ANNALS OF HEPATOLOGY

Volume 1 *Number* 1 *January-March* 2002

Article:

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Annals of hepatology 2002; 1(1): January-March: 06-11

Annals
of
hepatology

Concise Review

Hepatosplenic schistosomiasis: a model for the study of portal hypertension*

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Schistosomiasis is an endemic disease of tropical areas. In American countries as Brazil, Venezuela, Puerto Rico, Antilles and Suriname the worm that causes schitosomiasis is the *schistosoma mansoni*. According to the World Health Orzganization more than 600 million people live in risk areas and about 200 million are infected in 75 countries.[1]

The biological cicle of the worm corresponds to three phases: when human feces containing the eggs of the parasite fall in water, they rupture liberating the miracide. The intermediate cicle occurs in a snail of the gender *biomphalaria*. The parasite multiplies inside the snail and after 20 to 30 days gives origin to the cercariae, that spread in warm water of about 20 to 25 degrees Celsius. Free in the water the cercariae enter through the intact skin and mucosa, suffering modifications and achieving maturation in the portal system, where sexuated adult worms lay their eggs. From the portal system eggs can spread to tissues and organs, specially the liver and intestines. As eggs are elimianted with feces they may contaminate water, closing the cycle.

Adults worms live in the portal system, where about 300 eggs per day are laid and about 2/3 of them carried to the liver. The typical egg has a characteristic lateral spine, useful for its diagnosis, not only in stools but also in the various tissues where the egg can be found *(Figure 1).* As various couples of adult worms can be found in the veins of the portal system, specially the mesenteric veins, this parasitic infection gives rise to a vascular disorder that may end up with an hepatic disease.

Worms and eggs are responsible for the pathopysiology of the disease. In the initial phases there is formation of immune complexes, rarely with acute manifestations. The chronic forms are very common, due primarily to the deposition of eggs and dead worms in different organs and tissues, particularly intestines and liver. In the later they obliterate small vessels, forming granulomas in the portal tract, obstructing the portal vein. The presence and degree of fibrosis depend on parasitic load, immune response and genetic factors.[2]

Clinical forms of the disease in humans are classically classified in slight and severe. Persons living in endemic areas usually have the so-called intestinal form or the hepatointestinal form. The later represents an intermediate phase in the evolution of the disease, when a palpable liver can be found at physical examination. Some authors, however, consider that all slight chronic forms of mansoni schistosomiasis are hepatointestinal. In fact, hepatic granumolas around the eggs can be found without evident hepatomegaly. Complains of these patients are scarce and non-specific, as fatigue and diarrhea. Besides Kato's test for the search of eggs in stools, a high percentage of eosinophils in the blood may call the attention for the diagnosis.

About 5% to 10% of infected individuals develop the hepatosplenic form, which gives origin to portal hypertension and is considered the severe form of the disease. As clinical presentation hepatomegaly, specially of the left lobe, and a huge splenomegaly are found. The main manifestation of this severe form is gastrointestinal bleeding due to portal hypertension, leading to high morbidity and mortality. Clinically, what is striking in this type of portal hypertension due to chronic liver disease is the lack of the typical physical signs of hepatic dysfunction as jaundice, spiders, palmar erithema, gynecomastia or ascites. Epidemiological data is very important for the diagnosis since other types of pre-sinusoidal portal hypertension may have a similar clinical presentation, including large splenomegaly. Stool examinations may be repeatedly negative, but abdominal ultrasound, histology of the liver or its angiographic study are usually conclusive for schistosomiasis.

Contrasting with cirrhosis, where fibrosis starts around portal tracts or hepatic veins and spreads forming bridges between hepatic and portal veins, in schistosomiasis the fibrosis is restricted to the portal area, with preservation of the lobular architecture of the liver *(Figure 2).* The macroscopic specimen may show large fibrous septa, the typical "pipestem fibrosis."

In the intra-hepatic vascular tree, the differences between cirrhosis and schistosomiasis are also remarkable. Tortuous vessels are characteristic of cirrhosis whereas the amputation of portal vein branches with formation of multiple thinny vascular channels is consistant with schistosomiasis. *"In vivo"* angiographic studies detect these differences.

Among the many conditions – pre-hepatic, hepatic and post-hepatic, that may lead to portal hypertension –Schisto-

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* This text corresponds to the State of the Art Lecture given in Fukuoka, Japan, during the Biennial Meeting of IASL in 2000.

