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Hepatopulmonary Syndrome, The First Step Begins with Suspicion. Case Report and Literature Review.

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Abstract

Hepatopulmonary syndrome (SHP) is an entity that represents the most common cause of respiratory failure in patients with chronic liver disease, with an incidence ranging from 25 to 40% in patients with liver cirrhosis, appears because of an alteration in the gas exchange mechanism of the alveolo-capillary barrier, specifically, the development of intrapulmonary vascular dilatations. (DVIP) which in turn produce a defect in oxygenation of varying severity, and is clinically defined by the triad of platipnea, orthodeoxy and the presence of the PVIDs. SHP can be classified according to the severity of hypoxemia, according to the criteria proposed by the European Society of Respiratory Diseases (ERS) in 2004, and ideally diagnosed with contrast-enhanced transthoracic echocardiography (ETMC), but other imaging studies are also useful. Despite many studies designed with the aim of finding methods that stop disease progression, early liver transplantation (TH) remains the only effective therapy for PHS and should ideally be performed within the first year of diagnosis, as patients with PHS and liver cirrhosis have mortality that increases by 75% in the first 12 months. In the following report, we present the case of a 59-year-old woman with a diagnosis of severe PHS managed without TH describing her evolution and current state.

Case Report

In the following case report, we present a patient with long-term liver cirrhosis secondary to hepatitis C virus infection. (HCV), which was presented with platypnea, orthodeoxy and was found with intrapulmonary vascular dilatations (DVIP) through ETMC, finally establishing the diagnosis of SHP that was not performed TH, but presented improvement after receiving HCV disease control, describing its evolution and current state.

We present the case of a 59-year-old female patient who was subsequently treated by the external consultation service of gastroenterology and internal medicine of our institution. He had an 8-year personal history of chronic hepatitis C virus infection with a genotype 1b, for which he was treated with pegylated interferon and ribavirin for 12 months on 2 occasions, developing liver cirrhosis classified as

CHILD B, with a history of 3 decompensations: high digestive bleeding, hepatic encephalopathy, and tension ascites, respectively. Other records were denied, including exposure to organic and inorganic agents, whether occupational and/or household.

She was referred to the pneumology service in 2016 for having developed mMRC 2 dyspnea of slow and insidious installation in the last 2 months, progressing to present during the activities of daily life, which worsened when she assumed the upright position: oppressive type chest pain of EVA 6/10 intensity and general discomfort during bipedestation. An initial physical examination showed a woman at rest, with SpO2 85% improving to 94% in dorsal decubitus; no increase in respiratory work, no data on muscle fatigue, teguments with ochre skin, highlighting the absence of conjunctival jaundice, observation of symmetrical chest movements, which were corroborated with amplification and amplexation; clear pulmonary in the posterior thoracic region, with adequate respiratory noises, symmetrical and without the presence of adventures.

In the initial interventions, a chest X-ray, considered normal by the radiology service, was observed (Figure 1) as well as post-bronchodilator spirometry, which was concluded to suggest a slight restriction due to the presence of vital capacity at 77% (2.53 L). An arterial gasometrical analysis taken at ambient air and sea level revealed pH 7.45, pCO2 32 mmHg, pO2 53 mmHg, EB -1.8, with an arterial alveolar gradient of 57 considered elevated for its age.

Subsequently, high-resolution tomography and subsequent pulmonary angiographic protocol were performed, where no alterations of the pulmonary parenchyma or defects of the pulmonary vascular structure were observed (Figure 2). A transthoracic echocardiogram with agitated saline solution revealed the passage of microbubbles to the left atrium in the first heartbeat. Later a cardiac catheterization ruled out the presence of some defect of the structure of the interatrial septum (Figure 3) ending in the diagnosis of SHP, so it was referred to TH assessment. However, this was not feasible for administrative reasons.

Finally, using direct-acting antivirals (sofosbuvir/velpatasvir) for 12 weeks in 2017, a sustained viral response was achieved, with undetectable viral load since then and to date. After this, gradual improvement of respiratory symptoms has been observed. Currently persisting dyspnea in mMRC1, SpO2 96% at rest, in addition to not having presented a new picture of hepatic decompensation.

