Diploma thesis

Hepatopulmonary Syndrome in Patients with Compensated Cirrhosis

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Graz, am 10. April 2012 Philipp Douschan

Graz, April 10th, 2012

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Abstract

Background: Hepatopulmonary syndrome (HPS) is an under-diagnosed complication in chronic liver disease. Although it is most commonly detected in patients suffering from cirrhosis of the liver, there are also records of HPS in patients with chronic hepatitis or Budd-Chiari syndrome. Due to intrapulmonary vasodilatation and increased intrapulmonary shunting, the average arterial oxygen partial pressure (PaO_2) decreases and leads to systemic hypoxemia. In patients with cirrhosis this hypoxemia may lead to further impairment of their general condition. It is reported that HPS influences perioperative mortality in patients who undergo orthotopic liver-transplantation (OLT). Therefore, HPS is most often recognized during the evaluation for liver transplantation in patients with decompensated cirrhosis. Its prevalence ranges from 5% to 32%. The aim of this study is to assess the prevalence of HPS in patients with compensated cirrhosis.

Methods: 105 consecutive patients with cirrhosis referred to the Medical University of Graz including inpatients (medical ward) and outpatients (liver clinic) were enrolled. Patients were evaluated for severity and etiology of liver dysfunction and screened for the presence of HPS. In all patients, arterial oxygen saturation (SpO2) was determined in the upright position by a portable pulse oximeter. Patients with a SpO2 $\leq$ 97% underwent further pulmonary work-up including spirometry, arterial blood gas analysis, contrast enhanced transthoracic echocardiography and lung perfusion scintigraphy.

Results: Mean SpO_2 of our study population was 98.06% (SD 0.9). 27.6% (n= 29) had a SpO_2 of 99%, 60% (n = 63) had a SpO_2 of 98%, 5.7% (n = 6) had a SpO_2 of 97%, 5.7% (n = 6) had a SpO_2 of 96% and 1% (n = 1) had a SpO_2 of 93%. Therefore, 13 patients (12.4%) had a $SpO_2 \leq 97\%$. Complete examinations were conducted in six patients. Finally, just one patient with clinical HPS could be detected.

Conclusion: Clinically significant HPS seems to be a rare finding among patients with compensated cirrhosis. Pulse oximetry is a convenient screening tool for detecting severe stages of HPS.

Zusammenfassung

Hintergrund: Das hepatopulmonale Syndrom, kurz HPS, ist eine im klinischen hepatologischen Alltag meist übersehene und unterdiagnostizierte Komplikation, welche meist auf Boden einer vorbestehenden Leberzirrhose entsteht. Hauptkennzeichen ist eine vermehrte perialveoläre Vasodilatation in den Lungenstrombahnen, welche eine verminderte Oxigenierung des Blutes zur Folge hat. Das Vorliegen einer solchen pulmonalen Komplikation bei Zirrhotikern hat nach aktuellem Wissensstand jedoch starke Auswirkungen auf den postoperativen Verlauf und die Langzeitüberlebensrate nach einer Lebertransplantation. Die bisher berichtete Prävalenz von HPS schwankt zwischen 5% und 32%. Die meisten Daten stammen von Lebertransplantationskandidaten und umfassen daher schwerere Formen von Lebererkrankungen. In wie fern das hepatopulmonale Syndrom in bereits früheren, gut kompensierten Stadien der Leberzirrhose vorkommt ist noch immer Gegenstand kontroversieller Diskussionen. Hauptziel dieses Projektes ist es daher die Prävalenz des hepatopulmonalen Syndroms in Leberzirrhose unterschiedlicher Stadien, insbesondere in kompensierten Stadien zu ermitteln.

Methoden: Zu diesem Zweck wurden 105 konsekutive Patienten auf das Vorliegen eines HPS evaluiert. Zu Beginn wurden sämtliche Patienten mittels Pulsoximetrie auf das Vorliegen einer verminderten arteriellen Sauerstoffsättigung (SpO_2) gescreent. Patienten mit einer $SpO_2 \leq 97\%$ wurden mittels arterielle Blutgasanalyse, Spirometrie, einer Kontrastmittelechokardiographie und Lungenperfusionsszintigraphie weiter evaluiert.

Ergebnisse: Der gemessene mittlere SpO_2-Wert unserer Studienpopulation betrug 98.06% (SD 0.9). 29 Patienten (27.6%) hatten eine SpO_2 von 99%, bei 63 (60%) betrug sie 98%, bei sechs Patienten (5.7%) 97%, bei weiteren sechs Patienten 96% und bei einem Patienten (1%) lag eine Sättigung von 93% vor. Somit erfüllten 13 Patienten (12.4%) unsere Screeningkriterien. Sechs von diesen konnten weiter bezüglich des Vorliegens eines HPS abgeklärt werden. Schlussendlich erfüllte jedoch nur ein Patient die Kriterien für ein klinisch signifikantes HPS.

Fazit: Klinisch signifikantes HPS scheint bei kompensierten Leberzirrhotikern äußerst selten vorzukommen. Die Pulsoximetrie ist ein geeignetes Screeninginstrument, um solche Verdachtsfälle zu identifizieren.

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1 Introduction

1.1 Historical background

In 1884, a case report was published by Dr. Flückiger, a resident physician, in the *„Wiener Medizinische Wochenschrift"*(see Figure 1-1) (1). In this report he described the case of a 35-year-old woman, admitted to his hospital due to nervous prostration. Physical examination revealed massive cyanosis and digital clubbing of the fingers and toes. Two days later, the patient started to cough up bright red blood. Later on, mental disorders occurred and the patient died four months after referral. The autopsy revealed hepatic cirrhosis, and dilated intestinal, gastroesophageal and pulmonary vessels. Furthermore, pulmonary blood volume seemed to be increased. Haemorrhaging from oesophageal varices were thought to be the reason for her bleedings. However, the reasons for her pulmonary vascular alterations, cyanosis and her digital clubbing remained unclear.

Flückiger described common findings of advanced hepatic cirrhosis, such as hepatic encephalopathy, portal hypertension and oesophageal varices. Moreover, to the best of our knowledge, this seems to be the first report describing a typical pulmonary complication of cirrhosis, which later became known as hepatopulmonary syndrome (HPS).

In the mid-20th century, several authors described again pulmonary vascular alterations found in patients suffering from hepatic cirrhosis (2, 3). However, in 1977, almost a century after Flückiger, Kennedy and Knudson (4) were there first who introduced the term "hepatopulmonary syndrome", defined as hypoxemia and intrapulmonary vascular dilatations (IPVD) associated with liver disease.

1884. Wiener Medizinische Wochenschrift Nr. 49.

Aus der Klinik des Herrn Geheimrathes Dr. Kussmaul in Strassburg.

Vorkommen von trommelschlägelförmigen Fingerendphalangen ohne chronische Veränderungen an den Lungen oder am Herzen.

Mitgetheilt von Dr. M. FLÜCKIGER, Assistent an der obigen Klinik.

Karoline Schimmel, 37 Jahre alt, Ehefrau, liess sich am 24. Juni 1884 wegen Nervenschwäche in die medizinische Klinik zu Strassburg aufnehmen. Die Haut des ganzen Körpers der Patientin war ziemlich intensiv, Gesicht und Hände im höchsten Grade blaugrau gefärbt; die Endphalangen der Finger und Zehen in sehr bedeutendem Maasse kolbenförmig verdickt. Nach bestimmter Angabe der Frau Schimmel selbst und ihrer Angehörigen bestanden diese Veränderungen erst seit 5 Jahren. An den Lungen, am Herzen, an den grossen Gefässstämmen konnte durch die physikalischen Untersuchungsmethoden durchaus nichts Abnormes nachgewiesen werden.

Am 26. Juni begann die Patientin plötzlich, hellrothes schaumiges Blut in grosser Menge auszuhusten, im Ganzen ungefähr 4½ Liter im Zeitraume von 5 Tagen, davon 2½ Liter allein am 29. Juni. Am 1. Juli hörte die Hämoptoë auf und kehrte nicht wieder. Im weiteren Krankheitsverlaufe traten dann psychische Störungen, die im Anfange den Charakter beginnender Dementia paralytica trugen, in den Vordergrund; der Tod erfolgte am 17. Oktober 1884 nach mehrtägigem Sopor. Bei der völligen Unmöglichkeit einer exakten Diagnose war intra vitam als Wahrscheinlichkeitsdiagnose eine physikalisch nicht nachweisbare Herzanomalie und dadurch bedingte venöse Stauung angenommen worden.

Von den Ergebnissen der von Herrn Prof. v. Recklinghausen ausgeführten Sektion möge nur das Wichtigste hervorgehoben werden: Im Herzen wurde nichts Abnormes gefunden; in den Lungen grosser Blutreichthum, stark erweiterte Venen, sonst keine chronischen Veränderungen. Bedeutend erweitert waren ferner die venösen Gefässe des Gehirnes, des Rückenmarkes, der Hirnhäute und die grossen Körpervenen; stark geschlängelte und dilatirte submuköse Venen fanden sich auch im Oesophagus.

Ganz besonders auffällig war die hochgradige Dilatation fast sämmtlicher Unterleibsvenen. Es wurden dann weiterhin syphilitische Knochenveränderungen und ausgebildete Lebercirrhose (am linken Labium minus bestand eine runde Narbe) konstatirt; die Vena cava inferior war nirgends komprimirt, ein Ast der Vena portae obliterirt.

Nach diesem Befunde musste eine durch die Lebercirrhose bedingte Zirkulationsstörung als Ursache für die Erweiterung der Unterleibs- und Oesophagusvenen, und die varikösen Oesophagusvenen als wahrscheinliche Quelle der oben beschriebenen Blutungen, die dem klinischen Bilde nach als Lungenblutungen aufgefasst worden waren, betrachtet werden. Dagegen für die Dilatation der übrigen Körpervenen und der Lungenvenen und für die dadurch intra vitam verursachten Stauungserscheinungen, die hochgradige Cyanose und die kolbenförmigen Fingerendphalangen konnte ein sicheres ätiologisches Moment um so weniger angegeben werden, als Veränderungen in der Struktur der Gefässwände nicht gefunden werden.

Ein ähnlicher Befund ist bisher nirgends beschrieben und dürfte deshalb der vorliegende Fall der Mittheilung werth erscheinen.

Figure 1-1. Case report; Flückiger et al. (1)

1.2 Hepatic cirrhosis

Cirrhosis of the liver was defined by the WHO as "diffuse process characterized by fibrosis and the conversion of normal liver architectures into structurally abnormal nodules" (5). Depending on its morphological and histological presentation, it can be classified into micronodular, macronodular and mixed cirrhosis. Furthermore, based on its clinical presentation, cirrhosis can be categorized as compensated cirrhosis, without clinical signs and symptoms, and decompensated cirrhosis, characterized by the appearance of complications.

Due to recurrent chronic injury of liver parenchyma, cirrhosis can develop by progression of fibrosis. Therefore it is considered to be a final stage of chronic liver injury, caused by different noxa. In the western world the leading cause of cirrhosis is alcohol, whereas in developing countries hepatitis is the main cause of chronic liver damage. (6–8)

1.2.1 Pathogenesis of Cirrhosis

The underlying mechanisms of disease are chronic irritation of hepatic tissue, inflammation, apoptosis, fibrosis, intrahepatic vasoconstriction and angiogenesis.

Inflammation seems to play an important role in the pathogenesis of hepatic cirrhosis. Although there are also non-inflammatory mechanisms of disease progression, for example in hemochromatosis, most of the time there seems to be an overlap of inflammatory and non-inflammatory processes. Due to iterative injuries, damaged hepatocytes initiate apoptosis. Apoptosis itself is not known to be an inflammatory trigger, but clearance of apoptotic substances could induce fibrosis. Moreover, in the presence of massive apoptosis, secondary necrosis can appear and lead to inflammation. Finally, besides the collapse of architecture, obstruction of intrahepatic vasculature can occur, resulting in hypoxic parenchyma damage.

Fibrosis is triggered by myofibroblasts and hepatic stellate cells (HSCs), stimulated by inflammation. HSCs are retinoid storing cells, located in the hepatic space of Disse (perisinusoidal space) between sinusoids and hepatocytes. They can be activated by leucocytes, endothelium, Kupffer cells, hepatocytes and platelets. Activation mediators are fibronectin, platelet derived growth factor (PDGF), epidermal growth factor from platelets and transforming growth factor β1 (TGF β1) from Kupffer cells. Stimulated HSCs transform into contractile myofibroblasts, accumulate in areas of injury and produce extracellular matrix, especially collagen I. Additionally, Kupffer cells and activated HSCs produce metalloproteinases (MMPs)

and tissue inhibitor metalloproteinases (TIMPs). TIMPs reduce the activity of collagenases and, therefore, lead to progression of fibrosis.
Active hepatic myofibroblasts also show an increased contractile activity. They could, therefore, be responsible for the development of portal hypertension. Perisinusoidal fibrosis also causes loss of sinusoidal fenestration and thus leads to functional shunting. Oxygen deficiency triggers the release of angiogenic substances and development of new blood vessels. For this reason portal-to-portal and portal-to-central connections appear and cause more anatomic and functional shunting, increasing parenchyma hypoxia.
There are still debates about whether it is possible to successfully resolve cirrhosis. (7)

1.2.2 Complications of cirrhosis

Cirrhosis of the liver affects many other body systems. Malnutrition is often seen in the setting of cirrhosis, as it is associated with a catabolic state. Hepatic encephalopathy is caused by astrocyte swelling due to neurotoxins and ammonia that bypasses the liver via portosystemic shunts. Furthermore, cirrhosis is the most common cause of the development of hepatocellular carcinoma (HCC). Sodium retention and abnormal haemodynamics lead to an impairment of renal function. There are also observations about cardiac dysfunction in patients with cirrhosis.
Hypersplenism may cause reduction of platelets, erythrocytes and white blood cell count. Reduced liver function further effects impaired production of coagulants and anticoagulants. Patients are, therefore, more likely to suffer from haemorrhaging. Nevertheless, there are also reports of the increased risk of thrombembolic events. As the liver is also responsible for the metabolism of hormones, feminization or hypogonadism may occur in some patients. However, one of the most profound hallmarks of cirrhosis is portal hypertension. (8, 9)

1.3 Portal Hypertension and the cardiovascular system

The portal venous system collects blood from the small and large intestines, pancreas and spleen and directs it to the liver. The vena portae is the confluence of the superior mesenteric, the right and left gastric and the splenic (including blood from the inferior mesenteric vein) veins. Normal portal pressure ranges from 1 to 5 mmHg. Elevated portal pressure becomes clinically significant at levels above 12 mmHg by developing collateral pathways between the portal and the central

venous system. The most important collateral systems are the gastro-oesophageal junctions, umbilical junctions, retroperitoneal collaterals and rectal collaterals. The most significant complication is gastrointestinal haemorrhage due to the bleeding of oesophageal varices. Other side effects of portal hypertension are ascites, splenomagaly and hypersplenism. However, portal hypertension also has an important influence on the vascular system of the human body. (8–11)

1.3.1 Pathogenesis of portal hypertension

Portal hypertension is mainly caused by an increased hepatic resistance. As already mentioned HSCs are activated in cirrhosis and accumulate in the space of Disse. Sinusoidal capillaries loose their fenestration and furthermore, the vascular architecture of the liver is impaired by development of nodules and fibrous septae. Besides anatomic and structural impairment, functional changes in the hepatic vasculature also occur. Activated HSCs are contractile and can therefore regulate microcirculation by capillary contraction. Moreover, there is an imbalance between vasoconstrictive and vasodilative components.

Increased shear stress normally results in an elevated production of nitric oxide (NO), a vasodilator, in vessels of the liver. In the setting of cirrhosis, NO levels are decreased and there seems to be less activity of endothelial NO synthase (eNOS) in cirrhotic patients. Furthermore reactivity to systemic NO is reduced in the cirrhotic liver.

Production and sensitivity to vasoconstrictive substances is increased in the hepatic vessels of cirrhotic patients. Elevated levels of endothelins can be detected and there seems to be a change in endothelin receptor patterns to a predominace of vasoconstrictive ET_B receptors in the setting of hepatic cirrhosis. In advanced cirrhosis a dramatic activation of the renin-angiotensin system (RAS) also occurs. Angiotensin II is suspected to cause contraction by interacting with activated HSCs. There is also evidence that HSCs themselves can produce components of the RAS. Other substances suspected to be associated with the development of portal hypertension are leukotrienes and prostanoids. (12)

1.3.2 Portal hypertension and hyperdynamic circulation

Hyperdynamic circulation, defined as presence of decreased vascular resistance, increased heart rate and arterial hypotension is one the main pathogenetic factors contributing to the development

of hepatorenal syndrome, ascites and hepatopulmonary syndrome. In contrast to hepatic vasculature, peripheral and splanchnic vasculature is affected by increased concentrations of circulating vasodilators, increased production of local vasodilators and decreased response to vasoconstrictors. One of the circulating mediators, which is meant to be involved in vasodilatation, is glucagon. In cirrhosis, glucagon released by pancreatic α cells is not cleared by the liver. In healthy humans glucagon induces a postprandial hyperaemia in splanchnic vessels.
Local vasodilators such as NO are released due to shear stress. Bacterial translocation can induce NO production. Initially, eNOS expression occurs in the arterioles of the intestinal mucosa. This seems to be induced by vascular endothelian growth factor (VEGF), which is released by endothelium due to hypoxemia.
Reduction of vascular resistance leads to a drop in blood pressure in the central circulation. Hypotension and central hypovolemia activate sympathetic counter-regulating mechanisms. Furthermore, the RAS and the hypothalamic/neuropituitary system are activated. All these counter mechanisms try to maintain systemic blood pressure and blood volume. Nevertheless, in advanced cirrhosis there is a relative hypovolemia in the central vascular system compared to a relative hypervolemia occurring in the splanchinic system.
As another consequence of sympathetic activation, heart rate and cardiac output increase. In some cases, cirrhotic cardiomyopathy develops. Cardiac hypertrophy, fibrosis, and subendothelial edema cause diastolic dysfunction and stiffness of the myocardium. (11, 12)

1.4 Hepatopulmonary Syndrome

HPS is defined as a triad of liver disease, intrapulmonary vascular dilatation (detected by lung perfusion scintigraphy and contrast echocardiography) and arterial deoxygenation (PaO_2 < 80 mmHg or alveolar-arterial oxygen gradient [$AaDO_2$] ≥ 15 mmHg, ≥ 20 mmHg for patients aged > 64 years). Its degree of severity can be graded according to the degree of hypoxemia as mild (PaO_2 ≥ 80 mmHg), moderate (PaO_2 < 80 – ≥60 mmHg), severe (PaO_2 < 60 – ≥ 50 mmHg) and very severe (PaO2 < 50 mmHg – ≥15 mmHg) (13, 14). HPS can be further categorized into clinically significant (PaO_2 < 70 mmHg) or subclincal (PaO_2 > 70 mmHg) HPS (15, 16). As there is the possibility of coexisting cardiopulmonary disease, exclusion of these conditions is not required for the diagnosis of HPS (15).

