*Mem. Inst. Oswaldo Cruz*, Rio de Janeiro, Vol. *87*, Suppl. IV, 183-186, 1992

# PORTAL HYPERTENSION IN SCHISTOSOMIASIS: PATHOPHYSIOLOGY AND TREATMENT

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In heavily infected young patients, there is a "non-congestive" phase of the disease with splenomegaly which can improve after chemotherapy. A strong correlation between hepatosplenic form and worm burden in young patients has been repeatedly shown. The pattern of vascular intrahepatic lesions, seems to depend on two mechanisms: (a) egg embolization, with a partial blocking of the portal vasculature; (b) the appearance of small portal collaterals along the intrahepatic portal sistem. The role played by hepatitis B virus (HBV) and C virus infections in the pathogenesis of liver lesions is variably considered. Selective arteriography shows a reduced diameter of hepatic artery with thin and arched branches outlining vascular gaps. A rich arterial network, as described in autopsy cases, is usually not seen *in vivo*, except after splenectomy or shunt surgery. An augmented hepatic arterial flow was demonstrated in infected animals. These facts suggest that the poor intrahepatic arterial vascularization demonstrated by selective arteriography in humans is due to a "funtional deviation" of arterial blood to the splenic territory.

The best results obtained in treatment of portal hypertension were: esophagogastric devascularization and splenectomy (EGDS), although risk of rebleeding persists; classical (proximal) splenorenal shunt (SRS) should be abandoned; distal splenorenal shunt may complicate with hepatic encephalopaty, although later and in a lower percentage than in SRS. Propranolol is currently under investigation. In our Department, schistosomotic patients with esophagoal varices bleeding are treated by EGDS and, if rebleeding occurs, by sclerosis of the varices.

Key words: *Schistosoma mansoni* – portal hypertension – treatment

Symmers' fibrosis of the liver, which may result in portal hypertension and congestive splenomegaly is the most severe form and the most common cause of morbidity or death.

Fibrosis and venous intrahepatic portal lesions are the main pathogenic factors in the production of portal hypertension. These factors are responsible for a presinusoidal block and for an increased resistance to portal blood flow. Later on, a high splenic blood flow is observed ("overflow component").

A hamster model of schistosomiasis showed that a progressive rise in intrahepatic resistance appears to play a major role in the initial stages of evolving portal hypertension. A gradual decline in portal blood flow was only partially compensated for by an increase in hepatic arterial flow (Morgan et al., 1990).

Later on, there is evidence of increased portal inflow in many conditions associated with portal hypertension. This has been confirmed in animal models in which an increased splanchnic blood flow (and decreased splanchnic vascular resistance) closely accompanies portal hypertension. This hyperdynamic splanchnic circulation is considered to be a part of a wider hyperdynamic state with a high cardiac output and low vascular resistance. A number of potential mediators have been proposed to account for these haemodynamic changes, particularly glucagon, bile acids and adenosine which are frequently raised in portal hypertension (Macdougall et al., 1991).

The portal systemic shunting is responsible for the raised systemic levels of glucagon and bile acids. As a matter of fact, increased levels of cholyglycine, a conjugated bile acid undergoing 95% or more first pass clearance in the liver, were detected in hepatosplenic schistosomiasis (HSS) (Zwingenberg et al., 1990). A normalization was frequently observed after chemotherapy in patients with compensated HSS but not with decompensated form.

Clearly, many more investigations are necessary to stablish the role, if any, of these biochemical changes in the pathophysiology of portal hypertension.

In heavily infected young patients, there is a "reversible" phase of the disease with splenomegaly, which can improve after chemotherapy (Bina, 1977). It remains to be defined the role of drug therapy after the appearance of esophageal varices. Thus, three out of seven patients with a history of gastrointestinal hemorrhage presented a recurrence of bleeding after chemotherapy (Domingues & Coutinho, 1990). Domingues & Coutinho (1990) also mentioned a first episode of hemorrhage after treatment with praziquantel in four out of 35 patients (11.4%).

The irreversibility of schistosomotic fibrosis has been seriously disputed. Experimentally, chemotherapy produces a striking decrease of mortality in infected mice soon after treatment (Silva et al., 1985, 1990). Later on periportal fibrosis can undergo degradation in a way similar to that of periovular granulomas (Andrade, 1989).

As pointed out by Andrade (1989), after removal of the causative agents, degradation of fibrosis should be expected in a matter of months or even years.

