been advanced (29).

Underfilling theory.

This theory proposes that ascites formation begins when a critical imbalance of Starling forces in the hepatic sinusoids and splanchnic capillaries causes an excessive amount of lymph formation, which exceeds the capacity of the thoracic duct to return it to the circulation. Consequently, excess lymph accumulates in the peritoneal space. Simultaneously, vasodilatation and opening of arteriovenous shunts expand the space in which the plasma volume is contained; renal sodium retention is activated and the relative disparity between plasma volume and the circulatory space is perceived as "effective" plasma volume contraction. The renal retention of sodium may be successful in restoring absolute total plasma volume to a normal or even supranormal value; however, because of the enlargement of the circulatory space in which this volume is contained, a state of relative "effective" volume contraction persists. This may explain the apparent paradox of unremitting renal sodium retention even with an apparently expanded absolute plasma volume.

The term "effective" plasma volume refers to the part of the total circulating volume that is effective in stimulating volume receptors. The concept is elusive because the actual "volume receptors" remain not completely defined. The reduced "effective" volume is thought to constitute an afferent signal that triggers events leading to augmentation of salt and water reabsorption in the renal tubule. In summary, renal sodium retention is a secondary rather than primary event.

The so called "peripheral arterial vasodilatation theory", already mentioned, is not really a separate hypothesis, but rather represents a revision of the "underfilling" theory. The theory states that peripheral arterial vasodilatation would be the initial determinant of the intravascular underfilling. An imbalance between an expanded capacitance (mainly in splanchnic circulation) and the available volume would unload high pressure baroreceptors and stimulate a compensatory neurohumoral response (renin-angiotensin system, sympathetic nervous system, vasopressin) leading to renal sodium and water retention.

There seems to exist a close chronological relationship between the onset of sodium retention and the decrease in BP. In rats with partial portal vein ligation, a model of presinusoidal hypertension, the fall in systemic vascular resistance occurs before a detectable increase in total body sodium is observed (3). The hypothesis was reaffirmed when careful studies using magnetic resonance imagining demonstrated a decreased central blood volume (64). Moreover, in some studies (81), head-out water immersion –a maneuver that increases central blood volume– corrects the abnormal renal sodium and water retention in cirrhotic patients with ascites, only when associated with concomitant maintenance of systemic vascular resistance with norepinephrine.

"Overflow" hypothesis.

The "overflow" hypothesis proposes that the primary event in the pathophysiology of ascites is an excessive (inappropriate) renal sodium reabsorption, with a resultant expansion of plasma volume. In the setting of abnormal Starling forces (portal hypertension with increased hydrostatic pressure, and reduction of plasma colloid osmotic pressure in the

portal venous bed and hepatic sinusoids), the expanded plasma volume is sequestered preferentially in the peritoneal space with ascites formation. Thus, according to this formulation, renal sodium retention and plasma volume expansion precede rather than follow the formation of ascites.

It is important to emphasize that cirrhosis of the liver is a chronic progressive disease, evolving usually over years and –as such– there is ample opportunity for perturbations in salt and water balance to develop, for compensatory mechanisms to come into play and for them to become overwhelmed. Moreover, physiological signals influencing the renal tubule are not identical in the ascites and in the preascitic phase of the disease. Elegant studies performed in patients and in experimental animals in the preascitic phase have shown that this theory is correct. Initially, plasma volume becomes overfilled and then ascites "overflows" from an expanded circulation.

Further evidence to support the existence of primary renal sodium retention was added by several studies performed in these patients. Trevisani *et al* (88) observed that plasma renin activity was low when measured in the supine position, a fact consistent with volume expansion, while Rector *et al* (76) found an increment in atrial size measured by two-dimensional echocardiography. These observations are consistent with the study of Wong *et al* (100), who reported a significant increment in GFR and renal plasma flow associated with a decrease in renal vascular resistance, in well-compensated patients.

Careful sodium balance studies, sequentially following experimental cirrhotic animals, confirmed that urinary sodium retention and plasma volume expansion precede the appearance of ascites (54). Interestingly, while cirrhosis was still developing, urinary sodium retention also preceded the appearance of ascites in animals without portal hypertension (with a porto-cava anastomosis) (56). Then, a sodium retaining signal, unrelated to mere sequestration of blood within the mesenteric vascular space, was present in preascitic animals.

