The role of the sympathetic nervous system and vasopressin in the pathogenesis of the abnormal sodium and water

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INTRODUCTION

Despite intensive investigation, the pathogenesis of sodium and water retention in cirrhosis remains controversial. In this article, investigations regarding the role of the sympathetic nervous system and vasopressin in the pathogenesis of cirrhosis will be reviewed.

A decrease in «effective blood volume» has been hypothesized to mediate some of the pathophysiological changes seen in cirrhosis [85]. This decrease in «effective blood volume» may be due to an increase in the capacity of the vascular system secondary to peripheral vasodilatation, increase in the splanchnic vascular capacity, the development of portosystemic fistulae, and/or decreased plasma oncotic pressure. Some authors have taken an absence of detectable decreases in total blood volume to mean that the pathophysiology of cirrhosis does not involve decreases in «effective blood volume» [68,69]. However, they have not considered the increase of vascular capacity in cirrhosis.

Decreased intravascular pressure in sensed by baroreceptors [51] in the great vessels of the thorax [46], the carotid artery [56], the left atrium [46,48,89] or juxtaglomerular apparatus [21,25,44]. Traction stimulation of the carotid baroreceptors results in large increases in urinary sodium excretion without changes in glomerular filtration rate or renal plasma flow [56]. Stimulation of the left atrial pressure receptors leads to decreased secretion of vasopressin by the supraoptic and paraventricular nuclei of the hypothalamus [26,75] and decreases in renal sympathetic efferent nerve activity [55,86].

Evidence that decreases in the «effective blood volume» leads to stimulation of the sympathetic nervous system is augmented by experiments where volume is repleted [22,32,36,101]. The volume expansion maneuvers have included infusion of isotonic mannitol [88], head-out water immersion [13,36], infusion of ascitic fluid [87,107], saline [104], and saline plus albumin [107].

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Evidence for a «Splanchnorenal» Reflex

Evidence that liver disease leads to alterations in the renal sodium and water metabolism comes from a number of sources.

Levy [62] has shown thar renal sodium retention precedes ascites formation by 10 days in nitrosamine-induced cirrhosis in the dog. López-Novoa et al [71] have induced cirrhosis in the rat by carbon tetrachloride inhalation and oral phenobarbital and also observed positive sodium balance which preceded the development of ascites by two weeks without a change in the glomerular filtration rate or renal plasma flow. In addition, the authors performed experiments in the rat where chronic portal hypertension was induced by ligature of the portal vein [18]. Hemodynamics were measured using the double microsphere method 80-90 days after ligature placement, and a decrease in systemic vascular resistance was found which is consistent with the «underfill» theory.

Furthemore, increased portal vein pressure in the rat caused increases in urine flow [52,81]. Increased perfusion pressure in the portal vein of the isolated guinea pig liver and increased portal vein pressure in the rabbit in vivo produced by intravenous fluid administration led to increased afferent hepatic nerve activity [80]. Furthermore, inferior vena cava occlusion at the diaphragm has been observed to increase hepatic and portal vein pressure by 5-30 mm Hg without affecting mean arterial pressure; hepatic afferent nerve activity and renal sympathetic efferent nerve activity also increased [59].

Applying the opposite experimental intervention, i.e. decreasing hepatic sinusoidal pressure by five minute periods of main portal vein occlusion in the rabbit caused decreases in mean arterial pressure and efferent renal sympathetic nerve activity that were unaffected by vagotomy [79]. Similarly, occlusion of the main portal vein in the dog increased urine flow rate, chloride excretion, renal plasma flow and glomerular filtration rate. These responses were reversibly abolished by application of local anesthetics to the renal neurovascular pedicle [67]. Furthermore, main portal vein occlusion in the dog produced a 40 % decrease in efferent renal sympathetic nerve activity from 9.8 to 7.4 Hz as well as a slight decrease in mean arterial pressure that should cause sinoaortic baroreceptor-mediated increases in efferent renal sympathetic nerve activity [28].

