INTRODUCTION

Portal hypertension is a serious clinical syndrome, which is heamodynamically defined by a pathological increase of the portal pressure gradient and by the formation of portal – systemic collaterals that shunt part of portal blood flow to the systemic circulation by bypassing the liver, normal values of the portal pressure is of 1-5 mmHg ***(Bosch et al., 2008).***

The presence and development of esophageal and gastric varices is a clinical manifestation of portal hypertension and its prevalence increase progressively in relation to severity of liver damage ***(Camma et al., 2009).***

The clinical relevance of EV is linked to the risk of bleeding that occurs when Hepatic venous pressure gradient (HVPG) is greater than 12 mmHg ***(De Franchis, 2003).***

One-third of the patients with varices will suffer variceal hemorrhage with a death rate between 30% and 50% during each bleeding episode ***(D'Amico and de Franchis, 2003).***

A generalized program of periodical upper gastrointestinal tract endoscopy in these patients might result in heavy economical burden even for developed countries. Furthermore, repeated examinations, when not performed under general anesthesia or profound sedation, are often poorly

accepted by patients who may refuse further follow up ***(Spiegel et al., 2003).***

Ziol et al. (2005) reported that liver stiffness measurement (LSM) using fibroscan represents a simple, reliable non-invasive parameter that would allow limiting the indications of upper tract endoscopy to a subgroup of patients especially at risk with large varices. Also, ***Robic et al. (2011)*** found that LSM proved as effective as HVPG in predicting clinical decompensation and portal hypertension related complications in patients with chronic liver disease.

AIM OF THE STUDY

The aim of our study is to evaluate the effectiveness, objectivity of transient elastorgraphy (Fibroscan), a new non-invasive technique in the diagnosis of esophageal and gastric varices in pediatric patients with portal hypertension comparing it with standard tool (upper endoscopy).

PORTAL HYPERTENSION

A portal system is one, which by definition, begins and ends with capillaries. The major portal system in humans is one in which the capillaries originate in the mesentery of the intestines and spleen and end in the hepatic sinusoids. Capillaries of the superior mesenteric and splenic veins supply the portal vein with nutrient and hormone rich blood supply. The partially oxygenated portal venous blood supplements the oxygenated hepatic arterial flow to give the liver unique protection against hypoxia ***(Shneider, 2007)***.

Portal hypertension is a serious clinical syndrome, which is heamodynamically defined by a pathological increase of the portal pressure gradient and by the formation of portal – systemic collaterals that shunt part of portal blood flow to the systemic circulation by passing the liver, normal values of the portal pressure is of 1-5 mmHg ***(Bosch et al., 2008).***

Patients who survived an episode of acute variceal hemorrhage have a high risk of rebleeding and death ***(de Franchis, 2010).***

HVPG of 10 mmHg or greater defines clinically significant portal hypertension as this pressure gradient predicts clinical course in patients with cirrhosis including development of varices, clinical decompensation (i.e.,

development of ascites, variceal hemorrhage and encephalopathy ***(Ripoll et al., 2007)***, decompensation or death after liver resection, and hepatocellular carcinoma ***(Ripoll et al., 2009).***

With values of portal pressure gradient below 10 mmHg but exceeding the normal value of 5 mmHg, portal hypertension is referred to as pre-clinical PHT ***(Bosch et al., 2008).***

Pathophysiology of Portal Hypertension and Esophageal Varices:

Obstruction of portal venous flow, whatever the etiology, results in a rise in portal venous pressure. The response to increased venous pressure is the development of collateral circulation that diverts the obstructed blood flow to the systemic veins. These portosystemic collaterals form by the opening and dilatation of preexisting vascular channels connecting the portal venous system and the superior and inferior vena cava ***(Ravindra et al., 2008).***

The lower end of the esophagus is virtually the most important site of these anastomosis at which the esophageal tributaries of the left gastric vein (portal tributary) and the esophageal tributaries of azygos vein (systemic tributary) anastomose. It is the site of esophageal varices which can give rise to haematemesis and melaena. Another important site of

anastomosis is at the lower end of the anal canal where anastomosis between the superior rectal vein (portal) and the middle and inferior rectal veins (systemic) occurs and gives rise to hemorrhoids. At the umbilicus there may be "caput medusa" which is formed by anastomosis of the left branch of portal vein (portal) and veins of anterior abdominal wall (systemic). Retroperitoneal anastomosis between veins of the retroperitoneal organs such as the duodenum (portal) and veins of the posterior abdominal wall (systemic). It can also occur at the bare area of the liver or even inside the liver and sometimes the ductus venosus remains patent and connects the left branch of portal vein (portal) and IVC (systemic) ***(Gimson, 2003)***