1.5 Pathology

Hepatopulmonary Syndrome is most often seen in the setting of cirrhosis of the liver and portal hypertension. Nevertheless, there are also records of HPS in Budd Chiari syndrome (15), ischemic hepatitis (17), Abernethy malformations (18) and acute or chronic hepatitis (15). The main underlying pathological condition is intrapulmonary vascular dilatation (IPVD). Another characteristic feature of HPS is hypoxemia due to ventilation/perfusion and diffusion/perfusion impairment in pulmonary vessels (see Figure 1-2). However, there is also evidence that IPVD may occur in normoxemic patients with cirrhosis without causing HPS and hypoxemia (19). Kalambokis et al. (19) detected intrapulmonary shunting (MAA shunt fraction $\geq$ 6%) in approximately 20% of normoxemic patients with cirrhosis. Furthermore, they found a correlation between intrapulmonary shunt fraction and severity of liver disease.

In 1966, Berthelot et al. (3) described the presence of capillary dilatations, portopulmonary and intrapulmonary shunts in patients with cirrhosis of the liver. Precapillary and capillary dilatations cause increased blood flow. Therefore, the time required for gas exchange is reduced (13). This condition may be worsened by the hyperdynamic circulatory state found in the setting of cirrhosis of the liver that encompasses low arterial blood pressure, increased heart rate and increased cardiac output (20). Furthermore, wall thickening in pulmonary capillaries leading to diffusion impairment was detected (14). Finally, aside from elevated functional shunting of mixed venous blood, anatomic right to left shunting in patients with HPS sometimes occur (14). There also seems to be less vasoconstriction of intrapulmonary vessels as a reaction to hypoxemia in the setting of HPS (14).

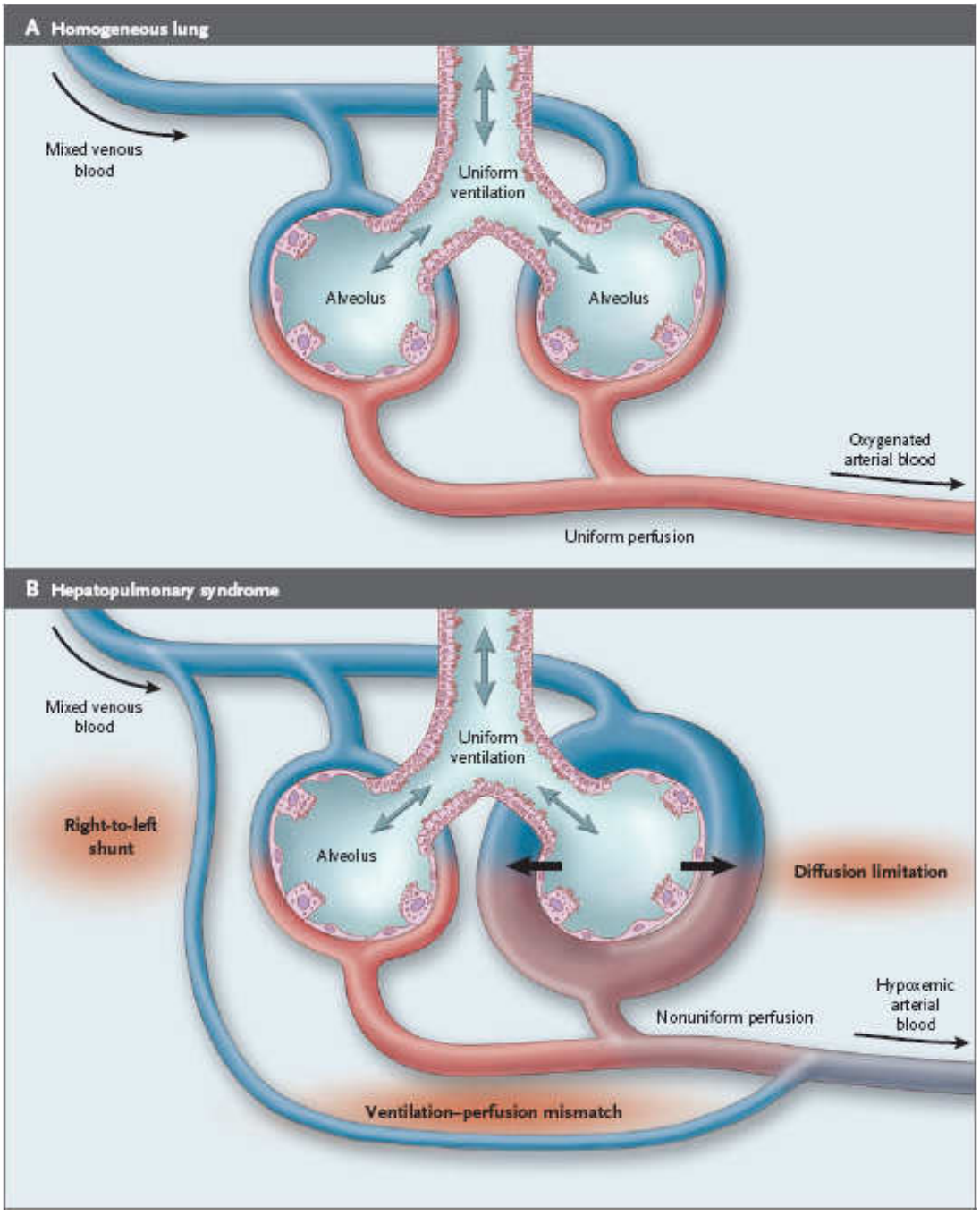

Figure 1-2. Underlying pathological conditions of HPS; Rodriguez-Roisin et al. (14);
Panel A shows physiological aspects of pulmonary perfusion and ventilation. In Panel B alterations, found in HPS, are illustrated.

1.6 Pathogenesis of HPS

Most data available dealing with the pathogenesis and pathobiology of HPS are experimental and were found by conducting chronic bile duct ligation (CBDL) in rats. Furthermore, ligation of the bile ducts seems to be the only procedure that can reproduce HPS in rats. Nevertheless, there are also some data available from human studies that underline experimental findings. Some of the most common attempts to explain pathogenesis of HPS are discussed in the following paragraphs. An overview is given in Figure 1-3.

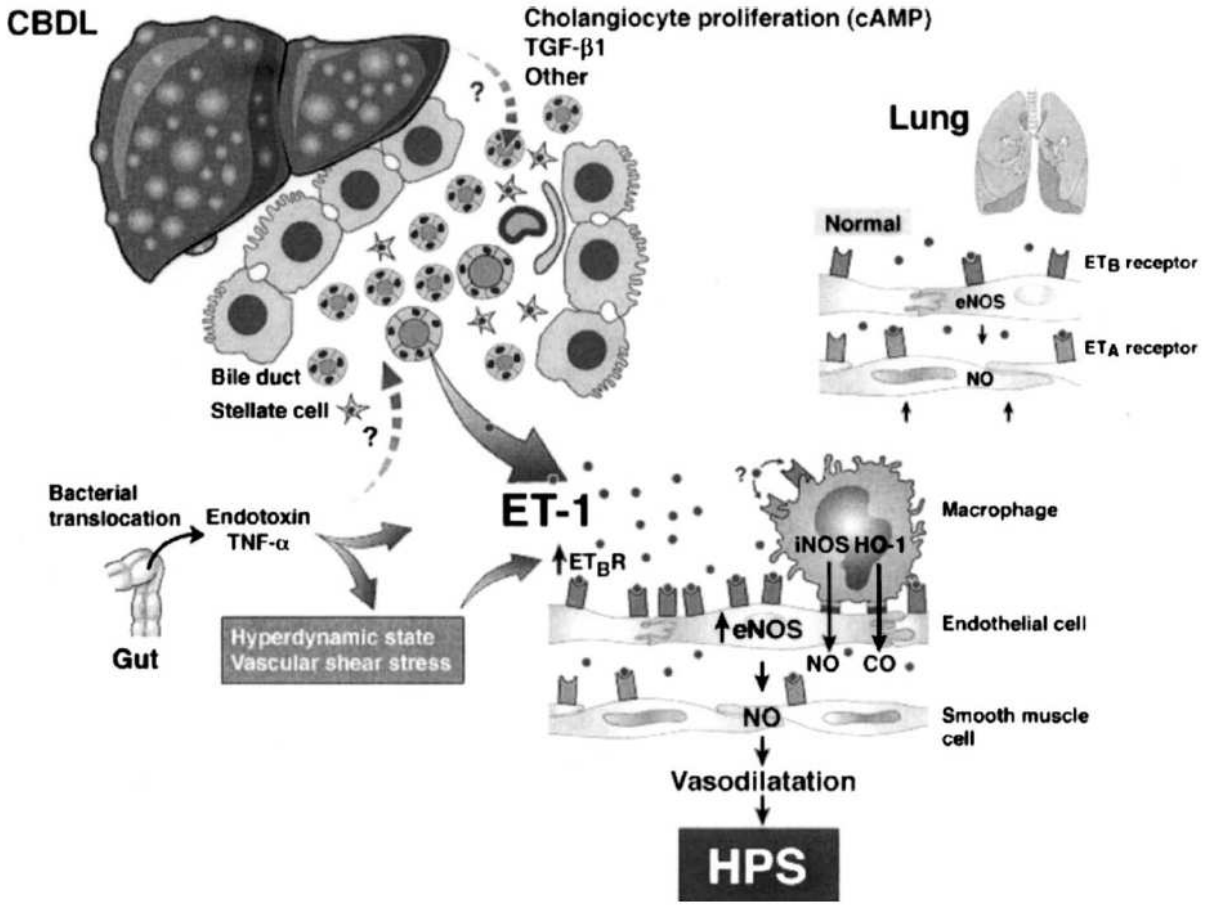

Figure 1-3. Pathomechanisms of HPS; from Fallon et al. (21)

1.6.1 ET-1, ET_B- receptor and bile duct proiferation

Pulmonary vascular defects in HPS appear to be mediated by an increased production of endothelin-1 (ET-1) in hepatic biliary cells and increased expression of endothelin B (ET_B) receptors in pulmonary vessels (15, 22). Apart from ET_B, there are also ET_A receptors in pulmonary vessels. Physiological ET-1 is a potent vasoconstrictor that is released paracrinely and autocrinely. It can cause vasoconstriction by targeting abluminal ET_A and ET_B receptors in the smooth muscle cells of vasculature (22–24). In contrast, ET-1 released to the luminal side of a vessel can interact with endothelial ET_B receptors (21, 23, 24). By targeting these ET_B receptors, ET-1 stimulates endothelial nitric oxide synthase (eNOS) causing higher amounts of nitric oxide (NO) to be synthesized. NO binds to the soluble guanylate cyclase in smooth muscle cells and thus leads to an additional production of cyclic guanosin monophosphat (cGMP) that causes muscular relaxation (15, 21, 22, 25). In experimental trials, the proliferation of bile ducts could only be triggered by CBDL (21, 24), whereas bile duct proliferation can occur in all forms of cirrhosis in humans (22). It is hypothesized that bile duct proliferation and cholangiocyte ET-1 production are induced by cytokines or endotoxines of translocated bacteria (21). Furthermore, expression of endothelial ET_B receptors is increased in the setting of HPS, leading to raised sensitivity of pulmonary vessels to ET-1 (24).

In an experimental trial by Ling et al. (24), regarding the role of ET-1 and ET_B receptors in the development of HPS, again CBDL rats were analyzed. After 2 to 3 weeks, elevated plasma levels of ET-1, ET_B receptor protein and eNOS could be detected. Administration of ET-1 in non CBDL rats lead to intrapulmonary vasoconstriction, whereas in CBDL rats it lead to further activity of eNOS and therefore elevated NO levels and the relaxation of pulmonary vessels. By inhibiting ET receptors, $AaDO_2$ could be reduced, indicating an improvement of HPS. Administration of N^G-nitro-L-arginine methyl ester (L-NAME), an inhibitor of the NO synthase could inhibit intrapulmonary vasodilatation.

These experimental findings could be verified by human conducting. Cremona et al. (25) revealed that exhaled NO is elevated in hypoxemic cirrhotic patients. Koch et al. (22) measured the amount of ET-1 in portal venous blood and found elevated ET-1 levels in patients with IPVD. Furthermore, increased ET-1 was associated with increased hepatic cholangiocytes (22). In another trial intravenous administration of methylene blue, an inhibitor of the soluble guanylat cyclase, lead to a decrease in shunt fraction, $AaDO_2$ and an improvement of hyperdynamic circulation in patients with HPS (26). In contrast to methylene blue, the use of L-NAME in a

cohort of patients suffering from HPS did not result in any significant improvement in HPS despite improvement of the hypercirculatory state (27). Hence, besides the cholangiocyte – ET-1 – NO pathway, other factors such as angiogenesis may play an important role in the pathogenesis of HPS in humans.

1.6.2 Bacterial translocation, cytokines and macrophage accumulation

Another condition that could contribute to the development of HPS is bacterial translocation. There is evidence of increased bacterial translocation, due to bacterial overgrowth and mucosal barrier dysfunction of the gut, in patients and CBDL rats suffering from cirrhosis of the liver (13–15, 21, 28–30). Bacteria seem to migrate to mesenteric lymph nodes, release large amounts of endotoxins and increase production of cytokines such as tumor necrosis factor alpha (TNFα) by immune cells (28, 31, 32). Under normal circumstances hepatic Kupffer cells would clear portal blood. Due to decreased liver function, reduced phagozytic activity of the reticuloendothelial system (RES) of the liver and portosytemic shunting these endotoxins and cytokines can easily reach the lung (31, 32). As a result of endotoxin stress in pulmonary vessels, there seems to be a shift in endovascular phagocytic activity from the liver to pulmonary capillaries (28, 29). This leads to pulmonary accumulation of CD 68+ macrophages and activation of these cells (29). Furthermore, activated macrophages produce inducible nitric oxide synthase (iNOS) and heme oxygenase 1 (HO-1) leading to vasodilatation via an increase in NO and CO levels (14, 21, 28, 29).

A study by Sztrymf et al. (28) revealed that CBDL rats with bacterial translocation are more likely to develop HPS, have higher plasma levels of TNFα and show more intravascular macrophage accumulation, compared to CBDL rats without bacterial translocation.

Rabiller et al. (31) tried to assess whether prevention of bacterial translocation could influence the severity of HPS. They used norfloxacin, a quinolon antibiotic effective against Gram negative bacteria. Norfloxacin lead to decreased growth and translocation of bacteria in CBDL rats. Moreover, reduction of bacteria also resulted in less severe HPS, lower expression of iNOS, lower NO levels and reduced vascular resistance. Antibiotic treatment could not affect eNOS protein expression. There was also no resolution of HPS or total reduction of NO levels in treated animals, indicating that bacterial translocation and macrophage accumulation is not the only cause of HPS.

Further investigations showed that by using pentoxifylline (PTX), a phosphodiesterase inhibitor that blocks TNFα production, macrophage accumulation could also be influenced (32). In CBDL rats treated with PTX, there are decreased levels of TNFα and NO (32). iNOS activity is lower in treated animals, compared to untreated CBDL rats (32). Additionally, PTX treatment in CBDL rats leads to resolution of HPS and a hyperdynamic circulatory state (32).
Thenappan et al. (29) could verify inflammatory activation of intrapulmonary macrophages by increasing levels of circulating endotoxins in CBDL rats. Intrapulmonary macrophages in HPS rats are positive for nuclear factor-κB (NF-κB), a transcription factor that usually transfers to the nucleus during inflammation. Furthermore, macrophages seem to be attracted by the lung via expression of monocyte chemoattractant protein 1 (MCP-1), mediating migration into pulmonary vessels. In this trial, depletion of macrophages with gadolinium and liposomal clodronate, both inducing apoptosis in macrophages, resulted in reduced accumulation and cell proliferation, normalization of oxygenation and hyperdynamic state and reduced vasodilatation, demonstrating a resolution of HPS.

1.6.3 Angiogenesis and abnormal vascular architecture

Current observations support the hypothesis that angiogenesis in pulmonary vasculature may play an important role in the pathogenetic processes of HPS. Again this seems to be mediated by macropahages accumulated in pulmonary vessels (29, 33). These macrophages express increased levels of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) (29, 33). VEGF and PDGF cause vascular remodelling through phosphorylation of extracellular signal-regulated-kinase (ERK) (29). High PDGF levels cause proliferation of pulmonary artery smooth muscle cells (PASMC) whereas VEGF leads to pulmonary capillary proliferation, endothelial tube formation and arteriovenous malformations (29).
Zhang et al. (33) underline this theory, revealing that markers for endothelial cells such as factor VIII (FVIII), von Willebrand factor (vWF), vascular endothelial cadherin (VE-cadherin) and proliferating cell nuclear antigen (PCNA) increase after performing CBDL in rats. There was a higher activity of angiogentic signalling pathways after CBDL, shown by significant increases in angiogenetic factors like phospho-Akt, VEGF A and phospho-VEGF receptor-2. Using PTX, Endostatin or Angiostatin, inhibitors of angiogenesis, could reduce vascular remodelling by

decreasing intrapulmonary macrophages and angiogenetic signalling. Endostatin and Angiostatin lead to an improvement in $AaDO_2$.

Thenappan et al. (29) detected high expression of PCNA in alveolar microvessels and phosphorylated ERK (pERK) in CBDL rats. Tube formation could be blocked by administration of imatinib, a tyrosine kinase inhibitor that can inhibit angiogenic signalling. Furthermore they observed an obstructive vasculopathy, characterized by thickening of the media and loss of lumen, in some of the resistance pulmonary arteries. Due to permanent vasodilatation in HPS this vasculopathy did not result in elevated pulmonary vascular pressure. However the response to vasoconstrictors like angiotensin II was significantly higher and by using L-NAME, an inhibitor of vasodilatation, the Euler-Liljestrand-reflex (hypoxic pulmonary vasoconstriction) was markedly increased in CBDL rats as compared to sham-operated rats. These findings suggest that there is additional vasoconstrictor capacity in pulmonary vessels in the setting of HPS.

Finally, a study by Roberts et al. (34) tried to detect genetic risk factors in patients suffering from HPS. They found that there are correlations between single nucleotide polymorphisms in genes associated with the regulation of angiogenesis and estrogen action and the presence of HPS. In contrast, genes encoding for NO, HO and ET_B receptors were not associated with HPS.

1.6.4 Further hypothesis

Furthermore, there are discussions of whether substances from the gut that are modified by the liver or other substances produced directly by the liver could be responsible for alterations in pulmonary vascular architecture (13, 14, 35). There are reports of patients suffering from congenital heart disease who develop intrapulmonary vascular malformations and vasodilatation after intervention via anastomosis of the superior vena cava and the right pulmonary artery (35). In contrast, total cavopulmonary anastomosis does not result in pulmonary vascular alterations and heart transplantation could lead to resolution of vascular abnormalities, indicating that reperfusion with hepatic venous blood could be necessary for regulatory processes in pulmonary vasculature (13, 35). This theory is supported by a record from O`Leary et al. (18). They described a patient suffering from a porto-caval shunt (type 2 Abernethy malformation) causing HPS and hepatic encephalopathy. The shunt was blocked via placement of a stent graft in the inferior vena cava. After intervention there was a complete resolution of HPS.

