

## Hemodynamic Changes in the Intra-Hepatic Circulation of Hepatosplenic Schistosomiasis: the Role of Hepatic Artery

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### ABSTRACT

Schistosomal liver disease represents a particular type of chronic liver disease, which presents unique characteristics that differentiate it from those found in cirrhosis, especially in the vascular bed. Changes in the vascular territory of hepatic artery are still controversial in literature, with some authors advocating no change, while others reporting a greater participation of this sector in hepatosplenic schistosomiasis (HSS). The purpose of this analytical review is to describe the pathophysiology of schistosomal liver disease, with special attention to intra-hepatic vascular alterations regarding the hepatic artery. In conclusion, the literature, to date, has divided opinions in respect to the role of hepatic artery in advanced

schistosomal liver disease. We believe this is an interesting field for future research in order to solve the intriguing pathophysiology of hepatic schistosomiasis and use this knowledge for the patients benefit.

**Key words:** Schistosomiasis; Hepatopathy; Hepatic Circulation

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### INTRODUCTION

Schistosomiasis is a parasitic infectious disease caused by worms of *Schistosoma* genus.

In 78 countries of Africa, Asia, Central and South America, it is considered an endemic infection, occurring in places with poor sanitation<sup>[1]</sup>. Although there are no specific global survey for schistosomiasis, it is estimated that about 200 million people are infected with *Schistosoma* in Africa, Asia and South America, 20 million with severe disease and other 600 million people are at risk of being infected<sup>[2,3]</sup>.

Schistosomal liver disease represents a particular type of chronic liver disease, which presents unique characteristics that differentiate it from those found in cirrhosis, especially in the vascular bed<sup>[4]</sup>. Advanced schistosomiasis produces one of the most characteristic presentations of liver diseases: Symmers fibrosis. In pathology cut surface, whitish fibrotic plaques occupying portal spaces are observed, surrounded by a hepatic parenchyma with normal appearance, without formation of fibrous septa and typical regenerative cirrhotic nodules<sup>[5]</sup>.

Vascular changes in hepatic artery territory are still controversial in literature, with some authors advocating no change, while others reporting a greater modification of this sector in hepatosplenic schistosomiasis (HSS)<sup>[4,6-12]</sup>. The purpose of this analytical review is to describe the pathophysiology of schistosomal liver disease

with special attention to intrahepatic vascular and hepatic artery alterations, since, unlike the portal venous bed, there is no consensus about the role of hepatic artery changes in severe forms of schistosomiasis.

## MATERIAL AND METHODS

In order to deepen the theme of the study, a literature research and review was carried out at the PubMed/Medline and Scopus database. The following descriptors terms were used: schistosomiasis pathology, schistosomiasis pathophysiology, schistosomiasis hemodynamics and schistosomiasis vascular changes. There were no restrictions on publication dates and were included on the analysis review articles and experimental studies as well as human and animal models. The adopted inclusion criteria were articles available at the electronic address, full version and be disclosed in English or Portuguese. The main goal of the studies analysis was evaluate the role of hepatic artery and possible changes in its hemodynamics in livers affected by severe forms of schistosomiasis.

## INTRAHEPATIC VASCULAR CHANGES

In *S. mansoni* infection, the female parasite produces a huge amount of eggs daily which are deposited on branches of mesenteric venules, to be excreted in host feces. Most eggs is retained in colonic wall or is excreted in the feces. However, about one third of them falls back into mesenteric circulation towards the liver and impact on small portal branches, causing partial obstruction to portal blood flow. Soluble antigens produced by the larva inside the egg stimulate a immune reactions cascade that culminates in formation of a periportal granuloma. The latter determines extensive damage to hepatportal vascular system. Thus, inflammatory and fibrovascular reactions of the host are the main factor responsible for the obstruction of portal venous flow and liver fibrosis is probably not significant by itself<sup>[13,14]</sup>. The space occupied by fibrosis in chronic liver diseases is not enough to have an impact on the physiology of an organ with such functional reserve. The importance of liver fibrosis is related to the fact that this changes act as a support for abnormal vascularization. Therefore, intrahepatic vascular derangement, venous and arterial, caused by chronic liver insults are the main background for physiological changes<sup>[15]</sup>.

