THE HEPATOPULMONARY SYNDROME

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As the liver goes, so goes the lung.
Stoller, 1990

BIOGRAPHIC INFORMATION

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Particular Interests: Interstitial Lung Disease, Atypical Mycobacterial Disease

Introduction

In 1884, Fluckiger described a 37 year old patient with hepatic cirrhosis, cyanosis and digital clubbing in the absence of apparent lung disease (1). Fifty years later, Keys and Snell reported that "relative arterial unsaturation is common among patients with cirrhosis of the liver and other conditions involving severe parenchymatous hepatic damage" (2). Moreover, it was evident that "circulatory disturbances, ascites and edema did not appear to account for the unsaturation...(and) must have resulted either from some interference with gas exchange in the lungs or from an abnormality of the blood itself" (2). Specifically, the desaturation was attributed to a decreased affinity of hemoglobin for oxygen and a rightward shift in the oxygen-hemoglobin dissociation curve (3, 4). This explanation proved inadequate, however, when it became feasible to directly measure arterial oxygen tension (PaO_2), and this too was low. Nevertheless, these early observations constituted the first descriptions of what is now called the hepatopulmonary syndrome (HPS). Kennedy and Knudson first applied this term to a cirrhotic patient who developed severe dyspnea, cyanosis, clubbing and orthodeoxia four years after a portocaval shunt (5). Today, it is used to describe the association of advanced liver disease with hypoxemia and intrapulmonary vascular dilatations (IPVD) (6-14).

Definition of the Syndrome

The hepatopulmonary syndrome is usually but not always associated with cirrhosis of the liver (Table 1) (7). The syndrome has also been reported in individuals with fulminant hepatic failure, noncirrhotic portal hypertension, chronic active hepatitis and rare disorders of metabolism which are associated with chronic liver disease (15-19). By definition, individuals must demonstrate an elevated alveolar-arterial oxygen gradient (>20 mm Hg) in the supine or standing position, and evidence of intrapulmonary shunting. The latter may be confirmed by a variety of imaging techniques.

TABLE 1

Disorders Associated with the Hepatopulmonary Syndrome

- Cirrhosis
  - Alcoholic
  - Cryptogenic
  - Post-necrotic
- Primary biliary cirrhosis
- Chronic active hepatitis
- Fulminant hepatic failure
- Chronic hepatic allograft rejection
- Noncirrhotic portal hypertension
- Congenital hepatic fibrosis
- Biliary atresia
- Alpha-1 antitrypsin deficiency
- Tyrosinemia
- Wilson's disease

Adapted from Krowka (7)

Hypoxemia in Liver Disease

There are many potential causes of hypoxemia in patients with liver disease, and sometimes the etiology is mixed (20-27). Tobacco abuse is frequent among alcoholics, and individuals may have concomitant airways disease. Pleural effusions, ascites and massive hepatomegaly may interfere with diaphragmatic function and cause atelectasis (28-31). Patients with liver disease may aspirate more frequently due to encephalopathy, alcohol intoxication or seizures. Pneumonia may also be more frequent in individuals with chronic liver disease due to altered host immunity (32). In addition, certain specific liver disorders are known to be associated with specific pulmonary complications. Alpha-1 antitrypsin deficiency, for instance, is associated with basilar predominant panacinar emphysema and occasionally with bronchiectasis. Sjogren's syndrome, common in patients with primary biliary cirrhosis, is associated with xerotrachea, bronchitis and bronchiectasis, as well as interstitial disorders like lymphocytic interstitial pneumonitis and a nonspecific cellular interstitial pneumonia (33). On rare occasions, cirrhotic patients with portal hypertension may develop a plexogenic pulmonary arteriopathy similar to primary pulmonary hypertension (32, 34-37).

Hypoxemia occurs in approximately one third of patients with cirrhosis (38, 39). Often it is mild ($PaO_2 \geq$ 70 mm Hg), but occasionally patients are profoundly desaturated. Debilitating dyspnea and hypoxemia affect 5-10% of cirrhotics, and arterial O_2 tensions below 40 mm Hg have been reported (11, 17, 40-44). Measurement of oxygen saturation by pulsoximetry often belies a significant gas exchange problem because cirrhotics typically hyperventilate, and the resultant respiratory alkalosis helps maintain normal saturations in spite of elevated alveolar-arterial oxygen gradients ($A\text{-}aDO_2$) (45, 46). Arterial blood gas determinations should therefore be obtained in all patients who complain of dyspnea, and even in asymptomatic individuals with advanced liver disease in an attempt to detect the syndrome early.

In Naeije's series of 100 cirrhotics being evaluated for portocaval shunts, 28% were found to have an arterial oxygen tension below 70 mm Hg, and 8% had a PaO_2<60 mm Hg while breathing room air (mean $A\text{-}aDO_2$ 34.4 mm Hg) (47). Eighty seven of these patients were chronic alcoholics, and all had unremarkable chest radiographs, but no correlation has been noted between the etiology of the liver disease and the incidence or severity of hypoxemia. Bashour and colleagues analyzed the blood gases of 26 patients with cirrhosis and found a mean $A\text{-}aDO_2$ of 44.8 mm Hg (21). Krowka and co-workers reported a higher incidence of more severe hypoxemia in their retrospective analysis of 22 patients specifically with HPS. Nearly 60% had arterial oxygen tensions below 60 mm Hg (11).

It appears that the incidence of hypoxemia is higher among individuals with more advanced liver disease. In 1960, Rodman and colleagues studied 56 patients with advanced cirrhosis. More than half had arterial O_2 saturations below 92% (48). In two other studies, 45% and 69% of liver transplant candidates had a widened A-a gradient

(39, 49). However, not all series indicate such a striking frequency of poor oxygenation. Hopkins and associates reported significant hypoxemia (PaO_2<70 mm Hg) specifically due to the hepatopulmonary syndrome in only 15% of individuals with end-stage liver disease (50). Likewise, Jensen et al. identified an arterial oxygen tension below 70 mm Hg **and** intrapulmonary shunting in just 13% of 47 consecutive liver transplant candidates (51). As a general rule, mildly affected individuals have excellent responses to 100% oxygen. Patients with severe hypoxemia due to the hepatopulmonary syndrome, however, demonstrate a highly variable response to breathing high inspired fractions of oxygen. Some achieve near normal oxygen tensions in excess of 600 mm Hg, while others show little change from room air levels. Most patients with a PaO_2<70 mm Hg will have at least moderate improvement (PaO_2>300 mm Hg), but individual responses correlate very poorly with the baseline arterial oxygen tensions in these severely affected individuals (9).

Clinical Features of the Hepatopulmonary Syndrome

The clinical features of the hepatopulmonary syndrome are summarized in Table 2. The majority of patients with HPS present with signs or symptoms related to their liver disease (and portal hypertension) such as ascites, splenomegaly or variceal bleeding (11). In the series by Krowka and colleagues, 18% of patients originally complained of dyspnea and were only subsequently diagnosed with liver disease. Breathlessness may occur at rest, but may be triggered only by exertion or moving from the supine to the upright position (platypnea) (53).

TABLE 2

Clinical Features of the Hepatopulmonary Syndrome

• Dyspnea	• Esophageal varices
• Platypnea	• Splenomegaly
• Orthodeoxia	• Ascites
• Hypoxemia	• Intrapulmonary shunting
• Good response to O_2	• Reduced DLCO
• Cyanosis	• Increased vascular markings in lung bases
• Digital clubbing	
• Cutaneous spider nevi	• "Spongy" network of vessels on angiogram

There does not appear to be a correlation between arterial oxygen tension and specific biochemical indices of hepatic function (prothrombin time, bilirubin, albumin, or transaminases), but most individuals with the syndrome have advanced disease (11). Nevertheless, profound synthetic dysfunction is not a prerequisite for the development of HPS, and oxygenation may continue to deteriorate despite apparently stable liver disease (11, 18, 54). The occurrence of HPS in noncirrhotic portal hypertension (18), a

reported association with the **severity** of esophageal varices (55), and Krowka's data indicating the presence of esophageal varices or splenomegaly in all 22 patients studied (11) suggest portal hypertension as the common thread. The syndrome has been reported to develop years after portocaval or splenorenal shunting, but the actual portal vein pressures in these patients when they developed HPS are unknown (5, 56-58).

Cutaneous spider angiomata are strongly associated with the development of the hepatopulmonary syndrome (28, 38, 59, 60); and patients with this finding frequently exhibit the hallmark intrapulmonary vascular dilatations and pleural spider nevi of HPS (61). Physical examination may also reveal cyanosis and digital clubbing in severely hypoxemic patients (62).

When obtaining arterial blood samples, it is best that the patients be sitting or standing. Early on, supine arterial oxygen tensions may be normal, but orthodeoxia (defined as a fall in PaO_2 of more than 3 mm Hg when moving from the supine to upright position) is typical of this syndrome (9,11). Healthy individuals show no change or a slight increase in PaO_2 after standing (63). Other disorders which may be associated with orthodeoxia are listed in Table 3.

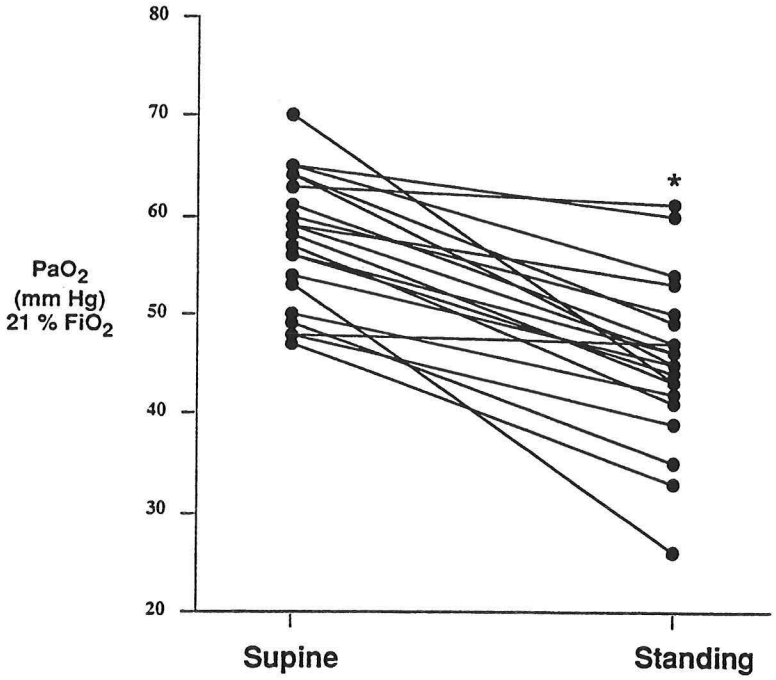
TABLE 3

Differential Diagnosis of Orthodeoxia

- Hepatopulmonary syndrome
- Pulmonary arteriovenous malformations
- Congenital heart disease
- Shunting through a patent foramen ovale due to altered geometry of the heart and elevated right-sided pressures
  - post-pneumonectomy
  - pulmonary embolism
  - chronic obstructive lung disease

Krowka and co-workers found that 14 of 16 HPS patients (88%) manifested orthodeoxia with a mean reduction in arterial oxygen tension of 18 mm Hg (11). Orthodeoxia persisted while breathing 100% inspired oxygen. In a series of 21 patients evaluated at the Mayo Clinic, the average decline in PaO_2 after standing while breathing room air was 12 mm Hg (9) (Figure 1). This finding is reliably present in individuals with more severe hypoxemia, but may be absent early on and is not required for the diagnosis (40, 64, 65).

FIGURE 1



(Figure 1). Orthodeoxia in the hepatopulmonary syndrome. Arterial oxygen tension of 21 patients with the hepatopulmonary syndrome in the supine and standing postions. Average decline 12 mm Hg.
From: Castro and Krowka (9)

In most persons with HPS, plain chest radiographs are normal, or demonstrate increased reticulonodular opacities in the lung bases (22, 39, 66-69) which likely represent the vascular dilatations. The identification of such interstitial or nodular shadows on plain films appears to correlate with a more advanced gas exchange disturbance and worse hypoxemia (22, 67-69).

Natural History of the Hepatopulmonary Syndrome

There have been no prospective, longitudinal studies of patients with the hepatopulmonary syndrome, and very little is known about its natural history. The disorder may affect adults or children, and gradual deterioration in gas exchange over several months should be expected (7, 70). However, abrupt worsening in oxygenation over several days with no other explanation has been reported to result in the death of one individual with hemochromatosis (71). Spontaneous resolution of the HPS may occur with recovery from severe hepatitis, but this has not been reported in cirrhosis (72, 73). Cadranal did report a single patient with chronic noncirrhotic hepatic failure due to angioimmunoblastic lymphadenopathy in whom hypoxemia resolved after an extended course of treatment with glucocorticoids and cyclophosphamide (74). In the series by Krowka and colleagues, overall mortality in HPS patients was 41%, and death occurred an average of 2.5 years after the diagnosis was made (11). The mean time to

diagnosis after the onset of symptoms, however, was almost 5 years, and the cause of death was frequently extrapulmonary (e.g., sepsis or gastrointestinal bleeding) (11).

