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SERUM NITRITE AND NITRATE LEVELS IN PORTAL HYPERTENSIVE GASTROPATHY: CORRELATION WITH ENDOSCOPIC AND MICROVESSEL CHANGES

THESIS

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PORTAL HYPERTENSION

Portal hypertension is the main complication of liver cirrhosis. It is characterized by a pathological increase in portal venous pressure and by the formation of portasystemic collaterals that divert portal blood to the systemic circulation bypassing the liver.[1] However, not all patients with an increased portal venous pressure should be considered to have "Clinically-significant portal hypertension". This is due to the fact that the complications of portal hypertension are only observed when the portal pressure gradient (the difference between portal pressure and the inferior vena cava pressure), is increased above a threshold value of approximately 10 mm Hg.[2]

A grasp of the biological mechanisms involved in the pathogenesis of portal hypertension is essential to an understanding of the complications of chronic liver disease and to the development of rational therapy.[1] When Ohm's law is applied to the vascular system, the blood pressure (P) in any vascular system is the product of the blood flow (F) in

that system and the vascular resistance (R) that impedes this flow and is defined by the equation: P= F x R

Therefore, the portal venous pressure is the result of the interplay between portal venous blood flow and vascular resistance offered to that flow. It follows that elevated portal pressure occurs as a result of an increase in portal blood flow, an increased resistance to that flow or a combination of both.[3,4]

I. Increased Resistance to Portal Venous Flow:

It is well established that the primary factor leading to portal hypertension is an increased resistance to portal blood flow as a result of an increase in both intra-hepatic and portasystemic collateral resistance in comparison with the low resistance of the normal liver.[1]

The normal liver is a very compliant organ. Hence, the intra-hepatic resistance decreases with increases in blood flow because of distension of the vascular tree in response to increased inflow. This compensatory mechanism maintains the portal pressure within normal limits with a wide range of portal flows in normal livers. This phenomenon is not seen

in the portal hypertensive states in which the intra-hepatic resistance becomes fixed and the hepatic vascular compliance is greatly reduced.[5]

In portal hypertension, increased resistance to portal venous flow may be localized to pre-hepatic, post-hepatic, or intra-hepatic (pre-sinusoidal, post-sinusoidal or sinusoidal) sites. In pre-hepatic and post-hepatic portal hypertension, increased resistance is secondary to obstruction of portal venous inflow or hepatic venous outflow respectively. Unlike pre- and post- hepatic portal hypertension, the intra-hepatic syndromes are more complex and rarely can be classified according to a single site of resistance.[1]

An early view of vascular resistance in cirrhotic livers hypothesized that portal hypertension is the consequence of a vascular obliterative process with scar tissue and regenerative nodules, both occluding and compressing vascular structures.[6] These pathologic changes in cirrhosis are associated with increased connective tissue deposition in the peri-sinusoidal region or the space of Dissë with capillarization of sinusoids and elevation of portal pressure.[7] Thus, earlier understanding of intra-hepatic portal hypertension emphasized the role of the "unmodifiable"

anatomical alterations leading to mechanical obstruction (irreversible component) in the increased intra-hepatic resistance.[1]

Recently, it has been demonstrated that along with this irreversible "mechanical" increase in hepatic vascular resistance, there is a "dynamic" component, due to the active contraction of the hepatic stellate cells, vascular smooth muscle cells and other contractile elements within or around the hepatic microcirculation.[8] These contractile elements in the liver are able to constrict in a reversible and graded manner in response to several agonists, promoting a further increase in the intra-hepatic resistance.[9] The hepatic stellate cells are pericyte cells strategically located in the peri-sinusoidal space of Dissë and have inter-hepatocellular branching processes that contain actin-like filaments and wrap around the sinusoids.[10] Activated stellate cells acquire contractile properties similar to myofibroblasts and may increase the resistance to flow in individual sinusoids and contribute to the dynamic modulation of intra-hepatic resistance.[11] Also, concomitant contraction of the abundant vascular smooth muscle cells located in the portal venules, is caused by same stimuli that contract hepatic stellate cells, and is able to increase the intra-hepatic resistance.[9]

In recent years, much attention has been paid to the potential role of vasoactive mediators in increasing the hepatic vascular tone in cirrhosis. These substances act in a paracrine fashion on the underlying vascular smooth muscles and modulate vascular tone.[1] Normal vascular tone is maintained by a delicate balance between these vasodilators and vasoconstrictors, or combination of both. An imbalance between endothelial vasodilators such as nitric oxide (NO) and prostacyclines and vasoconstrictors such as endothelins can affect the contractile elements in the liver.[12] It is possible that both a deficit of vasodilators and an increase in vasoconstrictors may be responsible for the increased vascular tone.[1] A study performed in isolated and perfused normal livers showed that endothelin-1 is able to increase the portal perfusion pressure by increasing intra-hepatic resistance.[13] Also, the stellate cells from cirrhotic livers exhibit an enhanced response to endothelins and the administration of endothelin A and B receptors antagonist, bosentan, produced a significant reduction in the portal perfusion pressure in cirrhotic livers.[14] Moreover, other vasoconstrictive factors such as norepinephrine, angiotensin II and vasopressin, which are usually increased in cirrhosis, are able to increase intra-hepatic vascular resistance.[15] Meanwhile, it has been shown that the synthesis of NO, a well known vasodilator, is decreased and unable to compensate for the