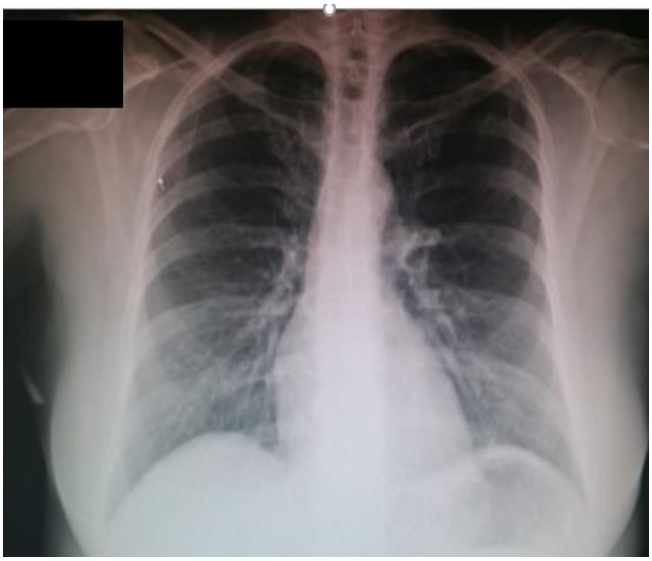

Figure 1 Normal chest X-ray

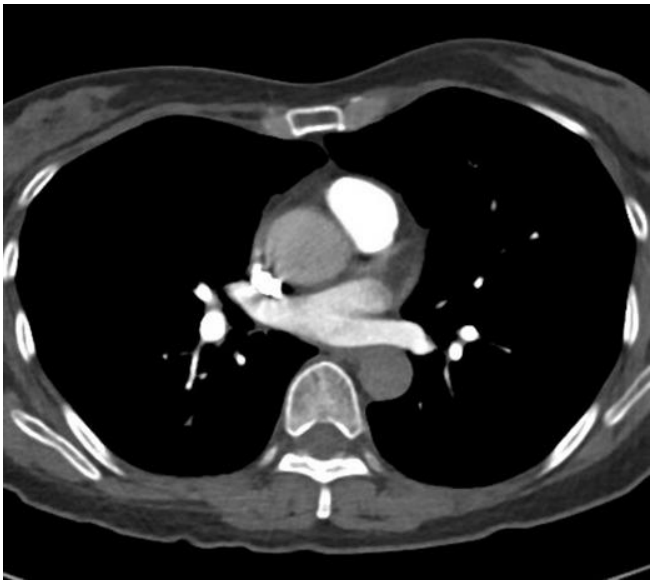

Figure 2 Pulmonary angiotomography without alterations

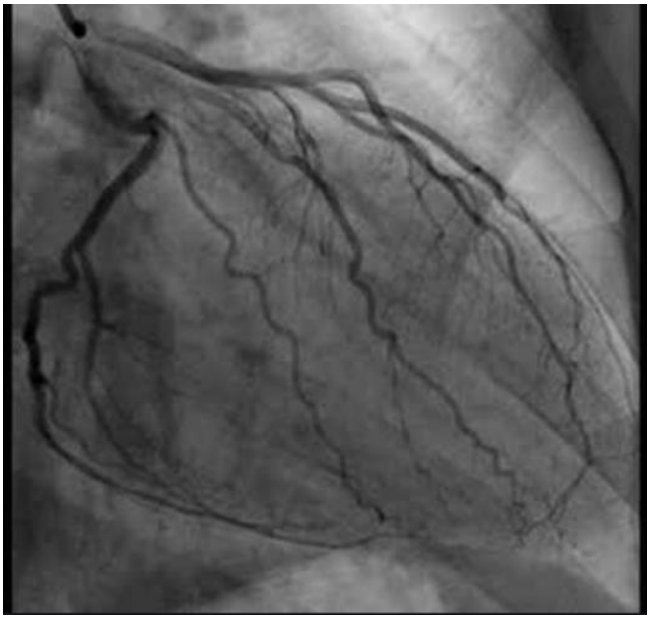

Figure 3 Coronary catheterization without alterations.

