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HEPATOPULMONARY SYNDROME ASSOCIATED WITH PORTOPULMONARY HYPERTENSION: CASE REPORT

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ABSTRACT

Case Presentation: Man, 48 years old, with cirrhosis due to non-alcoholic steatohepatitis (NASH) with portal hypertension, already decompensated with ascites, hepatic encephalopathy, esophageal varices, CHILD-PUGH C11 and MELD -Na 25, referred for pre - evaluation liver transplant. During the evaluation, an increase in the alveolar-arterial gradient (GA-aO2) was evidenced by blood gas analysis, continuing investigation with transthoracic echocardiogram (ECOTT), which showed passage of microbubbles after the sixth cardiac cycle, compatible with intra-pulmonary shunt, configuring hepatopulmonary syndrome (HPS), in this moderate case seen PaO2 of 69 mmHg. Furthermore, ECOTT revealed signs suggestive of pulmonary hypertension, with pulmonary artery systolic pressure (PASP) being 64mmHg. A hemodynamic study was indicated, through right heart catheterization, which confirmed moderate to severe pulmonary arterial hypertension with a mixed component (pre and post capillary), presenting the following parameters in the evaluation of the pulmonary artery trunk: Systolic pressure 59mmHg, diastolic pressure 33mmHg and mean pressure of 44mmHg. Therapy for pulmonary hypertension was initiated with sildenafil in association with ambrisentan, in addition to furosemide and spironolactone due to the hypervolemic component. The patient continues to be monitored by specialties to assess the response to therapy. **Discussion:** HPS is a complication resulting from portal hypertension and is the main cause of respiratory failure in cirrhotic patients. It is a priority on the liver transplant list and is the treatment of choice. Prevalence reaches 32% in cirrhotic patients, being the result of microvascular changes, hindering pulmonary gas exchange due to diffuse dilations at the pre -capillary level, or capillaries, or arteriovenous communications presenting changes in the ventilation-perfusion relationship and a decrease in gas exchange time. The diagnosis is: change in GA-aO2 or hypoxemia with evidence of intrapulmonary shunt, in a patient with chronic liver disease, and its severity is graded based on PaO2. Pulmonary hypertension can be a prohibitive condition for liver transplantation, depending on its severity (patients with mPAP >50mmHg), and even after responding to therapy, it presents a high mortality rate. This patient presented a mixed component of pulmonary hypertension, which was explained by portopulmonary hypertension (type I) and hypervolemic status (type II). Therapy was initiated for better clinical control of the disease and subsequent reevaluation for liver transplantation. **Final considerations:** HPS is a condition that should be investigated in all cirrhotic patients due to its prevalence and severity. The association with pulmonary hypertension is rare, directly interfering in the planning of liver transplantation and the survival of these patients.

KEYWORDS: Alveolar arterial oxygen gradient; Hypervolemia; Hepatopulmonary syndrome; Portopulmonary hypertension.

INTRODUCTION

Pulmonary hypertension is a chronic and progressive disease characterized by an increase in pulmonary artery pressure values and an increase in pulmonary vascular resistance, which can lead to right heart dysfunction. There are 5 types of pulmonary hypertension categorized according to etiology (Table 1). Its association with portal hypertension is rare, classified as type 1, with a prevalence of up to 10% of patients. This association directly influences the prognosis before, during, and after liver transplantation. It is not known whether there is a correlation between the severity of liver disease and the severity of portopulmonary hypertension, but it is observed that women, autoimmune liver disease, high levels of estradiol, and previous splenectomy are risk factors for its appearance.[1]

Table 1: Classification of pulmonary hypertension according to the World Health Organization.

WHO Group	Type of pulmonary hypertension	Average PCP	Examples of etiological causes
1	Pulmonary arterial hypertension	Normal	Idiopathic, hereditary, portal hypertension, congenital shunts, drug-induced
2	HP would be secondary to left heart disease	Increased	Valve disease, systolic dysfunction, diastolic dysfunction, pericardial disease, cardiomyopathies
3	HP would be secondary to lung disease	Normal	COPD, Asthma, Interstitial lung disease, Obstructive sleep apnea
4	PH due to chronic pulmonary thromboembolism	Normal	Chronic PTE
5	PH of unclear and/or multifactorial cause	Normal or increased	Systemic diseases, sarcoidosis, vasculitis, chronic kidney disease.