Pulmonary Function in Hepatic Cirrhosis

Pulmonary function abnormalities are common in patients with advanced liver disease (Table 4) (39, 75-78). The most commonly observed abnormality in pulmonary function is a low diffusing capacity for carbon monoxide (DLCO). Hourani and co-workers studied 116 patients being evaluated for orthotopic liver transplant and 52% had a DLCO <75% of predicted (39). No statistically significant relationship between smoking history and diffusion abnormalities could be discerned. In a prospective study by Krowka and colleagues of 95 patients before and after liver transplantation, an abnormal diffusing capacity was again the most frequently abnormal pulmonary function study (78). Fifty patients had a steady state DLCO below 80% of predicted. As a group, the Child's C patients demonstrated the lowest preoperative diffusing capacities. Interestingly, the DLCO in liver patients is often low even in the presence of a normal alveolar arterial oxygen gradient and despite negative tests for intrapulmonary shunting (39). This is true in about 40% of patients with a low diffusing capacity.

The cause of the low DLCO in liver disease continues to be debated (79). Theoretically, the abnormal diffusing capacity could reflect thickening of the alveolar-capillary membrane, an altered intracapillary phase of gas transfer (related to increased plasma volume and layering of erythrocytes), or changes in erythrocyte morphology (24). Anemia is common in these patients and it may contribute to an overall reduction in diffusing capacity. The interstitial edema commonly identified in cirrhosis due to high plasma volume and low oncotic pressure has been suggested as one contributing factor in the reduced DLCO in liver patients (80). Conceivably, it could also be related to the increased diffusion distance to red blood cells in the center of dilated intrapulmonary capillaries (discussed in the next segment). Some investigators have determined that the intracapillary phase of gas transfer (diffusion through the plasma and reaction kinetics with hemoglobin) are at least as important to the determination of diffusing capacity for oxygen as the thickness of the alveolar-capillary wall (81, 82). The impact of altered erythrocyte morphology on oxygen uptake has been discussed, but the importance of this factor in patients with liver disease is unknown (83). Of course, the presence of direct arteriovenous communications within the lung or pleural space bypassing alveoli entirely could also affect the gas transfer measurement. Furthermore, the vascular dilatations associated with HPS predominate in the lower lung zones; and in the upright position, the combination of gravitational effects and increased vascular capacitance may produce a perfusion "steal" from the upper lung zones causing a regional reduction in CO transfer. Diffusing capacity corrected for alveolar volume (DL/VA) does decrease in the upright compared to supine position (84), but in most healthy individuals, the concomitant increase in FRC results in an overall increase in total DLCO when sitting.

TABLE 4

Pulmonary Function Abnormalities in Hepatic Cirrhosis

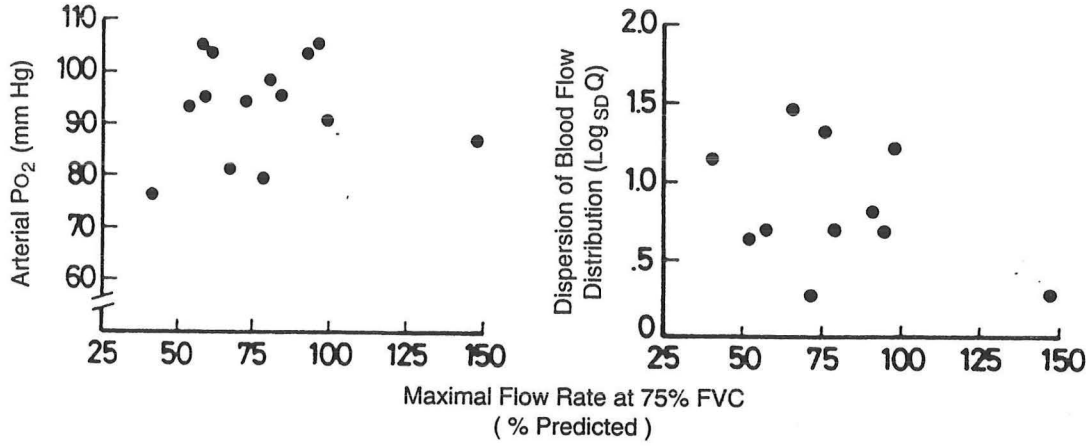
• Decreased DLCO	52%
• Restriction	25%
• Obstruction	3%
• Decreased MIP	56%
• Decreased MEP	86%
• Increased CV	>50%

DLCO= diffusing capacity for carbon monoxide
MIP= maximal inspiratory pressure
MEP= maximal expiratory pressure
CV= closing volume
Adapted from Hourani (39) and Furakawa (77)

Ventilatory restriction is the next most common PFT abnormality affecting about 25% of patients in Hourani's series (39). Notably, the DLCO may be severely abnormal even in the face of normal lung volumes. In fact, a minority of Hourani's patients with a low DLCO (only 35%) also had evidence of restriction. In patients with ascites, however, restrictive ventilatory defects are usual (76).

Even though 60% of Hourani's patients were current or former smokers, significant airflow limitation was quite uncommon, occurring in only 3% (39). Nevertheless, Ruff and coworkers found that closing volume is commonly increased above functional residual capacity (FRC) in patients with cirrhosis (80). Consequently, these individuals experience small airway closure during normal expiration which may contribute to microatelectasis. This finding was confirmed in a large study by Furukawa et al. (77) evaluating cirrhotics with no clinical or radiographic evidence of cardiopulmonary disease. Approximately 30% of the patients demonstrated hypoxemia with arterial oxygen tensions below 80 mm Hg. Interestingly, the average ratio of closing volume to vital capacity was significantly higher in the hypoxemic patients compared to those with normal oxygen tensions. In fact, on average, the FRC minus closing capacity yielded a **negative** and significantly lower value in the hypoxemic group (-90 ± 262 vs. 317 ± 363). This suggests that premature airway closure may be an important contributor to arterial hypoxemia and VA/Q mismatching in cirrhosis (63, 77). On the other hand, data from Rodriguez-Roisin et al. suggest that there is no correlation between mid-expiratory airflow (considered by some to reflect small airways function) and either the observed arterial oxygen tension or the degree of blood flow maldistribution (VA/Q mismatch) in these patients (Figure 2) (60).

FIGURE 2

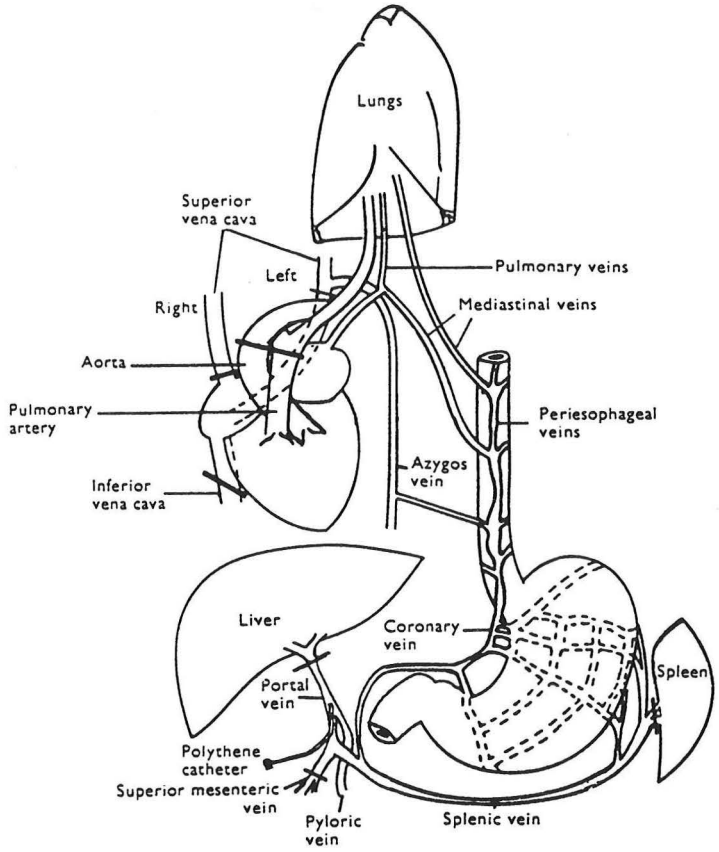


(Figure 2). Lack of correlation between maximal airflow at 75% of forced vital capacity and arterial oxygen tension or blood flow maldistribution (a measure of the severity of VA/Q mismatch) in hepatic cirrhosis.
Originally from Rodriguez-Roisin et al. (60)
Adapted from Agusti et al. (28)

Vascular Anomalies Associated with Shunting in Liver Disease

In the absence of hypoventilation, arterial hypoxemia must result in some way from erythrocytes passing through or around alveolar units without being fully oxygenated. Early physiologic studies in patients with cirrhosis and cyanosis indicated that affected individuals often demonstrated very high shunt fractions (up to 50% or more of the cardiac output) (15, 48, 66, 67, 72). Some of these early reports suggested that the source of the venous admixture might actually be extrapulmonary. The theory was that portal hypertension could potentiate abnormal flow of blood from the portal venous system to the pulmonary veins via dilated gastric, periesophageal and mediastinal collateral vessels, many of which have no valves to restrict bidirectional circulation (48, 66, 85-87). In a rat model of biliary cirrhosis, Khaliq and coworkers demonstrated that injection of the portal vein with barium led to opacification of the periesophageal and pulmonary veins on a post-mortem radiograph when a series of other vessels were ligated (88). Figure 3 depicts the pattern of histologically confirmed venous anastomoses in this case. In a similar experiment involving human cadavers, Calabresi and Abelmann injected the portal veins of 10 cirrhotics and 10 controls (87).

FIGURE 3



(Figure 3). Portopulmonary venous anastomoses in rats with experimental cirrhosis. The diagram shows the site of injection of a barium suspension into the portal vein following ligation of several vessels (indicated by the straight, black lines).
From: Khaliq et al. (88)

The cirrhotics, but not the controls, demonstrated extensive mediastinal venous anastomoses. The azygous system and superior vena cava filled with the injected material in all subjects, but the pulmonary veins and left heart filled in only two. Fritts and colleagues also found evidence for portopulmonary shunting in their study of hypoxemic cirrhotic patients injected with a certain dye and radioactive tracer (89). It was suggested that the mediastinal veins enlarge as portal pressures rise, increasing the likelihood that they may penetrate the pleura and drain into pulmonary veins to produce a right to left shunt (88). Although appealing on the surface, other considerations cast doubt on the importance of these "potential" shunts in patients with portal hypertension. Other investigators have not been able to demonstrate significant portopulmonary shunting in post-mortem human experiments (90). Even in Calabresi's study, only two of ten patients had aberrant "right to left" connections. The remainder were "right to right" and would not affect systemic oxygenation. Whether they exist commonly or not, it is now believed that flow through these collaterals is too low (because of their small size), and the oxygen content of portal venous blood too high ($PvO_2 \cong 50$ mm Hg) to result in important venous admixture (91).

Interest subsequently shifted toward identifying intrapulmonary sources for the shunting. In a post-mortem examination, Rydell and Hoffbauer were the first to identify numerous arteriovenous communications in the lung of a patient with chronic active hepatitis (92). Other reports followed implicating discrete arteriovenous fistulae in the pathogenesis of "hepatogenic cyanosis" (17, 19, 21, 56, 61, 67, 72, 85, 92-98). In 1968, Hutchinson and colleagues confirmed ante-mortem the presence of multiple intrapulmonary arteriovenous anastomoses by angiography (99). Such vascular anomalies might also explain the high cardiac output and low pulmonary vascular resistance commonly seen in liver disease, but they appear to be unusual findings (92, 100). Berthelot and coworkers performed post-mortem gelatin injections of the pulmonary arterial tree in thirteen cirrhotic patients and only one indicated the presence of precapillary arteriovenous connections (61). The striking finding in these patients, rather, was the presence of macroscopic spider nevi on the pleural surface in six subjects and marked precapillary arteriolar dilatations in all thirteen. Karlish et al. also noted numerous pleural spider nevi, especially over the lower lobes (Figure 4), and diffuse arterial vasodilatation in the lungs of one patient with cyanosis and clubbing (67).