The role played by hepatitis B virus (HBV) infection in increasing the morbidity of schistosomiasis was emphasized by several authors (Lyra et al., 1976) in the last fifteen years. It is our experience, that the higher frequency of HBV markers in hepatosplenic form as compared to the hepatointestinal is due to therapeutic measures in patients who seek for medical care (Strauss & Lacet, 1986). This point of view is defended by some authors (Madiwar et al., 1989) but not by others (Lyra et al., 1976). The participation of hepatitis C virus infection is not well established.

Ascites is an uncommon complication of portal hypertension in mansonian schistosomiasis, unless after some precipitating factors, such as hemorrhage and infection or in association with other liver lesions. However, in Egypt it seems to be a common finding, as shown by the studies of Habib et al. (1991) on blood levels of aldosterone and atrial natriuretic factor.

## HEMODYNAMIC ASPECTS

Some angiographic changes are very suggestive of hepatosplenic schistosomiasis, particularly an intrahepatic pattern of the portal system characterized by gross amputations of large branches, and by the appearance of a rich network around portal branches, as described by Bogliolo, (1957). As to the poor hepatic arterial vascularization demonstrated by selective arteriography and Doppler ultrasonography in human cases, in contrast to the rich arterial network described in autopsy cases, it might be due to a "functional deviation" of arterial blood to the splenic territory.

The gradient between hepatic vein wedged and free pressures may be normal or slightly raised (Coutinho, 1968; Mies et al., 1980).

It is not clear whether the mechanism of variceal development and rupture is identical in cirrhotic and non cirrhotic portal hypertension (Conn, 1990). On the other hand, the three main causes of bleeding in portal hypertension (variceal rupture, erosive gastritis and peptic ulcer) showed a similar incidence when bleeding patients with schistosomiasis and cirrhosis were submitted to an oral endoscopy (Silva et al., 1982). However, the mortality was significantly higher in the latter group.

## TREATMENT OF PORTAL HYPERTENSION

The management of patients with esophageal and gastric varices remains a challenging area, particularly when prophylactic procedures are considered.

Although a high portal pressure and large varices are associated with an increased risk of bleeding, the literature is still not clear and the methods of measuring size and pressure are still controversial (Spence, 1991).

Some endoscopic changes which are thought to indicate a high risk of bleeding include the large varices, cherry-red spots, varices on varices, erosions on varices (Spence, 1991) and hypertensive gastropathy.

These and probably other endoscopic signs should be used in the identification of patients for prophylactic procedures, including drug therapy, sclerotherapy and surgery.

As far as the non-surgical treatment of bleeding esophageal varices is concerned we

should mention that Braghirolli Neto, (1988) demonstrated that the beta adrenergic blockage with propranolol induced a 39.1% decrease in azygos blood flow and a study published by Mies et al., (1988), showed that propranolol seems to protect schistosomotic patients against GI rebleeding during the short period of time that precedes the definitive surgical treatment.

More recently, Kiire (1989) showed that continuous oral propranolol treatment is effective in preventing recurrent upper gastrointestinal bleeding in patients with non-cirrhotic portal fibrosis, most of whom were schistosomotic. Despite these favourable results, I wonder whether we could obtain a good compliance to this kind of treatment.

As far as sclerotherapy is concerned, a paper from Sakai et al. (1990) showed, in a retrospective study, that eradication of the varices was obtained in near 70% during a follow-up period between 48-132 months; sclerotherapy was effective in the control of rebleeding in 97.3% of the patients in the group with previous portal hypertension surgery and in 72.7% in the group without previous portal hypertension surgery, with lower number of sessions of sclerotherapy per patient in the former group; these differences were statistically significant. They concluded that previous surgical treatment for portal hypertension in patients with mansonian schistosomiasis, greatly benefitted the treatment of rebleeding esophageal varices by endoscopic esclerotherapy (Sakai et al., 1990). Cordeiro (1990) in a prospective non-randomized trial, comparing elective sclerotherapy with a control group with a 5-year follow-up, showed that the incidence of rebleeding was 28.1% and 44.5%, respectively a difference not statistically significant; but the mortality from rupture of esophageal varices was 3.1% in the sclerotherapy group and 27.7% in the control group, a statistically significant difference.

A poor long term compliance to theses non-surgical procedures and a significant number of failures justify a discussion on the surgical treatment.

Up to 1977, the main operations used for portal hypertension in hepatosplenic schistosomiasis were esophagogastric devascularization with splenectomy (EGDS), classical (proximal) splenorenal shunt with splenectomy (SRS) and distal splenorenal shunt (or selective shunt) (DSRS).