Different areas of ectopic varices (EcV) are the duodenum, jejunum, ileum, colon, rectum, peristomal, biliary tree, gallbladder, peritoneum, umbilicus, bare area of the liver, ovary, vagina, and testis ***(Toyonaga, et al., 2010).***

Although direct measurement of portal pressure may provide accurate condition, an invasiveness of portal venous catheterization limits the clinical application. Hepatic venous catheterization is the most common technique to determine the portal pressure. Wedged hepatic venous pressure (WHVP) reflects sinusoidal pressures, and hepatic venous pressure gradient (HVPG) is the difference between WHVP and free hepatic venous pressure (inferior vena cava), becomes

increased over the normal value of 5mmHg, and is associated with variceal bleeding when elevated above 12mmHg ***(Kumar et al., 2008)*** being a good predictor for the severity of portal hypertension.

The FHVP is subtracted from the WHVP to correct for intra-abdominal pressure to provide an accurate measure of the portal vein pressure. As in any other vessel, the pressure within the portal vein is determined by the product of blood flow and resistance to its egress, as defined by Ohm's law:

Portal pressure = portal venous inflow x outflow resistance

Portal hypertension is associated with both increased portal inflow and increased outflow resistance ***(Bosch et al., 2008).*** Intrahepatic vascular tone is modulated by endogenous vasoconstrictors (e.g., norepinephrine, endothelin-1, angiotensin II, leukotrienes and thromboxane A_2) and enhanced by vasodilators (e.g., nitric oxide). In cirrhosis, increased intrahepatic vascular resistance results also from an imbalance between vasodilators and vasoconstrictors ***(Abraldes et al., 2005).***

1- Hepatic Vasodilators:

Nitric oxide (NO) is a powerful endogenous vasodilator and it modulates the intrahepatic vascular tone. NO is produced from the amino acid larginine by NO synthases. It is the natural

ligand for soluble guanylate cyclase and is responsible for an increase in the levels of cyclic guanosine monophosphate, the final agent responsible for the relaxation of the vascular wall through the extrusion of cytosolic Ca^{2+}.

NO also promotes apoptosis of hepatic stellate cell through a signaling mechanism that involves mitochondria, is mediated by reactive oxygen species, and occurs independent of caspase activation ***(*Langer *et al., 2008).*** This NO-dependent apoptosis, which may maintain sinusoidal homeostasis, is expected as a future treatment of portal hypertension.

Carbon Monoxide (CO), a byproduct of heme group oxidation by heme oxygenases (HOs), is considered as an important modulator of intrahepatic vascular resistance. CO activates guanylate cyclase and thereby promotes smooth muscle relaxation, in spite of being less potent than NO. The inhibition of CO production increases portal resistance in normal livers, and HO/CO system is activated in patients with liver cirrhosis. In addition, plasma CO levels directly correlated with cardiac output and inversely with systemic vascular resistance and mean arterial pressure. Thus, CO may be closely related to the hyperdynamic circulatory state in cirrhosis ***(Tarquini et al., 2009).***

2- Splanchnic Vasodilatation:

Portal venous inflow tends to increase in cirrhosis, particularly in advanced stages of portal hypertension, due to the vasodilatation in the splanchnic organ. This increased blood flow is one of the key factors which contribute to the pathophysiology of portal hypertension.

NO is involved in the regulation of splanchnic and systemic hemodynamics in portal hypertension. Furthermore, the fact that cirrhotic patients show increased levels of serum and urinary concentrations of nitrite and nitrate, which are products of NO oxidation, also supports a role of NO in the pathophysiology of portal hypertension. . Further, there are some factors which may activate the constitutive NO synthase: shear stress, circulating vasoactive factors (e.g., endothelin, angiotensin II, vasopressin, and norepinephrine), and overexpression of the angiogenic factor vascular endothelial cell growth factor (VEGF) ***(Fernandez et al., 2005)***.

Glucagon is a humoral vasodilator which is associated with splanchnic hyperemia and portal hypertension. Two mechanisms are considered for vasodilation by glucagon; relaxing the vascular smooth muscle and decreasing its sensitivity to endogenous vasoconstrictors, such as norepinephrine, angiotensin II, and vasopressin. Plasma glucagon levels are increased in cirrhotic patients and

experimental models of portal hypertension, due to decreased hepatic clearance of glucagon as well as an increased secretion of glucagon by pancreatic α cells. The role of glucagon in the splanchnic hyperemia of portal hypertension provides a rationale for the use of somatostatin and its synthetic analogs to reduce glucagon level, thereby treating portal hypertension.