Posterior studies (89) have proposed that the above mentioned signal may be intrahepatic hypertension, initiated by a partial venous outflow block of the liver. Low pressure intrahepatic baroreceptors, sensitive to increments in sinusoidal pressure, activate renal sympathetic efferences, that increase tubular sodium reabsorption (40).

Renal sodium retention accompanying CLD is due primarily to enhanced tubular reabsorption rather than to alterations in the filtered load of sodium. Several observations indicate that a decrease in GFR cannot constitute the major determinant of this abnormality, because sodium retention occurs despite normal or even supranormal GFR.

The mediators of the enhanced tubular reabsorption of sodium in cirrhosis and their relative roles are only partially elucidated. Well demonstrated mechanisms are: a) hyperaldosteronism acting in cortical collecting tubule; b) an increment in renal sympathetic nervous system activity acting specially in the proximal tubule; c) alterations in eicosanoids, including a relative diminution of renal vasodilator prostaglandins; d) refractoriness to the natriuretic effect of atrial natriuretic peptide. Other suggested mechanisms are: alterations in renal blood flow distribution and perfusion pressure; altered vascular response to vasoconstrictor agents mediated by NO; a relative impairment of renal kallikrein formation; and modulation of other possible humoral natriuretic factors.

In summary, patients in the preascitic stage of CLD have an expanded blood volume as a consequence of primary sodium retention. As ascites accumulation progresses, the circulation becomes relatively "underfilled", thus creating an entire new set of pathophysiological disturbances. In this phase, physiological factors signaling the renal tubule are largely a consequence of a decreased "effective" arterial blood volume. Both theories are correct, but they apply to different "moments" of the disease.

ROLE OF NATRIURETIC PEPTIDES

Atrial natriuretic peptide physiology.

Atrial natriuretic peptide (ANP), discovered in 1981 (23), is a cardiac hormone with potent diuretic, natriuretic and vasodilator properties. This peptide and its precursors were found in storage granules observed in mammalian atria, initially in 1956 (48). The peptide –a 28 aminoacid molecule– belongs to a family of natriuretic factors (atriopeptine, brain natriuretic peptide, urodilantin, C-natriuretic peptide) whose functions have not been completely clarified.

Atrial natriuretic peptide is released from cardiac atria by multiple mechanisms, the most important being atrial stretch (26). For this reason, plasma levels of ANP are thought to serve as sensitive indicators of "fullness of the circulation", increasing when intravascular volume increases and *vice-versa*. Administered in pharmacological doses, ANP can induce potent renal (diuresis, natriuresis, increments in GFR), hemodynamic (decrease in BP, reduced cardiac output, hemoconcentration) and hormonal (suppression of renin, aldosterone) effects.

The physiological role of ANP in the day-to-day control of urinary sodium excretion remains unclear. The endogenous circulating ANP concentration in normal, euvolemic humans is approximately 10-70 pg/ml, and physiological maneuvers such as posture, exercise (27) and variations in sodium intake (78) cause modest (2- or 3-fold) changes in plasma ANP concentration. Increments in plasma ANP of about 25 pg/ml, by exogenous administration, produce a natriuretic response which is only about 10%-25% of that observed when a comparable change in ANP concentration is induced by increasing dietary sodium intake from 100 to 350 mEq/day (77). Moreover, in transgenic mice with an overexpression of ANP (chronic plasmatic ANP elevation), sodium balance remains normal and the only perturbation observed is a small decrease in BP (95). In these rats, renal sodium conserving mechanisms overcome the possible salt-wasting effects of chronic plasma ANP increase (95). Probably, in normal homeostasis, ANP serves mainly as a compensatory or modulating factor of sodium balance, occupying a third place in importance behind the renin-angiotensin-aldosterone and sympathetic nervous systems.

Natriuretic peptides interact with two biochemically and functionally distinct classes of receptors: a) clearance receptors, by far the most abundant, remove natriuretic peptides from the circulation and account for ANP's brief half-life of 3 min; b) signaling receptors or guanylate cyclase receptors that mediate the cellular, organ and systemic effects of the peptides, via the generation of cGMP. This second group is unique, because it contains in a single molecule the acceptor (ligand binding), the effector (membrane-bound enzyme guanylyl cyclase) and a modulator (protein kinase-like domain) of the activity of guanylate cyclase interposed between the other two (22).

In the kidney, ANP receptors have been clearly identified in the glomerulus and inner medullary collecting duct (13, 42). Interestingly, immunoreactive ANP and specifically ANP binding sites have also been localized in the gastrointestinal tract (13), where they modulate water and NaCl absorption.