Literature Review

PHS is characterized by arterial hypoxemia secondary to intrapulmonary vascular dilatations and elevation of the alveolo-arterial gradient in the context of liver disease and in the absence of previous lung disease that may justify hypoxemia. (1) It is usually a progressive disorder, whose presence worsens the prognosis of patients with chronic liver disease. (2) It has a prevalence of 4-32% of adult patients with chronic liver disease. (3) It most commonly occurs in portal hypertension and cirrhosis, however, it may also occur in patients with acute or chronic hepatitis, acute or chronic hepatic impairment, and some abnormalities in the hepatopulmonary vascular circulation, such as a congenital portosistemic bypass or cavopulmonary bypass. (2)

It was first named and described in 1977 by T.C. Kennedy and R.J. Knudson at the University of Arizona (4). However, there were no defined and widely used classification or diagnostic criteria. The study of the Working Group of the European Society for Respiratory Diseases (ERS) in 2004 on Hepatopulmonary vascular disorders marked the beginning of a new paradigm in this regard, establishing the first diagnostic criteria and classification of severity that have been widely accepted and used in the different guidelines of complications associated with liver cirrhosis, such as those of the European Association for the Study of the Liver (EASL), the American Association of Gastroenterology (AGA) and the International Society for Liver Transplantation (ILTS). (2) (5) (6)

The lung is one of the organs affected by hemodynamic and endocrine changes that occur in patients with cirrhosis of the liver, triggering a diversity of respiratory disorders, the most frequent being the presence of portopulmonary hypertension (PPH), hepatic hydrothorax and/or SHP. PPH occurs due to pulmonary vasoconstriction and increased pulmonary vascular resistance, which is manifested in approximately 10% of patients with portal hypertension (7) and hepatic hydrothorax appears when fluid from ascites in decompensated cirrhosis enters the pleural space through diaphragmatic defects. (8) Instead, SHP is defined as a pulmonary disorder secondary to DVIP. These pathologies appear in patients with chronic liver disease and are characterized by oxygenation disorders in the absence of other causes of lung failure. (9)

Mortality among cirrhotic patients with SHP increases by approximately 50%, (10) being mainly in those with very severe hypoxemia, although this is of multifactorial origin; adding complications of portal hypertension and hepatocellular disease (such as hepatic impairment, multi-systemic organic impairment secondary to sepsis, hepatocellular cancer, and gastrointestinal bleeding) and not due to type 1 respiratory insufficiency associated with PSHD. Due to the increased risk of death, patients with SHP are generally eligible for higher priority on the TH waiting list as it remains the only therapeutic intervention considered capable of modifying the prognosis of these patients. Therefore, at present, SHP should be suspected in any patient with severe liver disease or non-cirrhotic portal hypertension that occurs with dyspnea, as well as in those patients who are in study protocol for liver transplantation. (11)

Both platypnea and orthodeoxy occur due to gravitational redistribution of the pulmonary blood flow leading to an overperfusion of the lower areas of the lung during supine positioning and being the main areas in which dilatations and arteriovenous communications develop in the small pulmonary vasculature. Hyperdynamic circulation secondary to portal hypertension and this increase in the diameter of the pulmonary capillaries results in a misalignment of ventilation-infusion due to an excessive amount of blood passing through the pulmonary circulation without completing the gaseous exchange, leading to a higher alveolo-arterial gradient (GA-a) and subsequent hypoxemia. (6) (12)

These changes are explained physiopathologically because the pulmonary capillaries have an approximate diameter of 10 µm, however, it has been observed that this may rise between 15 and 100 µm and may even reach up to 500 µm, in patients with PHS. This increase is secondary to the endothelial effect of nitric oxide which is secreted by the enzyme nitric oxide endothelial synthetase (eNOS), which in turn is activated by binding endothelin-1 (ET-1) to the receptor in the pulmonary capillary beds. Bacterial translocation and subsequent accumulation of pulmonary macrophages also play an important role in the production of hypoxemia by releasing inflammatory mediators such as tumor necrosis factor alpha (TNF-a) that triggers the production of vascular endothelial growth factors (VEGF), which conclude in VEGF-mediated pulmonary angiogenesis that produces intrapulmonary shunts that replace the alveolar capillary circulation, further exacerbating the lack of oxygenated blood. (6) (12)

