INTRODUCTION

Approximately 8% of patients with liver cirrhosis without varices develop varices de novo each year, it is estimated that the majority of cirrhotic individuals will develop varices during their life time (Eugene et al., 2011).

All cirrhotic patients without a history of variceal hemorrhage should undergo endoscopic screening to detect presence of varices (Madhotra et al., 2002).

There is significant burden and cost on endoscopy unites for detection of varices, also patients having repeated unpleasant procedure-s even when up to 50% may still not have developed esophageal varices 10 years after the intial diagnosis (Merli et al., 2009).

Serotonin is known as 5-hydroxytryptamine (5-HT), a biogenic a-mine that functions as a ligand for a large family of 5-HT receptors, T-he majority of serotonin in the body (90%) is synthesised by entero-chromaffin cells of the gastrointestinal (GI) tract, where it regulates intestinal motility (Gershon et al., 2007).

With respect to the liver, it was found that serotonin has the ability to regulate hepatic blood flow at both the portal and sinusoidal levels (Ruddel et al., 2011).
Intraportal injections of serotonin were found to significantly increased portal pressure, this suggests that serotonergic mechanisms may contribute to maintaining portal hypertension in patients with cirrhosis (Mabuchi A et al., 2004).
AIM OF THE WORK

To determine the value of plasma serotonin concentration as a predictor of the presence of esophageal and/or gastric varices in cirrhotic patients.
PORTAL HYPERTENSION

Anatomy of the portal venous system:

Portal venous system carries capillary blood from the esophagus, stomach, intestines, pancreas, gallbladder, and spleen to the liver circulatory system of the normal liver-high compliance low-resistance system able to accommodate large blood volumes without substantial increases in portal pressure dual supply with 75% from PV and 25% HA, which converge into channels “hepatic sinusoids” Hepatic Arterial BufferResponse- when PV is reduced (i.e., PVT), arterial inflow increases to maintain total hepatic blood flow. In HAT, PV inflow increases in a compensatory mechanism as well (Sleisenger & Fordtran Gastrointestinal and Liver Diseases. 2010)

It is the unique circulatory system, which connects two systems of capillary beds; one in the wall of the small intestine and spleen and the second in sinusoidal area of the liver blood flow to the liver is unique in that it receives both oxygenated and deoxygenated blood.

As a result, the partial pressure of oxygen (pO2) and perfusion pressure of portal blood are lower than in other organs of the body.
Blood passes from branches of the portal vein through sinusoids of the liver. Blood also flows from branches of the hepatic artery and mixes in the sinusoids to supply the hepatocytes with oxygen.

This mixture percolates through the sinusoids and collects in a central vein which drains into the hepatic vein.

The hepatic vein subsequently drains into the inferior vena cava.

The hepatic artery originates 20% of vascular supply of the liver while the portal vein does remaining 80% (Cichoz-Lach et al., 2008).

Fig. (1): Sleisenger & Fordtran Gastrointestinal and Liver Diseases. 2010.
Definition of portal hypertension:

Portal hypertension, a major hallmark of cirrhosis, is defined as a portal pressure gradient exceeding 5 mm Hg. It is defined by a pathologic increase of portal pressure, in which the gradient between portal vein and inferior vena cava pressure is increased above the upper normal limit of 5 mmHg (Bosch et al., 2008).

Portal pressure is measured by angiography as hepatic vein pressure gradient (HVPG) which is a difference between wedged hepatic venous pressure (WHVP) (pressure in the venous sinuses) and free hepatic venous pressure (FHVP). Determined difference > 5-12mm Hg is considered as portal hypertension. Clinically it is diagnosed by catheterization of portal veins which is one of basic methods to detect portal hypertension (Henderson 2000).

