

# Hepatopulmonary syndrome (HPS)

By Alaa Haseeb , MS.c

## ***Definition:***

HPS is a disease process with a triad of:

1- Liver disease.

2- Widespread intrapulmonary vasodilatation.

3- Gas exchange abnormality presenting with increased alveolar arterial oxygen gradient ( $\Delta P(A-a)O_2$ ) while breathing room air, that results ultimately in hypoxemia.

- The most common liver disease responsible for HPS is liver cirrhosis.
- Other liver diseases may contribute ;
  - Non cirrhotic portal hypertension.
  - Extrahepatic portal vein obstruction.
  - Chronic active hepatitis.
  - Fulminant hepatic failure

## ***Prevalence:***

Studies on HPS report a wide range of prevalence of the disease which can be due to different patient groups and study designs. Usually it is reported to be between 9 to 29% of patients with liver disease.

# *Pathophysiology:*

## I) Vasodilatation:

Persistent pulmonary and systemic vasodilatation is mostly explained by the imbalance of vasodilator and vasoconstrictor agents favoring vasodilators. This could be due to:

- a- Overproduction of the vasodilators from injured hepatobiliary system.
- b- Decrease in their clearance by the liver.
- c- Production of a vasoconstrictor inhibitor.

d- Normal sensitivity of the pulmonary vessels to vasoconstrictors in response to hypoxemia is blunted in HPS.

- Numerous vasodilators are suspected but nitric oxide ( NO) is the most appreciated one. Other mediators include vaso-active intestinal peptide (VIP), calcitonin related peptide, glucagon, substance P and platelet activating factor.

## ***II) Hypoxemia:***

- The main pathophysiologic event underlying hypoxemia is widespread pulmonary precapillary and capillary vasodilatation. Pulmonary capillary diameter is normally about 8-15 micrometer ( $\mu\text{m}$ ) and this could rise up to 500  $\mu\text{m}$  in HPS.
- In addition, there is distinct arterio-venous (AV) malformations and direct AV communications.
- Pleural spider angiomas may also form.

These changes lead to the following:

**a- Ventilation perfusion ( V/Q) mismatch:**

- Results from widespread pulmonary vasodilatation and decreased V/Q ratio in alveolar-capillary units leading to low pressure of oxygen in arterial blood ( PaO<sub>2</sub>) and low oxygen (O<sub>2</sub>) content of the blood leaving these units. This hypoxemia is correctable by breathing 100% oxygen.

## **b- Right to left shunting of the blood:**

This results from direct arterio-venous communications that have no contact with breathed air. If numerous, they can give rise to severe hypoxemia unresponsive to breathing 100% oxygen.

### c– Diffusion impairment:

Excessive vasodilatation causes O<sub>2</sub> molecules not to reach the center of dilated capillaries readily. Increased cardiac out put and decreased transition time of blood through pulmonary vascular bed on the other hand impairs diffusion, this is called *diffusion-perfusion defect* or *alveolar capillary oxygen disequilibrium*.

#### d- Response to breathing 100% O<sub>2</sub> :

- In response to breathing 100% oxygen if PaO<sub>2</sub> rose to levels  $\geq 600$ mmHg, shunting of blood is unlikely.
- If it failed to exceed 500  $\mu$ mmHg, shunt can't be ruled out.
- If it didn't rise to levels above 150-200mmHg, shunt is most probably the main mechanism of hypoxemia.

## ***Clinical Manifestations:***

- More than 80% of patients present with symptoms and signs of liver disease.
- In less than 20%, the presenting symptoms and signs are related to lung disease. These include dyspnea, cyanosis, clubbing, platypnea and orthodeoxia.
- There is controversy on a correlation between the severity of liver disease and HPS.

Some studies have shown that the severer the liver disease the severer the HPS, but others have failed to show so.

- Mortality is high among HPS patients and is reported to be around 40% within 2-3 years after presentation. Curious enough, the causes of mortality are most commonly non respiratory (e.g., GI bleeding, sepsis, renal failure).