Caption: PH pulmonary arterial hypertension; WHO: world health organization; PCP: pulmonary capillary pressure; COPD: chronic obstructive pulmonary disease; PTE: pulmonary thromboembolism.
Adapted from Galiè, N. (2015).

Portopulmonary hypertension is multifactorial but has three main pathophysiological mechanisms: pulmonary artery vasoconstriction due to intimal proliferation, smooth muscle expansion leading to medial wall hypertrophy, and the development of plexiform arteriopathy, as well as platelet aggregation and thrombosis.[2]

In addition to these, we can highlight the following characteristics (figure 1) in the pathophysiology of the disease.

1- Increased Pulmonary Vascular Resistance: Portal hypertension induces vasodilation in the small pulmonary arteries. This, coupled with the diversion of blood from the portal system to the systemic circulation, results in an elevation of pulmonary vascular resistance due to increased blood flow in this system.
2- Endothelial Dysfunction: This leads to an imbalance of inflammatory and angiogenic mediators, contributing to vasoconstriction and vascular remodeling in the pulmonary arteries.
3- Formation of Portopulmonary Shunts: High pressure in the portal system leads to the creation of abnormal communications between the portal circulation and the pulmonary circulation. These shunts divert blood rich in vasoactive substances, such as nitric oxide, directly to the lungs, contributing to pulmonary vasodilation and pulmonary arterial hypertension.
4- Vascular Remodeling: Over the long term, chronic pulmonary hypertension induces structural changes in the pulmonary arteries, causing thickening of the vascular wall and lumen obstruction. This process further elevates pulmonary vascular resistance.
5- Cardiac Volume Overload: Overloading of the right heart results in right ventricular dilation and dysfunction. This phenomenon arises due to the heightened pulmonary vascular resistance, necessitating additional effort from the right ventricle to pump blood into the lungs.[2, 3, 4]

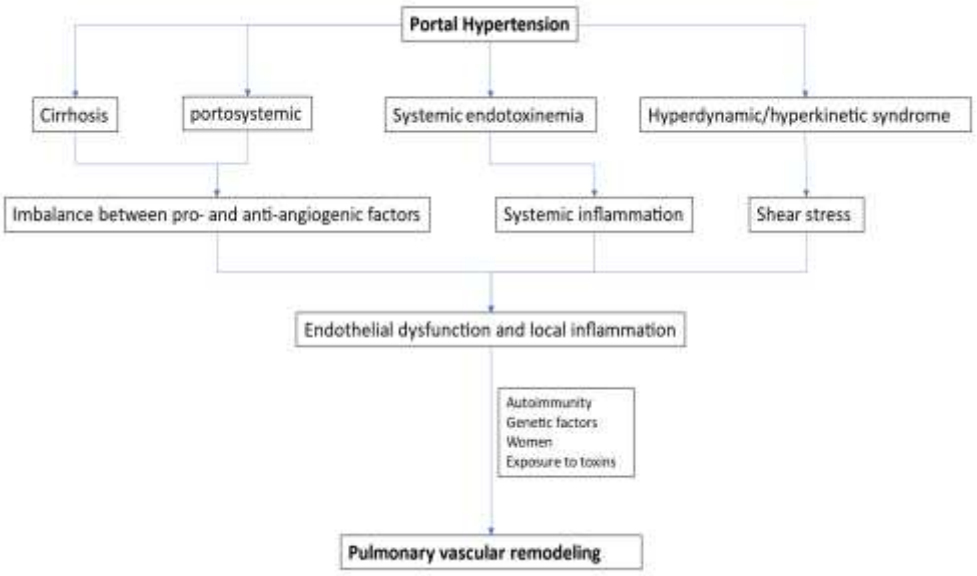


Figure 1: Pathophysiological mechanism of portopulmonary hypertension.

Adapted from Jasso -Baltazar, EA et al. (2023).