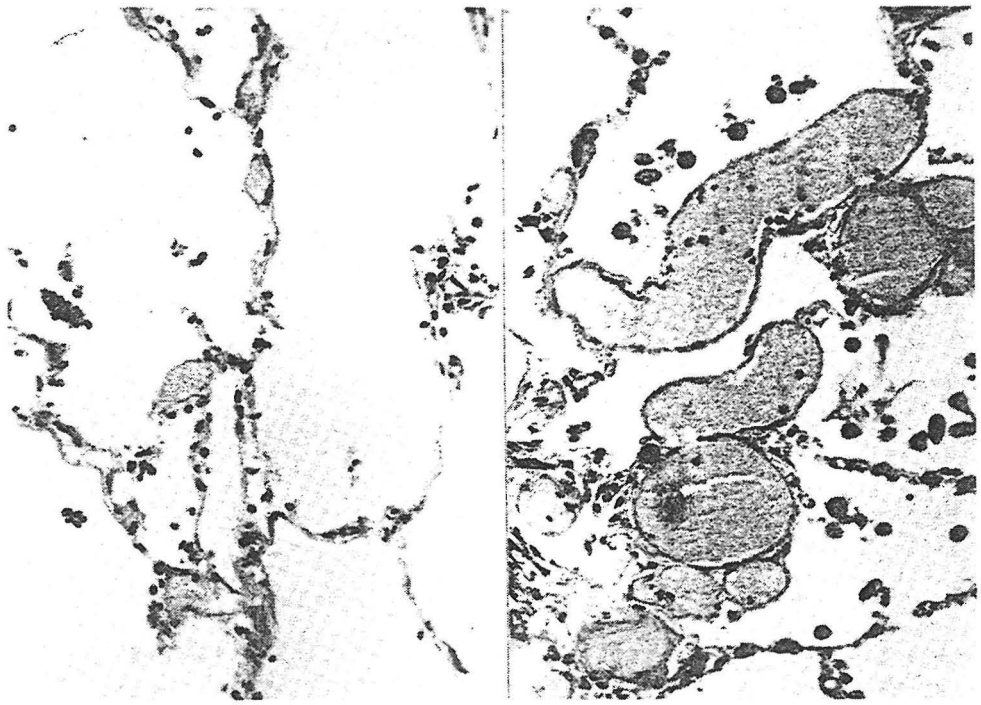
FIGURE 4

(Figure 4). Pleural surface demonstrating a large number of spider nevi injected with a barium suspension.
From: Karlish et al. (67)

In addition, this patient demonstrated direct arteriovenous connections in the proximal infrahilar regions, but diffuse dilatation of small intrapulmonary vessels without discrete fistulas is the most conspicuous finding in most studies (68). Identical changes can be induced in rats by ligating the common bile duct to cause biliary cirrhosis (101, 102).

These intrapulmonary vascular dilatations are now believed to be responsible for most of the apparent "shunt" identified in patients with liver disease. Precapillary vessels close to gas exchanging surfaces may reach 500 μm in diameter (normal < 175 μm) (15, 61); and Davis et al. found thin-walled intra-alveolar vessels (capillaries) measuring 60-80 μm (normal 8-15 μm diameter) throughout the lower lobes of one hypoxemic cirrhotic (Figure 5) (103). Interestingly, chronic liver disease is not a prerequisite for the development of IPVD. Quite similar but less severe dilatations were seen in one series of 12 patients who died from fulminant hepatic failure (15). Two-thirds of these patients also had pleural spider nevi identified. It is likely that these microvascular changes are not limited to the pulmonary circulation as systemic arteriovenous shunting is also increased in experimental liver cirrhosis (104).

FIGURE 5



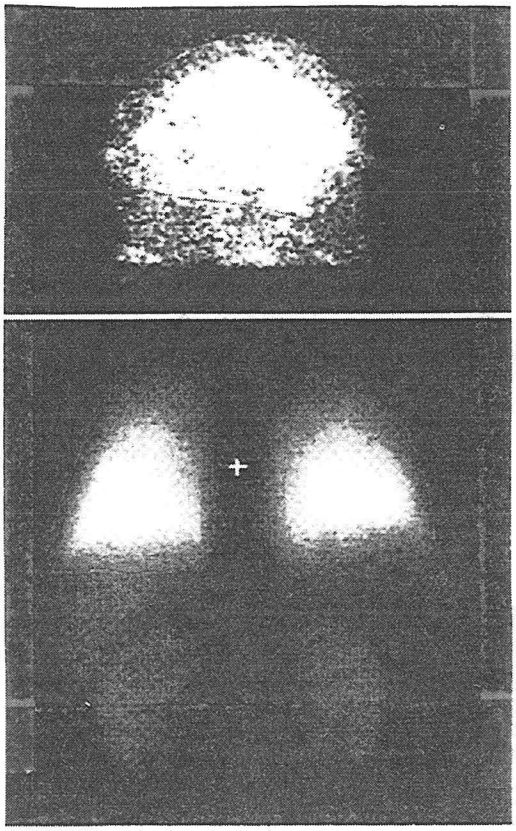
(Figure 5). Histologic sections of lung from the right upper lobe (left) and right lower lobe (right) after Hypaque injection demonstrating marked dilatation of alveolar vessels in the lung bases (average minimal luminal diameter of the largest vessels is 60-80 μm).
From: Davis et al. (103)

Diagnosis of the Hepatopulmonary Syndrome

The diagnosis of hepatopulmonary syndrome is predicated upon identification of these intrapulmonary vascular dilatations in the appropriate clinical setting. IPVDs can be diagnosed noninvasively by either technetium-99 macroaggregated albumin (^{99m}Tc-MAA) perfusion scanning or contrast-enhanced "bubble" echocardiography (CEE) (50, 54, 57, 96, 105-109). MAA particles range in size from 20-60 μm in diameter and

normally over 95% lodge proximal to the pulmonary capillaries (8-15 μm). A whole body scan is performed and the shunt fraction is estimated by the ratio of extrapulmonary to pulmonary "counts" (54, 57, 107, 110). In patients with liver disease and IPVD, more of these particles traverse the pulmonary capillary bed and deposit in systemic capillary beds (Figure 6). Unfortunately, ^{99m}Tc-MAA scans do not distinguish between intracardiac and intrapulmonary shunts.

FIGURE 6

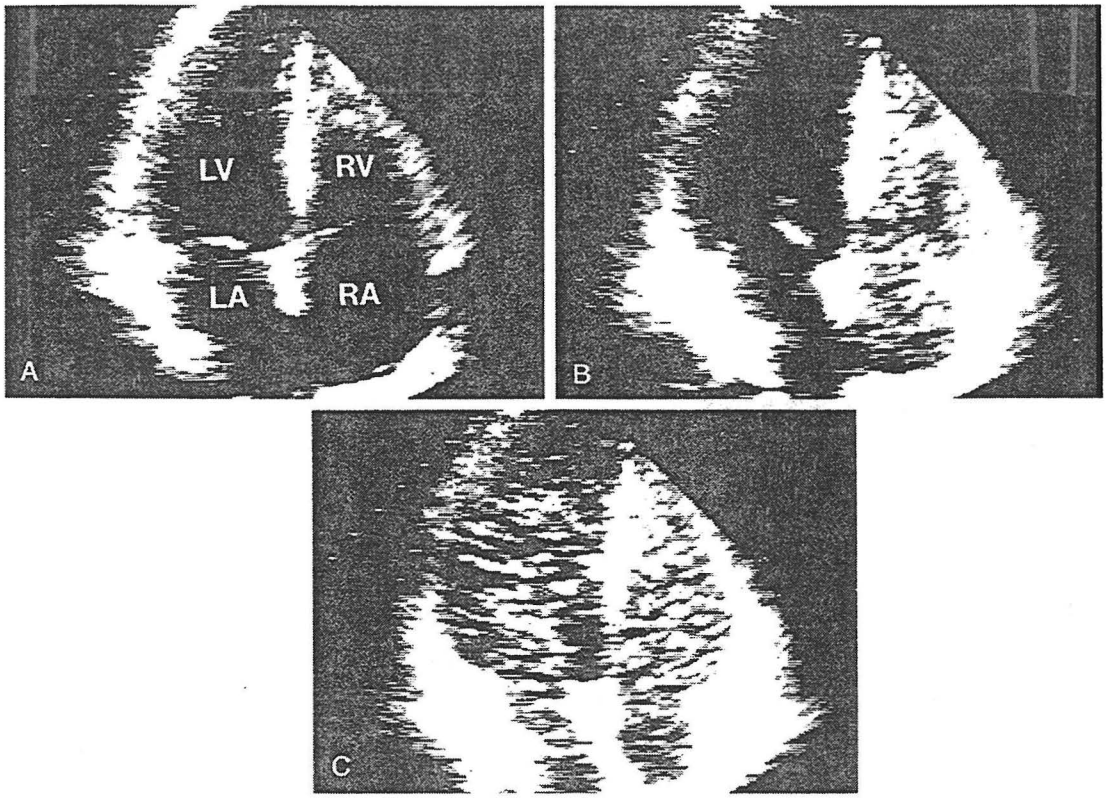


(Figure 6). ^{99m}Tc-MAA perfusion scan in a patient with the hepatopulmonary syndrome. Intrapulmonary shunting of the tagged aggregates is indicated by their appearance in the brain (above). The lower figure indicates uptake in the lungs and mild uptake in the kidneys and liver.
From: Castro and Krowka (9)

Agitation of normal saline or an indocyanine green solution creates microbubbles 15-90 μm in diameter which are normally trapped and resorbed in the pulmonary capillaries after peripheral intravenous injection (9, 108). In the presence of IPVD, some bubbles pass through the pulmonary capillary bed, or discrete arteriovenous fistulas, and arrive in the left heart within three to six cardiac cycles resulting in "delayed" opacification of those chambers (Figure 7). If the left atrium opacifies within one or two beats ("early" opacification), an intracardiac shunt is indicated. Unlike nuclear medicine scans, echocardiography also allows us to exclude significant pulmonary hypertension in these patients, another cause for hypoxemia in patients with portal hypertension. If the right heart appears dilated or early opacification is seen,

doppler imaging can be performed to estimate pulmonary artery pressures and rule out intracardiac shunting. A further advantage of CEE over nuclear medicine scans is its apparent superior sensitivity for detecting IPVD. In one study, 13 of 33 consecutive cirrhotic patients had positive CEEs, but only three of the 13 had shunting by MAA perfusion scanning (106). No individuals had a positive MAA scan and a negative CEE, and all control patients had negative CEEs.

FIGURE 7



(Figure 7). Contrast-enhanced echocardiogram in a patient with the hepatopulmonary syndrome. "Delayed" opacification of the left-sided chambers is noted five cardiac cycles after the appearance of bubbles in the right ventricle indicating an intrapulmonary shunt.
From: Krowka and Cortese (4)