A case report from 2010 (36) brought up the possibility of involving mu-receptors and opiates in the pathogenesis of IPVD and HPS. They described a patient suffering from hepatic cirrhosis and HPS, who had been on methadone substation treatment to remain abstinent from drug abuse. After the withdrawal of methadone, there was a complete resolution of intrapulmonary shunting and symptoms. Therefore, Lau et al. (36) hypothesized that chronic administration of methadone could lead to increased production of NO intrapulmonary via opiate receptors. These receptors are also present in vascular endothelium of rats. Nevertheless there are currently no experimental data available about the role of opiate-receptors in human vasculature.

1.7 Diagnosis

Diagnosis of HPS relies on demonstration of arterial hypoxemia, age-adjusted increases in $AaDO_2$ and intrapulmonary vasodilatation.

1.7.1 Current screening guidelines

Current European Respiratory Society (ERS) Task Force guidelines (see Figure 1-4) recommend screening in all hepatic patients and patients evaluated for OLT, who show typical symptoms. Such symptoms are shortness of breath, platypnoea, orthodeoxia (13). Platypnea is defined as shortness of breath exacerbated by sitting up and improved by lying down. Orthodeoxia is an exacerbation of hypoxemia after changing from supine into upright position. Other signs such as spider naevi, digital clubbing and cyanosis do not seem to be specific for HPS. (13) Pulse oximetry (see below) could be used as non-invasive screening tool to quantify hypoxemia (15, 16, 37).

For patients who are suspected to have HPS, further evaluation is recommended. This evaluation includes arterial blood gas analysis (to assess PaO_2 or increased age adjusted $AaDO_2$), contrast-enhanced echocardiography (CEE [see below]; to diagnose arteriovenous communications and IPVD by injection of agitated saline into a brachial vein and visualization of microbubbles in the left heart chambers after three or more heart beats) or lung perfusion scintigraphy (MAA scan [see below]; diagnosis and quantification of the extra-pulmonary shunt fraction (brain-to-lung ratio), value >6% is considered pathological) (13).

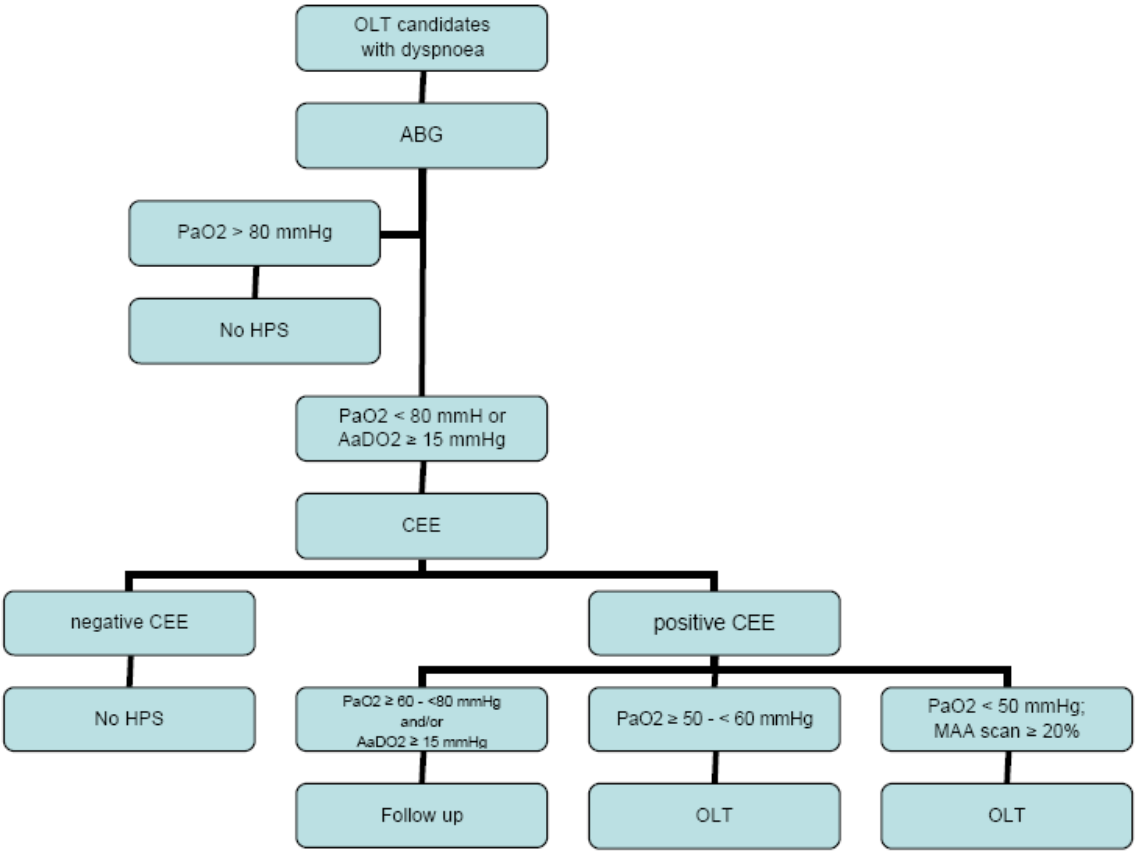

Figure 1-4. ERS Task Force screening guidelines; from Rodriguez-Roisin et al. (13)

In their 2006 review about HPS, Palma et al. (15) recommend that patients with liver disease or evaluated for OLT, who show clinical signs or a decreased SpO_2, should undergo further evaluation such as arterial blood gas analysis (ABG) and CEE. In patients with suspected intrinsic cardiopulmonary disease, the underlying conditions should be treated first and if symptoms persist, CEE and lung perfusion scintigraphy could be performed.

However, many different screening criteria and definitions were used by different study groups in clinical trials to detect HPS. Some of these adapted screening criteria are shown in Table 1-1.

	Schnek et al.; Gastroenterology 2003	Swanson et al.; Hepatology 2005	Krowka et al.; Liver Transplantation 2004	Moller et al.; Liver international 2009	Fuhrmann et al.; Gastroenterology 2006	Roberts et al.; Gastroenterology 2010*	Abrams et al.; Gastroenterology 1995	Deibert et al.; BMC Gastroenterology 2006*	Arguedas et al.; Clinical Gastroenterology and Hepatology 2007	Schenk et al.; GUT 2002
diagnostic criteria:	1.presence of chronic liver disease 2.increased AaDO2 (age related 3.intrapulmonary vascular dilatation (CEE) 4.absence of intracardiac or pulmonary disease	1. chronic liver disease + clinical manifestations of portal hypertension, 2. AaDO2 ≥ 20mmHg + PaO2 ≤ 70mmHg, 3. positive CEE,	1. liver disease that meets OLT listing criteria, 2. AaDO2 ≥ 20mmHg or PaO2 ≤ 70mmHg, 3. positive CEE + MAA scan	1. presence of liver disease, 2. AaDO2 ≥ 20mmHg, 3. positive CEE	1. presence of liver disease, 2. increased AaDO2 (age related), 3.positive CEE	1. positive CEE, 2. AaDO2 ≥ 15mmHg or 20mmHg (64a)	1. PaO2 ≤ 70mmHg, 2. absence of intrinsic cardiopulmonary disease, 3. positive CEE or MAA scan	1. oximetry: SaO2 ≤ 92mmHg or decrease of ≥ 4%, 2. positive CEE and MAA scan	1. positive CEE, 2. AaDO2 ≥ 20mmHg, 3. no significant findings on chest radiography or lung function test	1. chronic liver disease, 2. arterial hypoxaemia (impaired PaO2 and AaDO2), 3. positive CEE or MAA scan

Table 1-1. Variation of screening criteria

1.7.2 Other diagnostic techniques:

Lung function testing is not required for diagnosis of HPS. In the absence of cardiopulmonary comorbidity, patients with HPS show normal results for lung function testing (13, 15). Due to diffusion impairment in pulmonary vessels, the diffusion capacity of carbon monoxide (DLCO) is decreased in HPS. Therefore, DLCO seems to be a functional marker. In a study conducted by Moller et al. (38) the study group showed that there is a significant correlation between DLCO and other parameters such as liver function (indocyanine green clearance [ICG] and galactose elimination capacity [GEC]) and splanchinic and systemic hemodynamics. There was no correlation between DLCO and MELD or Child-Pugh scores (38). Nevertheless, DLCO is not recommended as screening parameter because it is also elevated in conditions such as chronic interstitial lung disease and anemia. (13, 30, 31)

Pulmonary angiography could be useful for distinguishing between two vascular patterns of HPS. The Type 1 pattern ("diffuse" pattern) can be divided into "minimal" or "advanced" patterns and is characterized by arterial abnormalities. The Type 2 pattern shows arteriovenous malformations (35). Pulmonary angiograms are recommended for patients with severe hypoxemia to localize intrapulmonary shunts (14). CT scanning could also detect dilatation of intrapulmonary arteries. (13)

The 100% oxygen test could be used to differentiate between anatomic and functional intrapulmonary shunts in patients with HPS (20, 39, 40). In contrast to functional shunts, there is no increase in the arterial oxygen saturation (SaO_2) while breathing 100% oxygen in pulmonary disorders caused by anatomic shunting (Typ 2 pattern). As there may be both anatomic and functional shunts in HPS, this test should not be used as screening tool. However, Krowka et al. (40) showed that it could help to detect severe anatomic shunting. They concluded that patients with a PaO_2 response less than 300 mm Hg while breathing 100% oxygen should undergo angiography to detect severe shunts and may benefit from therapeutic embolization (40). In their 2009 study, Moller et al. (38) also evaluated the utility of the 100% oxygen test in patients with liver dysfunctions and HPS. They determined that patients suffering from severe liver dysfunction (Child C) have a significant reduced change in $AaDO_2$ and a significant lower decline in the heart rate (HR) while breathing 100% O2 (38).

Currently there are no screening biomarkers available for HPS. Nevertheless, there seem to be higher serum levels of progesterone and oestradiol in patients suffering from HPS (13). Increased exhaled NO levels could also be detected (13). A prospective study conducted by Koch et al. (22)

showed that there is a positive correlation between elevated levels of endothelin 1 and the presence of intrapulmonary vascular dilatation and HPS.

1.8 Prevelance

The reported prevalence of HPS differs according to chosen cut-off values and screening criteria. Hence, it is reported that HPS prevalence ranges from 1.3% to 32% (13–16, 41). Diverse surveys tried to assess its frequency in different study populations. A detailed overview is given in Table 1-2.

In 2003, Schenk et al. (42) published a paper about the prognostic significance of HPS. 111 patients with biopsy-proven cirrhosis of the liver, mainly evaluated for OLT, were included into this prospective study. The diagnosis criteria were the presence of chronic liver disease, increased age related $AaDO_2$, positive findings on CEE and absence of cardiac and pulmonary disease. 27 patients (24%) fulfilling these criteria were found, most of them suffering from alcohol-induced cirrhosis (59%). 18% of the patients with detected HPS had Child A cirrhosis, 26%, Child B cirrhosis and 56% Child C cirrhosis. Mean MELD score of the patients with HPS was 20.6 (SD 8.4).

In a study conducted by Swanson et al. (43) 61 patients with HPS detected in the Liver Transplantation Clinic at the Mayo Clinic in Rochester were retrospectively analyzed. 3% of these patients were detected in the Child A group, 46% in the Child B group and 51% in the Child C group with an average MELD score of 14 (SD 2.8). The highest prevalence of HPS was found among patients suffering from alcohol induced cirrhosis (33%).

As shown in these two trials, there seems to be a higher prevalence of HPS in patients with more severe liver damage. Nevertheless, there are some aspects that may conflict with this conclusion. Both groups used patients evaluated or listed for OLT to perform their evaluations. Therefore, few patients with compensated cirrhosis were screened for the presence of HPS.

In contrary to the findings by Schenk et al. (42) and Swanson et al. (43), there are also clinical surveys that show different frequency scales of HPS.

In a study by Krowka et al. (44) the prevalence of HPS was assessed in liver transplant candidates and also in pediatric patients. HPS was defined as presence of liver disease that meets OLT criteria, $AaDO_2 \geq 20$ mmHg, $PaO_2 \leq 70$ mmHg and positive findings in CEE and MAA

scan. 40 patients with HPS were found; 22.5% in the Child A group, 57.5% in the Child B group and 15% in the Child C group.

Arguedas et al. (45) detected 41 (32%) patients suffering from HPS among 127 patients referred for OLT evaluation. The highest rate of HPS was observed among Child B cirrhosis (73%), followed by Child A (6%) and Child C (5%). However, most of the patients screened already belonged to Child-Pugh stage B (69%). Average MELD score was 14 (SD 4).

There are no data available about whether the frequency of HPS correlates with the etiology of the underlying liver disease. Although in most studies alcohol-induced liver damage is the leading cause of cirrhosis associated with HPS and its frequency ranges from 15% to 59% (34, 42–44). One study, in which also pediatric patients were included, showed that bilary artresia was seen in 37.5% (all pediatric subjects) of the patients with HPS (44). In the study by Roberts et al. (34) hepatitis C (44%) was the leading underlying trigger of liver damage.

In 2006, Deibert et al. (41) revealed much lower prevalence of HPS. In contrast to other trials they analyzed unselected groups of patients suffering from cirrhosis of the liver, portal hypertension and chronic hepatitis. Just four (1.3%) of 316 consecutive patients had HPS. However, data from this trial may be of limited use as the main aim of this study was to detect clinically significant HPS by the use of pulse oximetry and not to reveal the true frequency of HPS.

As already mentioned chosen screening thresholds have an important influence on the prevalence of HPS. In their 2002 study, Schenk et al. (16) tried to assess the influence of different thresholds on the detected frequency of HPS in a population of 98 patients evaluated for OLT or transjugular intrahepatic shunt. HPS was defined by the presence of chronic liver disease, intrapulmonary vascular dilatation (shown by MAA scan or CEE) and arterial hypoxemia detected by a decreased PaO_2 or increased AaDO2. They compared different cut-off values of arterial hypoxemia (PaO_2 <80 mmHg, <70 mmHg, <65 mmHg, <60 mmHg, <age related and $AaDO_2$ >15 mmHg, >20 mmHg, >age related) and found that the PaO_2 <65 mmHg was associated with the highest positive predictive value (100%) for the diagnosis of HPS and that the $AaDO_2$ >15 mmHg correlated with the highest prevalence of HPS (32%) in their study population.

	Schnek et al.; Gastroenterology 2003	Swanson et al.; Hepatology 2005	Krowka et al.; Liver Transplantation 2004	Deibert et al.; BMC Gastroenterology 2006	Arguedas et al.; Clinical Gastroenterology and Hepatology 2007
Results:					
HPS prevalence	24% (27)	61	40	1.3% (4)	32% (41)
mean Child Pugh Score:	10.8 ± 2.5	-	-	-	-
CHILD CLASS:			in 5% (2) not reported	no data	
CHILD A	18% (5)	3% (2)	22.5% (9)	-	15% (6)
CHILD B	26% (7)	46% (28)	57.5% (23)	-	73% (30)
CHILD C	56% (15)	51% (31)	15% (6)	-	12% (5)
MELD Score	20.6 ± 8.4	14 ± 2.8	-	-	14 ± 4
etiology:	Alcohol 59% (16); HCV 19%; HBV 3.7% (1); Hemochromatosis 3.7% (1); PBC 3.7% (1); Autoimmune Hepatitis 3.7% (1); Cryptogenic 7.4% (2);	Alcohol 33% (20); HCV 13% (8); PBC 8% (5); Autoimmune hepatitis 10% (6); Cryptogenic 16% (10); others 20% (12);	Bilary atresia (pediatric) 37.5% (15); Alcohol 15% (6); HCV10% (4); Autoimmune hepatitis 7.5% (3); NASH 5% (2); Hemochromatosis 2.5% (1); PSC 2.5% (1); Cryptogenic15% (6); others 5% (2);	HCV (1); Portal vein thrombosis (1); chronic EBV (1); nodular regenerative hyperlasia (1);	HCV 45%

Table 1-2. Reported prevalence of HPS

Summarizing previous data and cohort analysis, there seems to be a lack of evidence concerning the prevalence of HPS among patients with compensated cirrhosis and whether there are correlations between the severity (see Table 1-2) and the etiology of the underlying liver disease.

1.9 Natural history and prognosis

Hepatopulmonary Syndrome has an important influence on survival and perioperative complications of OLT (13, 15, 30, 37).

In a recent trial by Kochar et al. (46) 121 patients with and without HPS evaluated for OLT were prospectively screened with pulse oximetry to assess hypoxemia and its progress over time. Baseline SpO_2 values were different between HPS- and non-HPS patients listed for OLT (96.8% vs. 98.4%). Furthermore, HPS patients were more likely to have a deterioration in SpO_2 of more than 2% and a faster decline in oxygen saturation. A decline in oxygenation was associated with a worsening of the general condition and earlier transplantation.

Schenk et al. (42) assessed the prognostic influence of HPS. They could indentify HPS as an independent risk factor. Median survival in patients with HPS was significantly lower, especially in patients with severe liver dysfunction (Child C, 2.9 months) as compared to non-HPS patients (Child C, 14.7 months). Moreover, the degree of hypoxemia correlated with survival time in HPS patients. Causes of death were mainly associated with liver dysfunction and portal hypertension. The leading cause of death was hemorrhagic shock due to gastrointestinal bleeding.

In another study, Swanson et al. (43) analyzed 61 HPS patients retrospectively. There was a significant difference in median survival between patients with (24 months) and without HPS (87 months) who did not undergo OLT. In contrast, median survival in both OLT groups was similar. Low PaO_2 ($\leq$ 60 mmHg) was associated with worse long-term survival before and after OLT. Swanson and his partners, therefore, hypothesized that higher priority for OLT is required.

These findings are supported by a multicenter study by Krowka et al. (44). Again, non-survivors of OLT had a significantly reduced pre-OLT PaO_2.

Gupta et al. (47) assessed the direct influence of HPS on the perioperative period in patients undergoing OLT. In the pretransplantation period there was a progressive decline in arterial oxygenation in 87% of the patients. Mean decline in PaO_2 was 13.5 mmHg (SD 16.5) per year. The postoperative mortality rate was 5% in all subjects and 9% in patients suffering from severe hypoxemia. In 23.8% of HPS patients, early respiratory complications developed in the postoperative period. All of these complications could be successfully treated with Trendelenburg positioning, NO inhalation or high frequency oscillator ventilation. There was an increase in mean PaO_2 after transplantation from 65.1 mmHg (SD 9.4) to 90.9 mmHg (SD 8) with a mean increase rate of 3.1 mmHg (SD 2.3) per month. All in all, there was a 100% peritransplant and 93% one-year survival rate after OLT in HPS patients.

There are also reports about the development of portopulmonary hypertension after OLT (37).

1.10 Treatment

Over time there have been many attempts to treat HPS with different pharmaceuticals and invasive procedures (15, 48). Based on current pathological theories, interventional trials were conducted that tried to influence vascular tone of intrapulmonary vessels, bacterial translocation, syntheses of cytokines or modulators of vascular tone (see Figure 1-5). Most of these case records or pilot studies resulted in conflicting and inconsistent data. Therefore, large randomized and multicenter trials are needed to prove the utility of these procedures and pharmaceutical treatments.