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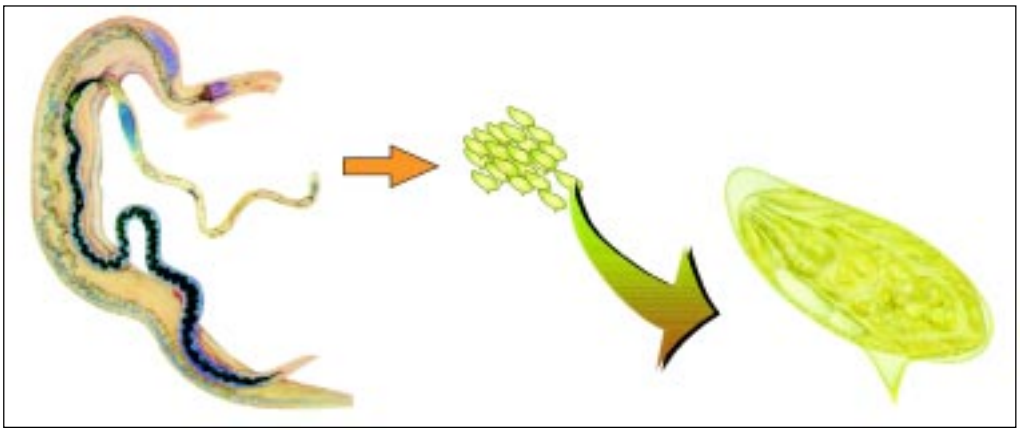


Figure 1. Adult sexuated worms live in the mesenteric veins, where they lie about 300 typical eggs per day, carried mainly to the liver.

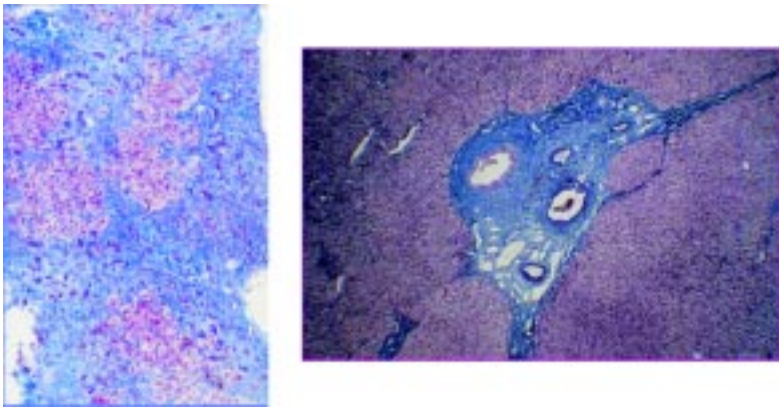
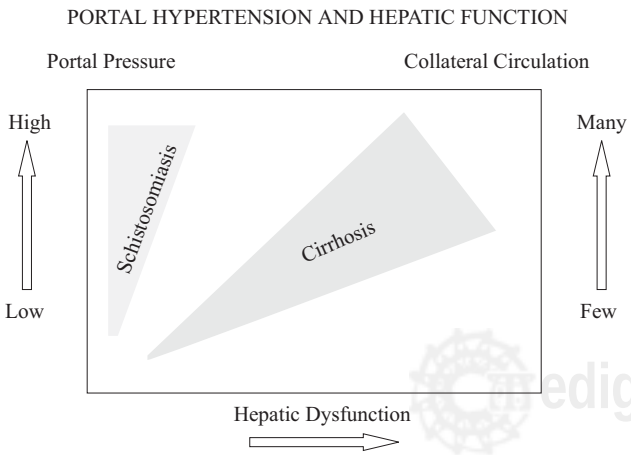


Figure 2. Liver histology of alcoholic cirrhosis in the left showing fibrosis in blue (Masson's trichromme) and a complete alteration of hepatic architecture. On the right, liver histology in schistosomiasis showing fibrosis again in blue, restricted to the portal tract and with preserved liver architecture.



Figures 3. In the severe form of schistosomiasis high portal pressure may lead to the formation of many collateral vessels and severe bleeding due to varices, but differently from cirrhosis, with minimal hepatic dysfunction.