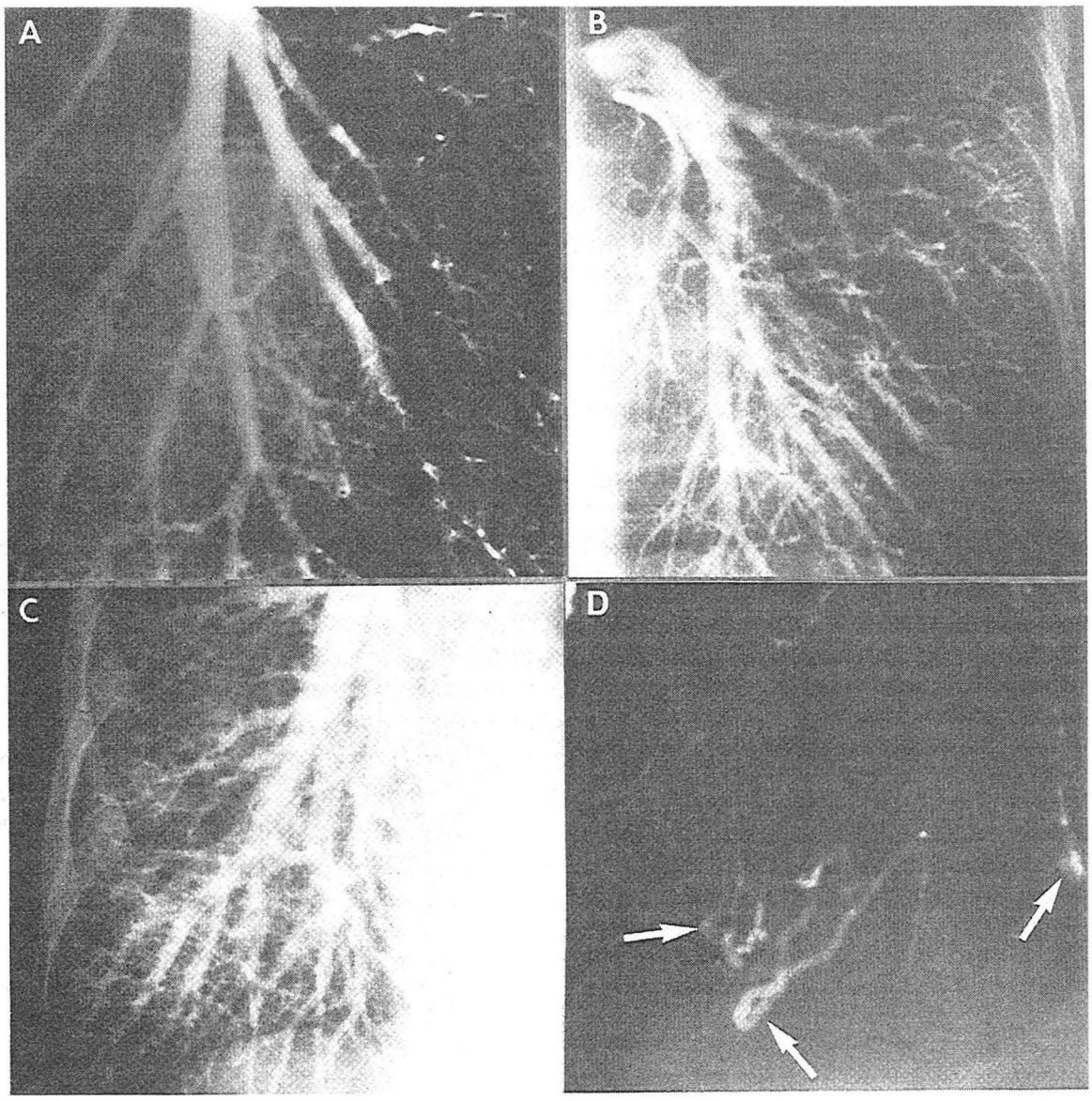
The reported incidence of positive contrast enhanced echocardiograms among patients with advanced liver disease has varied considerably from 13% to 47% (50, 51, 106, 108, 111). A positive study does not necessarily mean the patient has HPS. Perhaps 50% or more of individuals with positive studies have normal alveolar-arterial oxygen gradients and therefore do not fulfill currently accepted diagnostic criteria for the syndrome (50, 51, 106, 108).

The natural history of patients with IPVD and normal alveolar-arterial oxygen gradients is unknown, but it is likely that some (perhaps most) will progress to HPS if they survive long enough. In Hopkin's study, there was actually no significant

difference in the measured PaO_2 between patients with positive and negative contrast studies (76 ± 11 mm Hg vs. 82 ± 11 mm Hg) (50). However, most of the patients with positive CEEs were qualitatively graded as 1^+ (minimal) left ventricular opacification. When only the group with 2^+ to 4^+ (moderate to extensive) opacification were examined, the mean PaO_2 was lower at 66 ± 3 mm Hg ($p < 0.01$) and all had resting arterial oxygen tensions below 70 mm Hg (50). The same pathophysiologic events are undoubtedly taking place in IPVD with and without hypoxemia, and the hepatopulmonary **syndrome** should simply be considered one end of the disease spectrum.

Pulmonary arteriography is not required to secure a diagnosis in HPS. It is much more invasive and less sensitive at identifying IPVDs than either CEE or ^{99m}Tc-MAA scanning. However, in patients demonstrating a poor response to 100% inspired oxygen, it may furnish important prognostic information and suggest a change in therapy. Two distinct angiographic patterns may be seen or the study may be normal (Figure 8). Krowka and colleagues refer to these patterns as type I, diffuse (minimal or advanced) and type II, focal (6, 9, 11). The minimal type I pattern consists of a fine lattice of branching "spidery" vessels on the arterial phase. With advanced type I changes, a more dense "spongy" network is identified (11, 68, 90, 111). Any of the patterns may be associated with significant hypoxemia and orthodeoxia, but patients with the minimal type I pattern typically demonstrate a near normal response to breathing 100% oxygen ($PaO_2 > 500$ mm Hg). This may not be true of patients with the more advanced type I pattern or the focal type II pattern which indicates the presence of discrete arteriovenous fistulas (11). Type II shunts are identified much less commonly than type I abnormalities, but a poor response to supplemental oxygen increases the likelihood that direct arteriovenous connections will be seen which can be embolized. It has therefore been suggested that individuals with IPVD by a noninvasive study and a standing $PaO_2 < 150$-200 mm Hg on 100% O_2 should undergo angiography (7, 9).

FIGURE 8



(Figure 8). Pulmonary angiographic patterns identified in patients with the hepatopulmonary syndrome. A and B depict the "minimal" type I pattern with spidery dilatation of vessels. C indicates the "advanced" type I pattern with a diffuse "spongy" appearance of vessels in the lung base. D reveals the type II pattern of discrete arteriovenous fistulas.
From: Krowka et al. (11)

Failure of Hypoxic Pulmonary Vasoconstriction in Cirrhosis

What physiologic alterations accompany these IPVDs? Vasodilatation of the pulmonary microcirculation results in a reduction in the calculated pulmonary vascular resistance of many patients with cirrhosis. In 1972, Daoud and coworkers studied a group of ten patients with severe alcoholic cirrhosis and hyperdynamic circulatory states

while breathing either room air or a hypoxic mixture of 10% oxygen in nitrogen (112). The mean room air A-aDO_2 in these patients was 28 ± 9 mm Hg indicating mild to moderate hypoxemia. The principal abnormality identified was a lower than normal baseline pulmonary vascular resistance (PVR) and a complete failure of pulmonary vasoconstriction in response to alveolar hypoxia. Hypoxic pulmonary vasoconstriction (HPV) is a unique property of pulmonary vascular smooth muscle and occurs in the small precapillary arterioles (<300 μm in diameter). It is a critical component of the control system which matches ventilation with perfusion to preserve arterial PaO_2 (112, 113). Impairment of this mechanism with the resultant loss of arteriolar tone and dilatation of the vascular bed would result in relative overperfusion of some lung units and contribute to hypoxemia.

In 1981, Naeije and associates performed a similar analysis of the pulmonary vascular response to acute inspiratory hypoxia (12.5% oxygen) in 24 patients with mild to moderately severe cirrhosis (114). Pulmonary vascular resistance was reduced at baseline in cirrhotics, but a mean increase in PVR of 50% occurred when breathing the hypoxic gas mixture (81 ± 8 to 126 ± 13 dyne s cm^{-5}), and this was interpreted as normal. However, a significant fraction of the patients (7/24) were classified as "nonresponders" indicating an increase in PVR of less than 20% (Table 5). Rodriguez-Roisin and coworkers subsequently confirmed Naeije's finding that HPV is not absent in all patients with cirrhosis (60). These patients did not have severely decompensated liver disease either, and most had normal or only mildly elevated resting alveolar-arterial O_2 gradients. Nonetheless, an interesting correlation was noted in this study between the presence or absence of cutaneous spider angiomas and a variety of physiologic observations. Patients with spiders had significantly higher cardiac outputs, more systemic and pulmonary vasodilatation, reduced HPV, and lower arterial oxygen tensions than patients without them. In addition, these patients showed evidence of more hepatocellular dysfunction.

TABLE 5

Hypoxic Pulmonary Vasoconstriction in Hepatic Cirrhosis

	"Responders" (n=17)		"Nonresponders" (n=7)	
FiO_2	0.21	0.125	0.21	0.125
PaO_2 (mm Hg)	76.8 ± 3.4	41.6 ± 1.7	81.2 ± 3.3	41.8 ± 2.2
A-aDO_2 (mm Hg)	31.2 ± 3.2	8.1 ± 1.4	28.6 ± 2.7	8.2 ± 1.9
CI (L/min/m^2)	3.8 ± 0.2	4.3 ± 0.3	3.8 ± 0.2	4.2 ± 0.2
PVR (dynes s/cm^5)	82.6 ± 10.1	140.8 ± 15.7	85.3 ± 18.4	88.4 ± 18.8

Adapted from Naeije (114)

More recently, Kobayashi and colleagues reported a single case of a patient with cirrhosis, severe hypoxemia and a very low PVR who actually demonstrated a

paradoxic **increase** in PVR under hyperoxic conditions (115). Normally, PVR falls in response to increasing concentrations of inspired oxygen (116). To explain this unusual finding the authors hypothesized that short-acting vasodilatory substances might be tonically released in the presence of severe hypoxemia even during room air breathing (115). Indeed, several vasodilating candidate molecules exist which will be discussed later including nitric oxide, certain prostaglandins, atrial natriuretic factor, platelet activating factor, and purine nucleotides.

Chang and Ohara were the first to study pulmonary circulatory dysfunction in an animal model of the hepatopulmonary syndrome and have made significant contributions to our understanding of the vasoregulatory disturbance in cirrhosis (117). They induced cirrhosis in rats by chronic bile duct ligation, then measured systemic and pulmonary hemodynamics while breathing room air and 8% O_2. Cirrhotic rats had an increased A-aDO_2 (23 ± 1.9 mm Hg vs. 15.7 ± 1.1 mm Hg in controls) and markedly reduced HPV. The pulmonary vascular response while breathing hypoxic gas increased an average of 42% in control animals but was essentially absent in cirrhotic rats (Table 6).

TABLE 6

Hypoxic Pulmonary Vasoconstriction in Cirrhotic Rats

	Control Rats	Cirrhotic Rats
C.I. (ml/min/100 g BW)	33.2 ± 1.8	42.7 ± 2.8*
T.S.R. (mm Hg/min/100 g BW)	3694 ± 270	2628 ± 264*
T.P.R. (mm Hg/min/100 g BW)	577 ± 22	455 ± 42*
Δ T.P.R. during hypoxia	42 ± 14%	0.9 ± 3.6%*

- HPV not restored by perfusion with autologous blood from healthy rats
- Angiotensin II infusion restored HPV in isolated perfused lungs and in vivo

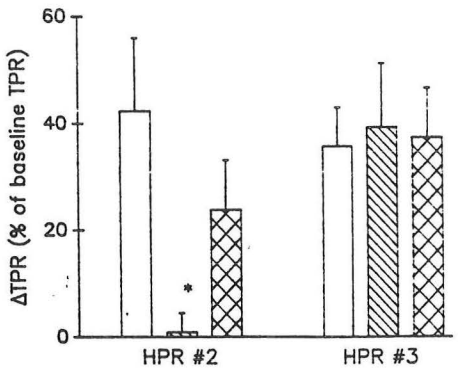
C.I.= cardiac index T.S.R.= total systemic resistance
T.P.R.= total pulmonary resistance * indicates significant difference

Adapted from Chang and Ohara (117)

Further studies involved isolating the lungs of cirrhotic rats and perfusing them with autologous blood from normal rats (117). If the depressed HPV were due to some systemically circulating vasodilator, infusion of autologous "normal" blood should reverse it; but the loss of HPV persisted suggesting that the problem was intrinsic to the pulmonary circulation. Interestingly, HPV was restored to control levels after infusion of angiotensin II both *in vivo* and in isolated perfused lungs (Figure 9). This indicates that the process responsible for the development of IPVD may be responsive

to pharmacological manipulation. Angiotensin II is known to stimulate cGMP hydrolysis in vascular smooth muscle cells (118). Chang and Ohara suggested that the intracellular accumulation of cGMP and/or cAMP due to prolonged stimulation from various circulating vasodilators might be responsible for the observed reduction in vascular reactivity in cirrhosis (117, 119-121). Angiotensin II, then, might improve vascular responsiveness by increasing hydrolysis of these vasodilating purine nucleotides (122).

FIGURE 9



(Figure 9). Effect of angiotensin II on hypoxic pulmonary vasoconstriction in cirrhotic rats. Angiotensin II was infused between the second (HPR #2) and third (HPR #3) hypoxic challenges. Hypoxic pulmonary vasoconstriction, as assessed by a change in total pulmonary resistance (ΔTPR) occurred only in the cirrhotic group. Open bars = control rats; Hatched bars = cirrhotic rats; Cross-hatched bars = cholestatic control rats.
From Chang and Ohara (117)

Mechanisms of Impaired Gas Exchange in the Hepatopulmonary Syndrome

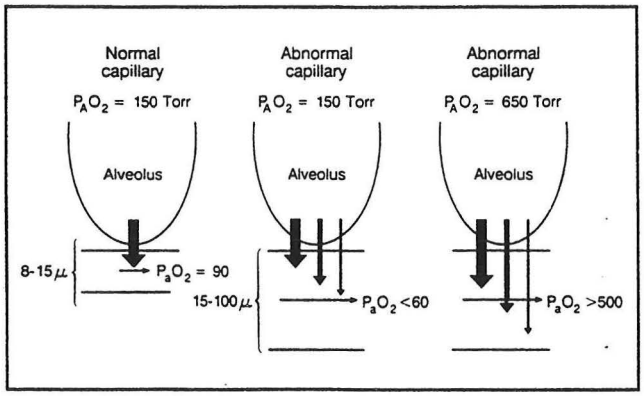
Generally speaking, hypoxemia may occur as the result of one or more of the following conditions: hypoventilation, ventilation-perfusion mismatch, shunt, or diffusion limitation. Patients with hepatic disease typically hyperventilate, but the remaining three mechanisms may each be important in producing a widened alveolar-arterial oxygen gradient in this population. The precise mechanisms of impaired oxygenation continue to be debated, but most investigators agree that the hallmark vascular dilatations are ultimately to blame.