Atrial natriuretic peptide receptor density correlates inversely with plasma ANP concentrations (38), but density is also regulated by renal sympathetic nerve activity. Glomerular ANP receptor density increases in denervated kidneys, a finding suggesting that denervated kidneys present an increased maximal response to the peptide's natriuretic effect (24).

Atrial natriuretic peptide increases the GFR by raising the glomerular hydraulic pressure; this is accomplished by dilating the afferent arteriole and constricting the efferent arteriole. In addition, by relaxing mesangial cells, ANP increases the glomerular ultrafiltration coefficient (28). Certainly, these mechanisms increase sodium filtered load and explain in part the natriuresis. However, it has been demonstrated that the natriuretic effect also

occurs in the absence of changes in GFR, reducing tubular sodium reabsorption in inner medullary collecting duct cells (41), where ANP inhibits the opening of sodium channels (57).

Recently, Boric and Croxatto (14) observed that ANP's excretory actions are antagonized by bradykinin and/or other kinins. This effect, observed with small kinin doses, is mediated by activation of B-2 receptors, independently of changes in systemic BP. The authors postulate that this inhibitory action could be particularly relevant in post-prandial periods.

ANP in cirrhosis.

Over the past decade, numerous studies have investigated the role of ANP on renal sodium retention in cirrhosis. In 1985, working at Dr Croxatto's Lab, before ANP radioimmunoassay was available in Chile, we (90) infused normal rats with atrial extracts obtained at autopsy from cirrhotic patients (with variable ascites) and from normal subjects that died accidentally. Interestingly, we found that extracts from cirrhotic patient's atria provoked higher natriuretic and diuretic effects than those of atria taken from controls, but their BP lowering effect was similar for both groups. We proposed then that an ANP deficiency was not responsible for the remarkable antinatriuresis observed in these patients.

Later, several investigators (39, 98) confirmed that –in the preascitic phase of cirrhosis– plasmatic ANP levels are normal or high, in association with an expanded total blood volume. Campbell *et al* (17) studied a group of sodium-retaining pre-ascitic cirrhotic patients, and submitted them to head-out water immersion. They demonstrated a significant hyperresponsiveness to the test when compared to controls. This maneuver provoked a greater elevation of plasma ANP and an exaggerated natriuretic response; this occurred in parallel with a rapid suppression of plasma aldosterone. The rise in plasma ANP concentrations in the cirrhotic patients was also much greater than that seen in the control subjects. This finding in pre-ascitic patients is consistent with the presence of an expanded extracellular blood volume, which –on central redistribution– produces a greater rise in atrial stretch and ANP release.

In summary, the increment in ANP levels observed in well compensated CLD patients seems to be a compensatory response to volume expansion.

In an animal model of canine cirrhosis (common bile-duct ligation), Levy *et al* (55) performed sequential measurements of plasma ANP, showing that levels present a biphasic profile. They decrease in the first two weeks after ligation, but they increase as dogs become progressively cirrhotic and their extracellular fluid volume is expanded. Once ascites appeared (and blood volume decreased?), plasma ANP levels returned to baseline or below. In the same experimental model, we (19) found that cholestatic rats presented larger extracellular fluid volume and also high plasma ANP concentrations; however, they showed a reduced sodium excretion after an oral sodium overload.

The biphasic ANP profile described by Levy *et al* (55) in the canine model is not observed in humans. Actually, in the most advanced stages of cirrhosis, plasma levels of ANP remain high, even in the presence of ascites and decreased central blood volume (30), and this is due to its increased cardiac release and not to impaired hepatic metabolism of the peptide. This apparent paradox has no clear explanation. Although in advanced cirrhosis, the effective arterial blood volume falls, there might be sufficient residual expansion of the vascular volume to keep ANP increased.

Perhaps, there might be activation of sympathetic afferents from the cirrhotic liver –due to intrahepatic hypertension– that reflexly augment ANP release. Levels of ANP have been correlated to intrahepatic sinusoidal pressure (97), suggesting that –as the disease progresses– more urinary sodium retention causes plasma volume expansion, which thus elevates ANP.