Thus, studies in four species of animals has led to the

conclusion that increases in hepatic sinusoidal pressure are associated with increased renal sympathetic nerve traffic as well as increased sodium and water reabsorption which precedes the formation of ascites. Indeed, ablation of the renal nerves decreases conservation of sodium by the kidney [29,49,93] in the case of a low sodium diet.

In contrast to the foregoing, Anderson et al [2] produced acute increases in portal vein pressure by partial main portal vein occlusion in dogs. Despite a constant renal arterial pressure; renal blood flow, glomerular filtration rate, urine sodium excretion, and free water clearance all decreased. Renal vascular resistance and renin secretion increased. Renal denervation prevented decreases in renal blood flow, glomerular filtration rate, and urinary sodium excretion as well as increases in renal vascular resistance and renin secretion rate, but it did not prevent antidiuresis. The authors felt the data were consistent with a «splanchnorenal» reflex.

Another model of experimental cirrhosis which has examined the pathophysiology of sodium and water retention is chronic bile duct ligation which has been shown to lead to sodium and water retention [10]. These findings were confirmed and cardiac output was found to be increased with a decrease in systemic vascular resistance [98]. Moreover, the conscious rat with chronic bile duct ligation was found to have decreased renal blood flow and increased renal vascular resistance with normal plasma protein concentration and plasma volume in another study [9].

Finally, renal sodium retention and ascites formation are abolished and normal mineralocorticoid «escape» is restored in experimental chronic bile duct ligation when the elevated intrahepatic sinusoidal pressure is relieved by a side-to-side portocaval shunt [103].

In contradiction to the above results, dogs with dimethylnitrosamine-induced cirrhosis were found to have sodium and water retention and increased renal sympathetic efferent nerve activity independent of changes in cardiac output, mean arterial pressure, splanchnic blood volume, hepatic arterial blood flow, glomerular filtration rate, renal blood flow, intrarenal hemodynamics, aldosterone, estrogen and progesterone levels [63]. Prevention of portal hypertension by prior construction of an end-to-end portocaval fistula before induction of cirrhosis did not prevent formation of ascites [65].

Finally, a balanced view may be gained from an early paper: renal denervation or alpha-adrenergic blockade does not totally abolish the antinatriuresis associated with various experimental models of liver injury in the dog [22]. Therefore, increased renal sympathetic tone cannot account entirely for the antinatriuresis of cirrhosis [22], but it is probably a contributing factor.

Mechanism of Increased Sympathetic Activity

The renal innervation is exclusively noradrenergic and involves the afferent and efferent arterioles, juxtaglomerular apparatus, and proximal and distal convoluted tubules. Increased renal sympathetic efferent nerve activity leads to renal vasconstriction [27]. Direct stimulation of the efferent renal nerves leads to frequency-dependent decreases in renal blood flow and glomerular filtration rate that are abolished by alpha-1 adrenergic blockade [83].

Moreover, direct as well as reflex changes in renal sympathetic efferent nerve activity lead to increased renal sodium and water reabsorption without changes in renal blood flow, glomerular filtration rate or intrarenal distribution of blood flow [8]. This occurs in the proximal convoluted tubule, and the more distal nephron, and this effect is not dependent on angiotensin II or prostaglandins [27,83].

However, angiotensin II receptors have been found on isolated proximal tubular cells and may enhance proximal tubular sodium reabsorption in the rat kidney [53]. Angiotensin II does decrease glomerular capillary permeability [77], probably by constricting mesangial cells and decreasing glomerular capillary surface area. In addition, increased renal sympathetic efferent nerve activity leads to increased secretion of renin and prostaglandins which is mediated by renal beta-1 receptors [83].

Evidence for an increase in sympathetic activity in man comes from data by Nicholls et al [78]. Elevated concentration of plasma norepinephrine were found in decompensated cirrhosis. These were not due to decreased clearance secondary to a diseased liver, but were associated with increased secretion. These high levels of norepinephrine were found to correlate with sodium and water retention by Bichet [17].

Epstein et al [34] were unable to reproduce these results, but he included patients with cirrhosis who excreted a water load normally, and, therefore, no pathologic state existed. Thus, is seems norepinephrine is important in so-called «non-excretor» cirrhotic patients.