A key piece of information in the gas exchange puzzle of advanced liver disease is the fact that most patients, including many with moderate to severe hypoxemia, will demonstrate a normal or near-normal response to breathing pure oxygen. This, of course, is inconsistent with true anatomic shunting. So how can these findings be reconciled with the CEE and ^{99m}Tc-MAA scan data?

In 1978, Davis et al. proposed a new mechanism for intrapulmonary "shunting" based on the established changes seen in the microcirculation of these patients. The theory was called the alveolar-capillary oxygen disequilibrium (103). Others refer to it

as the "diffusion-perfusion defect" (9, 22, 28, 107, 123-125). In normal capillary beds, erythrocytes circulate more or less in single file; but in cirrhotic patients, gas exchanging vessels may be dilated five or ten-fold with layering of red blood cells. This results in a much longer diffusion distance for oxygen, so erythrocytes in the center of the capillary may not fully equilibrate with alveolar oxygen prior to reaching the venous side of the circulation (Figure 10). With the exception of an isolated case report describing collagen deposition in the walls of capillaries and venules by ultrastructural analysis (126), the walls of these dilated vessels have not been found to be abnormally thick and would not be expected to impose an additional barrier to gas exchange. Raising alveolar oxygen tension by breathing a high fraction of inspired O_2 raises the pressure gradient for diffusion of the gas and thereby overcomes any ventilation-perfusion mismatch or diffusion limitation that may be present. This accounts for the generally good response to high-flow O_2 noted in patients with hypoxemia due to HPS.

FIGURE 10

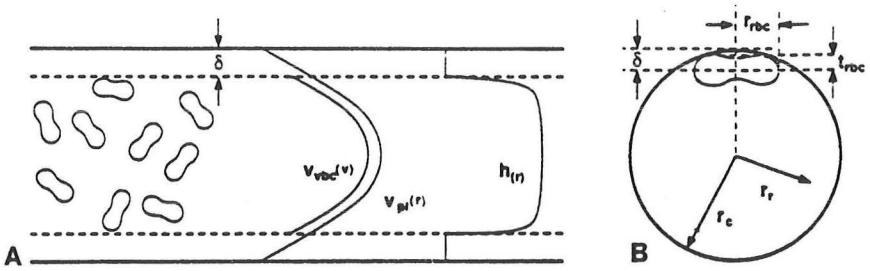


(Figure 10). The "perfusion-diffusion" defect. Effect of pulmonary vascular dilatation on oxygenation in patients with the hepatopulmonary syndrome under conditions of room air and 100% O_2 breathing.
From: Krowka and Cortese (22)

It has been shown that even in healthy well-conditioned individuals, diffusion can be limiting if either the mixed venous PO_2 is very low or erythrocyte transit time is very short (127, 128) as may occur in healthy persons during exercise at high altitude (129). Cirrhotic patients generally have a normal mixed venous oxygen tension (130-134), but they do often demonstrate reduced red cell transit time through acinar vessels. This is a result of the hyperdynamic circulatory state associated with advanced liver disease. Patients with cirrhosis often, though not always, have an increased cardiac output with diminished systemic and pulmonary vascular resistance (8, 47, 59, 60, 112, 117, 123, 135-142). In fact, the extent of this hemodynamic disturbance correlates with prognosis in liver disease (143). Moreover, in large capillaries it has been shown that blood flow assumes a parabolic profile due to shear forces between red blood cells and the vessel walls. Erythrocytes tend to move away from the walls of the capillary and flow accelerates toward the center of the bloodstream further decreasing transit time for the cells farthest away from the inspired gas (Figure 11) (144). This increases the odds that erythrocytes may fail to become fully saturated with oxygen (103).

FIGURE 11

$$\delta = r_c + t_{rbc} - \sqrt{r_c^2 - r_{rbc}^2},$$



(Figure 11). A. Schematic of the flow of erythrocytes in large capillaries. RBC and plasma velocity profiles and the hematocrit profile. B. Movement of cells away from vessel walls creates a layer of plasma that is depleted of cells, the "cell-free" layer (δ). Indicates the basis for calculation of the cell-free layer thickness. From: Nair et al. (144)

The commonly reduced diffusing capacity for carbon monoxide in liver patients was seen as further evidence in support of this diffusion-perfusion defect. Also, patients whose gas exchange is limited by diffusion will always desaturate further with exercise because of the obligatory decrease in erythrocyte transit time (127, 145). Indeed, studies have confirmed that the PaO_2 of cirrhotics often does fall during exercise (5, 124, 130). Average transit time under normal circumstances is about 0.75 seconds, but red blood cells achieve near complete partial pressure equilibrium with alveolar gas after approximately 0.25 seconds of gas exchange (one third of the average distance through the capillary) (131). This 0.50 second time "reserve" combined with additional capillary recruitment prevents exercise-associated diffusion limitation in healthy persons even if the cardiac output approaches its ceiling of 20-30 L/min.

MIGET Data

Our understanding of the pathophysiologic mechanisms leading to hypoxemia in liver disease was greatly enhanced by the development and application of the multiple inert gas elimination technique (MIGET) (146, 147). Previously physiologists relied on having patients breathe different concentrations of oxygen to help elucidate the cause of altered gas exchange in various disease states. This approach was problematic because of the non-linear nature of the oxy-hemoglobin dissociation curve and the fact that changing inspired oxygen concentrations can directly affect VA/Q ratios (148, 149). Farhi suggested that infusion of a series of dissolved inert gases with a wide range of solubilities and measurement of their elimination by the lungs and retention in the blood might circumvent these problems (150). This concept was refined in the development of MIGET by Wagner and associates (146, 147, 151). Prior to the development of this technique, investigators were largely limited to a conceptual model of the lungs consisting of three idealized compartments: one unventilated, one unperfused, and one

ideal (152). Now it became feasible to accurately quantify a virtually continous distribution of VA/Q relationships (50 compartments in all), and to distinguish low VA/Q units from true shunt, and high VA/Q units from dead space. With this technique, even diffusion limitation can be assessed, albeit indirectly. If the predicted arterial oxygen tension based on measurement of the VA/Q distributions and mixed venous O_2 tension exceeds the measured PaO_2, this implies the presence of diffusion limitation. Actually, there may be a small difference (predicted PaO_2 > measured PaO_2 by a few mm Hg) because the slight physiologic effect of shunting through the Thebesian and bronchial veins is not included in the calculations (153, 154).

Several studies utilizing MIGET have now been performed in patients with liver disease and varying degrees of hypoxemia (Table 7) (40, 59, 60, 125, 130, 131, 140, 155). In 1987, Rodriguez-Roisin and colleagues evaluated 15 consecutive patients with cirrhosis after recovery from acute variceal bleeds (60). All were Child's class A or B with arterial O_2 tensions between 76 and 105 mm Hg (mean 92.5 ± 2.5 mm Hg). Very little shunt was identified (mean 0.31 ± 0.3%, range 0.0-7.8% of the cardiac output), but there was an increase in blood flow to areas with low VA/Q ratios < 0.1 (mean 5.8 ± 1.8%, range 0.0-20.2% C.O.). No diffusion limitation was seen. This study found no correlation between tests of airflow limitation and VA/Q mismatching, and the authors suggested that it was the abnormal vascular tone associated with cirrhosis that was primarily responsible for the VA/Q inequality. However, it was not possible to separate the contributions of impaired pulmonary vasoconstriction versus the elevated cardiac output to the relative overperfusion of involved lung units.

TABLE 7

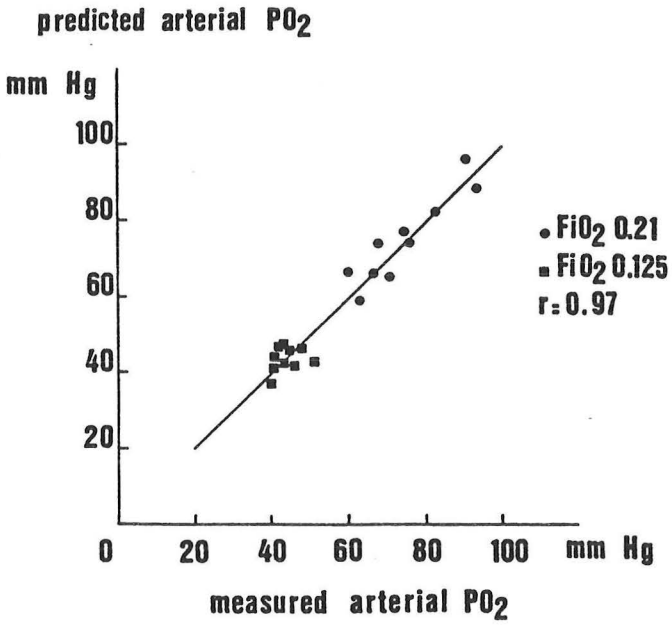
Summary of Multiple Inert Gas Elimination Technique (MIGET) Data

First Author	N	Mean PaO_2 (mm Hg)	%Shunt	VA/Q mismatch	Diffusion limitation
Rodriguez-Roisin	15	93	<1	mild-moderate	none
Agusti	6	99	5*	mild-moderate	none
Agusti	8	88	4	mild-moderate	none
Melot	3	89	0	mild-moderate	none
Melot	7	69	2	moderate	none
Eriksson	6	79	4	moderate	none
Hedenstierna	14	86	4	moderate	mild
Andrivet	9	64	20	mild	none
Edell	6	58	23	moderate	mild
Castaing	6	56	20	mild-moderate	mild
Van Obbergh	3	46	41	mild	none
Crawford	1	56	19	moderate	moderate

Adapted from Castro and Krowka (9)

Melot and associates utilized MIGET to evaluate ten cirrhotics (seven with hypoxemia) and confirmed the presence of significant VA/Q inequality, but negligible shunt and no diffusion limitation (131). There was no evidence for a limitation of oxygen diffusion even under conditions of alveolar hypoxia where such a disturbance should become obvious (Figure 12). In this study, unlike the previous one, hypoxemic patients did **not** have a statistically significant impairment of HPV compared to normoxemic patients. They also failed to find a close relationship between the clinical or laboratory assessment of the severity of liver disease and defects in vascular tone, but concurred that the hypoxemia of cirrhosis is best explained by VA/Q mismatch due to diminished HPV.

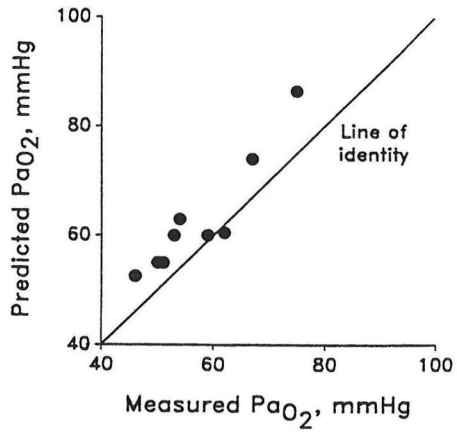
FIGURE 12



(Figure 12). Linear correlation between measured and MIGET predicted PaO_2 under conditions of room air and 12.5% O_2 breathing in 10 patients with cirrhosis. The solid line indicates the line of identity.
Squares = hypoxic breathing Circles = room air breathing
From: Melot et al. (131)

Edell and coworkers studied a group of cirrhotic patients with much more severe hypoxemia (standing PaO_2 35-59 mm Hg) and orthodeoxia (40). In addition to low VA/Q mismatching, these patients had large right to left intrapulmonary shunts (range 4-28% of the cardiac output) and higher predicted than measured arterial oxygen tensions indicating possible diffusion limitation (Figure 13). Breathing 100% O_2 did not reduce pulmonary artery pressures, implying blunted or absent HPV. Interestingly, pulmonary artery pressures fell and the shunt fraction increased in 3 patients who had measurements performed also in the sitting position, suggesting increased perfusion of dependent lung shunts.

