EDITORIALES

The impairment of sodium excretion in cirrhosis of the liver

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Advanced cirrhosis of the liver is associated with a significant derangement of hepatic architecture. These disturbances, evolving slowly over the years and consisting largely of areas of necrosis and fibrosis, as well as regenerative nodules, eventually produce a significant obstruction to hepatic venous outflow. To understand the role played by this partial hepatic venous outflow block in the impaired urinary excretion of sodium which appears in advanced cirrhosis, the following features of liver morphology and physiology should be considered.

1. The hepatosplanchnic circulation receives a considerable (about 25 %) portion of the cardiac output which must be directed through the hepatic veins before it can again reach the systemic circulation. Any significant degree of hepatic venous outflow block, will of necessity, influence the possible sequestration of blood and fluid balance over a considerable vascular territory.

2. Because approximately 60-65 % of the blood supply to the liver arrives there through the low pressure portal venous circuit, the resistance to flow through the hepatic sinusoids is very low, with the pressure drop across the liver between the hepatic and portal veins being very small. The implication is that the pre-sinusoidal: post sinusoidal resistance ratio for the arterial inflow must be very high. This in fact turns out to be so (50 to 1 for the liver versus 4 to 1 for other organs) and given the great degree of permeability of the sinusoids to albumin, means that increments in hepatic venous pressure, are virtually the only[3] mechanism whereby the trans-sinusoidal distribution of fluid can be influenced [1]. Thus, the hepatic formation of lymph is exquisitely dependent upon increments in outflow venous pressure and it can be demonstrated experimentally that for every millimeter of mercury rise in hepatic venous pressure, hepatic lymph flow will increase by some 63 % [2].

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3. Lymph normally derived from the hepatic sinusoid will be carried away either by the regional lymphatics and thoracic duct, or will percolate across the hepatic capsule into the peritoneal space, where the fluid will be reabsorbed by the sub-diaphragmatic lymphatics. Both the thoracic duct and the peritoneal cavity are capable of handling large amounts of lymph. Although the lymph flow through the thoracic duct is normally 800 to 1000 ml per day, in cirrhotic patients this value may rise as high as 20 litres per day. In addition, the extreme capacity of the peritoneal compartment (easily 25 to 30 litres), implies that a great deal of hepatic lymph can be formed before it may clinically appear as edema or ascites [3].

4. The sustained increment in intrahepatic pressure which may occur subsequent to partial hepatic venous outflow block will eventually be transmitted to the portal venous system where the classical response to a venous obstruction occurs ie. a rise in venous pressure, the formation of collateral vessels, and the formation of large amounts of lymph. Thus, the holding capacity of the splanchnic venous circulation will increase dramatically and the arterial blood volume will be gradually transferred to this capacious vascular territory. It is worth emphasizing at this point, that 75 % of the splanchnic circulation is normally held within the venous vessels. As the holding capacity of the splanchnic venous circulation dramatically increases, this must provide a salt retaining stimulus to the renal tubule in order to maintain the ratio of total plasma volume to total vascular holding capacity. If this did not occur, there would be a drop in venous return and therefore cardiac output.

5. The intrahepatic perisinusoidal area is richly innervated. The normally small pressures which exist in these channels, and the fact that 100 % of any increase in venous pressure is transmitted back to these sinusoids, makes them ideally situated to act as low pressure baroreceptors. Indeed, Kostreva and his colleagues [4] as well as other investigators [5], have shown that such baroreceptors exist in the dog and other animal species, and furthermore are capable of, when activated, of simultaneously sending efferent sympathetic discharges to the kidney.

The implication of these unique features of the liver, is that a period of urinary sodium retention must occur in

the cirrhotic patient as his disease is evolving and prior to the appearance of ascites. Such retention of sodium is mandated by the consequences of hepatic venous outflow block and must occur in order to keep central venous return, and therefore cardiac output at some reasonable physiological level. The larger question might be: is there any other cause for urinary sodium retention in the cirrhotic patient during the pre-ascitic phase, and if so, what are the mechanisms?