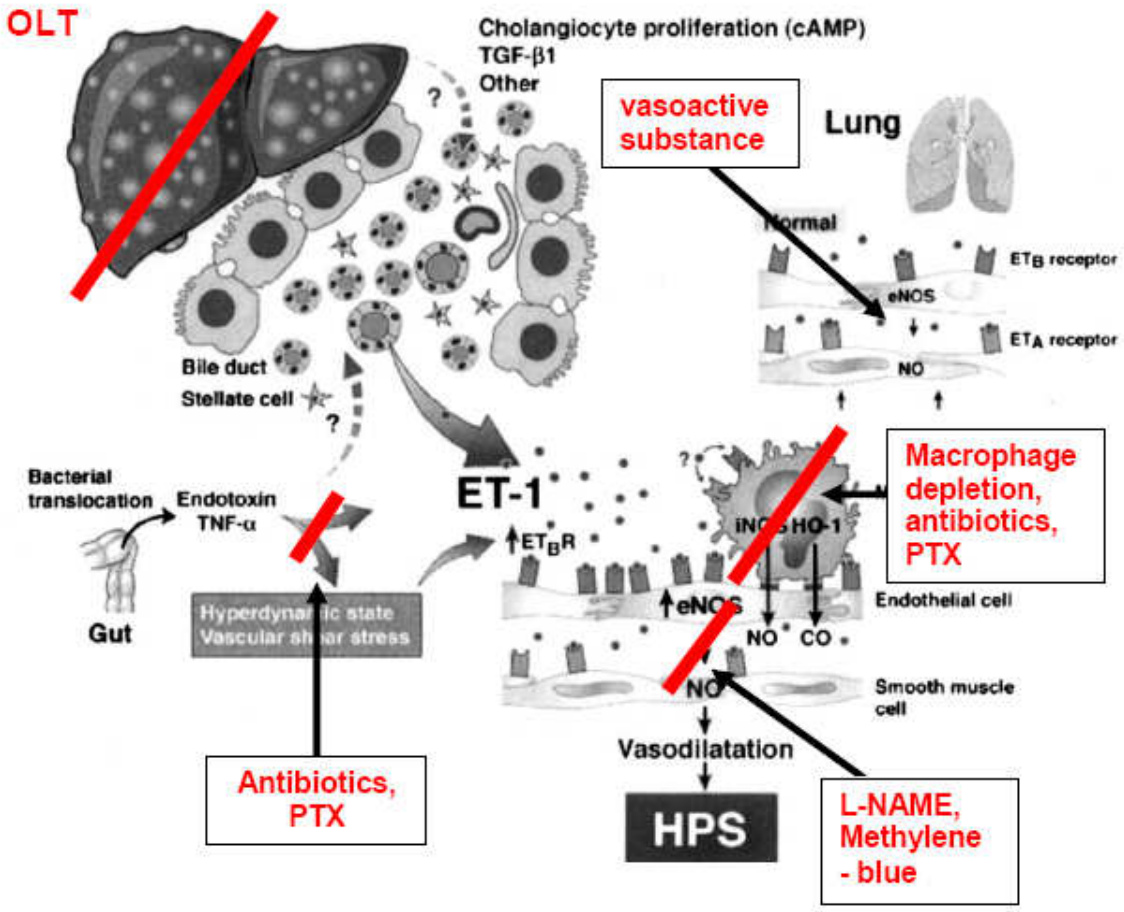

Figure 1-5. Different treatment options; from Fallon et al. (21), adapted by Philipp Douschan

1.10.1 Blocking the ET-1 – NO pathway

In 2000, Schenk and colleagues (26) tried to assess the effect of methylene blue, an inhibitor of the soluble guanylat cyclase, in the setting of severe HPS. Seven patients were included in this study. After intravenous administration of methylene blue (3 mg/kg body weight, injected over a period of 15 minutes), blood gas analysis and hemodynamic measurements were recorded. After administration there was an increase of PaO_2, due to decreased intrapulmonary shunting, an increase of mean pulmonary artery pressure, mean systolic artery pressure and systolic vascular resistance. There was a decline of $AaDO_2$ and cardiac output.

Gmoez et al. (27) used N^G-nitro-L-arginine methyl ester (L-NAME), an inhibitor of the NO synthase, to treat 10 patients with HPS. 162 mg L-NAME were administered nebulized. After inhalation there was a decrease in exhaled NO and again normalization in circulatory parameters. However, in contrast to Schenk et al., no significant changes in PaO_2, $AaDO_2$, intrapulmonary shunting and ventilation/perfusion (V_A/Q) mismatch could be detected.

1.10.2 Antibiotics and TNFα synthesis blocker

Data from experimental trials suggest that bacterial translocation, endotoxemia and increased amounts of cytokines contribute to the development of HPS (21, 28, 31–33).

Although evidence from CBDL rats treated with antibiotics suggests that antibacterial treatment could lead to an improvement of HPS, current clinical trials with humans could not fully approve the utilisation of antibiotics in the treatment of HPS (31, 49).

A single case record from Anel et al. (50) described a patient with HPS who underwent treatment with antibiotics due to a brain abscess. During treatment they recognized improvement of hypoxemia, therefore treatment with norfloxacin 400 mg was continued. After treatment SaO_2 increased to 95%. There was also a resolution of platypnea and orthodeoxia.

In a pilot study by Gupta et al. (49), nine patients suffering from HPS were treated with 400 mg norfloxacin twice daily for four weeks followed by a four weeks washout period. Due to the small cohort of patients and the high variability of changes in $AaDO_2$, no significant changes in gas exchange parameters could be found.

The utility of pentoxifylline (PTX), a phosphodiesterase inhibitor that blocks TNFα production, has also already been proven in experimental studies (32). Tanikella et al. (51) tried to use PTX in humans suffering from advanced HPS ($PaO_2 = 54 \pm 12$ mmHg). Seven patients were instructed

to take 400 mg tablets of PTX once daily for seven days, followed by twice daily for one week and thrice daily for 42 days. Due to adverse effects, most patients could not take the prescribed dose. Just one patient was able to complete full dose therapy. Furthermore, Tanikella et al. could not detect any improvement in PaO_2 during treatment with PTX.

However, Gupta et al. (52) conducted a trial where they included nine patients with HPS. They administered 400 mg of PTX thrice daily for three months. There was an improvement in nearly all clinical features of HPS. There were eight complete-responders (increase in $PaO_2 \geq 10$ mmHg or $PaO_2 \geq 80$ mmHg) and one non-responder. TNFα levels decreased significantly. Besides an improvement in oxygenation and symptoms, they also detected improved exercise tolerance among patients.

1.10.3 Modulating vasculare tone

As capillary and precapillary dilatations are responsible for increased shunting in HPS, the modulation of intrapulmonary vascular tone could help to normalize oxygenation in patients.

In some trials, almitrine bismesylate, a vasoconstrictor that increases hypoxemic pulmonary vasoconstriction, was used to treat patients (48). In a study by Nakos et al. (53) six patients were treated with almitrine bismesylate.

A significant increase in pulmonary vascular resistance (PVR), mean pulmonary artery pressure (mPAP) and systemic vascular resistance (SVR) was detected. Nonetheless, there was no improvement in oxygenation parameters such as PaO_2 and $AaDO_2$. However, in a case recorded by Milhe and colleagues (54), administration of this vasoconstrictor led to an increase of arterial oxygenation.

Another vasoconstrictor and analogue of vasopressin, terlipressin, was administered at a dose of 2 mg to a group of 15 patients with asymptomatic IPVD and hepatic cirrhosis (19). Terlipressin therapy led to a significant decrease of shunt fraction.

In another case record, Krug et al. (55) applied iloprost, a vasodilator that is normally used to treat patients suffering from pulmonary hypertension. It was administered nebulized six times a day. Eight weeks after the initiation of therapy, there was a marked increase in PaO_2 and in exercise tolerance. Furthermore, there was a resolution of symptoms such as dyspnoea. After conducting OLT, hypoxia was still present and iloprost therapy was continued. HPS resolved

three months after surgery. The underlying mechanism of action of iloprost in the setting of HPS remains unknown.

1.10.4 Garlic and other pharmaceuticals

Over several decades many different pharmaceuticals have been examined. The administering of somatostatin analogues, cyclooxygenase inhibitors and immunsupressive agents led to poor results (48). It was hypothesized that garlic could cause an improvement in oxygenation in people having HPS (56, 57). It was speculated that garlic leads to an uniform vasodilatation in the whole lung. Most of vasodilatation occurs in basal lung segments in HPS. So there is a significant V/Q mismatch in these regions. Administering of garlic could redistribute pulmonary perfusion from basal to apical and mid-lung fields and, therefore, could result in more homogeneous lung perfusion and less severe V/Q mismatch (56).

Abrams et al. (56) first conducted a pilot study to prove this hypothesis. 15 HPS subjects were treated with 500 mg garlic powder capsules twice a day. 40% (six patients) had a modest change in PaO_2 and $AaDO_2$. Garlic responders were younger and had lower extrapulmonary MAA shunting at baseline examination.

In 2010, De and colleagues (57) published a paper about a randomized controlled trial, again using garlic as therapy in patients with HPS. In contrast to the placebo group, HPS subjects treated with 250 mg garlic capsules had a significant increase in PaO_2 nine months after treatment. 14 (67%) patients out of 21 in the therapy group became HPS negative, whereas just one in the placebo group was a responder.

1.10.5 Invasive procedures

As mentioned previously, patients with HPS develop severe arteriovenous fistula in some cases causing severe hypoxemia. In angiography this pattern is called type 2 pattern. Due to its poor response to oxygen, interventional embolization therapy is recommended by some authors (15, 48). There are also reports of the successful treatment of Type 1 HPS pattern with coil embolization (48).

Reviewing articles about pathobiology of HPS, lowering portal venous pressure or restoring direct porto-caval connection could be considered a useful procedure to treat HPS. Indeed,

placement of transhepatic portosystemic shunts (TIPS) seems to have beneficial effects on patients with HPS (15, 48, 58). Benitez et al. (58) reported the case of a 46-year-old woman with cryptogenic cirrhosis and HPS. Due to her bad general condition (severe hypoxemia) OLT could not be considered. Thus TIPS placement was performed as bridging method. After four weeks there was a significant improvement of oxygenation. PaO_2 had changed from 60 mmHg to 72 mmHg. Six months later a 50% stenosis of the TIPS emerged and the patient presented with shortness of breath. There was complete improvement after dilatation of TIPS. Despite resolution of symptoms and increase in oxygenation, IPVD persisted and contrast enhanced CEE was still positive. Intrapulmonary shunts persisted, even after OLT.

Nevertheless, there are also reports of TIPS placements that did not lead to resolution of HPS (59). In fact, there are some reports about development of HPS in the setting of functioning TIPS (59). Some authors, therefore, claim that TIPS placement due to HPS is still an experimental treatment (15).

1.10.6 OLT and MELD exception

Currently the only effective treatment for HPS is OLT (14, 15, 37, 48). There are reports about total resolution of HPS after OLT (13, 15, 47, 48). However, as mentioned earlier in this work, depending on severity of hypoxemia, the outcome of OLT and the perioperative survival rate vary (42, 44, 47). Hence, to prevent further decline in oxygenation, a higher priority for transplantation is recommended. Fallon and colleagues (60) suggested an allocation of exception MELD points for patients with HPS. They also created a screening algorithm for HPS for daily clinical use (see Figure 1-6). People should be only screened by CEE and pulse oximetry. People with $SpO_2 < 96$ and positive findings on CEE should be further evaluated for the presence of IPVD. MELD exception protocol should be used in patients with HPS and a $PaO_2 < 60$ mmHg in the absence of severe alternative pulmonary comorbidity. Depending on the severity of hypoxemia and change in PaO_2 during follow up blood gas analysis, additional MELD points could be assigned (see Figure 1-7).

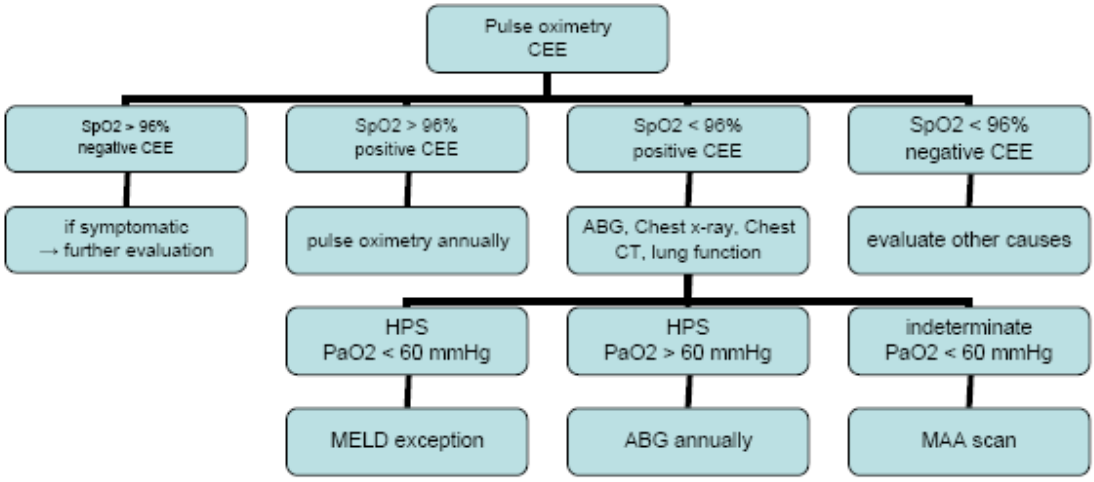

Figure 1-6. Screening algorithm by Fallon et al. (60)

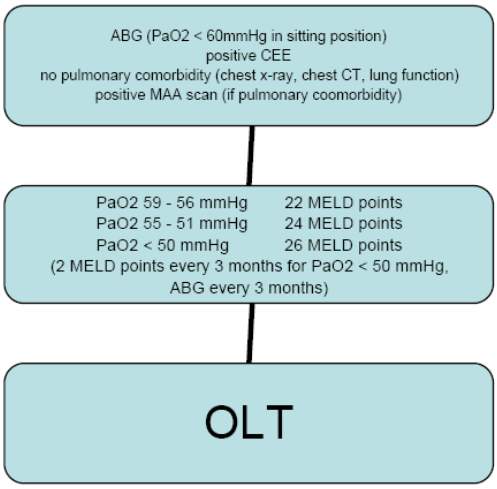

Figure 1-7. Proposed MELD-exception criteria by Fallon et al. (60)

1.10.7 Oxygen supplementation

Deterioration of oxygenation may lead to further impairment of hepatic function and general health condition. Thus it is suggested that long-term oxygen therapy (LTOT) should be used to prevent more reduction in oxygenation (15, 48). It is particularly recommended for patients with a PaO_2 < 60 mmHg (15). However, there are no long-term data available about its positive influence on the survival of patients with HPS and again, randomized controlled trials are needed to prove its utility.

In a case series of five subjects with severe and very severe HPS, who underwent liver transplantation, Chihara et al. (61) assessed the utility of non-invasive ventilation (NIV) after OLT to prevent postoperative adverse events. In the case of their first patient, a four-year-old boy with biliary atresia, NIV was started on the 9th postoperative day due to low oxygen saturation. In the other four cases, NIV was started immediately after extubation. In all cases no pulmonary complication developed during the postoperative hospitalisation period. NIV could, therefore, be useful for dealing with postoperative hypoxemia in patients with severe HPS.

1.11 Hypothesis and aims

There is a lack of information concerning the frequency of HPS in well compensated and early stage cirrhosis of the liver. Furthermore, there are no data available about whether the prevalence of this pulmonovascular complication of cirrhosis correlates with the severity or the etiology of the underlying hepatic disease.

After reviewing articles about HPS, we, therefore, hypothesized that HPS is present in all stages of hepatic cirrhosis, as well as in compensated. Our specific aims were:

1. To assess the prevalence of HPS in 100 patients, suffering from compensated cirrhosis seen in a referral center, using sensitive screening tools.
2. To relate HPS with gender, etiology of cirrhosis and the degree of liver dysfunctions estimated by the Child-Pugh score or the model of endstage liver disease (MELD).

2 Methods

2.1 Overview

Consecutive patients with cirrhosis referred to the Medical University of Graz, including inpatients (medical ward) and outpatients (liver clinic), were enrolled. Patients were evaluated for severity and etiology of liver dysfunction and screened for the presence of HPS. In all patients arterial oxygen saturation (SpO2) was determined in the upright position by a portable pulse oximeter. Patients with a SpO2 $\leq$ 97% underwent further pulmonary work-up including spirometry, arterial blood gas analysis (BGA), contrast enhanced transthoracic echocardiography (CEE) and lung perfusion scintigraphy.

An overview is given in Figure 2-1. HPS was defined as the presence of arterial deoxygenation, IPVD (positive CEE and positive MAA scan), hepatic cirrhosis and portal hypertension.

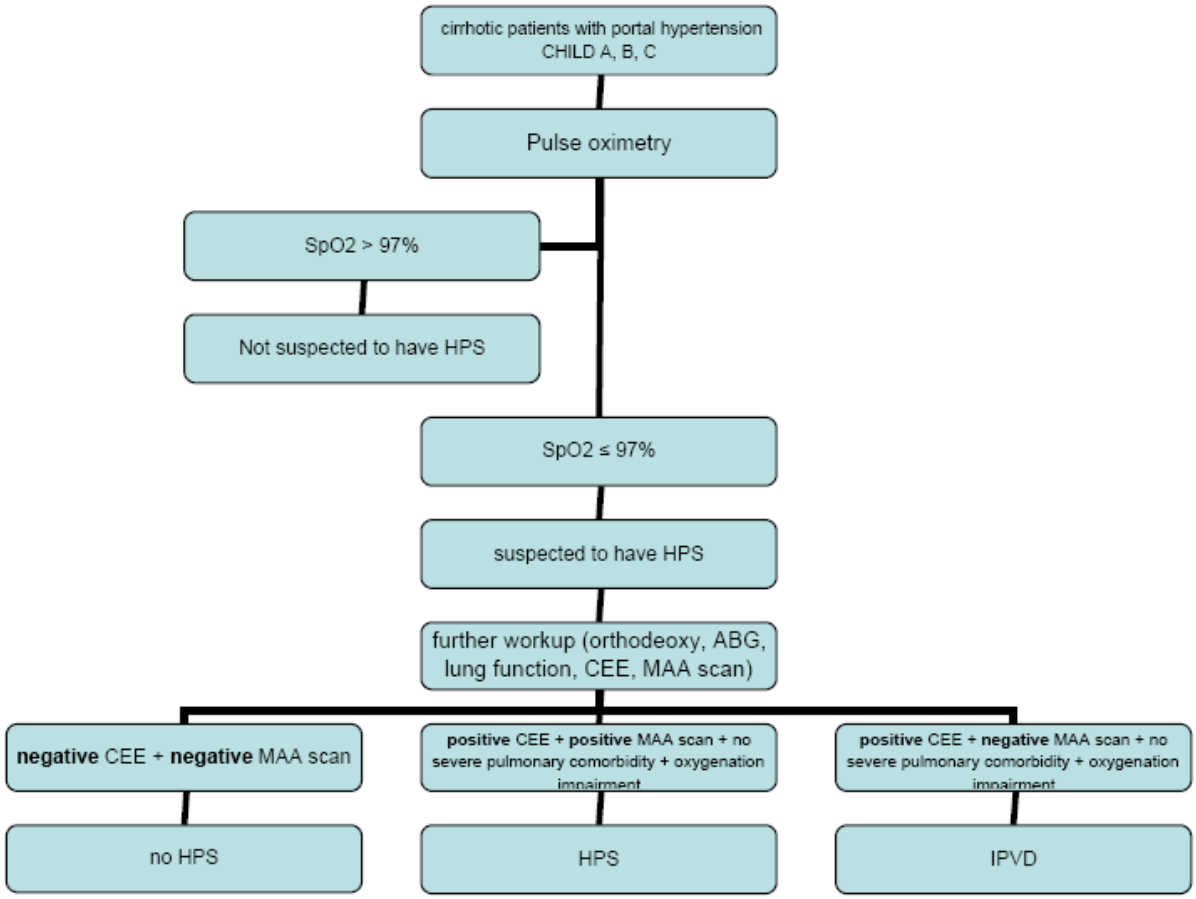

Figure 2-1. Study workflow

2.2 Patient selection

Consecutive patients with hepatic cirrhosis were enrolled, irrespective of severity or etiology of liver dysfunction. Diagnosis of cirrhosis was either confirmed by liver biopsy or by typical clinical findings such as signs of portal hypertension (esophageal varices, spider naevi, hepatic ascites, palmar erythema, splenomegaly, hepatic encephalopathy, reduced platelets), reduced hepatic synthetic function (impaired coagulation) and typical findings on ultrasound. We further defined inclusion and exclusion criteria for our study cohort.