Norepinephrine may at least partially exert its effect on sodium and water retention by reducing renal blood flow. Basal renal blood flow by radioactive xenon washout was less in cirrhotics versus normals [91]. Moreover, six normals had renal blood flow by radioactive xenon washout greater than 3.0 ml/min/g and peripheral plasma norepinephrine of 0.3 ng/ml; whereas, 24 cirrhotics with ascites and edema had renal blood flow 1.0-3.0 ml/min/g with norepinephrine of 0.2-2.0 ng/ml. Mean renal blood flow correlated inversely with norepinephrine [90]. If norepinephrine is exerting its effort on urinary sodium and water excretion by increased renal vascular resistance, thereby decreasing renal blood flow, it might be expected that renal vasodilatation would reverse this process [199].

Indeed, dihydroergocistine (an alpha-adrenergic antagonist) infused into the renal artery increased renal blood by radioactive xenon washout from 1.53 to 1.73

ml/min/gm (normal range 4.53 ± 0.97) without changing arterial pressure. These increases in urine flow rate as well as sodium and chloride excretion were were not larger, possibly due to a 13 % reduction in inulin clearance [45]. Intrarenal phentolamine has been given and was found not to increase renal blood flow in cirrhotics, but the majority had significant decreases in blood pressure [34].

The objection has been raised that assessment of increased systemic or regional sympatho-adrenergic activity is difficult when based on peripheral plasma norepinephrine [20,43,54]. However, in an elegant series of experiments this problem has been addressed. In the nonstimulated, innervated dog kidney renal vein norepinephrine is equal to or slightly greater than arterial blood [7,82]. Similiarly, in the nonstimulated, innervated human kidney the renal vein norepinephrine is equal to or slightly greater than arterial blood [73].

However, in 10 cirrhotic patients mean renal vein norepinephrine was 0.63 versus 0.47 ng/ml in arterial blood. Peripheral plasma norepinephrine in cirrhotics was greater than normals, and this increase was not due to decreased hepatic extraction. Peripheral plasma norepinephrine correlated with wedged hepatic venous pressure [91]. Using radioisotopes, both total norepinephrine release (1141 ng/min versus 399 ng/min) and renal norepinephrine release (305 versus 77 have been shown to be increased in decompensated cirrhotics versus normals [40].

Furthermore, when renal sympathetic efferent nerve activity is zero in the denervated kidney, renal vein norepinephrine is less than arterial blood [58]. With graded electrical stimulation of the renal nerves over the frequency range of 0.5 to 18 Hz, both the renal venoarterial norepinephrine difference and the renal norepinephrine secretion increased in a frequency dependent fashion [58,76]. Similar findings have been observed with baroreflex-mediated changes in renal sympathetic efferent nerve activity in the rat [76].

Evidence for Dysfunctional Response to Sympathetic Stimulation in Cirrhosis

In addition to elevated levels of norepinephrine, there is a dysfunctional response to sympathetic stimulation. A blunted pressor response to infused norepinephrine has been noted in the bile duct ligated dogs [41]. A blunted pressor response to infused norepinephrine and angiotensin II has also been observed in cirrhotics [1]. However, infusions of metaraminol have been successfully used to overcome the decreased sympathetic vascular resistance seen in cirrhosis, thereby increasing sodium and water excretion [50]. Moreover, some cirrhotics have been shown an extreme sensitivity to phentolamine [34].

Cardiovascular responsiveness to reflex autonomic stimulation may be impaired in cirrhotics including decreased vasoconstrictive response to ice on the forehead, mental arithmetic, negative lower body pressure, and the Valsalva maneuver [72]. This widespread interference in the peripheral and central autonomic nervous system in cirrhosis could be explained partially by increased catecholamine receptor occupancy [11].

In contrast, however, in advanced cirrhosis, when patients' blood pressure is decreased, there is a blunted pressor response to tyramine and a supranormal pressor response to exogenous norepinephrine [74] suggesting depletion of catecholamines resembling that seen after reserpine, guanethedine [47], or patients with autonomic failure [107].