Most patients are asymptomatic, but some may experience fatigue, dyspnea, and edema as primary symptoms, which can be indistinguishable from symptoms primarily related to cardiovascular and pulmonary congestion. Clinical signs may include hypoxemia (more common in HPS), tachypnea, and tachycardia, with the possibility of a galloping rhythm due to hypervolemia (B3).[1]

The diagnosis of pulmonary hypertension is suggested through echocardiographic evaluation, the primary screening test, revealing evidence of an increase in pulmonary artery trunk pressure. Confirmation is obtained through right heart catheterization. Diagnostic criteria for portopulmonary hypertension (PPH) rely on clinical, hemodynamic, and imaging assessments, as illustrated in Figure 2. These criteria can be complex due to the multifactorial nature of PPH and the necessity to rule out other causes of pulmonary arterial hypertension.

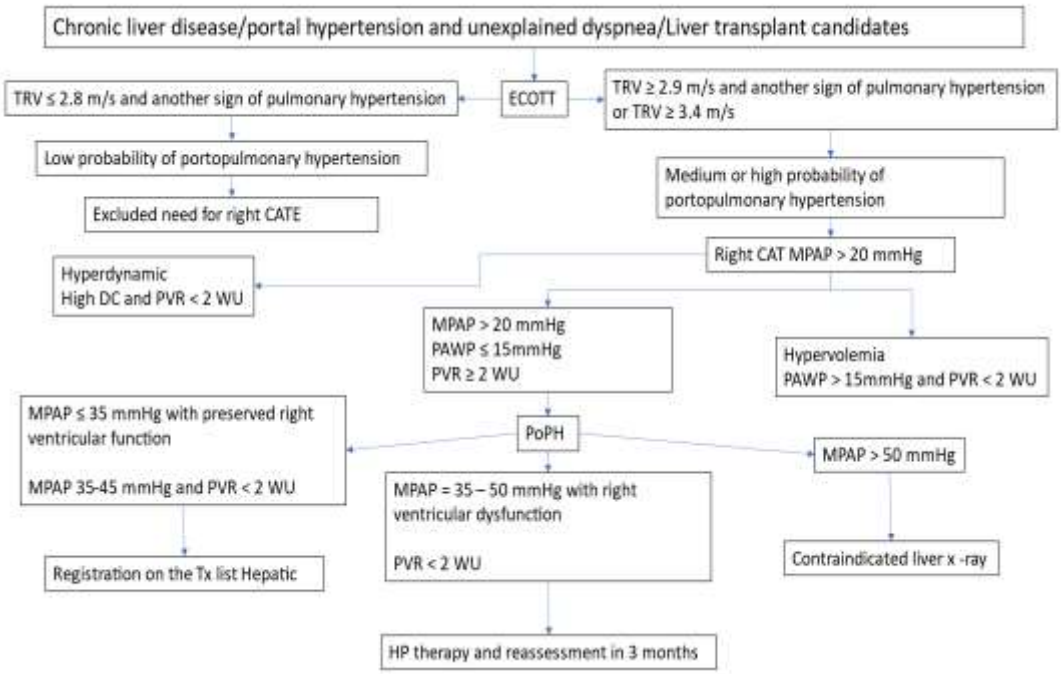
Clinical Criteria

1- Presence of portal hypertension: Portal venous pressure (PVP) ≥ 10 mmHg; evidence of clinical signs of portal hypertension, such as esophageal varices, ascites, thrombocytopenia with splenomegaly; transient elastography showing a kPa above 25, indicating chronic liver disease with clinically significant portal hypertension.

2- Evidence of pulmonary arterial hypertension (PAH) or pulmonary venous hypertension: Defined as a mean pulmonary artery pressure (mPAP) ≥ 20 mm Hg at rest, measured by right heart catheterization; Wedge pulmonary capillary pressure (PCP) ≤ 15 mm Hg; Pulmonary vascular resistance (PVR) > 3 Wood units (WU).

Exclusion Criteria: Exclusion of other causes of pulmonary arterial hypertension such as heart disease, chronic lung disease, chronic pulmonary embolism, and other known causes of PAH.

Hemodynamic Criteria: Mean pulmonary pressure gradient (mPAP) - wedge pulmonary capillary pressure (PCP) ≥ 5 mm Hg, which suggests the presence of PPH.
Imaging Criteria: Imaging findings that confirm the presence of PPH, such as dilated pulmonary arteries or portopulmonary shunts. Furthermore, the severity of portopulmonary hypertension is graded by blood pressure values, being mild (mPAP 20-35 mmHg), moderate (mPAP 35-45 mmHg), and severe (mPAP > 45 mmHg).[1, 5, 6]



Portopulmonary Hypertension (PoPH) diagnostic algorithm.