2.2.1 Inclusion criteria

- Adult patient with age > 18 years
- Presence of portal hypertension
- Cirrhosis of any etiology Child Pugh class A, B or C
- Informed consent

2.2.2 Exclusion criteria

- Presence of other causes of IPVD
- Presence of severe cardiopulmonary comorbidity
- Presence of hepatocellular or cholangiocellular carcinoma
- Status post liver transplantation
- HIV infection
- Pregnancy
- Esophageal variceal hemorrhage within the last six weeks
- Presence of hepatorenal syndrome
- Presence of hepatic encephalopathy (> stage 1)

We decided not to include patients with severe cardiopulmonary comorbidity, as it is known that sensitivity and specifity of screening tools could be influenced. The presence of other causes for IPVD could also affect our diagnostic approaches. Furthermore, we excluded patients who were at risk of developing any complication due to the severe stage of their disease. Such complications included esophageal varices bleeding, hepatorenal syndrome and the presence of malignant hepatic tumors. Patients who already underwent OLT were excluded. It is already known that transplantation could cause resolution of HPS or normalization of oxygen saturation.

2.3 Evaluation of liver dysfunction

In cirrhotic patients, the severity of liver dysfunction was estimated from routine parameters using the Child-Pugh score (see Table 2-1) and the MELD score (see Figure 2-2). Scores were assessed according to clinical and laboratory parameters obtained on the day of study inclusion.

score	1	2	3
Serum bilirubin (mg/dl)	<2,0	2,0 - 3,0	> 3,0
Serum albumin (g/dl)	> 3,5	2,8 - 3,5	< 3,0
Ascites	absent	mild	massive
Encephalopathy (grade)	none	1 and 2	3 and 4
INR	< 1,7	1,7 - 2,2	2,2
each parameter is scored 1 to 3: (CHILD A: 0-6, CHILD B: 7-9, CHILD C: 10-15)			

Table 2-1. Child-Pugh-score, Guha et al.(9), adapted by Philipp Douschan

$$3{,}8 \log_e(\text{bilirubin [mg/dl]} + 11{,}2 * \log_e[\text{INR}]) + 9{,}6 \log_e(\text{creatinine [mg/dl]}) + 6{,}4\ (\text{etiology: 0 cholestatic or alcoholic, 1 otherwise})$$

Figure 2-2. MELD formula, (9)

Routine laboratory procedure included measurement of haemoglobin, MCV, differential blood count, coagulation (INR, APTT, fibrinogen, antithrombin), renal function parameters (creatinine, blood urea nitrogen, uric acid), electrolytes (Na, K), CK, LDH, liver function parameters (AST, ALT, CHE, AP, GGT, bilirubine), total protein, albumin, cholesterol, triglycerides, glucose, and CRP.

The presence and measurement of ascites were assessed by using two dimensional abdominal-ultrasound. Depending on its degree it was graded into no (no evidence of ascites), mild (only detectable by ultrasound) and massive (massive volume of ascites detected by ultrasound and/or distension of abdomen) ascites.

Hepatic encephalopathy was graded from 0 to 4 depending on the level of consciousness, intellectual function and neurological abnormalities (see Table 2-2).

Grade	level of consciousness	intellectual function	neurologicl abnormalities
0	normal	normal	none
I	lack of awarness change in personlity day/night reversal	short attention span easy forgetfullness	slight tremor uncoordination asterixis
II	lethargy unsuitable behaviour	loss of orientation	asterixis abnormal reflexes
III	asleep but rousable confused	loss of interpersonal communication	abnormal rflexes
IV	unarousable	absent	Babinski/clonus decerebrate

Table 2-2. HE-grading, Häusinger et al. (62), adapted by Philipp Douschan

2.4 Pulse oximetry

Pulse oximetry was used as a simple and readily available screening tool. Measurement of oxygen saturation was performed with a portable pulse oximeter (Fingertip Pulse Oximeter MD300D HABEL Medizintechnik®). The SpO_2 measurment range is between 70% and 99%. Its reported accuracy varies: ± 2% in the range of 80% to 99% and ± 2% in the range of 70% to 80%. The pulse rate measurement range is between 30 and 350 beats per minute (BPM), with an accuracy of ± 2 BPM. Besides measurement of SpO_2 and heart rate, there is also the possibility of detecting SpO_2 waveform (plethysmography) on the display of the MD300D pulse oximeter.

Screening SpO_2 was measured at ambient O_2 partial pressure in upright position. The pulse oximeter was applied to the left or right index finger. SpO_2 was accepted after showing a regular SpO_2 wave and a stable SpO_2 value.

A positive result was defined by a $SpO_2 \leq 97\%$. The presence of orthodeoxia was demonstrated by a decrease of $SpO_2 \geq 4\%$ ten minutes after a change from supine to upright position.

2.4.1 Measurement principles

Pulse oximetry is a non-invasive technique that measures the oxygen saturation (SpO_2) of the blood. Measurement is based on Beer-Lambert law. It implies that the extinction (E) of light passing through a medium is dependent on the intensity of light before (I_0) and after (I) passing through the medium, the layer thickness (d), the type and the concentration of the medium (k) (63).

$$E = I_0/I = e^{k\,d}$$

To quantify this saturation, two dependent components, arterial pulsatile signal and different absorbtion spectra of oxy- and deoxyhemoglobin, have to be detected. The peak absorbtion frequency of haemoglobin is 660 nm (red light), whereas the peak absorbtion frequency of deoxyhemoglobin is 940 nm (infrared light). Normal tissues, nails and muscles also have different absorbtion peaks. Due to its pulsatile component, wave absorbtion by arterial blood can be distinguished from nonpulsatile and non changing absorption of the normal tissue and venous blood. In our pulse oximeter, two light emitting diodes (LEDs) are used to illuminate the vascular bed of one index finger with infrared (940 nm) and red light (660 nm). After penetrating through the vascular bed, a red and infrared receipt tube (photoreceptor) detects these photowaves. These signals are normalized by dividing nonpulsatile and pulsatile signals of each wavelength. An optical density ratio (ratio of normalized red signal / ratio of normalized infrared signal) is calculated. This optical density ratio can be compared by the processor of the sensor with empirically evaluated reference density ratios of different oxygen saturation values. Therefore, depending on the calculated density ratio, a specific SpO_2 value can be assessed. (64, 65)

There are many factors that could influence the accuracy of pulse oximetric measurement of SpO_2. Hypotension, low cardiac output, hypothermia and severe vascular constriction can cause reduced pulsatile volume and can, therefore, lead to reduced signal strength.

As arterial pulse plays an important role in calculation of SpO_2, motion artefacts are most often responsible for wrong measurements. Hence, the use of plethysmography, to differentiate between true and false signals, is recommended.

Carboxhemoglobin, methemoglobin, foetal haemoglobin and sickle red blood cells may also interfere with pulse oximetry. They have similar absorbtion peaks to physiological hemoglobin.

Other substances such as methylene blue, indocyanine green and indigo carnine can cause false low SpO_2 values.
Furthermore, blue, black and green nail polish and false finger nails lead to inaccurate assessment of oxygen saturation. Anemia does not cause wrong SpO_2 measurement. (64)
There is also no evidence of hyperbilirubinemia interfering with hemoglobin in pulse oximetry (66).
To reduce the risk of bias during pulse oximetry, we decided to use nail polish remover in patients with black, green or blue nail polish. Moreover, patients were instructed not to move during examination and we also used plethysmography, detected by the display of our pulse oximeter.

2.4.2 Backround

There have been many attempts to find screening tools for daily clinical practice. Therefore the utility of pulse oximetry has often been assessed by clinical trials.
Abrams et al. (67) tried to determine the utility of pulse oximetry to detect hypoxemia in 200 liver transplant candidates. Hypoxemia was defined as a PaO_2 level less than 70 mmHg. As most of those patients with hepatic cirrhosis and hypoxemia suffered from HPS, defining cut off values for pulse oxemetric screening could help to identify HPS in liver transplant candidates. They found that a SpO_2 of 98% had a sensitivity of 100% and a specificity of 53 %. A SpO_2 of 97% had a sensitivity of 96% and a specificity of 75% in detecting hypoxemia. Only one patient with HPS had a SpO_2 of 98% and a PaO_2 of 69 mmHg. Moreover, they revealed that pulse oximetry overestimates arterial oxygen saturation (SaO_2) by a mean of 3% to 4%. Due to the poor specificity of a SpO_2 cut-off value of 98%, Abrams et al. suggested conducting further arterial blood gas analysis in patients with a SpO_2 of 97% or less to detect hypoxemia.
As already mentioned in this work, Schenk and colleagues (16) stated that defining hypoxemia by different cut off values results in varying prevalence and positive predictive values. Lower prevalence (14%) was associated with a $PaO_2 < 70$ mmHg. Using $AaDO_2$ cut-off values led to higher prevalence (32%), but to a decrease of the positive predictive value (34% – 53%). $PaO_2 <$ 65 mmHg had the highest positive predictive value for diagnosis of HPS (100%), but only low prevalence (13%). Thus a $PaO_2 < 65$ mmHg definitely predicts the diagnosis of HPS.

Arguedas et al. (45) assessed different pulse oximetric cut-off values in the diagnosis of HPS. A $SpO_2 \leq 94\%$ had a sensitivity of 100% and a specificity of 93 % in detecting HPS patients with a $PaO_2 < 60$ mmHg. For patients with a $PaO_2 < 70$ mmHg, a SpO_2 cut-off value of $\leq 97\%$ showed 100% sensitivity and 65% specificity. In detecting all patients with HPS (including subclinical patients without hypoxemia), the 97% SpO2 threshold only had a sensitivity of 64% and a specificity of 68%. Hence, a screening threshold of 97% could help to detect all patients with clinically significant HPS with hypoxemia.

In a study by Deibert et al. (41) they tried to detect clinically significant HPS patients by the use of pulse oximetry. 316 cirrhotic patients were screened. Patients with a $SpO_2 \leq 92\%$ and presence of orthodeoxia were further evaluated by lung function testing, a chest x-ray, CEE and MAA scan. As already reported, they revealed much lower frequency of HPS but could detect significant cases.

There are many definitions of orthodeoxia. Some authors defined it as $\Delta SpO_2 \geq 4\%$, 10 minutes after changing from supine to upright position (39, 41). Withworth and partners (68) determined orthodeoxia as decline of oxygen saturation $\geq 6\%$ or as a decline to a level of ≤ 92 %. Others used a decrease of $PaO_2 \geq 5\%$ or ≥ 4 mmHg as the definition for orthodeoxia (13, 14).

We decided to use pulse oximetry as screening tool to detect suspected cases for further evaluation. Therefore, we had to choose screening thresholds. We chose a cut-off value of $SpO_2 \geq 97\%$ with a sensitivity of 100% for detecting all patients with clinically significant HPS. However, by choosing this threshold, we had to accept omitting some patients with mild and subclinical HPS. In our prospective study, orthodeoxia was defined as change in $SpO_2 \geq 4\%$, 10 minutes after changing from supine to upright position.

2.5 Pulmonary function tests and ABG

Pulmonary function tests were conducted to rule out severe pulmonary comorbidity and to assess functional and staging parameters of HPS. We performed bodyplethysmography, DLCO measurement and assessment of arterial blood gases.

For bodypletysmography and spirometry we used a Bodyplethymograph Master Screen Body / Jaeger® and a Spirometer + MS-PFT / Jaeger®. Before measurement started, patient ID, data for body weight, body height and smoking-anamneses were collected and saved. Afterwards the patient was informed about investigation procedure and a nose clip was attached.

The bodyplethysmograph chamber was closed and investigation started. The patient was guided to breathe into the mouthpiece slowly 5 to 10 times. Intrathoracic gas volume was assessed as follows. Occlusion was activated and the patient had to breathe in against this resistance. Thereafter, he had to breathe out for as long as possible and breathe in for as long as possible, followed by a period of normal breathing. Measurement results were calculated and the maneuver was repeated several times (3 to 8 times). The two best measurements were accepted.

After that, forced breathing maneuver was conducted. The patient was instructed to breathe within normal frequency, to breathe in deeply, to breathe out rapidly and powerfully, and again to breathe in deeply. This maneuver was conducted several times and the two best results were chosen for data collection.

DLCO single breath measurement was performed with a Spirometer + MS-PFT / Jaeger®. A nose clip was attached to the nose, the patient was instructed to breathe into the mouthpiece 4 times. Thereafter, he was guided to breathe out for as long as possible, followed by deep inhalation and ten seconds of holding his breath. Afterwards, the patient had to breathe out again and leave the mouthpiece immediately. Current haemoglobin was entered and DLCOc (hemoglobin adapted DLCO) was calculated by the computer.

Blood gases were analysed by Blutgasanalysator ABL 800 FLEX Radiometer Copenhagen®. Capillary blood was taken from an ear lobe, in sitting position, at rest and at ambient O_2 partial pressure. Before a blood sample was taken, a vasodilatative ointment (Finalgonsalbe Boehringer I.A.®) was administered locally to the left ear lobe. After ten minutes and disinfection of the prepared ear lobe, a lancet was used to prick the area. Blood, free from blood clots and air bubbles, was taken with glass capillaries. Thereafter, a clotcatcher was attached to the capillaries and they were put into the suction aperture of the blood gas analyser. After activating the analyser, the blood was absorbed and the capillary could be removed. Data were calculated automatically.

Collected data included FEV_1 (forced expiratory volume in 1 second), FVC (forced expiratory vital capacity), FEV_1/FVC (Tiffeneau index), DLCOc VA (haemoglobin and alveolar volume adjusted diffusion capacity for CO), DLCOc SB (haemoglobin adjusted single breathe diffusion capacity of CO), PaO_2, $PaCO_2$, SaO_2, FO_2Hb (fraction of oxygenated haemoglobin), FCO_2Hb (fraction of carbon dioxide haemoglobin), FMetHb (fraction of methemoglobin) and $AaDO_2$.

2.6 Contrast enhanced echocardiography (CEE)

Contrast enhanced echocardiography was used to detect intrapulmonary right to left shunting and to rule out intracardiac shunting. It was performed with a Vivid Five GE Vingmed Ultrasound® and a 3.5 mHz phased transducer. As a contrast medium we used 10 ml agitated saline drawn up into two or three 10 ml syringes. The patient was informed about the procedure and after disinfection, an intravenous line was inserted into a peripheral vein, mainly in the right forearm or the right antecubital fossa. Thereafter, the patient was instructed to lie on the left flank and a parasternal four chamber view was adjusted with the ultrasound transducer. Agitated saline was injected via the intravenous line. First of all, microbubbles appeared in the right atrium and the right ventricle. Intracardiac shunting was defined by appearance of microbbubbles within three heart beats after appearance in the right chambers. No arrival of microbubbles in the left chambers was defined as negative result. Appearance of contrast in the left chambers after three heartbeats was considered a verification of intrapulmonary shunting. CEE was repeated two or three times. All CEEs were conducted by the same investigator and recorded with a SVO-9500MDP Sony® video cassette recorder.

2.6.1 Measurement principles

Microbubbles of agitated saline consist of small bubbles of trapped air (≤90 μm). Therefore, they can be visualized with ultrasound. After injection into a peripheral vein, bubbles enter the right chambers, are pumped into the pulmonary arteries and enter the pulmonary capillary bed. The diameter of a normal pulmonary capillary bed in healthy people ranges from 8 μm to 15 μm (14). Under physiological conditions, microbubbles can not pass capillaries and are absorbed. Due to anatomic and functional shunting, as it seen in patients with HPS, bubbles pass the capillary barrier, enter the pulmonary venous system and appear in the left chambers. On average, it takes more than three heartbeats to pass the whole intrapulmonary vasculature. (13, 14)

2.7 Lung perfusion scintigraphy (MAA-scan)

Lung perfusion scintigraphy was used to detect intrapulmonary shunting and furthermore, to quantify shunt fraction. We used technetium-99m (Tc-99m) labelled macroaggregated albumin (MAASOL GE Healthcare®) as radionuclide contrast. The patient was informed about the

procedure and placed in the supine position. A maximal dose of 74 mBq (2 mCi) was injected with a syringe into a peripheral vein through an intravenous line. Scans were conducted with a Symbia T2 True Point SPECT CT Siemens® one minute after injection. Anterior, posterior, right-side and left-side scans of the lungs and the brain were performed and recorded on computer. The extrapulmonary shunt fraction was calculated as follows: (GMT brain / 0.13) / [(GMT brain / 0.13) + GMT lung]. A shunt fraction > 6% was considered a positive result.

2.7.1 Measurment principles

Detection of intrapulmonary shunting with lung perfusion scintigraphy is based on the same principles as CEE. Tc-99m labelled macroaggregated albumin has a particle size of between 10 µm and 100 µm. Under normal conditions it can not pass pulmonary capillary vasculature. In the presence of anatomic and functional shunts, it passes capillaries and is enriched in extrapulmonary organs such as the cerebrum. It is known that 13% of cardiac output is delivered to the brain. Thus shunt fraction can be calculated and quantified with MAA scan. (13, 14, 69)

2.8 CEE vs. MAA - backround

In 1995, Abrams and colleagues (69) published a paper about the diagnostic utility of CEE and MAA scans in patients with HPS. They compared both diagnostic techniques by screening 40 cirrhotic patients. CEE was positive in 15 (38%) patients, but only 7 (17.5%) patients had impaired oxygenation (PaO_2 < 70 mmHg) and only 3 out of 7 did not show pulmonary comorbidity and therefore met strict criteria for HPS. In contrast, MAA scans were only positive in patients with positive CEEs and hypoxemia without pulmonary comorbidity. Lung perfusion scintigraphy detected all patients who met criteria for clinically significant HPS. Hence, Abrams et al. stated that CEE has a higher sensitivity in detecting all patients with IPVD and subclinical HPS whereas MAA scans are less sensitive but have higher specificity for HPS. They recommended using CEE as screening tool for IPVD and to verify HPS by using MAA scan.