Extensive hepatic fibrosis seen in advanced HSS is dependent basically on two factors: high parasitic load due to massive embolization of eggs to portal system causing obliteration of small vessels of the peripheral portal system and immune response developed by the host. In the formation of periportal granuloma, there is a vascular proliferation that progressively affects the granuloma periphery as it grows by formation of fibrosis. When there is fusion of granulomas, as occurs in periportal fibrosis of advanced disease, small blood vessels proliferate and exhibit a prominent aspect in inter-granuloma tissue, assuming na angiomatoid feature. Despite this vascular proliferation, many portal vessels, in fact, are distorted, with thickening of muscular layer and occluded<sup>[4,5,13,16,17]</sup>.

Embolization of eggs and distal occlusion of portal branches causes an increase in intrahepatic portal venous pressure, which induces formation of periportal collaterals in larger diameter vessels, allowing a diversion of the blood flow. With the continuing arrival of eggs, damage to larger caliber veins will occur, with formation of granulomatous periportal inflammation, inter-granuloma fibrosis and vascular occlusion, which, in turn, promotes portal hypertension, increasing splenomegaly and portosystemic collaterals<sup>[4,13,16]</sup>.

The worm itself, on the other hand, participate on intrahepatic portal occlusive changes. After its death, it can function as microemboli occluding branches of portal venous bed<sup>[14]</sup>. These lesions caused by dead worms, although larger in extent, causes less impact, being fewer in number, and located though. Another mechanism involves soluble antigens secreted by the worm. These promote physiology changes of intrahepatic portal vasculature, characterized by an increased sensitivity of portal branches to vasoconstrictors such as serotonin and acetylcholine<sup>[18,19]</sup>. Coupled with increased extracellular matrix, vascular contraction contribute to increase the portal resistance<sup>[18]</sup>.

In advanced HSS, despite obliterative changes of portal venous system, total hepatic blood flow is maintained in the normal range<sup>[5]</sup>. This phenomenon may be due to hypertrophy/hyperplasia of hepatic arterial system<sup>[14,20,21]</sup>. Studies of vascularization in plastic models, obtained by injection in different vascular systems - portal vein, hepatic vein and hepatic artery - of plastic substance with different color could document the intrahepatic vascular changes in HSS<sup>[12,13]</sup>.

Portal branches are reduced and the less prominent of the three vascular sectors. Unlike cirrhosis, vascular changes in schistosomiasis affect larger portal branches, with considerable distortion and reduction of small peripheral branches<sup>[22]</sup>. Portal branches of medium and large calibers often have dilatation, tortuosity and sudden diameter reduction without emitting the terminals rami, with a network of thin newly formed vessels coming up of the main branches and anastomosing with each other<sup>[4,12,13,23]</sup>. The hepatic veins sector does not show any changes. But the hepatic artery sector shows considerable hyperplasia and hypertrophy with a vascular network more dense and tortuous, especially in peribiliary plexus<sup>[4,13,24]</sup>.

These changes in hepatic artery vascular bed may be considered compensatory to decreased portal venous perfusion<sup>[23]</sup> consequent to distortion of the portal venous system by occlusions or amputations of their branches. An intense arterial network is formed and grows through venous anastomotic and distorted branches around the thick trunks of portal veins, and fill the spaces that lack portal branches<sup>[20]</sup>. Thus, total hepatic blood flow remains unchanged. However, this increase in intra-hepatic arterial flow is responsible for a rise in sinusoidal pressure causing a greater accumulation of collagen fibers within the Disse space. These changes determine the capillarization of hepatic sinusoids and impairs the exchange surface between sinusoids and hepatocytes, contributing for episodes of bleeding and decompensated stage of HSS<sup>[4,13,20,25]</sup>.