From 1977 to 1983 our group performed (Silva et al., 1986; Strauss et al., 1990) a prospective trial comparing these three operations in 94 patients with previous gastrointestinal bleeding (GIB). A long term follow-up study showed that recurrence of GIB occurred in 24.1% of patients, without statistical differences among the three groups, but rebleeding due to varices was more frequent after EGDS. Lethality (42.9%) and hepatic encephalopathy (39.3%) were significantly higher after SRS when compared to DSRS (14.8% and 14.8%) and to EGDS (7.1% and 0%). Indirect hyperbilirubinemia was more frequent after DSRS (52%) whereas present after SRS (29.6%) and absent after EGDS. Peptic ulcer was more frequent after SRS (25%), occurring also in DSRS (12.5%) but absent after EGDS (25%).

This prospective study allowed us to conclude that: (1) the best operation for the treatment of variceal bleeding in hepatosplenic form of mansonian schistosomiasis is EGDS, although risk of rebleeding persists; (2) classical (proximal) splenorenal shunt should be abandoned; (3) DSRS may complicate with hepatic encephalopathy, although later and in a lesser percentage than in SRS.

In a recent paper Ezzat et al. (1990), concluded that DSRS is superior to EGDS, but that the latter operation, backed by endosclerosis for rebleeding is a good surgical alternative to DSRS. It is worth mentioning that the patients in this trial were not randomized and that in the schistosomotic group 50 patients were submitted to DSRS and only 15 to EGDS.

Summing up, in our Department of Gastroenterology schistosomotic patients with esophageal varices bleeding are treated by esophagogastric devascularization with splenectomy and, if rebleeding occurs, by sclerosis of varices.

## REFERENCES

ANDRADE, Z. A., 1989. Evolution and involution of hepatosplenic schistosomiasis. *Mem. Inst. Oswaldo Cruz, 84* (suppl. I): 58-75.

BINA, J. C., 1977. *Influência da terapêutica específica na evolução da esquistossomose mansoni.* Thesis, Faculdade de Medicina Bahia. Salvador.

BOGLIOLO, L. A., 1957. Esplenoportografia na esquistossomose mansonica hepato-esplenica, forma de Symmers. *Rev. Ass. Med. Bras., 2:* 263-267.

BRAGHIROLLI NETO, O., 1988. *Fluxo sangüíneo da veia azigos na esquistossomose hepatesplenica: Ação do Propranolol.* Doctoral Thesis. Faculdade de Medicina da Universidade de São Paulo.

CONN, H. O., 1990. *Hepatology* (Elsewhere) (Comments), 11: 1090-1092.

CORDEIRO, F., 1990. Variceal sclerosis in schistosomotic patients: a five-year follow-up study. *Gastrointest. Endosc., 36:* 475-478.

COUTINHO, A., 1968. Hemodynamic studies of portal hypertension in schistosomiasis. *Am. J. Med., 44:* 547-556.

DOMINGUES, A. L. C. & COUTINHO, A. D., 1990. Reduction of morbidity in hepatosplenic schistosomiasis mansoni after treatment with praziquantel: a long term study. *Rev. Soc. Bras. Med. Trop., 23:* 101-107.

EZZAT, F. A.; ABUD-ELMAGD, K. M. & ALY, M. A., 1990. Selective shunt versus nonshunt surgery for management of both schistosomal and nonschistosomal variceal bleeders. *Ann. Surg., 212:* 92-96.

HABIB, Y. A.; KIRA, L. H.; ELSHERBINI, H. A.; ASSER, L. A.; EL-SHAMY, E. A.; HATEM, Y. A., 1991. Role of atrial natriuretic factor in sodium and water retention in patient with schistosomal hepatic fibrosis. *J. Trop. Med. Hyg., 94:* 272-276.

KIIRE, C. R., 1989. Controlled trial of propranolol to prevent recurrent variceal bleeding in patients with non-cirrhotic portal fibrosis. *Brit. Med. J., 298:* 1363-1365.

LYRA, L. G.; REBOUÇAS, G. & ANDRADE, Z., 1976. Hepatitis B surface antigen carrier state in hepatosplenic schistosomiasis. *Gastroenterology, 71:* 641-645.

MACDOUGALL, B. R. D.; WESTABY, D. & BLENDIS, L. A., 1991. Portal hypertension: 25 years of progress. Gut Supplement S18-S24.