Other Mediators: Carbon Monoxide: is one of the vasodilators; an expression and activity of HO are increased in splanchnic tissues in portal hypertension .HO also stimulates VEGF production, resulting in the development of hyperdynamic splanchnic circulation ***(Angermayr et al., 2006).***

Prostacyclin is an endogenous vasodilator produced by vascular endothelial cells (***Abraldes et al., 2003).*** It causes vascular smooth muscle relaxation by activating adenylate cyclase and augmenting the intracellular level of cyclic adenosine monophosphate.

3- Hyperdynamic Circulation:

Portal venous inflow is affected by hyperdynamic circulation, which is characterized by systemic and splanchnic vasodilatation, low systemic resistance, plasma volume expansion, and high cardiac index. Splanchnic vasodilatation contributes to increasing substantial blood volume which returns to portal venous system. Peripheral vasodilatation activates endogenous neurohumoral systems that cause sodium

retention, which leads to expansion of the plasma volume, followed by an increase in the cardiac index ***(Sanyal, 2008).***

Hyperdynamic circulation is a usual finding in PHT and is characterized by an increased heart rate, stroke volume, cardiac output in the face of a reduced systemic vascular resistance ***(Martell et al., 2010).***

4- Portosystemic Collateral Circulation:

Porto-systemic collaterals are involved to some extent in the pathogenesis of hyperdynamic circulation in the intrahepatic as well as the extrahepatic PHT. These vessels act like an arteriovenous fistulae that shunt the splanchnic blood towards the IVC. So, the venous return to the heart and the cardiac output are increased and these are important contributors for the development of hyperdynamic circulation and increased portal blood flow ***(Bosch et al., 2010).***

Traditionally, the formation of these collateral vessels was considered a mechanical process that leads to opening of the minimally perfused naturally occurring vascular channels that connect both the portal and systemic circulations. As a result, diversion of up to 90% of the portal flow through porto-systemic collaterals back to the heart, resulting in flow mediated remodeling and enlargement of these vessels ***(Bosch et al., 2008).*** Recently, it is believed that angiogenesis is involved in this process by the formation of new blood vessels

under the effect of many mediators like VEGF, PDGF and other mediators. So, it is not a simple process of opening of the preexisting vascular channels as was believed before ***(Fernandez et al., 2005 and Bosch et al., 2010).***

5- Vasoconstrictors and Hepatic Vascular Bed:

Endothelins (ETs) ET- 1 is a powerful vasoconstrictor synthesized by sinusoidal endothelial cells that has been implicated in the increased hepatic vascular resistance of cirrhosis and in the development of liver fibrosis. Activation of ET-B receptors located on the vascular smooth muscle cells promotes vasoconstriction, whereas activation of ET-B receptors located on endothelial cells promotes vasodilatation, which is mediated by enhanced NO and prostacyclin production by the endothelial cell. Plasma levels of ET-1 and ET-3 are increased in cirrhotic patients. The level is dominant in patients with ascites.

Angiotensin II is a powerful vasoconstrictor, which may contribute to increasing hepatic resistance ***(Tandon et al., 2010).*** A-II antagonists, inhibitors of the converting enzyme, or A-II receptors blockers may have a potential to reduce portal pressure, though their effects may be accompanied with systemic hypotension.

Norepinephrine is also a vasoconstrictor, which is involved in the regulation of hepatic vascular tone. The

administration of α-adrenergic antagonists, such as prazosin, inhibits the increase of resistance by norepinephrine.

6- Endothelial Dysfunction:

This endothelial dysfunction is defined as impairment of normal endothelial functions, which are caused by the loss of balance between several factors such as vasoconstrictors and vasodilators, growth promoting and inhibiting factors, pro-atherogenic and anti-atherogenic and pro-coagulant and anti-coagulant factors. It is regarded as an early key event in multiple diseases and in PHT it is considered the initiating event and the cause of all the subsequent derangements occurring afterwards ***(Bosch et al., 2010 and Martell et al., 2010).***

Endothelial dysfunction may have a potential role for the treatment of portal hypertension by improving the endothelial dysfunction. The other is "statins," which decreases intrahepatic vascular resistance and improve flow-mediated vasodilation of liver vasculature in cirrhotic liver, due to increase of NO production and improvement of hepatic endothelial dysfunction ***(Abraldes et al., 2009).***