Even today, the SpO2 is still considered as the main method available for screening this sick woman and a SpO2 < 96% as the cutting point for detecting patients who are candidates to expand their approach. (2) However, the low sensitivity and specificity of this method for detecting patients with HPS is also recognized, at least in early stages and only 40% of patients with moderate HPS will meet this initial criterion. According to this, low levels in pulsioximetry will suggest the presence of HPS, however, normal levels will not be sufficient to exclude its presence. (13) On the other hand, it has been observed that exhaled nitric oxide (FeNO) measurement will be higher in patients with HPS compared to controls; as well as the decrease of these after liver transplantation, suggesting that this measurement might be useful in screening HPS, but further studies are still required to establish the role of FeNO in this pathology. (14)

In symptomatic patients, the intake of arterial gases is justified even in the absence of hypoxemia since the definition of the latter is debatable because it does not consider the age or altitude of the patient. Therefore, the calculation of GA-a is suggested and although in the current definition they still recommend the cut-off point greater than 15 mmHg, the use of GA-a adjusted to the patient's age could be debated to avoid the added bias of lung growth and aging that occurs in the early and late stages of life respectively. (15) Hypoxemia, on the other hand, serves to classify the severity of the disease into four groups: mild, moderate, severe, and very severe (Figure 4) (16)

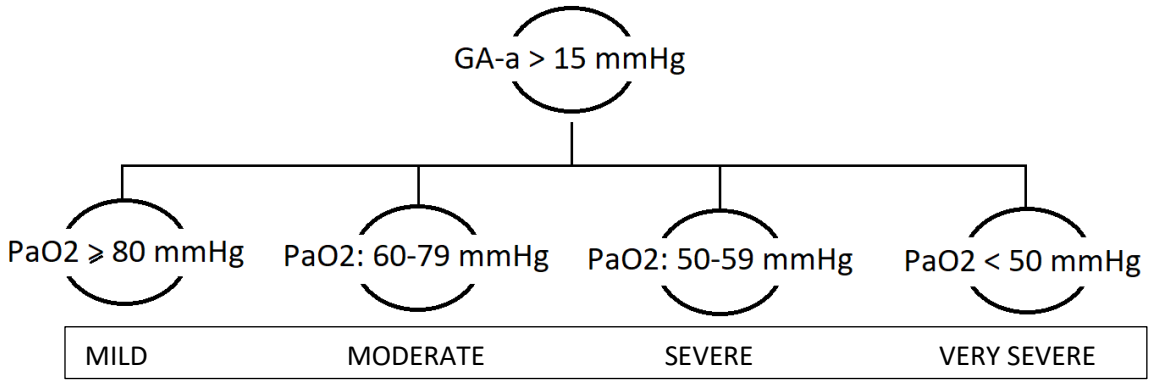

Figure 4. Classification of severity of hepatopulmonary syndrome

High resolution computed tomography can show reticulonodular strokes consistent with septal thickening distributed in basal regions mainly, in addition to exposing arteriovenous malformations, increased cardiac silhouette, and widening of the trunk of the pulmonary artery. Also, intrapulmonary dilations can cause a mosaic pattern. Finally, it may show the expansion of vessels to the subpleural region. (17)

The best tool, and even considered the gold standard, to establish the diagnosis is ETMC, (18) which uses agitated saline solution to produce microbubbles of < 10 µm in diameter. These bubbles are usually trapped in the pulmonary circulation and absorbed by the alveoli, as they are not small enough to pass through non-dilated capillaries. However, in patients with IVD, these microbubbles reach the left atrium and can be detected by echocardiography approximately in the fourth and sixth cardiac cycles after atrial filling. (2) (17) A severity classification of intrapulmonary shunt has also been suggested based on the number of microbubbles passing to the left heart, with stage 1 defined as < 30 microbubbles, stage 2 as 30-100 microbubbles or 3 > 100 microbubbles (19), however, this proposal has not been universally adopted, and its effect as a predictor of mortality still needs to be studied.