The relative contribution of natriuretic peptides in normal physiology and in cirrhosis was assessed by administering

HS-142-1, a specific antagonist of guanylate cyclase-coupled ANP-receptors (6). This interesting study was performed in conscious control and cirrhotic rats with ascites and their typical circulatory abnormalities. Administration of HS-142-1 did not alter systemic hemodynamics in the two groups of animals. Therefore, natriuretic peptides do not seem to be directly responsible for the hyperkinetic circulation observed in cirrhosis. In contrast, cirrhotic rats showed an increased sensitivity to the renal effects of ANP-receptor blockade. Administration of HS-142-1 induced a significant reduction in renal plasma flow and GFR. Natriuretic peptides –probably acting in concert with other vasodilator agents– seem to play an important role in the maintenance of renal perfusion and GFR in decompensated cirrhotic patients with ascites.

Renal unresponsiveness to ANP.

Renal unresponsiveness to ANP in CLD emerges as the logical consequence of finding a combination of high serum levels and urinary sodium retention.. It has been well confirmed by experimental (49, 58, 59, 60, 69, 72, 91, 92) and clinical (1, 12, 33, 51, 65, 79, 83, 101) research, but the exact explanation for this interesting fact remains unknown.

Experimental studies. We (91) evaluated the renal resistance to ANP in anaesthetized, chronic cholestatic rats without ascites and also in their isolated perfused kidneys. Cholestatic rats presented blunted natriuretic and diuretic responses to iv injections associated with reduced increments in GFR and fractional excretion of sodium when compared to controls. Similarly, the diuretic-natriuretic response of isolated kidneys was greatly attenuated: ANP did not increase perfusion pressure in cholestatic rats as it did in controls (91). To explore the possible mechanism of this resistance, we also determined ANP-binding sites by *in vitro* autoradiography in control and CCl_4-induced cirrhotic rats. We (92) found decreased ANP-binding sites in renal medulla of cirrhotic rats, but these results have not been confirmed by other authors (60).

Levy *et al* (59, 60) evaluated this resistance performing careful studies in two experimental models: cirrhotic dogs (59) and dogs with thoracic inferior vena cava constriction. The molecular composition of atrial extracts, the ANP release, its plasma half-life and metabolic clearance were identical in cirrhotic dogs and controls (60). Nevertheless, dogs with ascites infused with ANP divided in two groups: some presented a natriuretic response, some did not. Several variables were examined trying to determine which factors could discriminate between these apparently different populations with regard to the sensitivity of the natriuretic response to ANP. Atrial content of ANP, renal or systemic hemodynamics, plasma levels and urinary excretion of cGMP, inner medullary collecting duct receptor density, and binding and cGMP generation when tested in medullary slices were not different between both groups (60).

Reversal of ANP unresponsiveness in experimental animals has been accomplished with several maneuvers, that help to unravel the pathophysiology of this abnormality. The most successful have been renal denervation (49), normalization of BP with vasoconstrictor agents (58), and the use of phosphodiesterase inhibitors, to avoid excessive destruction of cGMP in renal target cells (69).

Clinical studies. Some authors use bolus and/or continuous intravenous infusions of ANP, markedly elevating its concentration; others employ the head-out water immersion technique to stimulate endogenous ANP release and suppresses plasma renin activity and plasma aldosterone levels. Head-out water immersion studies (33, 83) confirmed that these patients have no impairment in ANP release; moreover, they presented marked elevation in plasma ANP levels and a parallel significant increment in cGMP, its second messenger. Nevertheless, some patients achieved natriuresis (responders) and some did not respond (non-responders). Similar results were observed

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after ANP infusions. Interestingly, in head-out water immersion, urinary cGMP excretion increased to the same degree in both groups (83).

A more careful analysis of these studies disclosed that responders differed from non-responders in several respects: a) non-responders as a group, had more severe liver disease and more avid sodium retention, higher plasma renin activity and aldosterone levels (51, 79); b) urine potassium excretion was higher in responders, suggesting that volume expansion in these patients might allow sodium to be delivered to the distal cortical nephron for Na^+/K^+ exchange (101); c) significant hypotension followed ANP administration in all cirrhotic patients, but it was more marked in non-responders.

Reversal of "resistance to ANP" in clinical investigation is achieved by: a) combining head-out water immersion and ANP infusion, with a parallel suppression of antinatriuretic factors (101); b) the use of a peritoneo-venous shunt (97); and c) the administration of mannitol, to increase sodium distal delivery, by reducing proximal sodium reabsorption (1, 65).

Interestingly, renal resistance to ANP might be a more generalized phenomenon, affecting other organs. In a preliminary study, we also found that female cirrhotic rats presented resistance to ANP effect in the ileum. In these animals, ANP was unable to modify the mucosal electrolyte transport, as measured by short-circuit current (74).