In a second study by Abrams et al. (70), 25 diagnosed HPS patients, 25 cirrhotic non-HPS patients and 15 hypoxemic subjects with intrinsic lung disease were investigated using a MAA scan. The MAA scan was positive in 21 of 25 HPS patients, and negative in all other cases. All 4 HPS patients with a negative MAA scan had a PaO_2 > 60 mmHg. They concluded that lung

perfusion scintigraphy could be used to detect moderate to severe HPS and has an overall sensitivity of 84% and a specificity of 100%.

Nevertheless, there is evidence that an MAA scan could detect IPVD in normoxemic cirrhotic patients (19).

In a pediatric HPS study by El-Shabrawi et al. (71), they revealed higher sensitivity of MAA scans compared to CEE. However, El-Shabrawi and partners used different diagnostic criteria and a different formula for calculating extrapulmonary shunt fraction. Thus their results may be incorrect.

Due to the previously reported specificity and sensitivity of MAA scan and CEE, we decided to use both techniques to detect subclinical and clinical cases of HPS in our study cohort of patients with $SpO_2 \leq 97\%$.

2.9 Ethical considerations

An application for this study has been filed at the Ethics Committee of the Medical University of Graz. Informed consent was obtained in accordance with the Declaration of Helsinki. Most of the methods used in this study were non-invasive (lung function tests, pulse oximetry) or minimally invasive (CEE, lung perfusion scintigraphy) and, therefore, not associated with adverse events.

Written informed consent was obtained from each patient fulfilling inclusion criteria and presenting with a $SpO_2 \leq 97\%$.

2.10 Statistic analysis

Data collection was performed with Microsoft Office Excel 2003. Further data analysis with descriptive statistics was conducted with SPSS 19. Quantitative variables are presented as means, standard deviation (SD), median, maximum, minimum and range. Normal distribution was tested by using the Kolmogorov-Smirnov test. Mean and standard deviation are used for normal distributed variables, whereas the median is used for non-normal distributed variables. Qualitative variables are presented as absolute and relative frequencies.

3 Results

3.1 Study population

Between March 2011 and December 2011, 105 consecutive patients were screened using pulse oximetry. All patients underwent basic clinical investigations and blood laboratory assessments. An overview is given in Figure 3-1. Patients' characteristics are illustrated in Table 3-1 and Table 3-2.

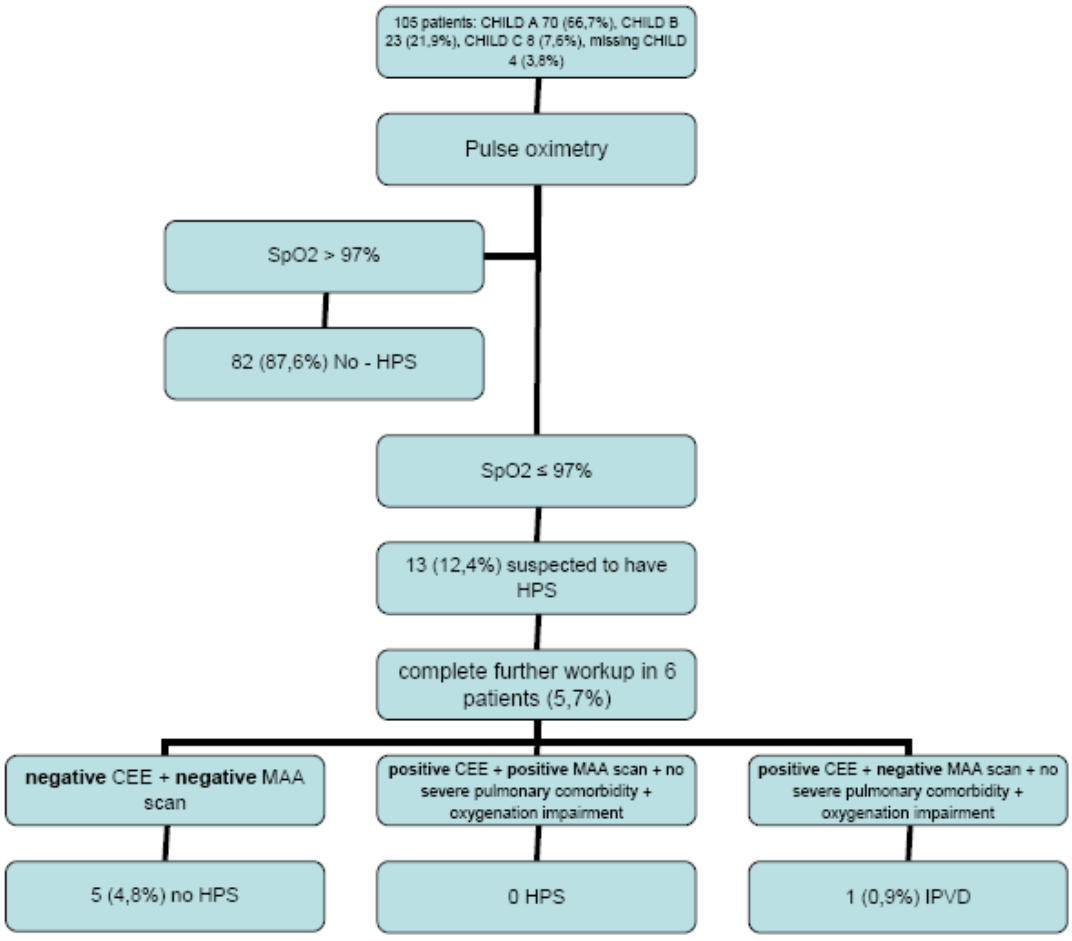

Figure 3-1. Results overview

Variable	Valid N	Mean	Standard Deviation	Median	Maximum	Minimum	Range
age (years)	105	56,6	10,5	57	77	29	48
height (m)	103	1,72	0,09	1,72	2	1,49	0,51
weight (kg)	105	77	16	74	124	40	84
BMI (kg/m2)	103	26,0	4,9	24,8	39,1	13,8	25,3
MELD	101	12	4	11	27	6	21
CHILD PUGH Score	101	6	2	5	14	5	9
Hb (g/dl)	105	12,5	2,2	12,8	17,1	6,6	10,5
MCV (fl)	105	91,2	7,7	90,1	116,2	71,4	44,8
Leucocytes (G/l)	105	6,0	3,2	5,4	23,2	1,1	22,1
Thrombocytes (G/l)	105	122	79	104	612	24	588
Neutrophile Granul. (%)	98	58	13	59	95	31	64
PT (%)	103	69	18	67	113	27	86
INR	103	1,32	0,28	1,27	2,49	0,94	1,55
Na+ (mmol/l)	105	138	5	140	147	119	28
K+ (mmol/l)	105	4,2	0,5	4,2	6,1	2,7	3,4
Creatinine (mg/dl)	105	0,93	0,30	0,85	2,01	0,53	1,48
blood urea nitrogen (mg/dl)	105	37	28	29	173	11	162
uric acid (mg/dl)	103	5,8	1,68	5,7	11,2	1,5	9,7
LDH (U/l)	104	209	83	188	625	75	550
AST (U/l)	105	63	42	48	271	15	256
ALT (U/l)	105	45	34	34	226	10	216
GGT (U/l)	105	167	221	102	1613	9	1604
AP (U/l)	104	129	115	102	1140	45	1095
CHE (U/l)	83	4287	2212	3955	9934	735	9199
total bilirubin (mg/dl)	105	2,3	3,4	1,2	18,5	0,3	18,2
total serum protein (g/dl)	103	7,5	0,7	7,5	9,1	5,5	3,6
Albumin (g/dl)	105	3,8	0,6	3,9	5,2	2,0	3,2
Cholesterol (mg/dl)	101	154	53	150	340	38	302
Triglycerides (mg/dl)	101	98	75	83	629	23	606
Glucose (mg/dl)	104	107	36	96	275	64	211

Table 3-1. Patient characteristics 1

Variable		Count	Column N %
gender (n = 105)	female	36	34,3%
	male	69	65,7%
etiology (n = 105)	ASH	54	51,4%
	NASH	2	1,9%
	HBV	5	4,8%
	HCV	24	22,9%
	autoimmune	4	3,8%
	other	8	7,6%
	cryptogenic	2	1,9%
	mixed	6	5,7%
CHILD CLASS (n = 101)	CHILD A	70	69,3%
	CHILD B	23	22,8%
	CHILD C	8	7,9%
Ascites (none, mild, massive) (n = 104)	none	79	76,0%
	mild	11	10,6%
	massive	14	13,5%
HE (Grade) (n=105)	none	95	90,5%
	grade 1	7	6,7%
	grade 2	3	2,9%
	grade 3	0	,0%
	grade 4	0	,0%

Table 3-2. Patient characteristics 2

The majority of our patients were male (65.7%). Mean age was 57 years (SD 11). 51.4% had alcoholic steatohepatitis (ASH) as the underlying cause of hepatic cirrhosis. 24% of our patients had chronic hepatitis B (HBV), 4.8% chronic hepatitis B (HBV), 3.8% autoimmune hepatitis (AIH) and 1.9% non-alcoholic steatohepatitis (NASH). In 5.9% two underlying causes could be detected and in 1.9% etiology of cirrhosis remained unclear. Other causes (7.6%) included primary biliary cirrhosis (PBC), secondary sclerosing cholangitis (SSC), Wilson's disease, papilla tumor and alpha 1 antitrypsin deficiency. Etiology of cirrhosis is summarized in Figure 3-2.

Median Child-Pugh score was 5 and median MELD score was 11. 66.7% of the patients had Child-Pugh stage A, 21.9% had Child-Pugh stage B and 7.6% had Child-Pugh stage C (see Figure 3-3). Four patients could not be characterized by Child-Pugh or MELD scores due to missing data.

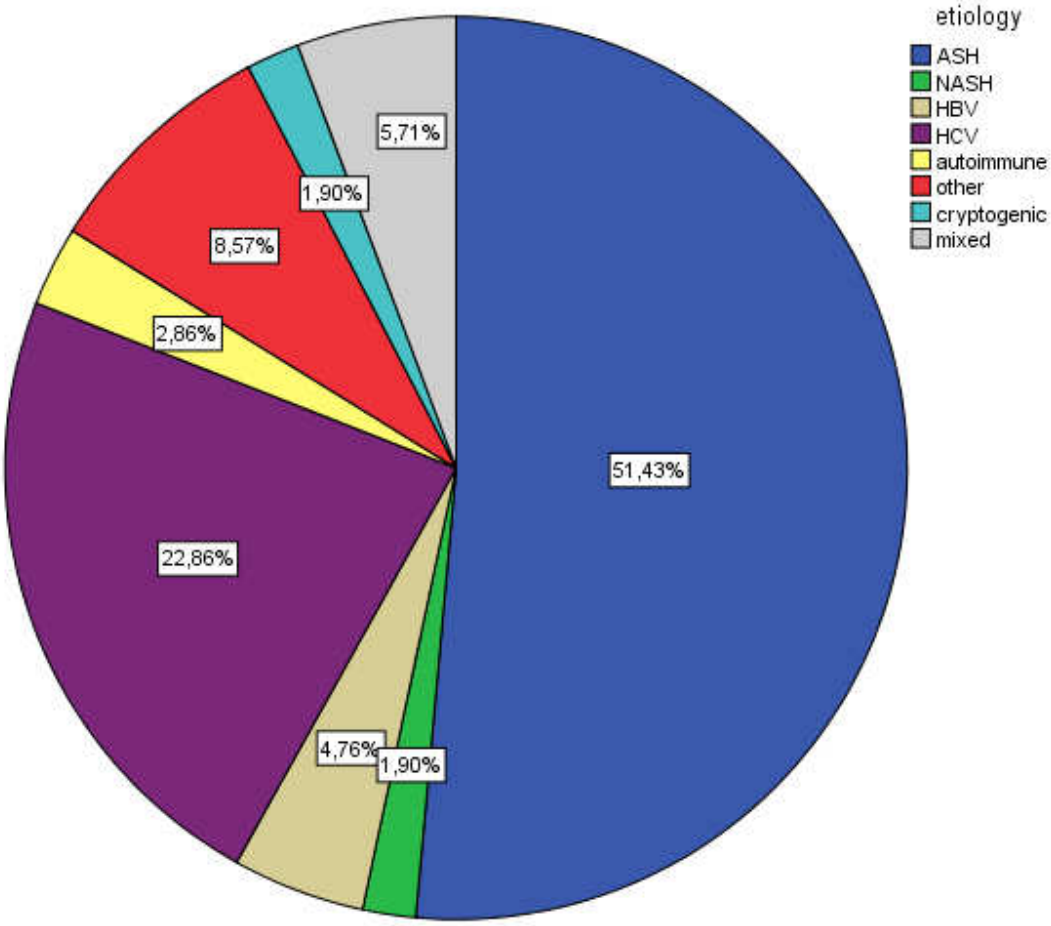

Figure 3-2. Etiology of cirrhosis

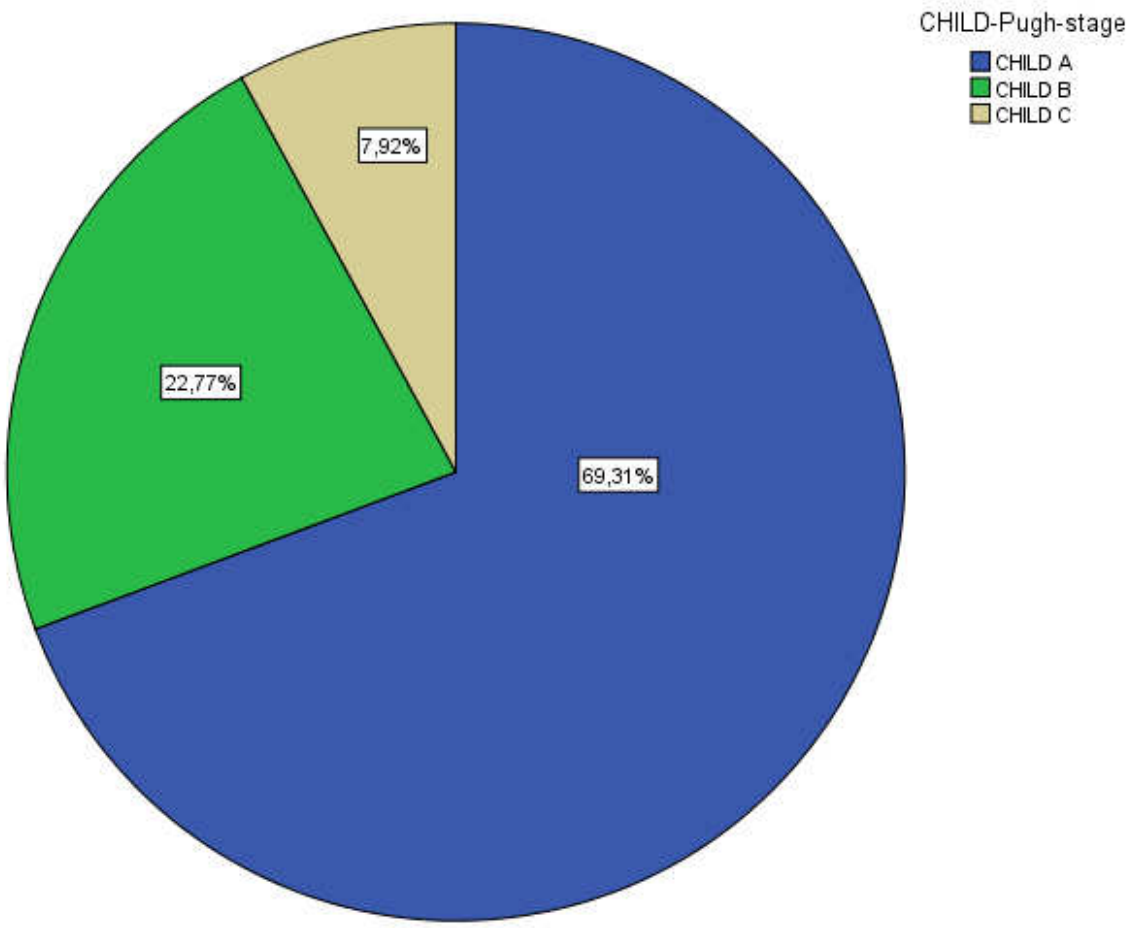

Figure 3-3. Child-Pugh-stage of study population

Ascites was measured and assessed in 101 patients. 75.2% had no ascites, 10.5% had mild ascites and 13.3% had massive ascites. In 90.5% of our patients no symptoms and signs of hepatic encephalopathy could be detected. 6.7% had grade 1 HE and 2.9% had grade 2 HE. No patient in our cohort was suffering from grade 3 or grade 4 HE.

The median total bilirubin was 1.2 mg/dl, median AST 48 U/l, median ALT 34 U/l, median GGT 102 U/l, median AP 102 U/l, mean total serum protein 7.5 g/dl (SD 0.7), median albumin 3.9 g/dl, mean PT 69% (SD 18), median INR 1.27, median creatinine 0.85 mg/dl, median blood urea nitrogen 29 mg/dl, median uric acid 5.7 mg/dl, median thrombocyte count 104 G/l, median leucocyte count 5.4 G/l and mean hemoglobin 12.5 g/dl (SD 2.2).

3.2 Pulse oximetry

The median heart rate was 70.5 bpm. The median SpO_2 was 98% in all subjects (see Table 3-3). 27.6% had a SpO_2 of 99%, 60% had a SpO_2 of 98%, 5.7% had a SpO_2 of 97%, 5.7% had a SpO_2 of 96% and 1% had a SpO_2 of 93% (see Figure 3-4). Therefore 13 patients (12.4%) fulfilled screening criteria ($SpO_2 \leq 97\%$) for further investigation. Four patients denied further participation, one patient died before investigations started, two patients became ill and could, therefore, not be examined. However, in one of the last two patients, lung function parameters and arterial blood gasses were assessed. Overall, six patients could be examined with lung function testing, ABG, CEE and MAA scan (see Table 3-4). The mean Child-Pugh score of the seven patients who were fully or partially evaluated was 6 (SD 1), the mean MELD score 10 (SD 2).