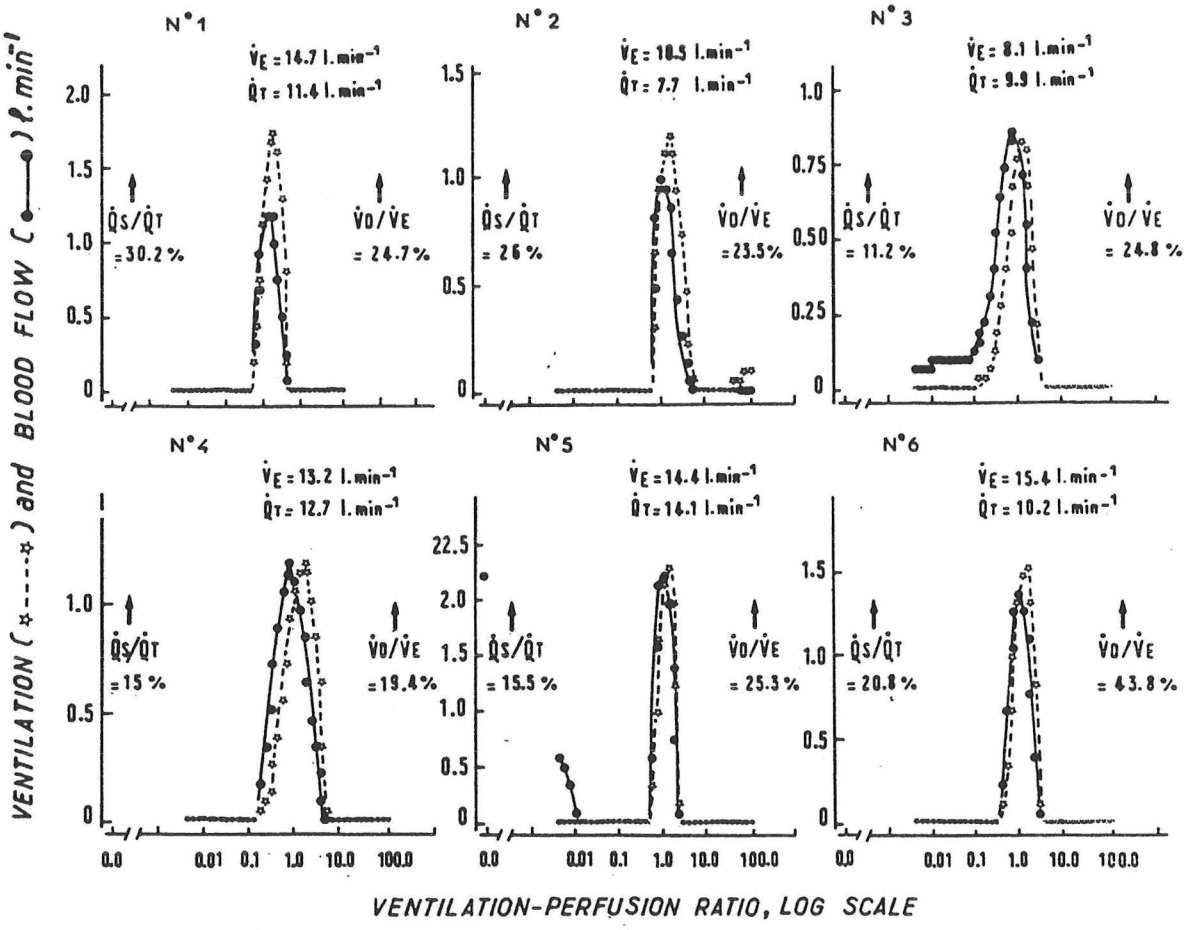
FIGURE 13



(Figure 13). Predicted PaO_2 as a function of measured PaO_2 in nine patients with severe hypoxemia. The predicted PaO_2 was significantly larger ($P<0.01$) indicating possible diffusion limitation.
From: Edell et al. (40)

Castaing and Manier (140) and Andrivet and coworkers (59) also used MIGET and hemodynamic monitoring to evaluate individuals with severe hypoxemia and cirrhosis. All patients exhibited high cardiac outputs, systemic and pulmonary vasodilatation. Intrapulmonary shunting was a critical factor in the observed gas exchange abnormality (mean shunt 20% C.O. in both studies) (Figure 14). No evidence for diffusion limitation or an extrapulmonary (e.g., portopulmonary) shunt was seen in Andrivet's group, but Castaing and Manier could not exclude these possibilities. In their study, predicted O_2 tensions were significantly higher than measured O_2 tensions (by 9.3 ± 5.9 mm Hg).

FIGURE 14

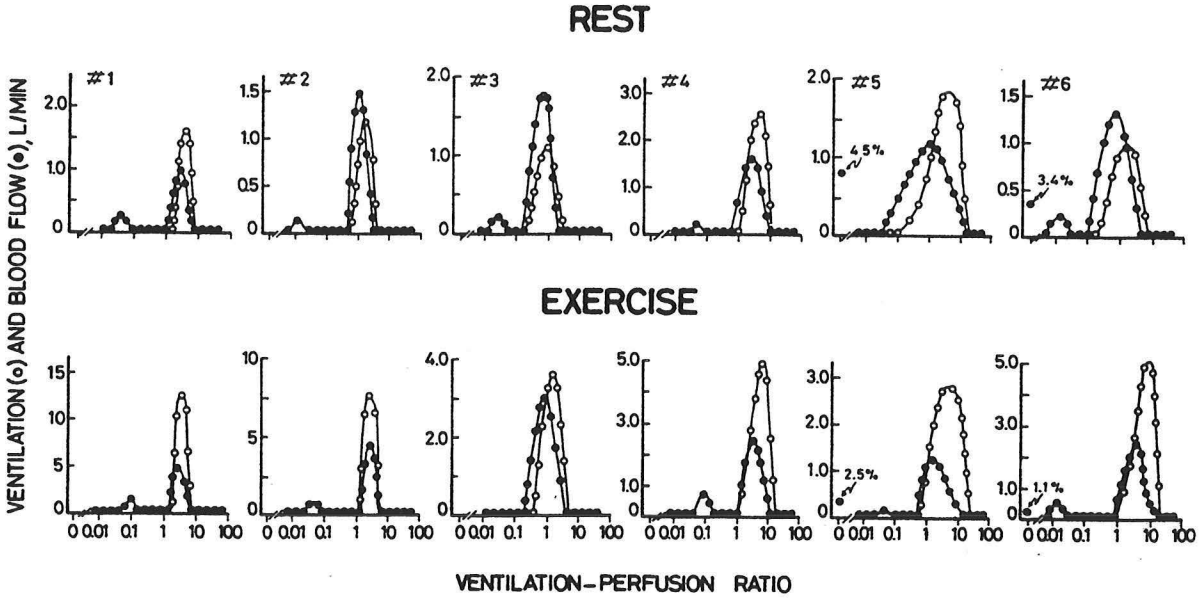


(Figure 14). Patterns of VA/Q distribution in patients with severe hepatopulmonary syndrome. High shunt fractions are noted in all 6 individuals.
From: Castaing and Manier (140)

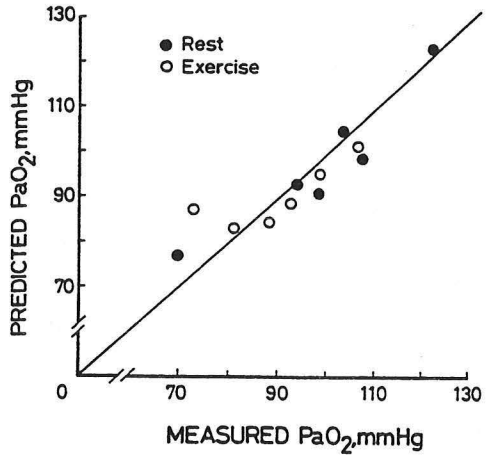
Hedenstierna and colleagues studied 14 patients with non-alcoholic cirrhosis and varying degrees of hypoxemia (155). Shunting was again significant only in the patients with the lowest arterial oxygen tensions (PaO_2<60 mm Hg). Calculated PaO_2 exceeded the measured value in hypoxemic but not normoxemic individuals.

To clarify the role for actual diffusion limitation in patients with IPVD, Agusti and coworkers utilized MIGET to evaluate exercising patients (130). Since exercise results in a further reduction in erythrocyte transit time through alveolar capillaries, any diffusion defect should be amplified under these conditions. Mild to moderate VA/Q mismatch was seen at rest in these patients, but PaO_2 was maintained within normal limits (99 ± 7 mm Hg) by the high resting cardiac output and hyperventilation ($PaCO_2$ 29 ± 2 mm Hg). With exercise, PaO_2 trended down (90 ± 5 mm Hg) and $PaCO_2$ trended up (35 ± 2 mm Hg) while mixed venous oxygen tension fell significantly (41 ± 2 to 33 ± 0.3 mm Hg). No diffusion impairment was identified even with exercise and the degree of ventilation-perfusion inequality did not worsen (Figure 15).

FIGURE 15



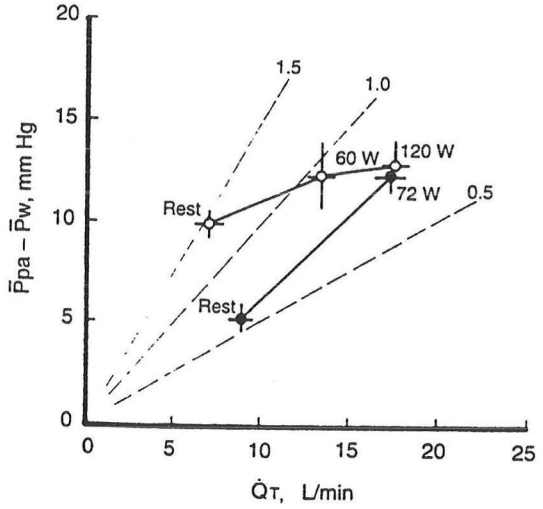
(Figure 15a). VA/Q distributions in six patients with cirrhosis at rest and during exercise. Five of six patients showed a bimodal distribution of blood flow indicating perfusion of poorly ventilated areas. Patients 5 and 6 also demonstrated small true shunts. Neither the degree of VA/Q mismatch nor the shunt fraction worsened during exercise in these patients.



(Figure 15b). Predicted PaO_2 as a function of measured PaO_2 at rest (closed circles) and during exercise (open circles). No significant differences from identity were noted under either condition indicating no diffusion limitation.
From: Agusti et al. (130)

Contrary to what was expected, the efficiency of the lung as a gas exchanging organ did not decrease with exercise. The authors further demonstrated that the hyperdynamic circulation seen in cirrhotic patients at rest is maintained during exercise. In fact, while oxygen consumption during exercise was comparable to that observed in normals at a similar workload (52), the patients with cirrhosis had cardiac outputs equivalent to those of healthy subjects exercising at almost twice the workload (Figure 16).

FIGURE 16



(Figure 16). Relationship between pulmonary driving pressure and cardiac output at rest and during steady state exercise in six patients with cirrhosis (closed circles) and eight healthy subjects (open circles) (control data from Wagner et al.) (52). At rest, cirrhotic patients demonstrate a lower mean Ppa-Pw and higher Q_T than controls. PVR decreased with exercise in normals but did not change significantly in cirrhotic patients. Consequently, Ppa-Pw increased much more as Q_T rose during exercise in the patient group.
From: Agusti et al. (130)

In normal individuals, pulmonary artery pressures do not rise much with exercise because of pulmonary vasodilatation and capillary recruitment; but in patients with cirrhosis, the pulmonary capillaries and arterioles are already dilated at rest, and there is a more linear increase in pulmonary arterial pressure with increasing cardiac output during exercise. Essentially, the cardiac output and minute ventilation exceed the actual metabolic demands of the patient at rest, but become more "matched" during exercise, thereby exposing the true degree of hypoxemia that would be expected for the measured degree of VA/Q mismatch (130). Arterial CO_2 tension fails to fall appropriately and may even increase with exercise, while mixed venous O_2 falls as a result of increasing peripheral extraction. The resting "buffer" of hyperventilation and the hyperdynamic circulation is thus diminished. Melot and colleagues also demonstrated that hyperventilation and the rightward shift of the oxyhemoglobin dissociation curve in cirrhosis help counteract the hypoxemic effect of abnormal ventilation-perfusion relationships at rest in these patients (131). Thus, even normoxemic cirrhotics may have hidden VA/Q disturbances.

