Pathophysiological Basis Of Ascites In Cirrhosis

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Ascites, the excessive accumulation of fluid in the peritoneal cavity, constitutes one of the commonest and most serious manifestations of cirrhosis. The probable mechanisms whereby the cirrhotic liver gives rise to this clinical phenomenon, as far as our present state of knowledge is concerned, consist of four inter-related factors;

They are:
1. Portal Hypertension.
2. Decreased Plasma Colloid Osmotic Pressure.
3. Increased Hepatic Lymph Flow.
4. Sodium and Water Retention.

To deal first with *portal hypertension*, there is much to suggest that it alone cannot produce ascites. I shall refer here to a paper published by Hans Krook in 1956 from Department of Medicine at the University of Lund and Malmo Hospital, Sweden. The study consisted of 67 cases of liver cirrhosis treated at Malmo General Hospital, 1951-55. The cirrhotic group was compared with 35 controls and 38 cases of other liver disease.

In this study normal portal pressure as established by Wedged Hepatic Vein (W.H.V.P.) pressure proved to be 10 mm. of Hg. or less (range 2-10). Ascites was found to be most common at W.H.V.P. of 18 mm. Hg. or more. Yet, of 49 cases of cirrhosis showing W.H.V.P. of this level or higher 27 were free from ascites and six of these had W.H.V.P. of 25 mm. Hg. or more.

Hence it may be said that portal hypertension alone does not cause ascites.

Further support was furnished by Guindlay and Bollman in 1950 when experimental occlusion of the portal vein in dogs was not followed by ascites unless the dogs were rendered hypoproteinemic by plasmaphoresis, which time ascites would develop

On the other hand, however, reducing portal hypertension by porta-caval shunt frequently relieves ascites in cirrhotic patients despite the persistence of hypoalbuminemia. Also, hypoalbuminemia alone may result in generalized edema but not specifically located in the peritoneal cavity.

Thus we may conclude that while portal hypertension does not act alone in production of ascites in cirrhosis, it is one of the major factors. I will elaborate further on this when I discuss the relationship of hypoalbuminemia to ascites in cirrhosis.

With regard to the cause of portal hypertension in cirrhosis, there still exists some controversy. The earliest explanation was obstruction to portal flow caused by partial obliteration and distortion of the vascular bed by fibrosis and regenerating nodules. Another widely accepted school of thought to explain the phenomenon of portal hypertension, is the shunting of blood under pressure directly from the hepatic arterioles into the portal venules.

The decreased hepatic vascular bed in cirrhosis can be demonstrated by pressure studies and hepatic blood flow studies.

Hepatic blood flow studies in the cirrhotic liver have been performed for several years using the injection technique. As we know, blood flowing into the normal liver follows two routes, the portal vein and hepatic artery. Blood from both enters individual sinusoids in the liver lobules and the sinusoids are then drained via the hepatic vein. Since the sinusoids also communicate with one another, there are at the sinusoidal level arteriovenous anastomoses. It has been demonstrated anatomically that arterio-portal communications also occur pre-sinusodidally in the vascular plexus surrounding the bile ducts.

Hepatic blood flow studies by the injection method performed by MacIndoe in 1928 on cirrhotic livers showed a pronounced decrease in the total vascular bed. The main branches of the portal vein were irregularly stenosed and the finer branches were extremly tortous and merged into a network of shrunken venules from which terminal branches were given off in an irregular arrangement. Similar changes were seen in the hepatic vein and to a lesser extent in the hepatic artery. In more advanced cases of cirrhosis the vessels of the liver tended to disappear, first the readily compressed veins and then the arteries.

Hence we may conclude that in cirrhosis blood entering the liver via the portal vein and hepatic artery encounters a markedly contracted vascular bed. The hepatic artery being less subject to the changes just described delivers blood into a smaller space than normal and hence increases the pressure in this space. Thus there is an increase in intrasinusoidal pressure. Furthermore the changes outlined in the hepatic vein by injection studies suggest that there is increase resistance to outflow from the sinusoids. This too then would further increase the intrasinusoidal pressure. Finally, blood in the portal vein by virtue of flowing into a contracted vascular bed plus the increased pressure in the sinusoids caused by the two previously mentioned factors reach great heights, the blood flow in the portal vein may actually reverse. This would and does move under increased pressure. Should the intrasinusoidal pressure reversal is by no means a rare finding in cirrhosis.