	SpO2 values	n (%)
	SpO2 Screening (mean ± SD)	98 ± 1
cut-off values	SpO2 ≤ 97%	13 (12,4%)
	SpO2 > 97%	92 (87,6%)
frequency of SpO2 values	SpO2 = 93%	1 (1%)
	SpO2 = 96%	6 (5,7%)
	SpO2 = 97%	6 (5,7%)
	SpO2 = 98%	63 (60%)
	SpO2 = 99%	29 (27,6%)

Table 3-3. SpO2 values of study population

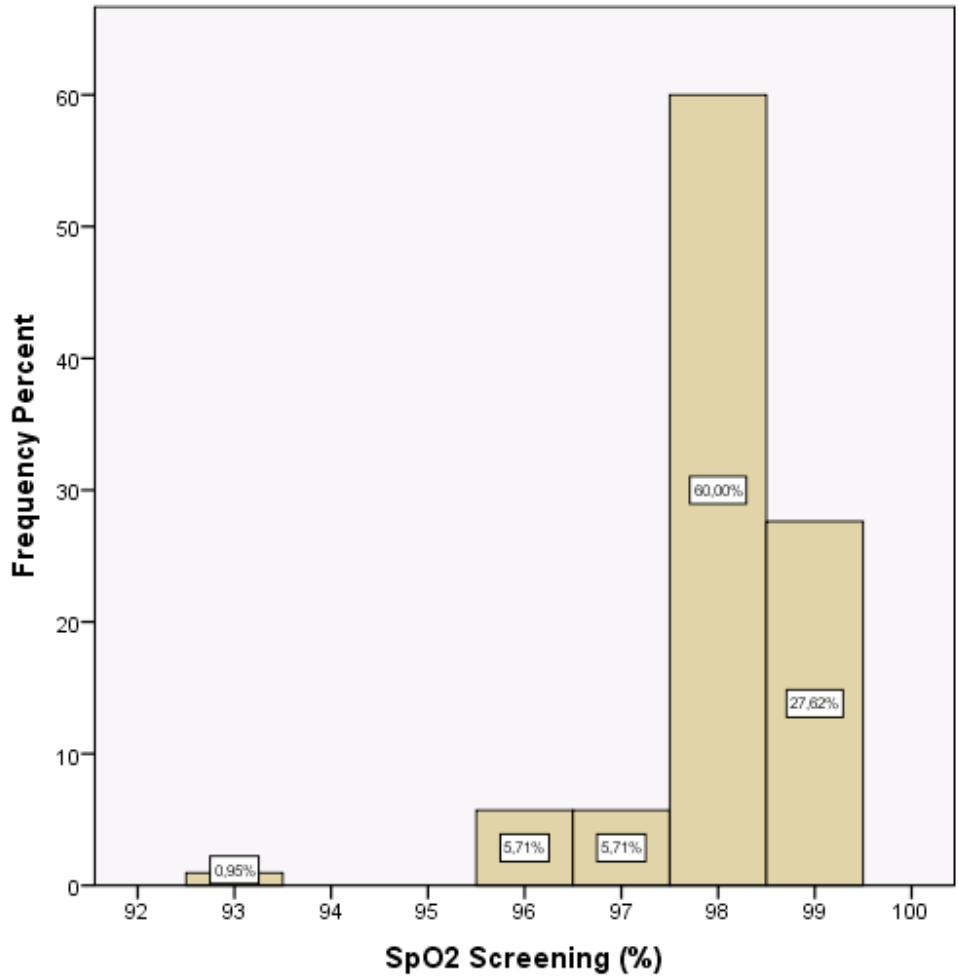

Figure 3-4. SpO2 screening values

Orthodeoxia testing was conducted in six patients see Figure 3-5. Patients 18 and 63 showed no decline of SpO_2 ten minutes after changing from the supine to the upright position. In patient 28 there was an increase of SpO_2 of 1%. Patient 13 had a decline of 1%, patient 88 of 2% and patient 51 of 3%. Hence, no patient fulfilled our criteria (SpO_2 change of 4%) for orthodeoxia.

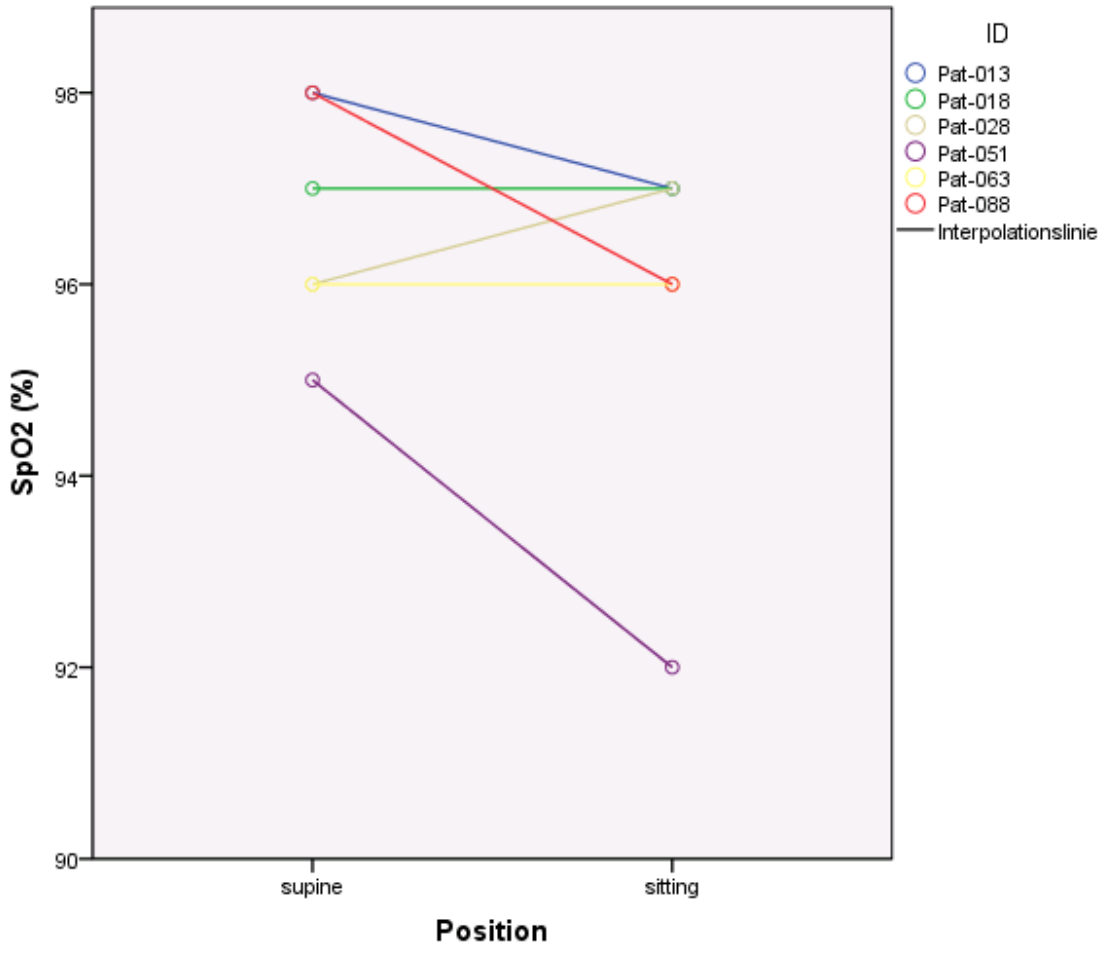

Figure 3-5. Orthodeoxia testing

3.3 Lung function testing and ABG

Data from body plethysmography, spiroergometry and arterial blood gases are available for 7 patients (see Table 3-4). Mean FEV1 was 85.2% (SD 12.6), mean FVC 87.4% (SD 15.5), mean FEV1/FVC 79.5% (SD 5.8) and mean DLCOc VA 80.6% (SD 28).

No severe pulmonary comorbidities could be detected. Mild bronchial obstruction could be detected in patients 13 and 63. Mild restriction was present in patients 18 and 28. Patient 63 had moderate restrictive ventilation impairment. Mild airway collapse was seen in patients 13 and 18. Diffusion-impairment was detected in patients 13, 28, 51, 88 and 92. Hyperventilation during examination was found in patients 13, 51 and 63. Furthermore, patient 63 showed mild partial respiratory insufficiency. Exertional dyspnea (NYHA 2) was present in patients 51 and 88.

	Patient - ID:	13	18	28	51	63	88	92	mean	SD
basic clinical parameters	age (years)	61	70	70	68	54	64	39	61	11
	gender	male	male	male	female	male	female	female		
	etiology	ASH	NASH	ASH	HCV	HCV	HCV	ASH		
	CHILD CLASS	A	A	A	A	B	A	A		
	CHILD PUGH Score	6	6	5	6	8	5	5	6	1
	MELD	14	9	9	10	12	9	8	10	2
pulse oximetry	SpO2 Screening (%)	96	96	97	93	96	97	96	96	1
	SpO2-supine (%)	98	97	96	95	96	98	.	97	1
	SpO2-sitting (%)	97	97	97	92	96	96	.	96	2
	SpO2 difference (%)	1,00	,0	-1,00	3,00	,00	2,00	,0	,83	1,47
ABG	pH	7,39	7,43	7,41	7,46	7,47	7,44	7,44	7,43	0,03
	PaO2 (mmHg)	81,2	66,9	67,8	53,8	69,4	74,2	82,1	70,77	9,7
	PaCO2 (mmHg)	28,2	38,8	38,5	25,3	26,1	41,0	39,3	33,9	7,0
	SaO2 (%)	97,3	94,7	94,7	90,0	96,9	95,5	97,7	95,3	2,6
	FO2Hb (%)	95,3	.	93,3	88,2	94,4	.	94,3	93,1	2,8
	FCOHb (%)	1,2	.	1,0	1,3	2,0	.	2,5	1,6	,6
	FMetHB (%)	,9	.	,5	,7	,6	.	1,0	,7	,2
	AaDO2 (mmHg)	26,5	32,0	30,2	58,5	42,7	22,7	16,7	32,8	13,9
	BE (mmol/l)	-7,5	1,5	,1	-5,2	-4,0	3,3	2,2	-1,4	4,2
lung function	FEV1 (%)	84,5	78,4	86,7	105,9	64,9	92,8	83,5	85,2	12,6
	FEVC (%)	97,1	79,7	79,2	111,9	63,4	93,9	86,4	87,4	15,5
	FEV1/FVC (%)	68,4	75,3	84,0	79,7	82,6	83,0	83,6	79,51	5,76
	DLCOc VA (%)	75,7	134,2	67,6	56,0	.	65,5	84,5	80,6	28,0
	DLCOc SB (%)	76,2	99,6	98,4	64,0	.	50,0	75,4	77,3	19,3
	GMT ratio	< 1%	< 1%	< 1%	1,8	< 1%	< 1%			
	CEE	-	-	-	+	-	-			

Table 3-4. Characteristics of patients with SpO2 ≤ 97%

Arterial blood gas analysis revealed a mean pH of 7.4 (SD 0.03), mean PaO_2 70.8 mmHg (SD 9.7), mean $PaCO_2$ 33.9 mmHg (SD 7), mean SaO_2 95.3 (SD 2.6), mean FO_2Hb 93.1% (SD 2.8), mean FCOHb 1.6% (SD 0.6), mean FMetHb 0.7 (SD 0.2) and mean $AaDO_2$ 32.8 mmHg (SD 13.9). All patients met the criteria for elevated age-adjusted $AaDO_2$. Five patients had a PaO_2 of less than 80 mmHg. Compared to SaO_2, SpO_2 overestimated oxygen saturation in four patients by a mean of 2% (SD 0.78). However, in three patients SaO_2 was higher than SpO_2. Therefore, the overall SO_2 difference was 0.6% (SD 1.87).

3.4 CEE results

CEE was conducted in six patients. CEE was positive in patient 51 (see Figures 3-9 to 11). Microbubbles could be detected in the left chambers four heart beats after appearance in the right chambers. A normal CEE result for patient 28 is shown in Figures 3-6 to 8.

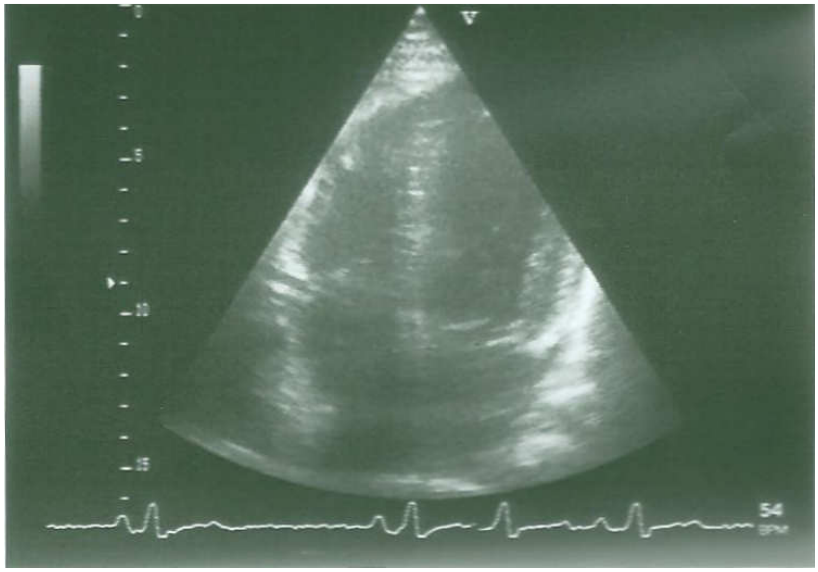

Figure 3-6. Four-chamber-view (patient 28)

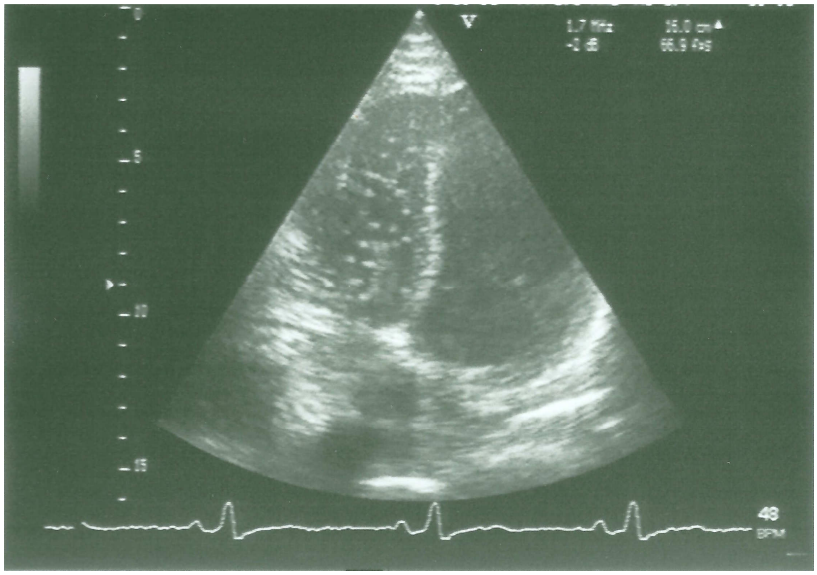

Figure 3-7. Appearance of microbubbles in right chambers (patient 28)

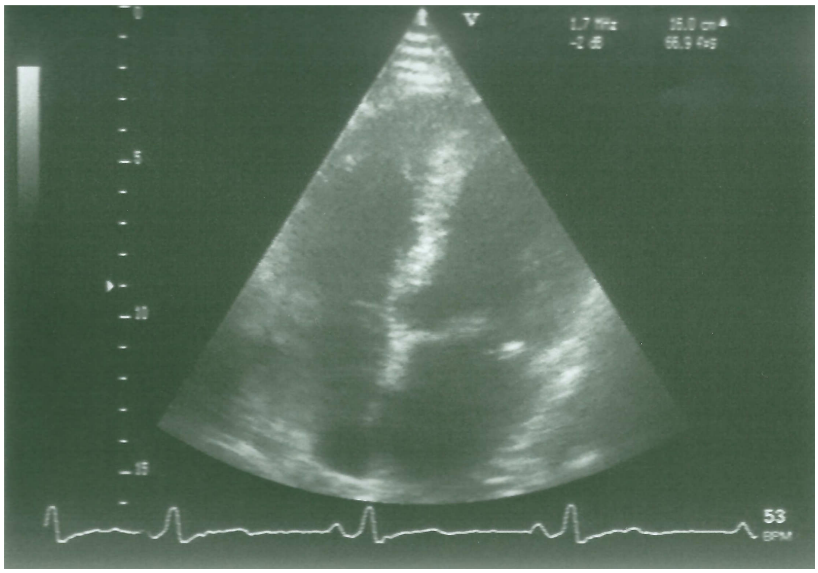

Figure 3-8. No microbubbles in left chambers (patient 28)

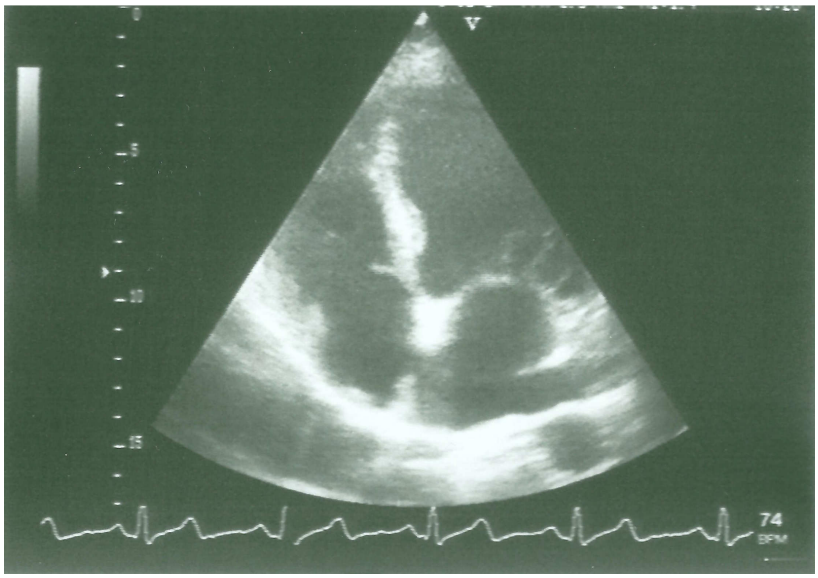

Figure 3-9. Four-chamber-view (patient 51)

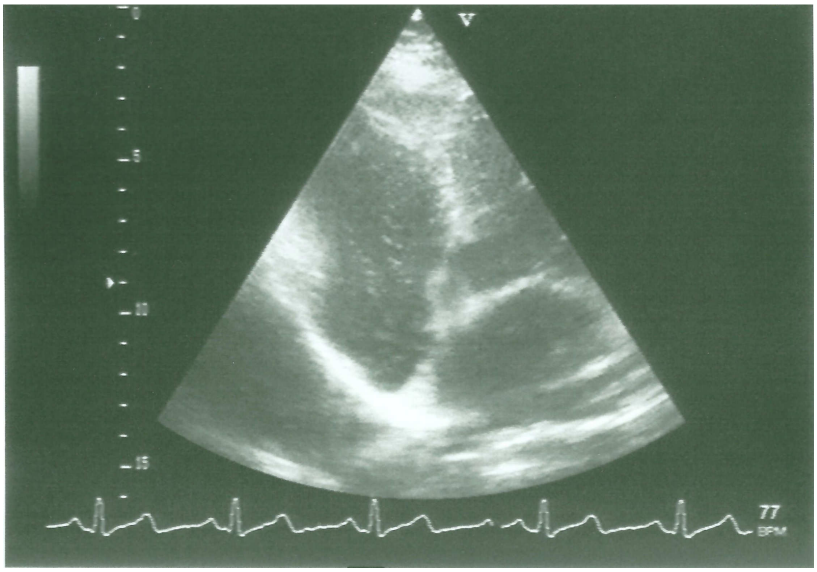

Figure 3-11. Appearance of microbubbles in right chambers (patient 51)

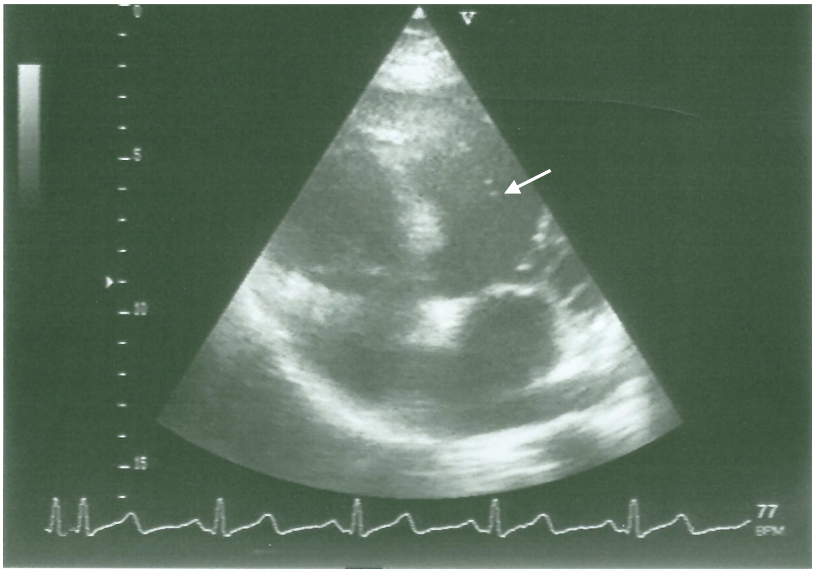

Figure 3-10. Appearance of microbubbles in left chambers (patient 51)

3.5 MAA results

Lung perfusion scintigraphy was negative in all six patients. A normal MAA scan is shown in Figure 3-12. A minimal brain uptake of 1.8% was found in patient 51 (see Figure 3-13). However, it did not meet diagnostic criteria for HPS (shunt fraction ≥ 6%).