Pulmonary infusion with macroaggregated albumin can also be performed to identify DPIV, injecting into the peripheral albumin circulation marked with a radionucleotide (technetium-99m), the former is usually trapped in the pulmonary capillaries and would be shown to concentrate in the lungs in the scan. However, in patients with SHP, this labeled albumin reaches other organs, especially the brain and kidneys. A more than 6% intrapulmonary or intracardiac shunt, but it cannot distinguish between one or the other, (8) However, it is an alternative method that is useful to quantify the extension of short-circuits which in addition to ruling out other possible causes of hypoxemia is especially useful in patients with multiple causes of dyspnea. (11) (20) (15)

Pulmonary angiography is useful for characterizing and differentiating the dilations that by their appearance are divided into type I, those that are small, ramified spider-shaped dilatations observable in early stages and that later become tortuous; and type II showing spider-shaped arteriovenous malformations. Also, this procedure allows to evaluate and perform embolization. It is mainly used in patients with refractory hypoxemia to supplemental oxygen. (17)

The only treatment considered effective and shown to improve survival is TH. In addition, it has shown reversibility of SHP in a range of 52 to 100% over a period of 6 to 12 months. In the evolution of this, a faster improvement in oxemia has been observed than in intrapulmonary short-circuits demonstrated by ETMC. (20) The only accepted medical alternative is supplemental oxygen treatment, which, although it has not been shown to improve survival, improves patients' quality of life and symptoms. (15)

It is not clear which is the best cut to indicate the performance of TH, however, the companies in charge agree on the cut-off point of PaO2 < 60 mmHg regardless of liver damage. On the other hand, questionably high mortality has been observed in patients transplanted with PaO2 < 54 mmHg and it is therefore doubtful which pre-operative risk factors can be affected to improve survival. (15) (21)

Discussion

Platipnea is a clinical disorder characterized by positional dyspnea and sedent desaturation. Orthodeoxy, on the other hand, is defined as a 4 mmHg drop in PaO2 or a 5% decrease in SpO2 when a person changes from supine to sedative position. Being able to divide the causes of this into intracardiac and intrapulmonary mainly. Foramen ovale persistence is the most common intracardiac cause, although it has also been described in aortic aneurysm, pericardial effusion, tumors in the right atrium, dilation of the right ventricle among others. Intrapulmonary causes include arterial-venous malformations, PHS, mainly interstitial diseases. (22)

The differential vascular diagnoses of PHS are PPH and hereditary hemorrhagic telangiectasia (HHT), being the first two acquired disorders and the last hereditary. (18) The pathophysiological differences are the presence of pre and capillary dilations in HPS, obstructive arteriopathy in PPH and dilation of postcapillary venules in lung, liver, brain, spinal cord, and digestive tract in HHT. In addition, PSHD is directly related to the severity of liver disease, as opposed to PPH. The risk factors described for PPH are female sex and autoimmune hepatitis, while hepatitis C virus infection is associated with a decreased risk. (18) Symptoms are characterized by dyspnea to stress, fatigue, palpitations, reinforcement of the second cardiac tone, elevated GA-a hypoxemia, pointing to the presence of echocardiographic findings due to increased systolic pressure of the pulmonary artery and possible data of right ventricular dysfunction. Unlike the others, HHT is considered with the following diagnostic criteria: spontaneous recurrent epistaxis, multiple telangiectasias, visceral telangiectasias; pulmonary, hepatic, cerebral and spinal arteriovenous malformations; as well as family history of HHT.

The patient in question presented with a more hypoxemic elevated A-a gradient of 53 mmHg, which classified her as severe HPS (9). Presenting the classic triad of SHP characterized by chronic liver disease, arterial hypoxemia with elevated GA-a and the presence of intrapulmonary vascular dilatations demonstrated by ETMC. (15) (23) Spirometry and computed tomography were also performed to rule out other causes of hypoxemia. (15) Surely it would have been useful to carry out a diffusion test to document its baseline decrease and follow-up, however, it was omitted due to lack of availability in the locality at the time of evaluation.