# ***DIAGNOSIS***

Diagnostic criteria for HPS are

- 1) Liver disease, and
- 2) Gas exchange abnormality manifested by hypoxemia ( $\text{PaO}_2 < 70 \text{ mmHg}$ ) and/or  $\Delta\text{P}(\text{A-a})\text{O}_2 > 20 \text{ mmHg}$  due to widespread intrapulmonary vasodilatation, in the absence of any primary cardiopulmonary disease.

# ***Diagnostic Procedures:***

## ***a) Arterial blood gas analysis :***

Performed in the supine and sitting positions.

## ***b) Chest X-ray and chest CT:***

Are normal or show non-specific minor reticulonodular changes in the base of the lungs *and /or dilatation of the peripheral pulmonary vasculature.*

***c) Pulmonary function tests:***

commonly show decreased diffusion ability of the lungs pointing to intrapulmonary vasodilatation.

***d) Two dimensional contrast enhanced echocardiography (CEEC):***

Is the method of choice for diagnosing intrapulmonary vasodilatation and is the most sensitive procedure designed for this purpose.

CEEC , however, lacks specificity in that in chronic liver disease the prevalence of pulmonary vasodilatation is about 20% by this method despite normal gas exchange status. Contrast enhanced trans-esophageal echocardiography is more sensitive than trans-thoracic echocardiography, and correlates more with gas exchange abnormality.

***e) Macro aggregated albumin scanning:***

Technetium 99m- labeled macroaggregated albumin is used. The estimated sensitivity of this method for diagnosing intrapulmonary vasodilatation is about 84% and its specificity is 100%. In addition, shunt fraction can be calculated by this procedure.

**f) *Pulmonary angiography:***

Two different angiographic patterns in HPS:

*Type I:* more common. There are minimal changes with diffuse spider like branches to more advanced changes with a blotchy, spongy appearance ( the type that responds to breathing 100% oxygen).

*Type II:* less common. There are vascular lesions as vascular dilatations representing A-V communications ( the type that responds poorly to breathing oxygen and liver transplantation is not as suitable as for type I vascular lesions).

**g) *Pulmonary artery catheterization:***

Is not used commonly for diagnosing HPS.

# ***Treatment:***

## ***I) Medical therapy:***

There are currently no medications proved to have persistent, adequate or acceptable effect on HPS. The following are tried:

***a- Almitrin bimesylate*** :is a stimulator of arterial chemoreceptors ( used in COPD).

***b- Indomethacin*** :

To cause inhibition of prostaglandin production which has a putative role of vasodilatation.

### *c- Methylene blue :*

Is a potent inhibitor of NO and its intracellular mediator, guanylate cyclase and is potentially effective for treatment of HPS although transiently. It might be used in the post-operative period of liver transplantation in cases with transient hypoxemia, however its routine and long term use is not recommended yet.

## ***II) Interventions other than liver transplantation:***

### ***a- Embolotherapy:***

It is recommended that pulmonary angiography be done for HPS patients who respond poorly to breathing 100% oxygen i.e.,  $PaO_2 < 150-200\text{mmHg}$ . If type II vascular lesions are diagnosed, embolotherapy with 22-coil spring devices must be tried.

***b- Portal decompression with transjugular intrahepatic portosystemic shunt (TIPS):***

There is controversy regarding the beneficial effects of this technique on HPS. Some studies confirmed the improvement of hypoxemia and others ruled out any usefulness of TIPS. More researches are needed undoubtedly.

### ***III) Orthotopic Liver transplantation (OLT):***

Previously, hypoxemia was considered as an absolute contraindication for OLT.

Today the trend is to give a chance to this group of patients with the logic that HPS is a progressive and fatal disease and there isn't an effective therapy which could improve oxygenation significantly.

The rate of improvement of HPS patients with type I vascular lesions undergoing OLT is about 80% , but is much less in those with type II lesions.

Thank you

Alaa Haseeb , MS.c