Conventional explanations for the impaired sodium excretion that is commonly observed in the patient with advanced alcoholic cirrhosis of the liver have tended to ignore the mandatory demands placed on the renal tubule by the sequence of events outlined above. Remembering that the alcoholic cirrhotic liver may evolve it's full spectrum of pathological disturbances over many years, or indeed decades, it is clear that the gradual increase in portal venous pressure with the subsequent augmentation of its holding capacity will be an important cause for the urinary retention of sodium. Indeed, it has commonly been observed that patients early on in the course of cirrhosis may have significant expansions of the plasma volume. There is nothing magical about the cirrhotic liver in this process, it is simply a mechanical response to a gradual increase in the venous reservoir of the splanchnic circulation. Indeed, patients who have non-cirrhotic and extrahepatic portal venous obstruction for a variety of causes, are also seen to have significant expansion of the plasma volume [6].

The conventional view has been that the disturbed Starling forces in the hepatoportal circuit will eventually cause the accumulation of ascites and the subsequent contraction of the arterial blood volume will cause the kidneys to retain sodium. It is clear however, that there must be a prolonged preascitic phase, where there must be extensive renal retention of sodium simply to keep the splanchnic lymph will be easily handled by the ability of the thoracic duct to handle increased lymph flows, as well as the fact that the peritoneal compartment can process large volumes of lymphatic effluent before ascites actively accumulates.

If the gradual sodium retention over the years (so gradual that it probably cannot be significantly measured), were simply occuring to fill up an expanded venous reservoir, one would not expect to find suppression of the plasma levels of renin and aldosterone. Yet at least three groups of investigators [7-9] have demonstrated that early on in the course of cirrhosis in the preascitic phase, this is exactly what happens. Moreover as the volume of ascites increases with corresponding decrement of the effective arterial blood volume, the plasma levels of renin and aldosterone begin to rise and are highest in those patients bearing large volumes of ascites and where there is sufficient arterial hypovolemia to produce pre-renal azotemia [9]. This sequence of events suggests that the circulating plasma volumes becomes expanded or «overfilled» during the earliest phases of cirrhosis, and that ascites forms as an «overflow» phenomenon because of this feature and disturbed Starling forces within the hepatoportal compartment. As ascites accumulates in significant quantity, the vascular compartment becomes «underfilled». But what factors, unrelated to extracellular fluid volume considerations could initiate the renal retention of sodium early in the cirrhotic process? My associates and I have adduced evidence that an intrahepatic factor, unrelated to the volume status of the circulation may be the cause for this secondary sodium retention [10-14]. Working with canine models of cirrhosis (both portal and biliary) we have demonstrated that sodium retention in the cirrhotic dog and the formation of ascites will be present even when there is a end-to-side portocaval fistula preventing the rise of portal venous pressure, and the sequestration of blood within the splanchnic circulation. This implies, that sodium retention and plasma volume expansion is a derivative of disturbances to the liver itself. We have also demonstrated that sodium retention and plasma volume expansion precedes any change to cardiac output or peripheral vascular resistance [15]. Since these two variables are the determinants, both in terms of filling and emptying, of the so called effective arterial blood volume, it is clear that the sodium retention precedes in the absence of any compromise to this hypothetical but significant blood volume.

Our laboratory has also demonstrated for dogs, and other workers have demonstrated for the human cirrhotic [16], that if ascites is mobilized completely with a LeVeen peritoneovenous valve resulting in normalization of the arterial blood volume, such that cardiac output rises and plasma levels of renin and aldosterone fall to normal values, that both cirrhotic dog and man cannot normally handle urinary sodium under these circumstances. This also implies that there is some intrahepatic cause for sodium retention independent of volume or circulatory considerations.