Crawford and associates studied a single patient with severe hypoxemia at rest (PaO_2 52 mm Hg) and a 40% shunt estimated by quantitative perfusion scanning (125). MIGET identified an abnormally large gap between the predicted and measured arterial oxygen tensions indicating possible diffusion limitation. The authors indicated that this observation was consistent with the findings of other groups who had studied severely hypoxemic patients (40, 140), and that physiological postpulmonary shunting was unlikely to be sufficient to account for the difference. Shunt, VA/Q mismatch, and

diffusion-limitation appeared to contribute equally to this patient's venous admixture (125). ^{99m}Tc-MAA scanning in this case indicated a 40% shunt which was much larger than the 25% shunt identified with MIGET, or the 18% shunt predicted by the standard 100% O_2 breathing method. Quantitative radionuclide scans dramatically overestimate shunt fractions in liver disease (as opposed, for instance, to hereditary hemorrhagic telangiectasia), because they merely detect the presence of capillary beds with vessels too large to capture all of the macroaggregated albumin. They do not confirm the presence of true anatomic shunts. This explains why technetium scans may identify sizable "shunts" in patients who demonstrate a completely normal response to breathing 100% oxygen. High inspired concentrations of oxygen will overcome VA/Q mismatch, but not shunt.

An interesting observation was made by Crawford and colleagues when MIGET was applied during 100% O_2 breathing. The measured arterial oxygen tensions actually exceeded those predicted by the MIGET (the opposite of the usual finding). Edell and colleagues had identified the same anomaly in severely hypoxemic patients during O_2 breathing (40). Crawford suggested that this might be the result of diffusion-limitation of SF_6, the retention-excretion characteristics of which are the main determinant of shunt estimation by MIGET. Inert gases are supposed to equilibrate with blood and gas much faster than O_2 and CO_2 and should not be diffusion limited in the setting of a normal sized capillary (127). However, the authors propose that since the effective "diffusivity" of a gas is proportional to its solubility in blood and inversely proportional to its molecular weight, and since SF_6 is the least soluble and second heaviest of the inert gases, there may not be sufficient time for complete equilibration of this gas between blood and alveolus in the setting of marked IPVD. Under conditions of pure O_2 breathing, the alveolar O_2 tension overwhelms any diffusion-limitation that might be present for oxygen, but may further increase the diameter of acinar vessels by releasing residual HPV, thus increasing the diffusion distance for SF_6. If SF_6 is diffusion limited under these circumstances, relatively more of the gas will be retained and less excreted; but since the MIGET calculation **assumes** complete equilibration of the inert gas between blood and alveolus, the increased retention of SF_6 would be interpreted as increased shunt or low VA/Q inequality (125). This could explain why the MIGET predicted PaO_2 is lower (and the shunt fraction higher) than measured in cases of advanced HPS when breathing 100% O_2. In an editorial addressing this paper, however, Wagner casts doubt on Crawford's theory and suggests two alternative explanations (156). It is possible that the MIGET overestimated the shunt fraction due to its inability to separate very low VA/Q units (VA/Q<0.01) from true shunts. Also, there could be regions of lung that are very poorly ventilated such that expired gas (e.g., containing inert gas) has difficulty escaping the alveoli despite the presence of some ongoing gas mixing with inspiration (156). Some bronchioles may open during inspiration because their diameter increases with increasing lung volume due to radial traction on the airway walls. However, expiratory collapse of the airways could prevent measurement of "excreted" inert gas from these units. The increased closing volume frequently noted in patients with cirrhosis lends some credibility to this concept (77, 80).

Considering all of this data, it would appear that mild to moderate degrees of hypoxemia in liver patients are usually explained by VA/Q mismatch. The diffusion-perfusion defect represents this VA/Q imbalance more than actual diffusion limitation as originally thought. The hypoxemia results from perfusion of **relatively** underventilated lung units (actual ventilation may be normal, but perfusion is excessive) creating low VA/Q mismatches. In more severely hypoxemic patients, true shunting of a sizable portion of the cardiac output also occurs. There are several possible sources for these true shunts (VA/Q=0): direct arteriovenous fistulas (i.e., type II anastomoses), pleural spider angiomata, perfusion through unventilated atelectatic zones in the lung bases as a result of failed hypoxic pulmonary vasoconstriction, and perhaps occasionally, flow through portopulmonary collaterals. In some severely hypoxemic patients, diffusion limitation may also contribute to arterial desaturation, especially during exercise, but this is usually not a critical factor.

Mediators of Vascular Dilatation in Cirrhosis

A variety of endocrine and paracrine factors have been implicated in the hyperdynamic circulatory state and pulmonary and systemic vasodilatation seen in hepatic cirrhosis and other forms of advanced liver disease (157) (Table 8). These include glucagon (158-165), atrial natriuretic factor (ANF) (166-175), vasoactive intestinal peptide (VIP) (176, 177), calcitonin gene-related peptide (CGRP) (178-181), substance P (179, 182), prostaglandin I2 or E1 (183-187), platelet activating factor (188, 189), and nitric oxide (190-197). The hemodynamic disturbances most likely result from overproduction or reduced metabolism of one or more of these vasodilating substances produced by the gut or endothelial cells in the presence of a dysfunctional liver. In addition, certain pulmonary vasoconstrictor substances may be reduced in liver disease further upsetting the regulation of vascular tone.

TABLE 8

Potential Mediators of Intrapulmonary Vascular Dilatation
in the Hepatopulmonary Syndrome

Increased Vasodilators	Decreased Vasoconstrictors
Glucagon	Endothelin
Atrial Natriuretic Factor	Tyrosine
Vasoactive Intestinal Peptide	Serotonin
Calcitonin Gene Related Peptide	Prostaglandin $F_{2\alpha}$
Substance P	Angiotensin I
Platelet Activating Factor	
Prostacyclin (PGI_2)	
Prostaglandin E_1	
Nitric Oxide	

Adapted from Castro and Krowka (9)

Glucagon has a wide variety of effects on the heart and circulation (159). In one study, newborn calves with experimental pulmonary hypertension demonstrated an increase in cardiac output and 50% reduction in pulmonary vascular resistance with glucagon infusion (158). It is known that serum glucagon levels are increased two to six-fold in patients with portal hypertension due to cirrhosis (160-163). This may be related to either portosystemic shunting or disturbed metabolism secondary to hepatocellular insufficiency, and the pancreas may even hypersecrete this hormone in cirrhotics (161, 163, 164). Glucagon probably can cause vasodilatation and may have direct inotropic effects at levels seen in patients with cirrhosis (159, 160). However, it has been shown that desensitization occurs to the vasoactive effects of glucagon in cirrhosis and it is unlikely to be responsible for the chronic hyperkinetic circulation seen in these patients (160, 165).

CGRP is another potent vasodilator which is found in increased levels in patients with cirrhosis (178-181). CGRP receptors have been identified in high density within the pulmonary arterial tree (178). This molecule may function as a neurotransmitter in the non-adrenergic non-cholinergic (NANC) regulation of vascular tone (178). The levels of CGRP in serum increase with more advanced cirrhosis and there is evidence of widespread release of this peptide in many tissues (181). Substance P is another vasodilating neuropeptide that might be important in pulmonary and systemic vasoregulation in health and disease (179). It has been shown to be increased in the plasma of patients with hepatic coma, and is associated with augmentation of cardiac output and a reduction in systemic vascular resistance (182).

Atrial natriuretic factor is a peptide hormone released from the heart with diuretic, natriuretic and vasodilating properties (166, 167, 173-175, 198). Circulating levels also are commonly elevated in patients with cirrhosis and ascites, and ANF has been shown to attenuate the pulmonary pressor response to hypoxia (166, 167, 175). It may also function as a protective endogenous vasodilator in various primary or secondary pulmonary hypertensive states (198). The mechanism of vascular smooth muscle relaxation by ANF appears to involve the production of cyclic GMP (122).

Platelet activating factor has a wide spectrum of biologic activities including peripheral vasodilatation (188, 199). Caramelo and colleagues identified increased levels of PAF in the blood of patients with cirrhosis, and the levels were higher in decompensated patients (188). What role this molecule plays in the hyperdynamic circulatory state of chronic liver disease is unclear, but one study of experimental cirrhosis in rats did indicate rapid reversal of the low systemic vascular resistance in these animals by administration of a specific antagonist to PAF (189).

Certain vasodilating prostaglandins, especially prostacyclin (PGI2) and perhaps PGE1, have also been implicated as possible humoral mediators of the abnormal systemic and pulmonary vascular tone in liver disease. Prostacyclin is known to contribute to the splanchnic hyperemia and portal hypertension of cirrhosis (184). These substances are potent pulmonary vasodilators whose effects may be mediated

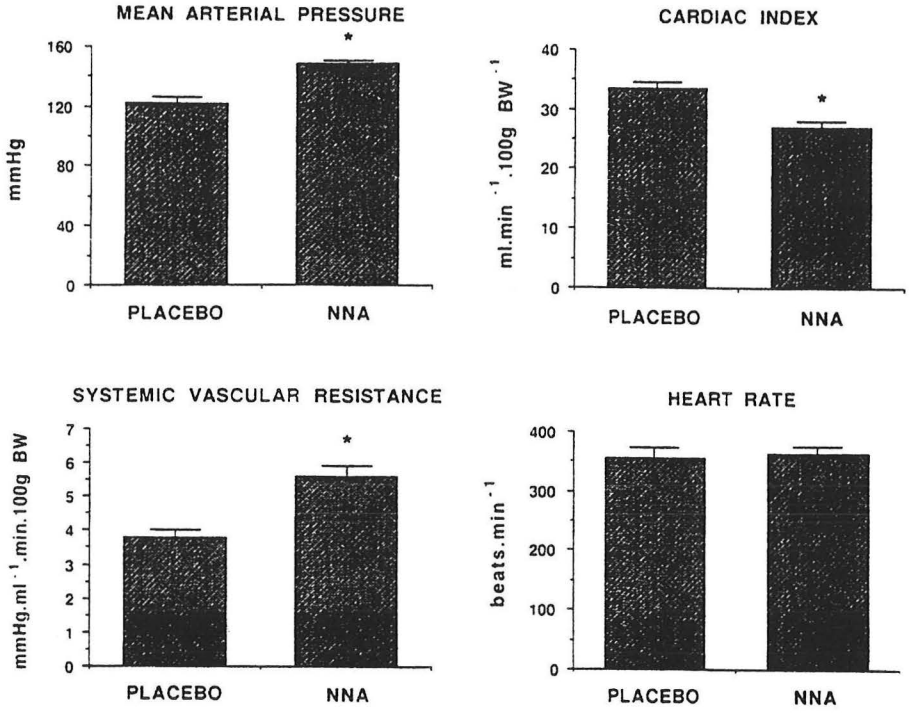
by stimulation of adenylate cyclase and guanylate cyclase, and indirectly by inhibition of sympathetic neurotransmitter release from autonomic nerve terminals (120, 183).

It is reasonable to assume from the above data that no one humoral factor is responsible for all of the circulatory disturbances associated with hepatic dysfunction and portal hypertension, but one molecule in particular has received a great deal of recent attention. Nitric oxide (NO) may be a critical link in the pathogenesis of the hepatopulmonary syndrome. NO is a powerful vasodilator derived from the amino acid L-arginine which is responsible for the biologic activity of endothelium-derived relaxing factor (EDRF) (200). Endogenous NO is produced throughout the body and appears to be an important tonic vasoregulatory substance because administration of L-NMMA (N-monomethyl-L-arginine), a specific inhibitor of NO synthesis, will cause a substantial increase in systemic blood pressure (195, 201). When NO is inhaled, it functions as a selective pulmonary vasodilator and reverses hypoxic pulmonary vasoconstriction (202). The vasodilatory effect of some of the peptide hormones and cytokines which are elevated in cirrhotics may be mediated by NO release.

Baseline NO production occurs via a calcium-dependent constitutively expressed nitric oxide synthase (NOS) enzyme. There is, however, a calcium-independent NOS which can be induced in vascular tissue after stimulation with endotoxin or cytokines (200, 203, 204). Sustained NO release, then, leads to the hypotension and attenuated response to vasoconstrictors seen in septic shock (119, 196, 197, 205-209). Interestingly, elevated circulating levels of endotoxin and cytokines are characteristic features of cirrhosis, even in the absence of infection (193, 194, 210-212). In the dog, infusion of even minute doses of endotoxin (too small to cause hypotension) have been shown to abolish the pulmonary pressor response to hypoxia, thus worsening ventilation-perfusion imbalance (213).

Vallance and Moncada first suggested that induction of NOS might by linked to the circulatory abnormalities associated with cirrhosis (192). In cirrhotic rats, infusion of NOS inhibitors results in an increase in systemic and splanchnic vascular resistance and a fall in cardiac output (Figure 17) (193, 194, 214, 215). Correction of systemic hemodynamics also appears to effect an increase in renal sodium excretion and a reduction in ascites and plasma volume expansion (193, 215).