MADIWAR, M. A.; EL TAHAIVY, M. & STRICKLAND, G. T., 1989. The relationship between uncomplicated schistosomiasis and hepatitis B infection. *Trans. R. Soc. Trop. Med. Hyg., 83:* 233-236.

MIES, S.; MORI, T.; LARSSON, E.; ROSA, P. & RAIA, S., 1980. Hepatic vein in mansonic schistosomiasis. Angiographic and hemodynamic pattern (abstract). *Gastroenterology, 78:* A1314.

MIES, S.; PEREIRA, M. B.; ORLANDO, C. D.; SETTE, M. & RAIA, S., 1988. Propranolol na prevenção da recidiva de hemorragia digestiva em pacientes com esquistossomose hapetoesplenica. *Rev. Ass. Med. Brasil., 34:* 24-28.

MORGAN, J. S.; GROSZMANN, R. J.; ROJKIND, M.; ENRIQUEZ, R., 1990. Hemodynamic mechanisms of emerging portal hypertension caused by schistosomiasis in the hamster. *Hepatology, 11:* 98-104.

SAKAI, P.; BOAVENTURA, S.; ISHIOKA, S.; MIES, S.; SETTE Jr., H. & PINOTTI, H. W., 1990. Sclerotherapy of bleeding esophageal varices in schistosomiasis. Comparative study in patient with and without previous surgery for portal hypertension. *Endoscopy, 22:* 5-7.

SILVA, A. O.; BRANDÃO, J. F.; CARVALHAES, A.; LEANDRO, P. A.; SILVA, A. T.; RAIA, S. & SILVA, L. C. da, 1982. Endoscopia de urgência na hemorragia digestiva alta em pacientes esquistossomóticos ou cirróticos com hipertensão portal. *GED, 1:* 19-24.

SILVA, L. C.; ALVES, V. A. F.; ABRANTES, C. P.; LIMA, D. M.; CHRISTO, C. H.; DE BRITO, T., 1985. Effects of chemotherapy on mice submitted to multiple Schistosoma mansoni infection. A controlled randomized prospective study. *Trop. Med. Parasitol., 36:* 150.

SILVA, L. C.; STRAUSSS, E.; GAYOTTO, L. C. C.; MIES, S.; MACEDO, A. L.; SILVA, A. T.; SILVA, E. F.; LACET, C. M. C.; ANTONELLI, R. H.; FERMANIAN, J.; FORSTER, S. C.; RAIA, A.; RAIA, S., 1986. A randomized trial for the study of the elective surgical treatment of portal hypertension in mansonic schistosomiasis. *Ann. Surg., 204:* 148-153.

SILVA, L. C.; VIANNA, M. R.; ABRANTES, C. P.; LIMA, D. M. C.; FALAVIGNA, A. L.; ANTONELLI-CARDOSO, R. H.; GALUCCI, S. D. D. & de BRITO, T., 1990. Liver morphology with emphasis on bile ducts changes and survical analysis in mice submitted to multiple Schistosoma mansoni infections and chemotherapy. *Rev. Inst. Med. Trop. S. Paulo, 32:* 328-337.

SPENCE, R. A. J., 1991. Prevention of recurrent bleeding; nonshunting surgery, p. 533-547. In K. Okuda & J. P. Benhamou (eds) *Portal Hypertension, Clinical and Physiological Aspects.* Springer-Verlag, Tokyo.

STRAUSS, E. & LACET, C. M. C., 1986. Hepatite e esquistossomose mansônica. In L. C. da Silva – *Hepatites Agudas e Crônicas.* Sarvier, S. Paulo.

STRAUSS, E.; RAIA, S.; da SILVA, L. C.; FORSTER, S. C.; GAYOTTO, L. C. C.; MIES, S.; MACEDO, A. L. V.; da SILVA, A. T.; FUKUSHIMA, J. & RAIA, A., 1990. Portal hypertension in schistosomiasis. Long term follow-up of a randomized trial comparing three types of surgery (abstract A-66). *Hepatology 12:* 854.

ZWINGENBERG, K.; RICHTER, J.; SIQUEIRA VERGETTI, J. G. & FELDMEIER, H., 1990. Praziquantel in the treatment of hepatosplenic schistosomiasis: biochemical disease markers indicate deceleration of fibrogenesis and diminution of portal flow obstruction. *Trans. R. Soc. Trop. Med. Hyg., 84:* 252-256.