In recent years advancement in methods of indirectly estimating portal pressure has led to further study of portal hypertension in cirrhosis. Thus by advancing a catheter into the hepatic vein until it has occluded the lumen, one obtains the wedged hepatic vein pressure which represents the pressure of a static column of blood from the sinusoids and hence is a measure of intrasinusoidal pressure. It is found to range

in normal individuals from 2-10 mm. Hg. and correlates remarkably well with portal pressure taken at open surgery. Other methods involve the measure of pressure in collaterals and intrasplenic pressure.

In cirrhotic patients the value of the W.H.V.P. is virtually always increased. The cause for the increase must be either increased blood flow into the sinusoid, obstructed flow from the sinusoid or compression of the sinusoid or a mixture of these mechanisms.

In a recent study done on Hemodynamic Changes in Cirrhosis by Warren and Muller of Virginia, they concluded that since hepatic blood flow in cirrhosis was either normal or diminished (usually the latter), then the chief factor in production of increased intrasinusoidal pressure was obstruction to outflow. I feel, however, that since as shown by blood flow studies, which I have mentioned earlier, that the hepatic vascular bed is decreased in cirrhosis, and since the hepatic artery is not severely affected by the process as are more compressible structures, then even with decreased flow via the hepatic artery the vascular bed into which it flows is decreased to a greater degree and hence it can still play a very significant role in production of increased intrasinusoidal pressure, hence, the main causes for increased intrasinusoidal pressure are blood from the hepatic artery flowing into a contracted vascular bed and increased resistance to outflow from the sinusoid, mainly the former mechanism.

Another theory offered to explained increased portal pressure in cirrhosis is the development of shunts between branches of the hepatic artery and portal veins in the peribiliary vascular plexus in the portal area. Such shunts could result in arterial blood under high pressure passing directly into the portal veins, thus leading to portal hypertension. Such pre-sinusoidal arteriovenous shunts have been demonstrated by injection technique by MacIndoe and other workers and hence their existence proven.

However, their significance in production of portal hypertension is another matter. If they are significant, then one would expect that after side to side porta-caval shunt resulting in return of portal pressure to normal, the arteriovenous fistulae would pour blood into the portal venous system to be shunted through the porta-caval anastomosis and completely by-pass the liver. If there is remarkable blood loss in this way, it should be manifested by a markedly increased O_2 saturation in the portal vein and by a diminished O_2 saturation in the hepatic vein due to diminished perfusion volume to the sinusoids.

In O_2 saturation studies conducted by Warren and Muller following side-to-side porta-caval shunt, they found that:—

1. Blood leaving the liver via the portal vein was distinctly venous in character although showing higher O_2 saturation than blood in the hepatic vein.
2. O_2 saturation in the hepatic vein following side-to-side shunt was normal.

They concluded from this, even though realizing the small number of cases, that serious doubt is raised as to the significance of presinusodial arteriovenous shunts in production of portal hypertension in cirrhosis. Whether these doubts prove to be true must then await more experimental evidence.

It would appear then that the main cause for portal hypertension in cirrhosis is basically fibrosis and regenerating nodules in the portal areas and to lesser degree in the sinusoidal areas. These changes lead to contraction of the vascular bed affecting first the more compressible areas - veins and sinusoids and to a lesser extent the more resistant vascular structures - arteries. Thus in effect, in the cirrhotic liver blood in the hepatic arteries empties into a markedly contracted vascular bed and this plus obstruction to flow from the vascular bed by constricted hepatic veins leads to increased

intrasinusoidal pressure. Increased intrasinusoidal pressure plus constriction and tortuosity of the portal veins leads to markedly increased portal pressure. Whether presinusoidal shunts significantly aggravate the process remains to be seen.

Decreased Plasma Colloid Osmotic Pressure.

The second factor felt to be of significance in the production of ascites in cirrhosis is *hypoproteinemia.* The hypoproteinemia is due mainly to a decrease in serum albumin resulting from impaired production of this protein fraction by the diseased liver. The normal value for serum albumin is 4-5 gm./100ml. with slight variation, depending on methods of measurement in different centers.