One of the main physiological disadvantage of hypertrophy of hepatic artery sector is the hepatic parenchyma dependence on arterial flow. When there are episodes of massive gastrointestinal bleeding - common complication of HSS - there is liver hypoperfusion, because blood flow is more dependent on the mean arterial pressure. As a consequence of these ischemic insults, areas of hepatic necrosis appear, and become focal peripheral post-necrotic scars with formation of fibrotic septa isolating nodules indistinguishable in appearance from cirrhosis<sup>[4,13,20]</sup>.

Despite these morphological aspects described above, some angiographic studies of the hepatic vascular system in HSS revealed conflicting results, with a theory of little arterial participation in HSS abnormal liver hemodynamics. They observed reduction in the hepatic artery diameter, with decreased intrahepatic arterial vascularization<sup>[8,26,27]</sup>. The authors suggested that, as a result of massive splenomegaly, there would be a hypertrophy of the splenic artery with consequent diversion of the hepatic artery flow, a mechanism similar to the splenic artery steal syndrome, described in

vascular complication cases of liver transplantation<sup>[28,29]</sup>. However, the “siphon” mechanism described to explain this steal has been questioned. Reductions in the hepatic artery inflow has been assigned to the intrahepatic regulatory mechanism known as *hepatic arterial buffer response* (HABR)<sup>[30]</sup>. In this, portal blood flow caused by increased splenic flow from splenic artery, reduce the flow of hepatic artery in a compensatory mechanism<sup>[31]</sup>.

Cleva *et al.*, in angiographic evaluations of systemic hemodynamics in schistosomal patients prior to splenectomy with ligation of left gastric vein, observed poor intrahepatic arterial vascularization. The authors documented exuberant splenic vasculature both arterial, and splenic vein, with hemodynamic measurements suggesting systemic hyperdynamic state like in cirrhosis, with increased heart rate and cardiac work and reduction in peripheral vascular resistance. They suggested that the supporters of a systemic hyperdynamic state were splenomegaly, along with portosystemic collateral circulation working as arteriovenous fistula, shunting hypertensive portal flow<sup>[9,32]</sup>. Another study by the same author, using thermodilution techniques showed that 56% of 16 patients with HSS had portal flow above the range considered normal for a total hepatic flow (greater than 1500 ml / min) opposing the idea of a typical normal global liver flow in these patients<sup>[33]</sup>.

Mies *et al* also studied the systemic hemodynamics in patients with HSS to assess effects of treatment with propranolol. They observed the same findings of Cleva *et al* in relation to increased heart rate, decreased peripheral vascular resistance and preservation of total liver blood flow. They have also reported increased flow through the azygos vein, indicating a higher blood drainage through portosystemic collateral circulation, with significant reduction after treatment with propranolol. In this study the authors demonstrated a reduced flow through the hepatic artery that had increased after use of propranolol, accompanied by reduction in flow through the portal vein, splenic vein and superior mesenteric vein<sup>[11]</sup>.

Lacerda and Pereira evaluating hemodynamic effects of splenectomy associated with gastroesophageal devascularization and ligation of left gastric vein, respectively, showed an increase in caliber and flow through the hepatic artery, just after surgery, associated with a reduction in the diameter and flow in portal vein accompanied of a slight increase in sinusoidal pressure<sup>[34,35]</sup>. Lacerda suggests that, in patients with HSS, with large shunts, absence of increased arterial sector is justified by portal blood overflow, which maintain normal liver perfusion, diverting only the blood in excess and dispensable by colateral circulation. With surgery the overflow mechanism would cease, reducing portal perfusion, with a compensatory increase in arterial circulation<sup>[35]</sup>.