To determine what this might be, our laboratory recently published studies in a canine model of cirrhosis where there was a side-to-side porta-caval anastomosis [14]. This experimental manipulation normalizes pressure within the liver and the entire portal circuit thus preventing the formation of lymph in both liver and from splanchnic capillaries and preventing the formation of ascites. As well, by nature of the fistula, the sequestration of blood within the portal circuit is prevented. This leaves us essentially with a model where only a «sick» cirrhotic liver and its metabolic consequences could be a stimulus for the urinary retention of sodium. In such animals, followed sequentially over a two to three month period, no such urinary sodium retention appeared. We have concluded from these experiments, that intrahepatic hypertension is a important determinant for urinary sodium retention. We have recently confirmed these observations in dogs, in

the presence of low grade supradiaphragmatic caval constriction, where intrahepatic pressure was elevated just enough to increase portal venous pressure, but insufficient to cause ascites [17]. Under these circumstance sodium retention could be demonstrated and this was abolished in the presence of hepatic dennervation.

A summary of the factors disturbing sodium excretion in the cirrhotic patient is shown in Figure 1.

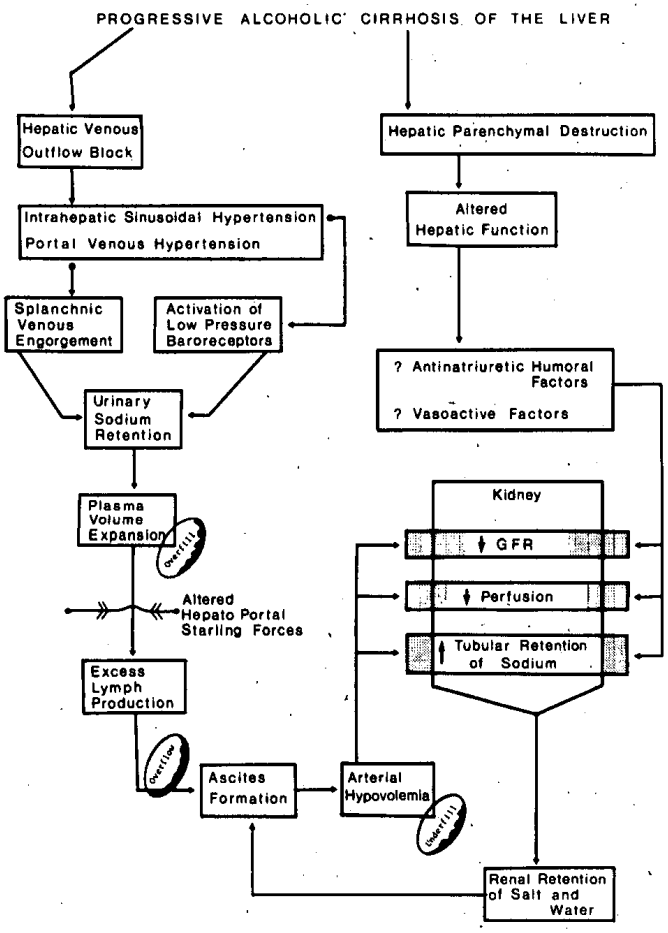

Fig. 1.—*Factors thought to be important in causing urinary sodium retention in the cirrhotic patient.*