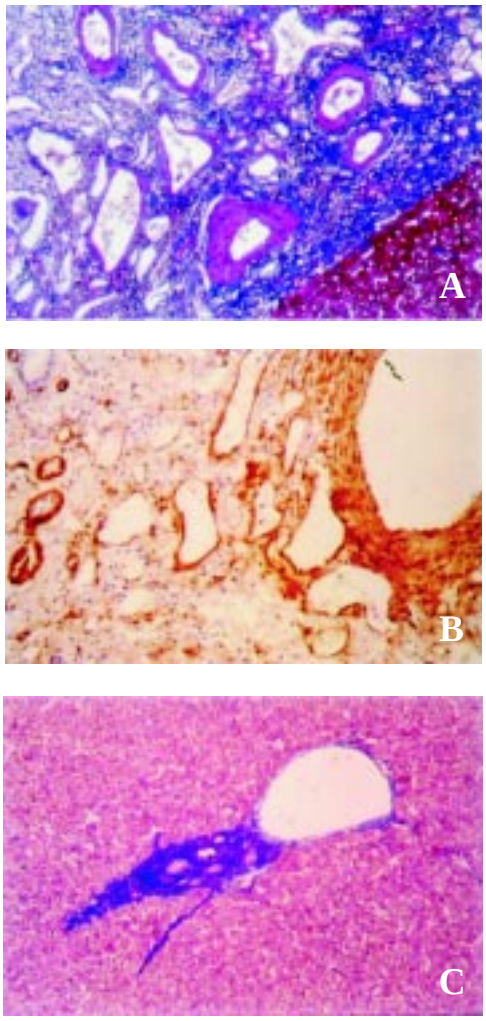


Figure 4. The characteristic histological appearance of the altered venous vessels in the portal tract. Top left (A) shows telangectasias: many small portal vessels instead of a large portal vein. Top right (B): special staining to show the thickness of the walls of the portal vessels, Bottom (C) showing a small portal tract with a kind of "varice" of the portal vein.

Table I. Hyperdynamic circulation is present in portal hypertension due to both cirrhosis and schistosomiasis, but its consequence on systems and organs may be similar or different as depicted here.

	Portal hypertension Effects of Hyperdinamic Circulation	
	Cirrhosis	Schistosomiasis
Splanchnic and hepatic area	Portal flow Portal pressure	Portal pressure Normal hepatic blood flow
Systemic	Cardiac output Arterial pressure	Normal wedged venous pressure
Renal	Water and Na^+ retention Hepatorenal syndrome	Glomerulonephritis related to immune complexes of *schistosoma*
Pulmonary	Arterial O_2 Hepatopulmonary syndrome	Pulmonary hypertension related to porto-collateral circulation (shunts)
Brain	Edema Coma	Rare cases of Hepatic Encephalopathy related to surgical shunts

somiasis is classified as a pre-sinusoidal cause of portal hypertension whereas cirrhosis is typically classified as sinusoidal and post-sinusoidal. It is universally accepted that, regardless the causing disorder or disease, the physiopathologic mechanisms of the syndrome of portal hypertension is basically the same, but there are some differences.[3]

The starting point for the elevation of the portal pressure is the increase in vascular resistance and/or an augmentation of blood flow, which gives origin to collateral circulation. This is true for any type of portal hypertension leading to the presence of varices and its consequent bleeding tendency.[4] In the last twenty years we have learned that due to collateral circulation, vasodilating substances reach the systemic circulation creating splanchnic and systemic vasodilation with the consequences of hypervolemia and increased blood flow, closing the vicious cycle of a persistent hypertension in the portal system.

The clinical consequences of portal hypertension, as disease progresses, affect various organs and systems, besides the liver, as kidneys, lungs and brain. In *table I* consequences of the hyperdinamic circulation in cirrhosis is compared to those found in the same organs or areas for schistosomiasis, where similarities and differences can be found. Usually, some of the clinical manifestations may be related or aggravated by a very poor hepatic function. In schistosomiasis, however, some manifestations are absent or very rare, what has been attributed to a preserved hepatic function.

In a recent review of liver function tests,[5] comparing hepato-intestinal and hepatosplenic forms of schistosomiasis with controls, the authors found slight alterations of liver enzymes: ALT, AST, Alkaline Phosphatase, as well as low platelets and prothrombin time in the hepatosplenic form of the disease. Although albumin levels remain similar to control, other proteins as transthyretin and protein C have shown lower values, attesting a minimal hepatic dysfunction. The altered coagulation test, a constant report in hepatosplenic schistosomiasis is related to hyperesplenism and/or consumption coagulopathy. In conclusion, a direct correlation between portal hypertension and hepatic dysfunction occurs in cirrhosis but not in schistosomiasis *(Figure 3).*

As concomitance of cirrhosis may occur in patients with schistosomiasis, it is essential to differentiate pure forms of hepatosplenic schistosomiasis from the association with the most frequent causes of cirrhosis as alcoholism and hepatitis virus. Hepatitis B has been associated with mansoni schistosomiasis for a long time.[6] Our data,[7] in accordance with others,[8,9] shows that the infection is more frequent in the hepatosplenic forms associated with bleeding episodes, blood transfusions or other medical manipulations, whereas the earlier forms of schistosomiasis have the same prevalence of HBsAg as control regional groups. A recent work from Pereira and co-authors,[10] shows that in Brazil the more advanced forms of hepatosplenic schistosomiasis, with decompensation, are due to the association with hepatitis C virus.