Other *in vivo* dynamic studies, however, have documented opposite results. Coutinho in 1968 conducted a hemodynamic study with measurement of intra-splenic, intrahepatic, direct portal vein, free and occluded hepatic vein pressures, associated with na angiography study with splenopography. He observed an increase in intra-splenic and portal pressures, normal or slightly increased sinusoidal pressure, and total liver flow maintained. In the angiographic study, the author documented dilation of right and left portal vein branches with reduced venous ramifications, described as Bogliolo signal, and preservation of the arterial system. Thus, the author raises as possibilities for maintenance of total liver blood flow, the arterial system conservation that would allow a compensatory increase in the liver flow<sup>[36]</sup>.

In another angiographic study, Ramos *et al* documented an intrahepatic presinusoidal block of portal flow, with maintained total liver blood flow, indicating a compensatory increase in arterial

blood flow<sup>[37,38]</sup>. Alves *et al*, studying 5 schistosomal patients during splenectomy, positioned a catheter in the hepatic vein to measure intrahepatic pressures. The next step was clamping the hepatic artery in its main trunk, observing a decrease in sinusoidal pressure over 15 mmHg. Then, individuals in control group, with splenomegaly secondary to a cavernous hemangioma, the same pressures were measured during splenectomy with normal sinusoidal pressures findings and unchanged sinusoidal pressures after clamping the hepatic artery. With these findings the authors highlight the importance of the arterial sector in HSS<sup>[10]</sup>.

Dynamic studies in animal models also described changes in arterial circulation of mice livers. Morgan *et al* studied a HSS model in hamsters showing that, with progression of liver disease, there was a significant decline in portal blood flow partially compensated by na increase in arterial flow<sup>[39]</sup>. Sarin *et al*, in a murine model of HSS, using radioactive microspheres technique, demonstrated that the decline in portal flow of infected animals was 61% greater than in healthy animals and observed an increase of two times in arterial inflow of animals with HSS compared to controls. In addition to these observations, the authors highlighted measures consistent with hyperdynamic circulatory state like described by Cleva *et al*, with increased heart rate, decreased peripheral and splanchnic vascular resistance<sup>[7]</sup>.

These observations can be explained by the double hepatic blood supply and a unique mechanism that allows an intimate relationship between these two vascular systems, determining an intrinsic regulation of blood inflow. This inter-relationship is the so-called *hepatic arterial buffer response* (HABR), described initially by Lautt<sup>[40]</sup>, in which hepatic artery can produce compensatory changes in its flow in response to changes of portal blood flow, to maintain a constant total liver flow<sup>[41]</sup>. In association with classic mechanism of arterial auto-regulation, in which there is a myogenic contraction of vessels in response to increases in blood pressure and, in the case of the hepatic artery is considered low, there is a second mechanism in which hepatic artery dilates when portal flow decreases and contracts when portal flow increases<sup>[42,43,41,44]</sup>. This HABR mechanism has been demonstrated not only in physiological conditions, but also in fetuses, liver cirrhosis and liver transplant<sup>[43,45-51]</sup>. The increased arterial flow can compensate 25 to 60% of decreases in portal flow. Kollmar *et al* showed that 14 days after ligation of the portal vein left branch of rats there was an increase in flow through hepatic artery so significant that reached levels close to the initial arterial and portal flow<sup>[52]</sup>. Since the portal vein is unable to control its flow, which is the sum of outflows of splanchnic organs, there is no reciprocity of HABR, i.e. changes in the perfusion of hepatic artery does not induce compensatory changes within the portal vein<sup>[42,43]</sup>.