A false neurotransmitter hypothesis has also been advanced to explain the autonomic changes. Precursors of false neurotransmitters are produced in the bowel by the bacterial degradation of protein. These are usually cleared by the healthy liver, mainly by monoamine oxidase. In cirrhosis, the false neurotransmitters bypass the liver and enter the nervous system where they are degraded locally by beta-hydroxylation. In the central nervous system, they may replace normal neurotransmitters, thereby disrupting normal synaptic transmission. This would explain autonomic dysfunction, hepatic coma including extrapyramidal changes as well as peripheral vasodilatation [42,60].

In summary, cirrhotics and animals with experimental liver damage have widespread central and peripheral autonomic dysfunction which may contribute to the peripheral vasodilatation of cirrhosis. Increased adrenergic tone and plasma catecholamines in advanced cirrhosis may increase renal vasoconstriction and renal sodium and water retention. False neurotransmitters may contribute to autonomic dysfunction, but probably don't dominate in the kidney since they would be expected to cause renal vasodilatation [11].

Role of AVP

Patients with cirrhosis with ascites or peripheral edema exhibit impaired water excretion; however, patients without ascites or edema excrete water normally [16,31,57]. Hyponatremia is a marker of abnormal water metabolism and frequently complicates the clinical course of patients with cirrhosis [6,11,16,57,87,88,104].

The pathogenesis of this impairment in water metabolism is controversial. Three mechanisms have been proposed: intrarenal factors such as decreased delivery of filtrate to the diluting segments of the nephron, enhanced nonAVP- mediated back diffusion of water in the distal nephron, and increased AVP activity.

Furosemide can improve free water clearance in cirrhosis which supports a role for decreased distal delivery in the pathogenesis of cirrhosis. Moreover, the free water clearance induced by furosemide was unaffected by infusion of AVP which supports an intrarenal mechanism in cirrhosis [96]. However,

furosemide may also block the renal effect of AVP [101]. It is, however, difficult to test the role of decreased distal delivery in cirrhosis because maneuvers which expand the intravascular volume and increase distal delivery also suppress AVP release [13].

The next mechanism proposed for impaired water excretion is enhanced nonAVP-mediated back diffusion of water [104]. It is proposed that when tubular flow rate is low, water exits the distal nephron approaching osmotic equilibrium with the papillary interstitium even in the absence of AVP. It is unclear of this mechanism is important in the impaired water excretion of cirrhosis, because it is difficult to evaluate.

The possible mechanisms for increased AVP activity in liver disease include: a reset osmostat, decreased metabolic degradation, enhanced tubular sensitivity, and increased release of AVP.

A reset osmostat is suggested by data of Earley and Sanders [30] who studied 6 patients with decompensated cirrhosis and hypoosmolality. Their serum osmolalities were manipulated with hypertonic saline and they demonstrated that AVP release responded quantitatively in a normal fashion about a lower serum osmolality. However, these patients may have responded to non-osmotic factors which caused the release of AVP.

Abnormalities in AVP clearance in patients with liver disease is controversial; some investigators have found normal clearance [100,106] and others have found decreased clearance [3,99]. Thus far, no evidence has been published which supports enhanced tubular sensitivity of the distal nephron to AVP in cirrhosis.

Evidence that increased release of AVP occurs in cirrhosis comes from a number of sources. Before a sensitive assay for AVP became available, there was suggestive evidence that AVP levels were elevated in cirrhosis. Strauss et al [100] showed that ethanol ingestion increased flow and decreased urine osmolality in decompensated cirrhotic patients with normal glomerular filtration rate. This was interpreted as an effect of ethanol to inhibit the release of AVP.