Jaundice, a symptom of hepatic decompensation is not related to portal hypertension and not found in schistosomiasis. But it may appear after surgical treatment, with predominance of the non-conjugated fraction of bilirubin. Comparing surgeries with and without a shunt procedure, hyperbilirubinemia was present only in those with shunt. Some years ago we have conducted an investigation (Ref) to evaluate the role of splenomegaly or the shunt itself in the production of hemolysis, comparing different groups of patients with presence or absence of these factors. Biochemical parameters: haptoglobin, hemopexin, total and non-conjugated bilirubins were analysed in the 4 groups and compared. The statistical analysis was clear in showing that presence of shunt was the main factor for the development of hemolysis and splenomegaly was only a contributing factor.[11]

Hemodynamic studies in schistosomiasis, on the other hand, have shown an important role of splenomegaly. When systemic and hepatic hemodynamics were studied, Brazilian authors[12,13] have found high cardiac outflow and low periph-

Table II. Results of two human hemodynamic studies about the effects of propranolol are shown here, as well as an experimental one. The Brazilian clinical trial was interrupted due to the need of very high doses of propranolol and the Egyptian trial, showing good results, has high percentage of dropouts. A better clinical evaluation is needed.

Treatment of portal hypertension
Propranolol in hepatosplenic schistosomiasis

Authors	n	Design	Results
Braillon et al. 1989	4 patients	Hemodynamic study	Hypercinetic circulatory syndrome Azygos blood flow
Strauss et al 1990	23 patients	Randomized trial Prop X Sclerotheraphy	Rebleeding > P Higher doses P
Sarin et al 1991	20 animals	Chronic murine schistosomiasis	Portal pressure systemic shunting portal flow
El Tourabi et al 1994	82 patients	Randomized trial Prop X Placebo	Rebleeding mortality (high dropout)
Mies et al 1997	11 patients	Hemodynamic study	Hypercinetic circulatory syndrome azygo blood flow portal pressure ~ portal flow ~ pulmonary hypertension

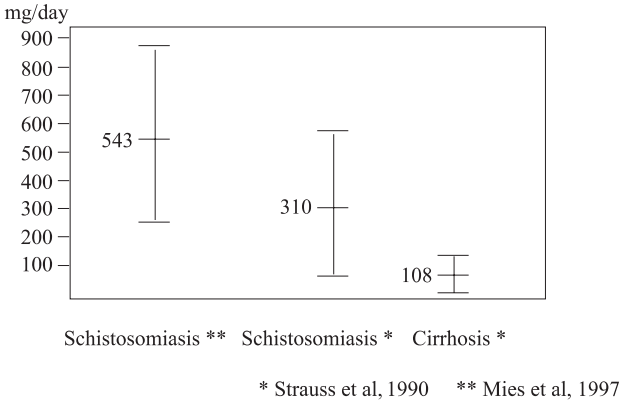


Figure 5. Blockade doses of propranolol are much higher in patients with portal hypertension due to schistosomiasis than those due to cirrhosis.

eral resistance, confirming the existence of a hypercinetic circulation, although cardiac rate and mean arterial pressure remained normal, differently from cirrhosis. As far as hepatic hemodynamics is concerned, besides the very high portal pressure, evaluated by transhepatic measurements, free and wedged venous pressures are usually normal.

Differently from cirrhosis, where hepatic blood flow is lower than normal, many authors, including ourselves[14] have described that total hepatic blood flow is normal in portal hypertension due to hepatosplenic schistosomiasis. It has been demonstrated that portal flow remains in the normal range, although splenic flow is extremely high and mesenteric flow is lower than normal. Azygos blood flow is also high, but not as high as the values found in cirrhosis.