Several studies have demonstrated maintenance of HABR in cirrhotic livers. Moeller *et al*, in an animal model of cirrhosis, have demonstrated reduced resistance and increased hepatic artery flow in cirrhotic rats even without portal hypertension, i.e. with normal portal vein resistance<sup>[51]</sup>. Richter *et al*, also in rodent models of cirrhosis, showed decrease in total hepatic blood flow with marked decrease of portal blood flow and compensatory increased flow through hepatic artery. He demonstrated that the ratio of total hepatic flow changed from 79.8% via portal vein and 20.2% via hepatic artery before chemical induction of cirrhosis to 59.2% through the vein and 40.8% through the hepatic artery in cirrhotic animal group. The author mentions also that, although the absolute value of blood flow is similar to control animals, the proportion of increase was much higher<sup>[47]</sup>. Aoki *et al*, in a study using human clamping of portal vein in cirrhotics during transplantation surgery,

demonstrated that portal vein flow was reduced while hepatic artery flow was increased and clamping of portal vein induced an additional increase in the arterial flow<sup>[48]</sup>. Gulberg *et al.*, evaluating HABR in cirrhotic patients undergoing TIPS (Transjugular intrahepatic portal shunt) placement, showed that the hepatic artery resistance index was decreased in cirrhotic patients, with further reduction after fall of the portal perfusion induced by TIPS placement<sup>[45]</sup>.

The most accepted theory, however, involves intrahepatic adenosine washout<sup>[40,44,53-55]</sup>. This hypothesis discloses that adenosine, a potent arterial vasodilator, is released at a constant rate in the space of Mall fluid that surrounds the portal vessels. This space is limited by a limiting plate that separates it from other compartments. The concentration of adenosine is regulated by its clearance through portal vein and hepatic artery. When there is a reduction on portal blood flow, less adenosine is cleared from the space of Mall and its accumulation leads to dilation of hepatic artery and increase arterial flow. Likewise, when portal blood flow increases, a larger amount of adenosine is cleared causing contraction of hepatic artery and decreasing its flow, demonstrating the inverse relationship between arterial and portal flows<sup>[42,43,48-50]</sup>. In association with adenosine, other vasoactive mediators have been described in the participation of HABR, such as nitric oxide, carbon monoxide, adenosine triphosphate (ATP) and hydrogen sulfide<sup>[42,43]</sup>.

Hepatic arterioles ramifies around portal venules, sending small branches to capillaries of peribiliary plexus and to venules that will form arteriolo-portal shunts. Thinner arterioles branches will supply venular portal walls as a vasa-vasorum<sup>[43]</sup>. Under normal conditions, about 30% of the flow through the hepatic artery is shunted to the portal circulation<sup>[50]</sup>. This deviation was demonstrated to guarantee the nutrient supply and oxygen supply by HABR in rats, with authors suggesting no change in vascular diameter, but the proportion of flow through the shunts<sup>[56]</sup>. Under normal conditions, most of sinusoids are perfused by portal blood with small portion further supplied directly by hepatic arterioles terminals. Conditions of reduced portal flow induces HABR, with preferred inflow through the shunts leading to a disproportionate increase in the contribution of hepatic artery to sinusoidal perfusion<sup>[43,56]</sup>.

Preliminary study conducted by our group, with not yet published data, used angioscintigraphy to evaluate hepatic perfusion with findings similar to those described in cirrhotic patients<sup>[57-60]</sup>. We observed a rise of radioisotope uptake in arterial phase of hepatic perfusion of patients with HSS<sup>[61]</sup>. Thus, it is suggested that, in fact, there is an increased arterial component in the total hepatic flow of schistosomal liver, similar to what occurs in cirrhosis. This increase would be secondary to impairment of intrahepatic portal flow caused by vascular distortion of this sector as a result of fibrociatricial phenomena of schistosomal hepatopathy.

In conclusion, literature to date has divided opinions in respect to the role of hepatic artery in advanced schistosomal liver disease. Various studies indicate a direct involvement of the hepatic artery to maintain a constant total liver flow, while others show little arterial involvement, assigning the maintenance of hepatic blood flow exclusively through to portal overflow. We believe this is an interesting field for future research in order to solve the intriguing pathophysiology of hepatic schistosomiasis. Using this knowledge, we might be able to understand the mechanisms of portal hypertension, not only in HSS, but also in other forms of non-cirrhotic portal hypertension. Moreover, many patients would benefit from the development of this field as HSS is a still prevalent disease in many eastern and subequatorial countries.

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