Caption: DC: cardiac output; MPAP: mean pulmonary artery pressure; Tx: transplant; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; CAT: Transarterial cardiac catheterization; ECOTT: transthoracic echocardiogram; TRV: tricuspid valve regurgitation velocity.

Adapted from Jasso -Baltazar, EA et al. (2023).

The treatment of portopulmonary hypertension (PPH) is complex and necessitates a multidisciplinary approach involving hepatologists, cardiologists, and pulmonologists due to its multifactorial nature. A support team, including a nutritionist, psychologist, and physical educator, is also crucial. The primary goals of PPH treatment are to alleviate symptoms, improve the quality of life, and, when possible, address the underlying causes of portal hypertension and pulmonary hypertension. Pharmacological interventions do not alter the natural progression of the disease and do not yield significant prognostic benefits in the first 6 months. The primary objective is to stabilize the clinical condition for liver transplantation, with a considerable increase in survival observed over 5 years with treatment. Among the therapeutic modalities, we can mention.

Treatment of Underlying Portal Hypertension: If PPH is associated with underlying portal hypertension, such as liver cirrhosis, it is essential to implement measures to reduce portal pressure, including the use of beta-blockers or consideration of liver transplantation. Addressing underlying portal hypertension may lead to an improvement in PPH.[8, 9]

Treatment of Pulmonary Arterial Hypertension (PAH): may include specific medications, such as phosphodiesterase-5 inhibitors and prostacyclin, aimed at reducing pressure in the pulmonary arteries.[10]

Oxygen therapy: Supplemental oxygen administration may be necessary to enhance oxygenation in patients with HPS, whether associated or not with HPH.[1,11]

Diuretics: An important support in managing hypervolemia and complications arising from portal hypertension, such as ascites.

Beta-blockers: An important tool in managing portal hypertension, indicated for the prophylaxis of upper gastrointestinal bleeding. Additionally, they offer secondary benefits in portal hypertension, particularly carvedilol. However, caution is advised in patients with portopulmonary hypertension, as many may exhibit right ventricular dysfunction. The recommendation for this patient profile is not yet well-established.

The specific treatment of pulmonary hypertension includes the use of prostacyclin agonists, endothelin receptor antagonists, phosphodiesterase inhibitors, and guanylate cyclase stimulants. The objective is to reduce mean pulmonary artery pressure (mPAP) and vascular resistance through vasodilation.[1]

Prostacyclin analogues are recommended for type 4pulmonary hypertension and can serve as bridge therapy for transplantation. Endothelin analogues are indicated for profiles 2 and 3 and can be employed as monotherapy or in combination with phosphodiesterase inhibitors. Phosphodiesterase 5 inhibitors are utilized in profile 1, while guanylate cyclase stimulants are

indicated for cases resulting from pulmonary thromboembolism.[1]

Beyond pharmacological therapies, liver transplantation stands as the definitive treatment for liver disease, portal hypertension, and hepatopulmonary syndrome. While this procedure can reverse portopulmonary hypertension, it is contraindicated in patients with untreated pulmonary hypertension exceeding 50 mmHg or when treatment fails to maintain values below 40 mmHg. Post-liver transplantation, pharmacological therapies for pulmonary hypertension may still be necessary.

On the other hand, hepatopulmonary syndrome constitutes a clinical syndrome characterized by a triad.
1 - Advanced liver dysfunction, portal hypertension, and congenital systemic portal shunts.[12]
2 - Intrapulmonary vascular dilation.
3 - Impairment of arterial oxygenation[13], with concentrations below normal levels and/or an increase in the alveolar-arterial gradient in oxygen partial pressure.

It is the primary cause of respiratory failure in cirrhotic patients[14], occurring without primary heart or lung disease and affecting up to 32% of cirrhotic individuals.[15] Notably, hepatopulmonary syndrome (HPS) can also manifest in patients with non-cirrhotic portal hypertension.[16] The genesis of HPS is predominantly linked to portal hypertension, resulting from an intricate interplay among vasoconstrictors, vasodilators, and hepatic factors that either inhibit or stimulate the growth of vascular cells. This leads to microvascular alterations in pulmonary gas exchange.[17] These alterations involve diffuse dilations at the pre-capillary level, capillaries, or arteriovenous communications (true shunt)[18], compromising the ventilation-perfusion (V/Q) relationship. Such changes, coupled with the hyperdynamic state observed in liver dysfunction, contribute to an accelerated blood flow within the pulmonary territory, thereby reducing the time available for effective gas exchange.