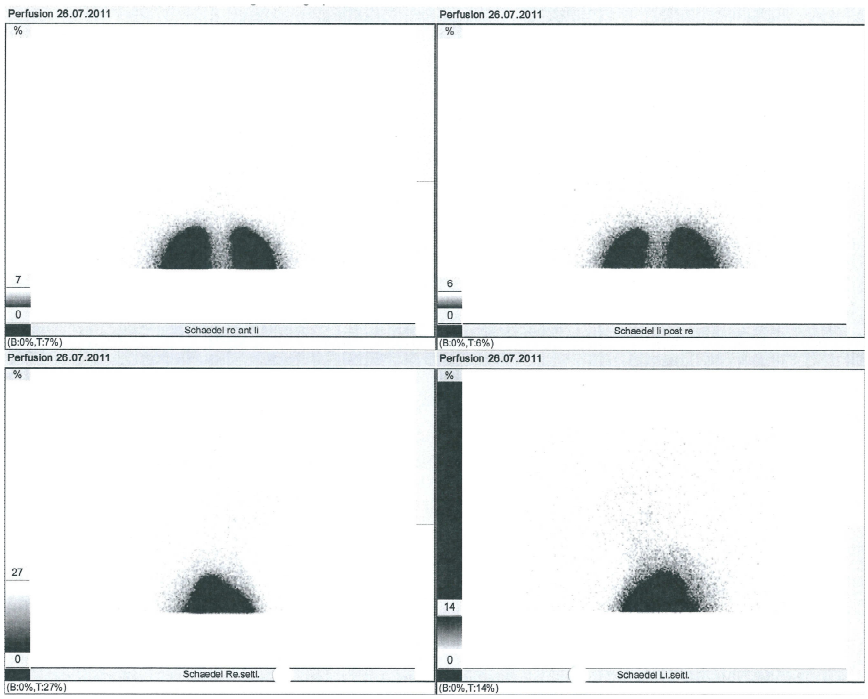

Figure 3-12. MAA-scan (patient 28)

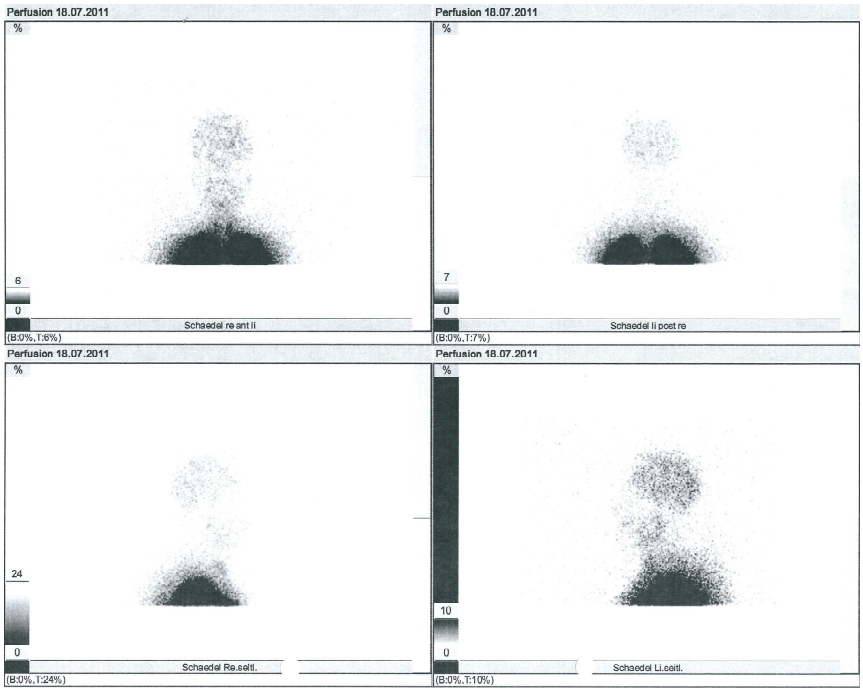

Figure 3-13. MAA-scan (patient 51)

3.6 HPS case report

Patient 51 had a screening SpO_2 of 93%. She was, therefore, investigated further. Due to the positive findings on the contrast enhanced echocardiography in case 51, this patient is suspected to have HPS. However, MAA scanning showed just minimal brain uptake and, thus, this patient did not fulfil our strict diagnostic criteria for HPS. Nevertheless, there is evidence of the presence of IPVDs in this case. Although pulmonary function tests and echocardiography did not reveal any signs of severe cardiopulmonary comorbidity, this patient complained of dyspnea, NYHA 2. Dynamic and static lung function parameters were within normal ranges. FEV1 was 105.9%, FVC 111.1%, and PEF was 101.8%. Arterial blood gases revealed diffusion impairment and partial respiratory insufficiency. DLCOc/V was 0.98 mmol/min/kPa/L (64%), PaO_2 53.8 mmHg, $PaCO_2$ 25.3 mmHg, $AaDO_2$ 58.5 mmHg and SaO_2 90%. We also conducted orthodeoxia testing in this patient. She had a SpO_2 of 95% in supine position. SpO_2 decreased by 3% to a stable level of 92% ten minutes after changing into upright position.

Although this change in SpO_2 again did not fulfil our criteria for orthodeoxia, it can be speculated that the deterioration was caused by HPS. The Child-Pugh score of patient 51 was 5 (Child A) and the MELD score 9.

4 Discussion

After screening of 105 consecutive patients, we only detected one single case with intrapulmonary vascular dilatation (0,95%). Due to the small number of cases, further analysis regarding any relation between prevalence and severity of liver disease or etiology could not be conducted. In most trials available, prevalence of HPS ranges from 10% to 40%. However, in one study by Deibert et al. (41), HPS was detected in 1.3% of all patients. So what are the reasons for our outcome?

4.1 Preselection and study population

In most studies, preselected groups of patients, especially patients listed for OLT were analyzed. Most of our consecutive patients were screened at the liver unit of our hospital and were not listed for OLT. Our study population had a mean Child-Pugh score of 6, a mean MELD score of 12 and was well compensated. Most patients belonged to Child-Pugh stage A (66.7%), 21.9% to Child-Pugh stage B and only 7.6% were characterized as Child-Pugh stage C. Therefore, our study cohort represents a more compensated group of patients, as is usually observed in outpatient clinics.

Schenk et al. (42) revealed that 24% of their study population were suffering from HPS. However, the aim of their study was not to detect the real prevalence of HPS among cirrhotic subjects, but to assess its prognostic significance for OLT. Therefore, they mainly used patients listed or evaluated for OLT. 28% of their 111 patients had cirrhosis Child-Pugh stage A, 27% Child-Pugh stage B and most of their patients had Child-Pugh stage C (45%). In another study with a detected overall prevalence of 32%, again OLT listed patients were evaluated and distribution of Child-Pugh stages were 20% (Child A), 69% (Child B) and 11% (Child C) (45). Therefore, it could be hypothesized that higher frequencies of HPS may be associated with a higher severity of liver disease. Nevertheless, although we screened more subjects with Child-

Pugh stage A, in both studies higher frequencies of HPS in this group of patients were detected. In the study by Schenk et al. (42) 18% (n = 5) of all HPS patients had Child-Pugh grade A. Arguedas et al. (45) detected 6 HPS patients (16% of all HPS patients) in this stage of cirrhosis.
In another survey by Deibert et al. (41) a much lower frequency of HPS, similar to our findings, was detected.
Just four patients (1.3%) of 316 consecutive patients with cirrhosis (n = 265), chronic hepatitis (n = 69) and non-cirrhotic portal hypertension (n = 2) had HPS. Furthermore, cirrhosis of the liver was found as underlying disease in just one of these four patients, resulting in an overall prevalence of HPS of only 0.4% in the group of cirrhotic patients. They evaluated a homogenous group of cirrhotic patients with 36.3% Child-Pugh stage A, 42.5% Child-Pugh stage B and 21.2% Child-Pugh stage C. Deibert et al. also used pulse oximetry as a screening tool for HPS and this leads us to another possible limitation of our study.

4.2 Pulse oximetry and HPS-screening

In contrast to former trials (41), we decided to use a higher SpO_2 cut-off value for pulse oximetric screening in cirrhotic patients, as it is suggested by Abrams et al. (67). Our threshold value of 97% should help us to detect all patients with clinically significant HPS ($PaO_2 < 70$ mmHg) (45, 67). With a PaO_2 of 53.8 mmHg, our single case fulfils criteria for severe and clinical significant HPS. However, some patients with mild ($PaO_2 \geq 80$ mmHg) and moderate ($PaO_2 < 80 – \geq 60$ mmHg) HPS, who may have had SpO_2 values above our cut-off value, may have been omitted.
Therefore, arterial blood gas analysis and contrast enhanced echocardiography would have been better screenings tools for detecting all patients with HPS in our consecutive cohort. Nevertheless, pulse oximetry has some important advantages in daily routine. First of all, it is readily available and easy to use. Another important aspect of pulse oximetry is its cost effectiveness. It was calculated that using pulse oximetry as screening tool for hypoxemia in liver transplant centers in the United States, instead of ABG, could lead to a reduction of screening costs by 68% or 90% (67).
It remains unclear as to how many subclinical cases were neglected and if subclinical HPS is more common among compensated stages of cirrhosis. Data from Schenk et al. (42) suggest that subclinical HPS is indeed a common finding in cirrhotic patients. Mean PaO_2 was 68.7 mmHg (SD 12.3). 48% of their patients with HPS had a $PaO_2 \geq 70$ mmHg. Four out of five cirrhotics

with Child-Pugh stage A had a $PaO_2 \geq 70$ mmHg. Two of these patients had a PaO_2 higher than 80 mmHg.

Kochar et al. (46) revealed even more subclinical HPS cases in their consecutive group. Mean PaO_2 was 77 mmHg (SD 12) and mean SpO_2 was 96.8% (SD 2.9). 72.7% (n = 16) of their HPS patients had a $PaO_2 \geq 70$ mmHg, 59% (n = 13) had a $PaO_2 \geq 80$ mmHg and 9% (n = 2) had a $PaO_2 \geq 90$ mmHg.

As HPS-patients with a $PaO_2 > 70$ mmHg are more likely to have normal SpO_2 values, higher than our 97% threshold, pulse oximetry is not an appropriate screening tool for detecting subclinical cases. Therefore, more studies are needed to reveal the frequency of subclinical HPS among compensated cirrhotics.

Clinical features such as digital clubbing, spider naevi, dyspnea and cyanosis are common findings among cirrhotic patients but are not specific to hepatopulmonary syndrome (15, 41, 45). Orthodeoxia has low sensitivity but is highly specific for HPS. Furthermore, its sensitivity seems to be lower among less severe stages of HPS (72–74). Hence, CEE and ABG are the only effective tools that could help to detect cases of subclinical HPS.

4.3 IPVD

Our definition of HPS included the presence of portal hypertension and hepatic cirrhosis, IPVD (positive findings on CEE and MAA scans) and oxygenation impairment ($PaO_2 < 80$ mmHg or alveolar-arterial oxygen gradient [$AaDO_2$] ≥ 15 mmHg, ≥ 20 mmHg for patients aged > 64 years). Our HPS patient met all criteria except our strict definition for IPVD. Other groups have positive findings on CEE or MAA scans as HPS criteria (13, 14). However, data from Abrams et al. suggest that MAA scan should be positive in clinically significant HPS (69, 70). It remains unclear as to why our HPS patient, who met oxygenation criteria for severe hepatopulmonary syndrome, had a positive CEE but no significant shunt fraction on the MAA scan. Perhaps there are other factors than IPVD and intrapulmonary shunting that contribute to hypoxemia in some patients with HPS. Therefore, more investigations are needed to assess pathophysiological mechanisms in humans.

5 Conclusion

Our study revealed that the real prevalence of clinical HPS in a group of consecutive patients with moderate stages of cirrhosis is much lower than previously reported. These data are consistent with the findings of other groups (41). However, the prevalence of subclinical HPS, characterized by poor oxygenation impairment, in a group of subjects with compensated cirrhosis remains unclear. Hence, more studies are needed to assess the overall prevalence of different stages of severity of HPS among patients with liver diseases.

Pulse oximetry is a simple and useful screening tool for detecting hypoxemia in patients with cirrhosis of the liver. It can target relevant cases that could be further evaluated with arterial blood gas analysis, lung function testing, contrast enhanced echocardiography and lung perfusion scintigraphy. Therefore, severe cases of HPS can be identified earlier, the general condition can be improved by long-term oxygen therapy and higher priority for OLT can be arranged to achieve an optimal outcome for these patients.

There are still many points of contention concerning the natural history, pathogenesis and the treatment of HPS. Nevertheless, much progress has been made since the first description of HPS by Dr. Flückiger 128 years ago. Nowadays, there is the chance of early detection of hepatopulmonary syndrome in patients suffering from cirrhosis of the liver. Moreover, there is the possibility of resolution of HPS after transplantation and by increasing the OLT-priority, we can achieve similar outcomes, compared to non HPS-subjects, in this group of patients.

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Appendix

Abbreviations

A

$AaDO_2$	alveolar-arterial oxygen gradient
ABG	arterial blood gas analysis
AIH	autoimmune hepatitis
ALT	alanine transaminase
AP	alkaline phosphatase
APTT	activated partial thromboplastin time
ASH	alcoholic steatohepatitis
AST	aspartate transaminase

B

BPM	beats per minute

C

CBDL	chronic bile duct ligation
CEE	contrast-enhanced echocardiography
cGMP	cyclic guanosin monophosphat
CHE	serum cholinesterase
CK	creatine kinase
CO	carbon monoxide
CRP	C-reactive protein
CT	computed tomography

D

d	layer thickness
DLCO	diffusion capacity of carbon monoxide
DLCOc SB	haemoglobin adjusted single breathe diffusion capacity of CO
DLCOc VA	haemoglobin and alveolar volume adjusted diffusion capacity of CO
DLCOc	hemoglobin adapted DLCO

E

E	extinction
eNOS	endothelial NO synthase
ERK	extracellular signal-regulated-kinase
ET-1	endothelin-1
ET_A receptor	endothelin A receptor
ET_B receptor	endothelin B receptor

F

FCO_2Hb	fraction of carbon dioxide haemoglobin
FEV_1	forced expiratory volume in 1 second
FMetHb	fraction of methemoglobin
FO_2Hb	fraction of oxygenated haemoglobin
FVC	forced expiratory vital capacity
FVIII	factor VIII

G

GEC	galactose elimination capacity
GGT	gamma-glutamyltransferase
GMT	geometric mean count of Tc-99m

H

HBV	hepatitis B virus infection
HCC	hepatocellular carcinoma
HCV	hepatitis C virus infection
HE	hepatic encephalopathy
HO-1	heme oxygenase 1
HPS	hepatopulmonary syndrome
HR	heart rate
HSC	hepatic stellate cell

I

I	light intensity
ICG	indocyanine green clearance
iNOS	inducible nitric oxide synthase
INR	International Normalized Ratio
IPVD	intrapulmonary vascular dilatation

K

k	medium concentration
K	potassium

L

LDH	lactate dehydrogenase
LED	light emitting diode
L-NAME	N^G-nitro-L-arginine methyl ester
LTOT	long-term oxygen therapy

M

MAA	macroaggregated albumin
MCP-1	monocyte chemoattractant protein 1
MELD	model of endstage liver disease
MMPs	metalloproteinases
mPAP	mean pulmonary artery pressure

N

n	count
Na	sodium
NASH	non-alcoholic steatohepatitis

NF-κB	nuclear factor-κB
NIV	non-invasive ventilation
NO	nitric oxide
NYHA	New York Heart Association

O

O_2	oxygen
OLT	orthotopic liver-transplantation

P

$PaCO_2$	arterial carbon monoxide partial pressure
PaO_2	arterial oxygen partial pressure
PASMC	pulmonary artery smooth muscle cells
PBC	primary biliary cirrhosis
PCNA	proliferating cell nuclear antigen
PDGF	platelet derived growth factor
pERK	phosphorylated ERK
PTX	pentoxifylline
PVR	pulmonary vascular resistance

R

RAS	renin-angiotensin system
RES	reticuloendothelial system

S

SaO_2	arterial oxygen saturation
SD	standard deviation
SpO_2	pulse oximetric oxygen saturation
SSC	secondary sclerosing cirrhosis
SVR	systemic vascular resistance

T

Tc-99m	technetium-99m
TGF β1	transforming growth factor β1
TIMPs	tissue inhibitor metalloproteinases
TIPS	transhepatic portosystemic shunts
TNFα	tumor necrosis factor alpha

V

VE-cadherin	vascular endothelial cadherin
VEGF	vascular endothelian growth factor
vWF	von Willebrand factor

Curriculum vitae

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