With the sensitive radioimmunoassay for AVP now available most investigators report elevated levels in cirrhosis [104]. In two recent studies we have demonstrated inappropriately elevated AVP levels relative to plasma osmolality in decompensated hyponatremic cirrhotic patients [16,17]. 26 patients were studied with a standard water load of 20 ml/kg, hormone profiles, and evaluation of renal function by inulin and para-aminohippuric acid clearances. They segregated into 2 groups: 7 patients had a normal water load excretion (i.e. greater than 80 %, mean 82.4±0.8 %), and 19 patients were «non-excretors» with less than 80 % excretion and a mean excretion of 29.0±3.4 %. The «non-excretors» were found to have higher urinary osmolality, lower basal serum sodium, and lower serum osmolality as compared to «excretor» patients. Other characteristics of the «non-excretors» were a significantly lower serum albumin, higher plasma renin activity, plasma aldosterone, and norepinephrine levels.

The release of AVP in spite of hypoosmolality suggests enhanced secretion in response to nonosmotic stimuli. The stimulus for AVP release as suggested by our data [13,16] and data provided by Epstein [92] seems to be a decrease in effective blood volume in decompensated cirrhosis. This may explain the elevated plasma renin activity, plasma aldosterone, and norepinephrine which we observed.

We have tested this hypothesis that central volume depletion stimulates AVP release by using head-out-water immersion to increase central blood volume in eight «non-excretor» cirrhotic patients [13]. Systemic hemodynamics were assessed by Swan-Ganz catheter. Head-out water immersion resulted in increased cardiac index, right atrial pressure, and pulmonary wedge pressure; and decreased systemic vascular resistance. There was a significant decrease in plasma renin activity, plasma aldosterone, norepinephrine, and AVP with head-out water immersion. In another study, we were able to completely reverse the abnormal water and sodium excretion of cirrhotic patients by the combination of head-out water immersion and norepinephrine infusion in 6 patients [97]. Head-out water immersion or norepinephrine alone caused only a modest increase in natriuresis and water excretion. These results suggest there may be a resetting of the baroreceptor response in cirrhosis, i.e. a reset «barostat».

In contradistinction to our results, in a recent report involving head-out water immersion, the investigators were unable to demonstrate a consistent suppression of AVP in cirrhosis [39] which may have been due to the heterogeneity of the cirrhotic population which they examined. In a previous study by the same group [37] an increase in free water excretion was demonstrated during head-out water immersion, unfortunately AVP levels were not measured.

In conclusion, experimental and clinical data suggest AVP plays a major role in the abnormal water metabolism of cirrhosis.

Prognosis and Treatment

We recently found a subgroup of «non-excretor» cirrhotic patients with a water load excretion less than 20 %, mean 12.9±1.2 % with a very poor prognosis [24]. In agreement with Bosch [19] and Arroyo's data [4], who found that cirrhotic patients with activation of the renin-angiotensin-aldosterone system have a poor prognosis, this subgroup also had activation of the renin-angiotensin-aldosterone system as well as elevated levels of norepinephrine and AVP.

We, therefore, propose a new classification of cirrhosis based on the work done in our center that has prognostic and possibly therapeutic importance. Class zero would be patients with early changes of cirrhosis on liver biopsy

who have not yet developed clinical stigmata of liver disease.

Class I would have a water load excretion greater than 80 % and essentially normal physiology. They are distinguished by the stigmata of cirrhosis, although only 2 of 7 were found to have ascites [17].

Class II would have a water load excretion from 20-80 %. We found 8 patients who fit in this group with a mean water load excretion of 40.2±4.7 % [24]. Their prognosis is good, if they avoid ethanol.

Class III has a water load excretion less than 20 %, with a mean of 12.9±1.2 % [24]. Only one patient lived longer than five months, and he is still alive at 26 months. He received a LeVeen shunt which converted his water load excretion to 100 %. The poor prognosis of Class III cluld be disassociated from continued ethanol use as only one of seven in Class III versus four of eight in Class II continued ethanol use. In view of their bleak prognosis with medical therapy alone, an intervention such as LaVeen shunt should be considered. This needs to be evaluated prospectively.

Class IV consists of those patients with the hepatorenal syndrome. We are studying correction of this pathophysiologic state by administration of colloid combined with pressor agents.

Thus, we have established cirrhotic patient profiles based on water load excretion and hormone levels which are helpful prognostically and may help guide therapy in the future.

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