As mentioned above, the best tool to establish diagnosis is CTMD, which in patients with IVD, it is observed that microbubbles reach the left atrium approximately in the fourth and sixth cardiac cycle after atrial filling. This patient presented the microbubbles detected in the first and second cardiac cycles, which suggested intracardiac short circuit, however, in cardiac catheterization there was no evidence of a permeable oval foramen or other cardiopathy that supported this possibility. (2) (6) (16) Therefore, it was concluded to be sufficient for the diagnosis of SHP. (6)

Regarding treatment, several pharmacological interventions have been attempted, such as the administration of somatostatin analogues in the hope that their antiangiogenic effect may improve hypoxemia, or intravenous administration of methylene blue to reduce intrapulmonary shunting, however, these have been a resounding failure or have shown slight improvement but exclusively in animal models, respectively. (24) (25) The only therapeutic intervention that has been shown to be effective is liver transplantation, which improves arterial oxygenation in the first year. Patients with liver cirrhosis and PHS who are transplanted generally have survival rates between 75% and 80% over a 5-year period (2) and patients who do not receive treatment generally have an annual decrease in arterial oxygenation of 5 mmHg and an increased mortality of almost double, in fact, the life expectancy without TH at 10 years is less than 5%. (10)

In the case of this patient, the remarkable thing is the improvement of its symptoms, decrease of dyspnea to mMRC1, improvement of oxygenation to SpO2 96% at rest, after the change of antiviral treatment and despite not having performed TH, it has not even presented a new picture of hepatic decompensation. One possibility is that the natural history of his disease is paused, with a decrease in the generation of DPIV. However, in the light of current evidence, it is essential that we continue to monitor the need for this procedure.

In conclusion, hepatopulmonary syndrome remains a very common complication of liver cirrhosis, its appearance in a cirrhotic patient increases annual mortality by almost 50%, therefore it remains essential that the risk criteria be improved, and that these are independent of the Child-Pugh or MELD score, in such a way that timely detection can be carried out.

All patients with chronic liver disease and dyspnea should be evaluated with EMC and arterial gasometry assessed even without decreased baseline SpO2.

Current HPS diagnostic criteria should be discussed and updated to incorporate variables such as age and altitude of patients at the time of GA-a calculation and avoid false positive diagnoses associated with lung aging.

An alternative to EMC is the realization of pulmonary perfusory gamagram with 99mTcMAA primarily useful when there are multiple causes of hypoxemia and that it is necessary to evaluate the extension of short circuits.

As previously mentioned, pulmonary angiography is not useful in the routine approach of these patients.

References

1. Raevens S., Geerts A., Steenkiste Cv., Verhelst X., Vlierberghe Hv., Colle I. Hepatopulmonary syndrome and portopulmonary hypertension: recent knowledge in pathogenesis and overview of clinical assessment. Liver Int. 2015;: p. 1478-3223.

2. Krowka MJ, Fallon MB, Kawut S, Fuhrmann V, Heimbach JK, Ramsay M, et al. International Liver Transplant Society Guidelines: Diagnosis and Management of Hepatopulmonary Syndrome and Portopulmonary Hypertension. Transplantation. 2016; 100: p. 1440–1452.

3. G., TUMGOR Cirrhosis and hepatopulmonary syndrome. World J Gastroenterol. 2014; 20(10): p. 2586-94.

4. Kennedy TC, Knudson RJ.. Exercise-aggravated hypoxemia and orthodeoxia in cirrhosis. Chest. 1977; 72: p. 305-309.

5. The European Association for the Study of the Liver. Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018.

6. Soulaidopoulos S, Cholongitas E, Giannakoulas G, Vlachou M, Goulis I. Review article: Update on current and emergent data on hepatopulmonary syndrome. World J Gastroenterol. 2018; 24(12): p. 1285-1298.

7. Kiafar C, Gilani N. Hepatic hydrothorax: current concepts of pathophysiology and treatment options. Ann Hepatol. 2008; 7: p. 313-320.

8. Fussner LA, Krowka MJ.Current Approach to the Diagnosis and Management of Portopulmonary Hypertension. Curr Gastroenterol Rep. 2016; p. 18-29.