The importance of this syndrome is defined by the frequency and severity of its complications (porto-systemic collaterals, variceal haemorrhage, ascites, hepato-renal syndrome, porto systemic encephalopathy, hepato-pulmonary syndrome); the appearance of these complications defines the progression from compensated to decompensated cirrhosis. The most important and direct consequence of portal hypertension is the formation of porto-systemic
collaterals and, in particularly, the formation of gastro-oesophageal varices, the rupture of which is responsible for the main and most lethal complication of portal hypertension, variceal bleeding. Even with current treatments, the morbidity and mortality associated with this condition is high, which emphasizes the need of effective preventive therapy (D’Amico G & deFranchis R 2003).

**Causes of portal hypertension:**

Cirrhosis of the liver is by far the most common cause of portal hypertension & The causes of portal hypertension are usually subcategorized as prehepatic, intrahepatic, and post hepatic as listed below causes of portal hypertension: (Garcia-Tsao G. 2006)

- **Prehepatic**
  - Portal vein thrombosis
  - Splenic vein thrombosis
- **Hepatic**
  - Pre sinusoidal
  - Schistosomiasis
  - Congenital hepatic fibrosis
  - Sinusoidal
  - Cirrhosis—many causes
  - Alcoholic hepatitis
- Post sinusoidal
- Hepatic sinusoidal obstruction (venoocclusive syndrome).

- **Posthepatic**
  - Budd-Chiari syndrome
  - Inferior vena caval webs
  - Cardiac causes
  - Restrictive cardiomyopathy
  - Constrictive pericarditis
  - Severe congestive heart failure.

---

**Fig. (2):** Classification of portal hypertension according to site of vascular obstruction, most common cause *(Colledge et al., 2010).*
Pathophysiology of portal hypertension:

The initial event in the development of portal hypertension in cirrhosis is an increase in resistance to outflow from the portal venous bed.

This results from a relatively fixed component from distortion of the intra hepatic vascular bed from the disruption of hepatic architecture and a dynamic component from impaired intrahepatic vasodilation.

An estimated 30% of the increased portal resistance is due to the hemodynamic changes, characterized by hepatic vasoconstriction and impaired response to vasodilatory stimuli (Shah V et al 1998)

An intrahepatic decrease in the production of the vasodilator nitrous oxide (NO) (Sarin S, et al 1991)in combination with an increase in the production of the vasoconstrictor endothelin-1, is the major contributor to the dynamic increase in hepatic vascular resistance (Pinzani M, et al 1996)

The hallmark of portal hypertension is a pathologic increase in the pressure gradient between the portal vein and the inferior vena cava, which is measured by the hepatic venous pressure gradient (HVPG).
Briefly, the wedged hepatic vein pressure (WHVP), a marker of sinusoidal pressure, and the free hepatic vein pressure (FHVP) are measured with radiologic assistance. HVPG is calculated by the following formula (Garcia et al., 2005).

$$HVPG = WHVP - FHVP$$

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: $\Delta P = Q \times R$ in which $\Delta P$ is the portal pressure gradient, $Q$ is the flow within the portal venous system, and $R$ is the vascular resistance of the portal venous system, which represents the sum of the resistance of the portal vein, the hepatic vascular bed, and of the portosystemic collaterals. It follows that portal pressure may be increased by an increase in portal blood flow, an increase in vascular resistance, or a combination of both (Bosch & Garcia, 2000).

However, it is well established that in cirrhosis, the primary factor leading to portal hypertension is an increased resistance to portal blood flow. Later on, an increase in portal venous inflow will help to maintain and aggravate portal hypertension (Aina Rodríguez et al., 2007).
Experimental studies have shown that the initial factor in the pathophysiology of portal hypertension is the increase in vascular resistance to portal blood flow. In cirrhosis, this increase in resistance occurs at the hepatic microcirculation (sinusoidal portal hypertension).

![Diagram of Portal Pressure](Paquet, 2000)

Fig. (3): Portal Pressure (Paquet, 2000).
It is important to emphasize that, contrary to what was traditionally thought, increased hepatic vascular resistance in cirrhosis is not only a mechanical consequence of the hepatic architectural disorder caused by the liver disease, but there is also a dynamic component, due to the active contraction of portal/septal myofibroblasts, activated stellate cells and portal venules (Wiest and Groszmann, 2002)

The following pathophysiological changes explaining the portal hypertension will be discussed:

1. Increase vascular resistance to portal blood flow.

2. Increase portal venous flow.

3. Hyperdynamic circulation.

1-Increased vascular resistance to portal blood flow:

In cirrhosis, the principal site of increased resistance to outflow of portal venous blood is within the liver itself. This results from 2 factors:

(1) Mechanical obstruction to flow because of fibrotic disruption of architecture.