In the study reported by Hans Krook which I have referred to earlier, he found that serum albumin was abnormally low in 81 *%of the cases studied* and was on the average 3.31 gm.%. In cases with ascites the serum albumin was 2.51 gm.% (range 1.65 - 3.67 gm.%) as against 3.72 gm.% in cases without ascites (range 2.4 - 5.22 gm.%). The difference was highly significant.

Many investigators in the past few years have felt that the level of albumin below which ascites would develop is less than 3.0 gm.% (ascites threshold). As we look at the figures just mentioned however, we see two things:—

1. Ascites did in fact develop in some cases with serum albumin levels as high as 3.67 gm.% (0.67 above threshold).
2. In some cases with serum albumin as low as 2.4 gm.% ascites did not develop (0.6 gm.% below threshold). Hence we must conclude that ascites formation does not depend on low serum albumin alone.

For several years it was thus felt that ascites formation depended on an interrelation between portal pressure and serum albumin rather than either alone. Because of difficulty in obtaining portal pressure this was hard to demonstrate. However, with modern methods of measuring portal pressure by hepatic vein catheterization, this principle can be demonstrated.

Thus, in Krook's series, 5 of the cases of ascites had a serum albumin above the ascites threshold, the highest value being 3.7 gm.%. All of these patients, however, had pronounced portal hypertension with a W.H.V.P. of 24-34 mm. Hg. (normal W.H.V.P. 2-10 mm. Hg.). On the other hand some patients had ascites despite fairly moderate portal hypertension - thus 4 patients with ascites had a W.H.V.P. below 19 m.m. Hg., but here the serum albumin was very low (2-2.5 gm.%). Three cases with no ascites had serum albumin of 2.4-2.8 gm.% (considerably below threshold) but in these the portal pressure was only slightly increased. Finally in no case where serum albumin was normal (greater than 4 gm.%.) was ascites demonstrated.

Therefore ascites does not depend on either portal hypertension or hypoalbuminemia alone but rather on an inter-relation between the two. With pronounced portal hypertension and slight hypoaluminemia ascites may develop; or with slight portal hypertension and pronounced hypoalbuminemia ascites may develop; or finally with moderate portal hypertension (above 18 mm. Hg.) and moderate hypoalbuminemia (below 3 gm.%) ascites may develop.

Increased Hepatic Lymph Flow

This brings us to the third possible mechanism in the production of ascites in cirrhosis, namely *increased hepatic lympatic flow.* It is postulated that obstruction of the hepatic veins within the cirrhotic liver leads to increased intrasinusoidal pressure with consequent spilling over into the lymphoid system and extravasation of protein rich lymph from the surface of the liver. As we have seen earlier, increased intrasinusoidal pressure can be due to more than obstructed hepatic outflow, namely arterial inflow and contracted sinusoidal space. Nevertheless, we do know that regardless of

mechanism in cirrhosis, intrasinusoidal pressure is increased. Hence increased hepatic lymph flow seems reasonable.

This increased flow has in fact been demonstrated and the fluid was collected directly from the surface of the liver for analysis. Such analysis showed that the fluid had a high protein content as did liver lymph. Ascitic fluid from cirrhotic patients however shows a much lower protein concentration. The discrepancy is explained by suspected dilution of the hepatic filtrate by transudation of water and electrolyte from extracellular tissue spaces.

In a recent paper published by Welch, Welch and Carter from the Department of Surgery, Albany, Medical College of Union University, they expressed their feeling that the major factor in ascites production was increased lymphatic flow with extravasation of lymph through the liver capsule. They felt that portal hypertension and hypoalbuminemia were contributory but only secondary since each may be seen without ascites.

As we have seen eariler however from Krook's study, it was the inter-relation between portal pressure and hypoalbuminemia which was significant in ascites production, and neither by itself. Hence, I feel that hypoalbuminemia and portal hypertension are major factors in ascites production. The significance of increased hepatic lymph flow, however, must not be overlooked.

The final factor felt to play a role in ascites of cirrhosis is *sodium and water retention.* Thus in cirrhosis with ascites, patients excrete only a small proportion of the ingested sodium. This low sodium excretion is found in urine, perspiration, saliva and feces. Hence it is a general phenomenon and not due to local causes in the kidney.