Natriuretic hormone.

The first evidence of the existence of a natriuretic hormone was given by De Wardener in 1961 (25). As yet, this molecule is not well characterized and appears to be a low-molecular weight substance eluted after Sephadex chromatography of plasma and urine. It inhibits Na^+/K^+-ATPase *in vitro* and sodium transport *in vivo*; it increases in response to maneuvers that expand the extracellular fluid volume, such as head-out water immersion, saline infusion or oral sodium load (32). The role of natriuretic hormone in sodium retention of cirrhosis is less clear. Naccarato *et al* (68) observed that the natriuretic activity of urine extracts obtained after volume expansion was significantly lower in cirrhotic patients without ascites, than in normal volunteers. Nevertheless, LaVilla *et al* (52) observed that its activity was increased in urine extracts from cirrhotic patients with ascites, suggesting that renal sodium retention could not be attributed to a deficiency in this hormone. Interpretation of these contrasting results is difficult; perhaps they might be explained because patients studied are in different stages of the disease.

CAN WE INTEGRATE CIRCULATORY ABNORMALITIES, RENAL SODIUM RETENTION AND RESISTANCE TO ANP IN A LOGICAL EXPLANATION?

The pathophysiology of sodium retention in CLD remains mysterious. Most authors consider "primary arterial vasodilation" as the major initiating event which, enhanced by hypoalbuminemia, promotes a decrease in "effective blood volume" that stimulates the sympathetic nervous system. Renal nerve stimulation increases proximal tubular sodium reabsorption (11) and stimulates the renin-angiotensin system leading to edema.

As presented in this review, three facts are well established: a) increased NO production by endothelial cells plays a major role in the pathogenesis of vasodilation; b) renal sodium reabsorption precedes ascites formation; c) renal resistance to atrial natriuretic peptide is present in early stages of the disease.

The behaviour of the renal circulation in early cirrhosis remains not well defined. Clearly, there is evidence that some intrarenal circulatory disturbance, is present even in early stages of the disease. Studies by Atucha *et al* (8) have demonstrated that cirrhotic animals present a reduction in diuretic and natriuretic response to mechanical increments of renal perfusion pressure. Moreover, they observed that cirrhotic rats with normal total renal blood flow and normal GFR,

presented a reduced renal papillary plasma flow, both in the basal state and also after volume expansion. This was associated with a lower increment in renal interstitial hydrostatic pressure during the expansion (9). These results are in keeping with a report by Schwab *et al* (80), who described a blunted increase in renal interstitial hydrostatic pressure after ANP administration. Thus, a selective papillary abnormality or a defect in medullary circulation might also explain the renal resistance to ANP.

Renal interstitial hydrostatic pressure is thought to be an important determinant of the renal response to extracellular volume expansion and vasodilator agents (34). It is possible that reduced papillary flow during volume expansion might induce a lower renal interstitial hydrostatic pressure, and hence facilitate sodium and water reabsorption in renal tubules.

Another enigma is the exact role of NO in cirrhotic patient's renal hemodynamics. It is well known that in normal animals, NO produces renal vasodilation, diuresis and natriuresis (84); thus, if the cirrhotic non-ascitic patient's kidney is vasodilated, it should eliminate, not retain sodium. As indicated above, cirrhotic animals exhibit an increased renal vasodilator response to acetylcholine, suggesting that cirrhotic patient's kidneys are able to release –under appropriate stimulation– more NO than controls (37). Moreover, iv administration of L-arginine in cirrhotic humans significantly reduced BP, and increased urinary volume and sodium excretion (87). Nevertheless, although cirrhotic animals and patients show elevated renal and systemic activity of NO, their kidneys –even vasodilated– seem to be refractory to its natriuretic effects, as it is to ANP; they seem unable to maintain sodium balance.

Nitric oxide synthesis blockade in cirrhotic animals should produce renal vasoconstriction and more sodium retention. Curiously, for unknown reasons, NOS inhibition with Nω-nitro-L-arginine methyl ester, infused in non-pressor doses to cirrhotic animals, far from increasing sodium reabsorption, produced natriuresis that was not due to changes in GFR (10, 61). The mechanism behind this paradoxical beneficial effect remains unknown. Perhaps, the intrarenal elevation of NO is produced as a compensation against antinatriuretic systems, which –as it appears– predominate and are responsible for sodium retention. In this situation, the increase in NO may not be enough to compensate.

New studies are needed to explain the abnormal sodium balance observed in this interesting disease.

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