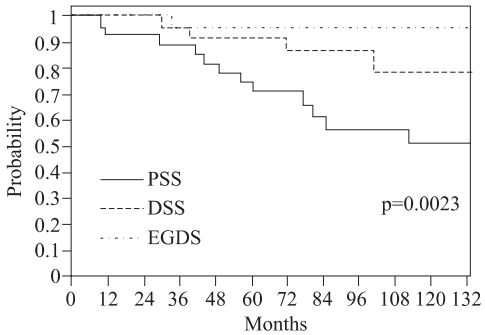
Morphological and morphometric studies of intra-hepatic portal veins have shown many telangiectasias *(Figure 4A)*,

Table III. The main results of our randomized trial comparing surgeries of portal hypertension in schistosomiasis have shown no differences in re-bleeding but higher percentages of hepatic encephalopathy for PSS and higher hemolysis for DSS.

Surgical treatment of portal hypertension in schistosomiasis

	PSS (n=28)	EGDS (n=28)	DSS (n=27)	"p"
UGIB	28.6%	21.4%	22.2%	NS
HE	39.3%	0.0%	14.8%	p=0.001
Hemolysis	29.6%	0.0%	52%	p<0.001

PSS = Proximal splenorenal shunt
EGDS = Esophagogastric devascularization with splenectomy;
DSS = Distal splenorenal shunt
UGIB = Upper gastrointestinal bleeding;
HE = Hepatic encephalopathy
Strauss E, 1989



Survival curves (Kaplan-Meier) of the three groups of patients, Raia et al. 1994.

Figure 6. A randomized controlled trial with 5 to 10 years follow-up and less than 10% dropout, has shown better survival rates for esophagogastric disconnection with splenectomy when compared to shunt surgeries: PSS and DSS.
PSS = Proximal Splenorenal Shunt
DSS = Distal Splenorenal Shunt
EGDS = Esophago-Gastric Disconnection with Splenectomy.

greater thickness of their muscular layer, as demonstrated in *figure 4B* and also, although rare, the formation of a type of "varice" of the portal vein *(Figure 4C).*

Another important contribution for the diagnosis of Mansoni's hepatosplenic schistosomiasis is abdominal ultrasound. Hyperechoic fibrotic bands can be recongnized along the portal vessels, as well as volumetric reduction of the right hepatic lobe with enlargement of the left one, splenomegaly and peri-vesicular fibrotic thickening. When associated with Doppler features collateral veins and flow abnormalities are also detectable.[15]

It is well known that treatment must have a physiopathological basis. If all cases of portal hypertension have a common physiopathological mechanism, efficacy of one type of treatment should be the same for all patients suffering from the syndrome. The efficacy of propranolol, for example, is well demonstrated in cirrhotic patients.[16] But few studies were done in hepatosplenic schistosomiasis, as shown in *table II.* Hemodynamic studies were initially performed by Lebrec's group[17] who have shown the hyperdiynamic circulation, confirmed in the studies of Mies.[12] We have interrupted a clinical trial comparing propranolol with sclerotherapy due to unfavorable results in the groups taking propranolol,[18] besides the need for very high doses, what may be risky *(Figure 5).* Although some authors have shown good clinical results, when compared to placebo, long-time follow-up was not available.[19,20] Other authors confirmed the need for very high doses of propranolol and also showed an increase in the pulmonary venous pressure.[12] In these studies a decrease in portal pressure was not achieved and the decrease of the azigos blood flow was low. These results proned us to avoid the usage of propranolol in Hepatosplenic Schistosomiasis.

For the surgical treatment of portal hypertension portocaval shunt was performed in schistosomiasis in the early sixties but with very bad results. A high percentage of complications were observed, specially hepatic encephalopathy, otherwise not seen in this parasitic disease. Other techniques, as proximal and distal splenorenal shunts were commonly performed in the seventies, whereas a different technical approach, the esophagogastric disconnection with splenectomy was popular in both Egypt and Brazil.[21]

We have conducted a randomized clinical trial to study the efficacy of 3 types of surgery namely Proximal Splenorenal Shunt, Distal Splenorenal Shunt and Esophagogastric Disconnection with Splenectomy.[22] After 5 to 10 years of follow-up, with only 9% of dropout, we could show that re-bleeding was the same for the 3 surgical groups, whereas hepatic encephalopathy was greater in the proximal splenorenal shunt, also occurring, after the distal shunt, although some time later *(Table III).* But the more striking results were the survival curves, showing that definitely the best option was esophagogastric disconnection with splenectomy[23] *(Figure 6).*

In summary, schistosomiasis is an interesting human model for the study of portal hypertension with minimal hepatic dysfunction. As we have shown, the physiopathological mechanisms seem to have similarities with cirrhosis, but with important differences. Pharmacological therapy showed low efficacy of propranolol besides the need of very high doses. Surgical treatment was the most interesting model to demonstrate that portal hypertension has a different behavior when dissociated from hepatic insufficiency.

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