Despite diminished excretion the serum sodium is found to be normal or low, more frequently the latter. The total body sodium is however increased.

The case for salt retention is by no means certain at the present time. On the one hand it has been assumed that fluid and electrolyte disturbances in association with the formation of ascites stimulates increased production of aldosterone by the adrenal cortex and antidiuretic hormone by the pituitary. On the other hand, it has been assumed that these disorders are a result of decreased destruction of the respective hormones in the cirrhotic liver.

To deal first with antidiuretic hormone (A.D.H.), its significance in cirrhosis and ascites continues to be challenged. Hence many workers have failed to demonstrate any increase in A.D.H. in the serum and urine of patients with cirrhosis and ascites. White in 1951 and Miller in 1954 could not find any definite difference between the capicity of normal and cirrhotic livers to metabolize A.D.H. Therefore, the significance, if any, of A.D.H. in ascites must await further study.

With aldosterone the story is somewhat different. It has been demonstrated and repeatedly confirmed that patients with cirrhosis and ascites, excrete in their urine large quantities of aldosterone. Patients with cirrhosis but without ascites, however, do not demonstrate this increase. Furthermore, it has recently been demonstrated that the rate of aldosterone secretion by the adrenal cortex over a 24-hour period is distinctly elevated above normal in patients with cirrhosis and ascites. Aldosterone levels in the plasma are similarly increased above normal in these patients.

The question therefore arises as to whether the increased aldosterone levels are due to cirrhosis per se with inadequate metabolization of the hormone or to ascites with stimulation of the adrenal cortex to produce greater amounts of the hormone.

The ascites could do this in virtue of containing a sizable portion of the body electrolyte with consequent apparent hyponatremia.[1]

The latter alternative, i.e. secondary hyperaldosteronism caused by ascites is suggested by:—

1. Increased aldosterone is not found in cirrhosis without ascites. We must remember here that the presence of ascites usually means greater liver damage and hence the possibility of more pronounced inadequacy of the liver to inactivate the hormone.
2. The actual secretory rate of aldosterone by the adrenal cortex in cirrhosis and ascites is increased.
3. Cases have been demonstrated in which abnormal sodium retention disappeared following correction of the ascites in cirrhotic patients by porta-caval shunts.

Hence, it appears that increased aldosterone in cirrhotic patients is due mainly to excessive secretion by the adrenals in response to ascites. Decreased inactivation of aldosterone by the damaged liver may also play a role, but probably a lesser one.

Thus it is probable that increased oldosterone is not a primary factor in the production of ascites in cirrhosis but rather an aggravating factor brought on by the ascites itself.

CONCLUSION

Ascites in cirrhosis is mainly the result of an inter-relation between portal hypertension and hypoalbuminemia; increased hepatic lymph flow sometimes playing a

major supporting role; sodium and water retention aggravating rather than causing the condition.

[1] Ascites per se is fluid retention, hence, increased extracellular volume with dilution of electrolytes. Thus, apparent hyponatremia even though total body sodium is normal or increased.

References:

1. Krook, Hans: *Circulatory Studies in Cirrhosis,* Acta Medica Scandinavica. Supplement 318, 1956.
2. Leevy, Cherrich, G., Davidson, C.S.: *Portal Hypertension,* New England Journal of Medicine. February 25, 1960, page 397. March 3, 1960, page 451.
3. Rousselot, L.M., Moreno, A., Panke, W.: *Studies on Portal Hypertension, Annal of* Surgery. September 1959, page 384-409.
4. Warren, W.D., Muller, W.H.: *A Clarification of Some Hemodynamic Changes in Cirrhosis and Surgical Significance,* Annals of Surgery. September 1959, page 423-426
5. Welch, C.S., Welch, H.F., Carter, J.H.: *Treatment of Ascites by Side to Side Shunt,* Annals of Surgery, September, 1959, page 428-439.

"It would seem that the study of medicine does not always contribute to broad-mindedness, as men who choose medicine as a profession are apt to lose rather than gain breadth of perception. It could be said rather that medicine develops individualism." —CHARLES H. MAYO