(2) Dynamic component produced by active contraction of vascular smooth muscle cells and activated stellate cells (Garcia-Pagan et al., 2005).
Although the former is not acutely modifiable, disease stabilization and improvement, eg, after successful treatment of hepatitis C or abstinence from alcohol, can improve fibrosis and the mechanical component (Rincon et al., 2006). The vascular, reversible component of the increased intra hepatic resistance is mainly the result of a deficit of the vasodilator nitric oxide (NO) in the liver microcirculation. This has led to the use of NO donors to decrease intrahepatic resistance and thereby portal pressure.

In this regard, recombinant adenovirus carrying the endothelial NO synthase (NOS 3) gene was injected intra portally into rats with cirrhosis induced by carbon tetrachloride (Van de Casteele et al., 2002).

One study suggests, however, that cirrhotic livers may have a lower vaso-relaxant response to NO donors. In this study, the vascular relaxation induced by either nitroglycerin, from which NO is liberated enzymatically, or the spontaneous NO donor, S-nitroso-Nacetylpenicillamine (SNAP), which liberates NO non enzymatically, was investigated using in situ perfusion of normal and cirrhotic rat livers. Compared with normal livers, cirrhotic livers exhibited lower vasorelaxant response to both nitroglycerin and SNAP, indicating an inability of the cirrhotic vasculature to respond to NO. In addition, nitroglycerin induced less vasorelaxation than SNAP, indicating impaired liver
metabolization of nitroglycerin to NO (Dudenhoefer et al., 2002).

An increased production of vasoconstrictors and an exaggerated response of the hepatic vascular bed to them, as well as an insufficient release of vasodilators together with an insufficient response to vasodilators of the hepatic vascular bed are the mechanisms that have been implicated in the pathogenesis of the dynamic component of the increased intrahepatic resistance of the cirrhotic liver (Aina Rodríguez et al., 2007).

**Different vasoconstrictive factors, that are detailed below, have been involved in the regulation of hepatic vascular tone in cirrhotic livers:**

**α-Adrenergic agonists**

The alpha-adrenergic agonist norepinephrine, that is usually elevated in decompensated cirrhosis, has been shown to increase intra hepatic vascular resistance. This is completely blunted by the administration of α-adrenergic antagonists, such as prazosin. This agent by itself markedly reduces hepatic resistance and portal pressure in patients with cirrhosis. On the other hand, the administration of β-adrenergic agonists, such as isoproterenol, reduces intrahepatic vascular resistance in perfused cirrhotic liver. These data
suggest that adrenergic receptors may be involved in the regulation of intrahepatic resistance in cirrhosis, and that α-adrenergic receptor blockers may decrease portal pressure in cirrhosis (Ballet et al., 1988).

b-Cysteinyl leukotrienes

Cysteiny1 leukotrienes (CT) are a group of highly potent vasoactive substances derived from the oxygenation and dehydration of arachidonic acid by 5-lipoxygenase that increases intrahepatic vascular resistance in normal and cirrhotic rat livers. However, this response is significantly greater in cirrhotic livers that in addition also have an increased expression of the 5-lipoxygenase mRNA and an increased production of CT. 5-lipoxygenase inhibition produces a marked reduction in portal pressure in cirrhotic livers, which suggests that 5-lipoxygenase–derived eicosanoids also contribute to the increased hepatic vascular resistance in cirrhosis (Graupera et al., 2002)

c-AngiotensinII:

Angiotensin II (A-II) is a powerful vasoconstrictor that increases hepatic resistance. Increased A-II is the result of the activation of the renin-angiotensin system (RAS), which is commonly observed in patients with cirrhosis.