The diagnosis of Hepatopulmonary Syndrome (HPS) significantly impacts the prognosis of patients with liver cirrhosis, doubling the risk of mortality.[19] Interestingly, there is no described relationship between the severity of liver disease and the presence of HPS.[13, 23] Consequently, HPS screening is recommended for all patients with chronic liver disease, particularly those on the liver transplant list. The diagnostic criteria, as proposed by Krowka et al., include an increase in the alveolar-capillary oxygen gradient exceeding 15 mmHg for patients under the age of 64 or 20 mmHg for those aged 65 or older in an upright position at rest. Diagnosis also involves the recognition of intrapulmonary vascular changes through transthoracic echocardiography with contrast (bubbles) and the presence of liver dysfunction, with a higher prevalence observed in cases of liver cirrhosis with portal hypertension.[20]

The severity of Hepatopulmonary Syndrome (HPS) is established based on PaO2 values: ≥80 mmHg (mild); <80 and ≥60 mmHg (moderate); <60 and ≥50 (Severe); <50 mmHg (Very Severe).[21] Clinically, in HPS, hypoxemia is more severe, with PaO2 possibly being less than 50 mmHg and accompanied by orthodeoxia.[13, 22]

The primary element of symptomatic treatment is oxygen therapy. Various therapeutic modalities have been explored in HPS, with inconclusive results, necessitating further clinical studies to better define their efficacy.[25, 26, 27,28]

A review of 73 HPS cases demonstrated that 82% of patients normalized their oxygenation changes within 9 to 15 months after liver transplantati.[22] This normalization was evidenced by contrast echocardiography and scintigraphy. Therefore, it can be inferred that the only effective treatment to date is liver transplantation, with better outcomes when performed in the early stages of the disease. A PaO2 below 60 mmHg is used as an indicative parameter for prioritizing the patient on the liver transplant list.[24] Survival at 5 years post-transplantation is 76%, and recurrence of the disease after this intervention is rare.[23]

CASE REPORT

Man, 48 years old, with cirrhosis due to non- alcoholic steatohepatitis (NASH) with portal hypertension, already decompensated with ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, medium-sized esophageal varices, with no history of upper digestive hemorrhage, having undergone elastic ligation of esophageal varices as primary prophylaxis, in addition to systemic arterial hypertension. Smoking for 30 years/pack with abstention for 18 years and Grade III obesity, with weight loss of 50 kg in 4 months, being referred for pre -liver transplant evaluation. Patient on outpatient use of Furosemide 160mg/day, spironolactone 100mg/day, omeprazole 20mg/day, Lactulose, alprazolam 0.5mg/day and ciprofloxacin 500mg/day.

During evaluation at the pre -liver transplant outpatient clinic, a reduced level of consciousness, disorientation in time and space, flapping, and diffuse crackles on lung auscultation were noted. Furthermore, the companion reported that the patient had not had bowel movements for more than 3 days, even after using medications at home.

In view of these changes, he was sent to the hospitalization department to follow up on the necessary therapeutic measures. On admission examinations, the classification was CHILD-PUGH C11 and MELD-Na 25, Urine type 1 with signs of urinary tract infection, a chest x-ray was performed, showing inversion of the vascular network with changes compatible with hypervolemic status, without other changes compatible with disease. chronic obstructive pulmonary disease despite a history of smoking. Therefore, antibiotic