SUMMARY

I believe that the traditional linkage of urinary sodium retention to ascites formation through arterial underfilling is an oversimplification of the pathophysiology of ascites formation. First, à priori considerations would dictate that there must be a period of relative sodium retention occurring early on in the cirrhotic process merely to replenish a gradually increasing splanchnic venous reservoir. This sequence of events would easily lead to the expansion of the plasma volume so generally seen in cirrhotic patients and in fact in patients with extrahepatic portal obstruction as well. However, if this were all that was occurring, one would not expect suppression of the plasma renin and aldosterone levels to below normal values. That this occurs, suggests that in the absence of any identifiable intrarenal cause, that there is an expansion of the plasma volume greater than what could be accounted for by a requirement simply to fill up the splanchnic venous reservoir. We have suggested, based on experiments with a canine model of cirrhosis that the activation of intrahepatic baroreceptors may cause the tubular retention of sodium independent of any volume requirements. This would gradually lead to an expanded plasma volume which, as well, might also explain the reduction in peripheral vascular resistance and increased cardiac output commonly observed in the cirrhotic patient. The continuous retention of sodium for this reason would cause significant plasma volume expansion. We would now have a situation where there was marked overfilling and marked expansion of the arterial blood volume in a pathophysiological setting where Starling forces over a wide vascular territory are becoming progressively disturbed. The eventual encounter between the overfilled plasma volume and these disturbed Starling forces would eventually cause ascites to overflow. The numerous observations by my laboratory in dogs, and as well several other laboratories in cirrhotic rats [18, 19, 20], supports the point of view that ascites forms by this overflow phenomenon. Once ascites begins to form, we then have an «emptying» phenomenon with regards to vascular fullness since fluid is now leaving the vascular space faster than it can return. We now enter a state of relative underfilling where there is gradual reduction in the blood volume even as ascites slowly begins to accumulate. Indeed, there is good evidence to show that as time passes the progress of the cirrhotic picture is associated with progressive hypovolemia and that as such hypovolemia develops it is associated not only with prerenal azotemia but with the eventual elevation of plasma levels of renin and aldosterone, ADH and catecholamines. While the plasma level of noradrenaline in the cirrhotic patient without ascites is normal, the highest values ever recorded have been observed in cirrhotic patients with ascites; particularly those that have been treated with diuretics [21].

Once a state of relative underfilling has been achieved, the determinants of sodium retention are different then what they were previously. Now there are many factors leading to underfilling of the vascular compartment. These include the continuous formation of ascites, the entrapment of blood and edema in the lower extremities, the continuous bleeding from the gastrointestinal mucosa, the possible bleeding from varices, the abuse of diuretics, the frequent occurrence of vomiting and diarrhea in alcoholic patients - all this coupled with a reduced salt intake. Patients therefore are poised to become hypovolemic, yet find it difficult to replenish the vascular compartment because it is difficult for ascites to be mobilized into the splanchnic capillaries (the only area where such fluid can move into). At this point in time the impaired sodium excretion is due directly to arterial hypovolemia and is mediated at least in part by the increased levels of aldosterone, catecholamines and perhaps other disturbances as well

such as a reduced intrarenal production of natriuretic prostaglandins.

Table 1 summarizes some of the evidence supporting this biphasic relationship between sodium retention and the magnitude of the circulating plasma volume. For a review of this controversial (but important) area, the reader is encouraged to read References 3 and 22.

TABLE I

EVIDENCE SUPPORTING AN INITIAL INCREMENT THAN A GRADUAL REDUCTION IN PLASMA VOLUME DURING EVOLUTION OF THE CIRRHOTIC PROCESS

1. Plasma volumes invariably elevated in cirrhotic patients (and those with extrahepatic portal obstruction) in «early» phases of disease. Such elevation may be associated with suppressed plasma levels of renin and aldosterone (markers for fullness of the circulation).
2. Progress of liver disease is marked by third space fluid sequestration (ascites), and a decrement in circulating plasma volume.
3. The progressive reduction in plasma volume is accompanied by a progressive rise in the circulating levels of renin, aldosterone, vasopressin and catecholamines.
4. The progressive reduction in plasma volume is also accompanied by azotemia and/or a reduction in GFR —presumably due to the contraction of the effective blood volume.
5. Patients and animals with cirrhosis but with normal systemic hemodynamics and suppressed levels of plasma aldosterone (due to mobilized ascites with LeVeen Valve) i.e. no third space will still retain urinary sodium, demonstrating non-volume related causes for sodium retention capable of causing plasma volume expansion.

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