9. Rodríguez-Roisin R, Krowka MJ, Hervé P, Fallon MB. ERS Task Force Pulmonary-Hepatic Vascular Disorders (PHD) Scientific Committee. Pulmonary-Hepatic vascular Disorders (PHD). Eur Respir J. 2004; 24: p. 861-880.

10. Fallon MB, Krowka MJ, Brown RS, et al. Impact of hepatopulmonary syndrome on quality of life and survival in liver transplant candidates. Gastroenterology. 2008; 135: p. 1168–1175.

11. Rodríguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome a liver-induced lung vascular disorder. N Engl J Med. 2008.

12. Zhang, J. & Fallon, M. B. Nat. Rev. Gastroenterol. Hepatol. 2012; 9: p. 539–549.

13. Sara Cardoso, Débora Vilela, Sandra de Barros, et. al. Correlation between hepatopulmonary syndrome and oxygen saturation pulse oximetry in cirrhotic patients. REV ASSOC MED BRAS. 2020; 66(11): p. 1577-1582.

14. Jeffrey Lam Shin Cheung 1, Madina Naimi 2, Jenna Sykes 2, Samir Gupta. A Role for Alveolar Exhaled Nitric Oxide Measurement in the Diagnosis of Hepatopulmonary Syndrome. J Clin Gastroenterol. 2020; 54(3): p. 278-283.

15. Forde, Kelley Weinfurtner & Kimberly. Hepatopulmonary Syndrome and Portopulmonary Hypertension: Current Status and Implications for Liver Transplantation. Curr Hepatology Rep. 2020 July.

16. Rodríguez-Roisin R, Krowka MJ, Hervé P, Fallon MB. Pulmonary- Hepatic vascular Disorders (PHD). Eur Respir J. 2004; 24: p. 861-880.

17. Du, Bi-Wei Luo and Zhi-Yong Advances in Diagnostic Imaging of Hepatopulmonary Syndrome. Front. Med. 2022; 8: p. 1-5.

18. Inna Krynytska, Mariya Marushchak*, Anna Mikolenko, Anzhela Bob, Iryna Smachylo, Ludmyla Radetska, Olga Sopel. Differential diagnosis of hepatopulmonary syndrome (HPS): Portopulmonary hypertension (PPH) and hereditary hemorrhagic telangiectasia (HHT). Bosn J Basic Med Sci. 2017; 17(4): p. 276-285.

19. Velthuis S, Buscarini E, Gossage JR, Snijder RJ, Mager JJ Clinical implications of pulmonary shunting on saline contrast echocardiography. J Am Soc Echocardiogr. 2015; 28: p. 255-263.

20. Israel Grilo-Bensusan, Juan Manuel Pascasio-Acevedo. Hepatopulmonary syndrome: What we know and what we would like to know. World J Gastroenterol. 2016; 22(25): p. 5728-5741.

21. Arun Jose, Shimul A Shah, Nadeem Anwar et al. Predictors of outcomes following liver transplant in hepatopulmonary syndrome: An OPTN database analysis. Respir Med. 2021; 190.

22. Abhinav Agrawal, MD, Atul Palkar, MD, Arunabh Talwar, MD FCCP. The multiple dimensions of Platypnea-Orthodeoxia syndrome: A review. Respiratory Medicine. 2017; 129: p. 31-38.

23. Gandhi KD, Taweesedt PT, Sharma M, Surani S. Hepatopulmonary syndrome: An update. World J Hepatol. 2021; 13(11): p. 1699-1706.

24. Söderman C, Juhlin-Dannfelt A, Lagerstrand L, Eriksson LS. Ventilation-perfusion relationships and central haemodynamics in patients with cirrhosis. Effects of a somatostatin analogue. J Hepatol. 1994; 21: p. 52-57.

25. Miyamoto A, Katsuta Y, Zhang XJ, Li HL, Ohsuga M, Komeichi H, Shimizu S, Akimoto T, Mizuno K. Effect of chronic methylene blue administration on hypoxemia in rats with common bile duct ligation. Hepatol Res. 2010; 40: p. 622-632.