therapy was started, laxative measures were started, and diuretics were removed. During hospitalization, an abdominal tomography was performed for pre -liver transplant evaluation and investigation of nodules due to significant weight loss. Upper digestive endoscopy was performed requiring elastic ligation of esophageal varices. Arterial blood gas analysis showed an increase in the alveolar-arterial gradient (GA-aO2) measuring 47.8 mmHg, with PO2 of 69.9 mmHg, PCO2 25.6 mmHg, pH 7.534, SatO2 94.8% in room air. continuing investigation with transthoracic echocardiogram (ECOTT), which showed passage of microbubbles after the sixth cardiac cycle, compatible with intra-pulmonary shunt, configuring hepatopulmonary syndrome (HPS), in this moderate case seen PaO2 of 69mmHg. Furthermore, ECOTT revealed signs suggestive of pulmonary hypertension, with pulmonary artery systolic pressure (PASP) being 64mmHg, and the presence of moderate enlargement of the left atrium and mild enlargement of the right chambers. A hemodynamic study was indicated that confirmed moderate to severe pulmonary arterial hypertension with a mixed component (pre- and post-capillary), presenting the following parameters in the assessment of the pulmonary artery trunk: Systolic pressure 59mmHg, diastolic pressure 33mmHg and mean pressure 44mmHg. Spirometry was requested to investigate chronic obstructive pulmonary disease (COPD) given the history of smoking, respiratory auscultation with crackles on admission and changes in GA-aO2, with a chest X-ray showing the absence of signs compatible with COPD.

Therapy for pulmonary hypertension was initiated with sildenafil in association with ambrisentan, in addition to furosemide and spironolactone due to the hypervolemic component. After finishing antibiotic therapy, the patient improved with hospital discharge criteria.

hepatorenal syndrome, progressing to hepatic encephalopathy and consequent death in an external service, without undergoing spirometry, and therefore it was not possible to exclude the diagnosis of associated COPD.

DISCUSSION

We present a case report of a patient with liver cirrhosis already decompensated by the disease, exhibiting clinically significant portal hypertension. The diagnosis of hepatopulmonary syndrome was established due to the presence of the three diagnostic criteria: chronic liver disease, alteration of the alveolar arterial oxygen gradient, and the presence of an intrapulmonary shunt. Furthermore, the patient was diagnosed with group 1 pulmonary hypertension, with an associated congestive component. This diagnosis justified respiratory auscultation, revealing crepitus, and the absence of changes compatible with COPD on the chest x-ray, despite the lack of spirometry. The diagnosis of portopulmonary hypertension was suggested by transthoracic echocardiography, with the screening test recommended and later confirmed with a hemodynamic study.

Once the diagnosis was defined, and the etiology was classified, as the patient had an mPAP of 44 mmHg without previous treatment, therapy with diuretics was initiated due to the hypervolemic component. Additionally, sildenafil and ambrisentan were prescribed to address the vasodilation mechanism, with the aim of reducing the mPAP below 40 mmHg for the possibility of liver transplantation.

Pharmacological therapy does not alter the natural course of the disease or its prognosis in the first 6 months, despite an increase in survival within the first 5 years. In this case, despite symptomatic improvement, the patient experienced complications three months after starting therapy, developing hepatorenal syndrome and subsequently succumbing to death, making long-term follow-up impossible to assess the response to therapy.

CONCLUSION

Portopulmonary hypertension (PPH) is a complication of liver cirrhosis that significantly impacts the patient's clinical condition for liver transplant planning and, in some cases, may even contraindicate the procedure despite being the only curative therapy. While it is a rare condition, it has well-established diagnostic criteria, and pharmacological therapy serves as a bridge to the possibility of transplantation. Although the pharmacological treatment does not alter the disease's course, it can enhance survival and pave the way for curative therapy, i.e., liver transplantation.

Another complication of cirrhosis affecting the pulmonary vascular system is hepatopulmonary syndrome (HPS), although its association with portopulmonary hypertension is uncommon. It is crucial to distinguish between HPS and PPH, as they are often confused despite presenting distinct symptoms. While they can occur in association, it is relatively uncommon. PPH clinically manifests similarly to right heart failure with symptoms such as edema, congestion, and dyspnea. On the other hand, hepatopulmonary syndrome presents with pulmonary symptoms like hypoxemia, clubbing, and dyspnea. Despite these differences, both conditions share the same therapeutic modality — liver transplantation.

In terms of pathophysiology, PPH primarily involves vasoconstriction in the lung bed, along with vessel changes resembling primary pulmonary hypertension. This includes plexogenic arteriopathy, leading to right heart dysfunction. In contrast, HPS features pulmonary vasodilation associated with arteriovenous shunts as one of the main elements of its triad.

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