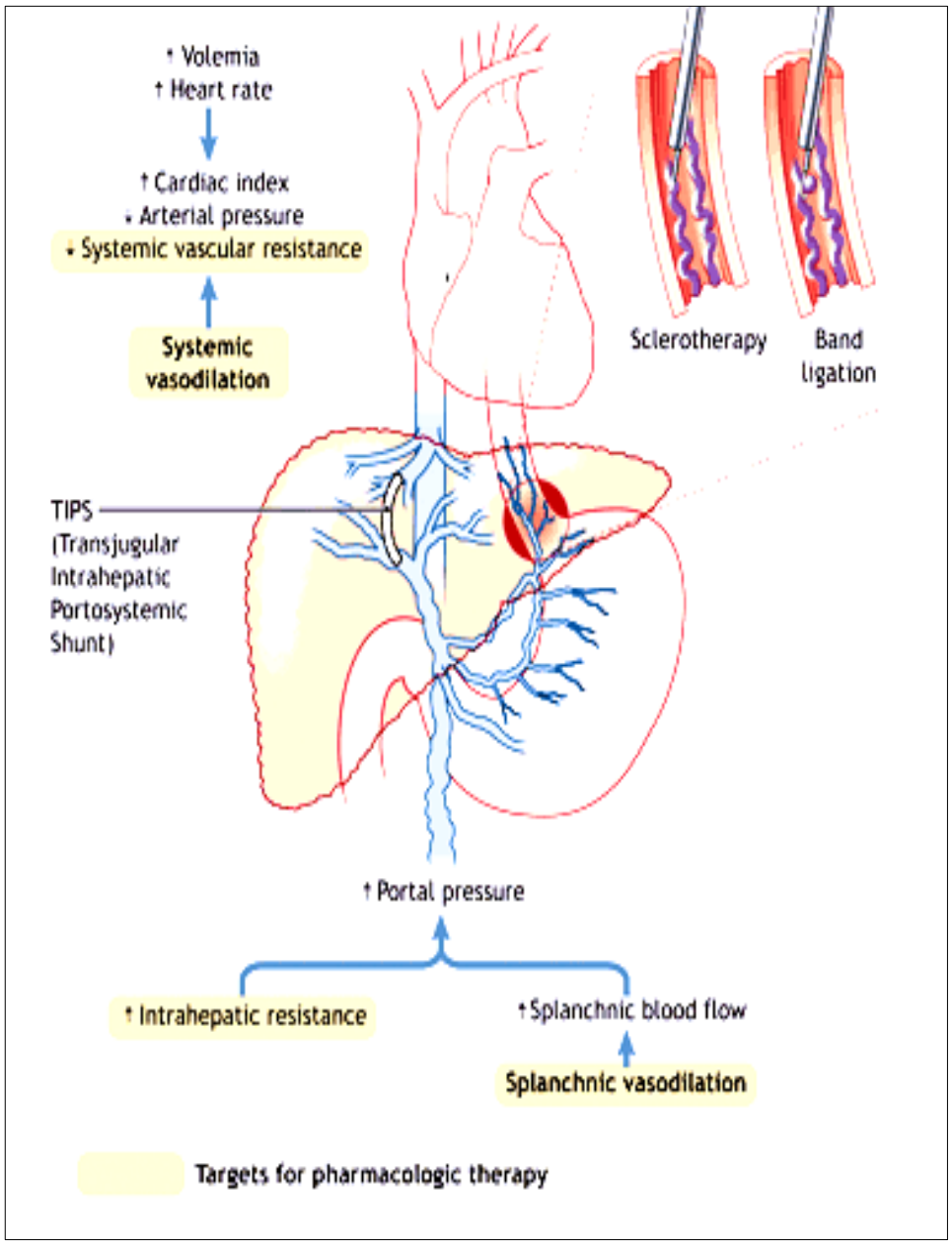

Figure 1: Pathophysiology of portal hypertension (with targets for therapy) *(Calès et al., 2006).*

The pathophysiology in portal hypertension is likely to be multifactorial in origin; various interactive regulations may be present to compensate for the effect of vasoactive mediators. It is a continuous challenge to unveil the mechanism and to develop more effective therapeutic measures.

The following are risk factors for variceal hemorrhage ***(Qureshi et al., 2005 and Dite et al., 2008)***:

- Variceal size - The larger the varix, the higher the risk of rupture and bleeding; however, patients may bleed from small varices too.
- The presence of endoscopic red color signs (eg, red wale markings, cherry red spots).
- Child B or C classification, especially the presence of ascites, increases the risk of hemorrhage.
- Local changes in the distal esophagus (e.g, gastroesophageal reflux). These have been postulated to increase the risk of variceal hemorrhage, but evidence to support this view is weak; studies indicate that gastroesophageal reflux does not initiate or play a role in esophageal hemorrhage.
- Bacterial infection. A well-documented association exists between variceal hemorrhage and bacterial infections, and this may represent a causal relationship.