FIGURE 17



(Figure 17). Systemic hemodynamics in portal hypertensive rats after a 6 day course of placebo or N^{ω}-nitro-L-arginine (NNA), a specific inhibitor of nitric oxide synthesis. NNA induced a significant increase in MAP and SVR, and a reduction in cardiac index.
From: Lee et al. (215)

NO is known to attenuate hypoxic pulmonary vasoconstriction (216). When inhaled, it produces a marked reduction in pulmonary vascular resistance but has no effect on systemic vascular resistance because it is rapidly inactivated by interaction with hemoglobin before reaching peripheral arteriolar beds (217-219). Interestingly, exhaled NO has been shown to be elevated (about three-fold) in patients with HPS compared to either normoxemic cirrhotics or healthy controls (190). One of these patients underwent orthotopic liver transplantation, and when evaluated three months later, the hypoxemia had resolved while exhaled NO levels decreased to normal. It is not believed that the reduced PaO_2 in HPS patients caused the elevated NO in expired gas since alveolar hypoxia actually caused a decrease in exhaled NO in the normals (190), which is consistent with previously reported animal data (220).

NO, like the atriopeptins, is believed to cause vascular relaxation by stimulation of soluble guanylate cyclase in smooth muscle cells with an attendant increase in cGMP levels (121, 200). Cyclic AMP is also known to attenuate HPV and appears to be an important mediator of vascular tone in response to vasodilating prostaglandins and VIP (121). Thus, the purine nucleotides may represent the final common pathways of vasodilatation in patients with liver disease and a generally disturbed humoral milieu. It is quite possible that selective inhibition of inducible NOS may lead to major

therapeutic advances in the treatment of shock states and the hepatopulmonary syndrome (192).

Medical Therapy for the Hepatopulmonary Syndrome

Thus far, medical therapy for HPS has been rather disappointing. The published experience on pharmacologic interventions is anecdotal, consisting of case reports and a few small observational cohort studies but no randomized controlled trials.

Propranolol has been used to reduce the risk of variceal bleeding in cirrhotics with portal hypertension (221). Theoretically, by blocking beta-adrenergic receptors in vessels it might increase pulmonary vascular tone while simultaneously reducing shunt fraction as a passive consequence of the drop in cardiac output. Agusti and colleagues examined eight patients with MIGET before and after propranolol (134). No change in arterial oxygenation occurred. The shunt fraction was reduced, but was countered by a decrease in mixed venous oxygen tension when systemic oxygen delivery decreased.

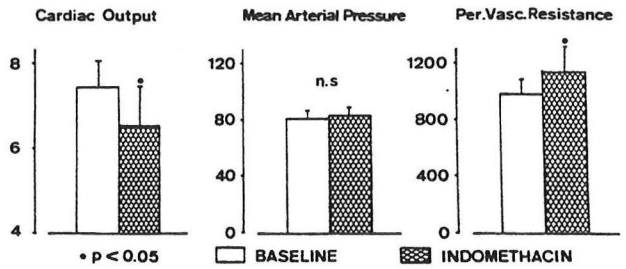
Other investigators have assessed the impact of direct pulmonary vasoconstrictors like almitrine bismesylate, an agent known to enhance HPV (22, 132). Nakos and colleagues found that administration of this drug produced a significant increase in pulmonary vascular resistance accompanied by a reduction in A-aDO_2 from 44 ± 5 to 34 ± 3 mm Hg (uncontrolled data) (132). Krowka and Cortese, however, demonstrated improvement in arterial O_2 tension in just one of five patients given almitrine, and this was modest (<10 mm Hg) (12). At any rate, this agent is not without significant untoward effects and is no longer available in the United States.

Somatostatin inhibits the secretion of vasodilating neuropeptides. In 1989, a single patient with severe hypoxemia (PaO_2 58 mm Hg on 6 liters of O_2) and a shunt fraction of 17% by quantitative radionuclide scan underwent one week of therapy with a somatostatin analog (222). The patient's oxygenation improved and the estimated shunt fraction decreased to 3%. OLT was then performed successfully. Subsequent investigations, however, have failed to identify a positive response to somatostatin analogs (11, 223-225).

Prostaglandin inhibition with indomethacin has been demonstrated to cause a significant decrease in cardiac output and portal pressure in cirrhotics while increasing peripheral vascular resistance (Figure 18) (185). Blockade of prostaglandin synthesis has also been shown to prevent (in dogs) the loss of hypoxic pulmonary vasoconstriction which occurs with infusion of endotoxin (Figure 19) (183, 226, 227) or following repeated hypoxic exposures (186). Similarly, in experimental bacterial pneumonia, cyclooxygenase inhibitors will reduce perfusion to consolidated lung and increase arterial oxygen tension (228). Slight improvement in the arterial oxygen tension of HPS patients has been reported after administration of indomethacin (229, 230). In a study of six patients with MIGET, however, this agent did not improve gas exchange or VA/Q distribution, and there was no change in cardiac output, systemic or pulmonary vascular resistance (59). Notwithstanding, this study investigated only the

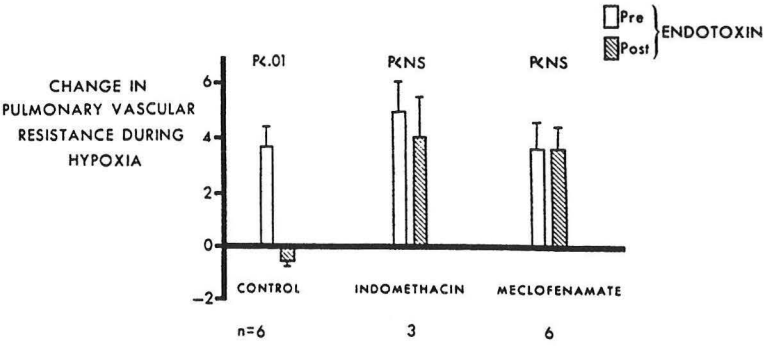
acute effects of intravenous indomethacin administration at 60 and 90 minutes post-infusion. It is possible that longer periods must elapse for accumulated intracellular stores of vasodilating purine nucleotides to decay. A single patient with severe HPS at this institution underwent a trial of indomethacin 50 mg p.o. t. i. d. with excellent results. The individual's pre-treatment arterial blood gas revealed a partially compensated but marked respiratory alkalosis and severe hypoxemia (7.46/20/63/97%, A-aDO_2 62 mm Hg). After two weeks of therapy with indomethacin, dramatic improvement was seen in the patient's gas exchange (ABG 7.44/29/92/98%, A-aDO_2 22 mm Hg). The patient also reported substantial relief of his exertional dyspnea. His oxygen saturation still fell with exercise, but remained $\geq$ 90%. Pre-treatment, desaturation to the low 80's was noted at a lower level of exertion.

FIGURE 18



(Figure 18). Effect of indomethacin on cardiac output, mean arterial pressure and peripheral vascular resistance in cirrhotics with portal hypertension.
From: Bruix et al. (185)

FIGURE 19



(Figure 19). The increase in pulmonary vascular resistance (mm Hg/L/min) seen during hypoxic breathing in dogs is eliminated by endotoxin infusion. Inhibition of prostaglandin synthesis by indomethacin or meclofenamate prevents loss of the hypoxic pressor response after endotoxin.
From: Alexander et al. (186)

Glucocorticoids, like dexamethasone have been shown to inhibit synthesis of the inducible calcium-independent NOS in vascular endothelium (204, 209), but no studies exist examining their efficacy in the HPS. In a single case report, methylene blue was

reported to temporarily reduce shunting and improve oxygenation in HPS (Table 9) (231). Methylene blue inhibits NO stimulation of soluble guanylate cyclase, blocking its vasodilatory effect. Interestingly, methylene blue has also been reported to increase systemic blood pressure in a patient with cirrhosis and hypotension that failed to respond to norepinephrine (232). Unfortunately, NO inhibition (at least inhibition of the constitutive NOS) may actually be associated with **increased** mortality in shock due to endotoxemia (209). Clearly, more must be learned about the specific NOS enzymes involved in the circulatory derangements of cirrhosis and the protective effects of NO before proceeding with human trials of selective NOS inhibitors (209, 233).

TABLE 9

Methylene Blue in a Patient with the Hepatopulmonary Syndrome

	Day 1 PaO_2 (mm Hg)		20 minutes after methylene blue		Day 2 PaO_2 (mm Hg)
	RA	100%	RA	100%	RA
Supine	62	325	70	480	60
Standing	56	115	68	390	53

Adapted from Rolla (231)

One cirrhotic individual elected to take a home remedy for her liver disease consisting of generous amounts of garlic powder (234). Pretreatment, her PaO_2 was 55 mm Hg on room air and 201 mm Hg while breathing 100% oxygen (25% shunt). After four months of "therapy", the PaO_2 on 100% O_2 was 547 mm Hg (shunt 8%). Oximetry on room air increased from 86% supine/82% sitting to 95%/90%. Allicin (allyl 2-propenethiosulfinate) may be the important biologically active compound in garlic. No untoward effects were reported (save for the smell), but as yet, no studies have been performed to assess the possible efficacy of such therapy.

Because estrogen levels are increased in cirrhotics with cutaneous spider nevi, and these are associated with the HPS, some investigators have hypothesized that there may be a role for estrogen blockade (e.g., tamoxifen therapy) in the treatment of HPS (6). No data exist to support or refute this concept.

Even plasma exchange has been attempted in the hepatopulmonary syndrome (70). If the high concentration of circulating vasodilators could be reduced by this method, perhaps improvement would be noted in VA/Q matching and oxygenation. Five patients with severe hypoxemia were studied following plasma exchanges on three successive days. No benefit was found.

Patients with HPS should be evaluated for both their need and response to supplemental oxygen. Indeed, all persons with advanced liver disease should have arterial blood gas determinations approximately every six months. Patients with arterial oxygen tensions below 70 mm Hg should be evaluated for further desaturation that may occur with exercise and sleep which might benefit from O_2 therapy. If high flow oxygen (i.e., in excess of four liters per minute) is required to maintain acceptable saturations, oxygen conserving pendants or reservoirs, or transtracheal O_2 delivery should be considered.

Nonpharmacologic Treatment of the Hepatopulmonary Syndrome

Three potential non-medical alternatives to treatment of severe hypoxemia in liver disease exist: angiographic coil embolization therapy, transjugular intrahepatic portosystemic shunt placement, and orthotopic liver transplantation. It has been suggested that failure to respond well to 100% O_2 (standing PaO_2 < 150-200 mm Hg) indicates a higher likelihood of identifying a type II pattern (discrete arteriovenous fistulas with true anatomic shunting) when arteriography is performed. If this pattern is identified, it is appropriate to proceed with coil embolization (235). Unlike the type I "spongy" pattern of vascular dilatations, type II lesions have not yet been demonstrated to resolve after OLT. Significant improvement in oxygenation may occur with vascular embolotherapy, although repeat procedures may be required (236). An attempt has been made to perform multiple embolizations in a patient with an advanced type I pattern on angiography with partial success (room air PaO_2 increased from 38 to 53 mm Hg) (237). Generally though, this therapy is reserved for type II abnormalities.

Transjugular intrahepatic portosystemic shunt (TIPS) is usually used to control variceal bleeding by reducing portal pressures, or as an adjunct to the management of refractory ascites (238-240). Two case reports suggest a possible role for TIPS in the treatment of severe hypoxemia due to HPS (241, 242). Allgaier and coworkers reported on a 22 year old with cirrhosis due to chronic Epstein Barr Virus infection and a resting PaO_2 of 45 mm Hg, positive CEE, and no evidence of lung disease. One month after TIPS, the room air PaO_2 was 79 mm Hg and follow-up ^{99m}Tc-MAA scanning revealed a reduction in intrapulmonary shunting from 34% (pre-stent) to 26% (242). A second report appeared in 1995 wherein TIPS was used as a bridge to OLT (241). TIPS greatly improved arterial oxygen tension while breathing 100% O_2 (Table 10) allowing transplantation to be performed on day 21 with a much greater margin of safety.

TABLE 10

Transjugular Intrahepatic Portosystemic Shunt in a Patient with the Hepatopulmonary Syndrome

	Pre-TIPS	Post-TIPS		
		Day 1	Day 7	Day 14
PaO_2 on room air (mm Hg)	45	43	47	56
PaO_2 on 100% O_2 (mm Hg)	123	105	152	442
Shunt fraction (% C.O.)	27%	28%	26%	11%

Adapted from Riegler (241)

It is unknown what fraction of patients might experience improved gas exchange with TIPS or the time course to maximal benefit. The mechanism itself is also unknown, but it is postulated that elevated sinusoidal pressures within the liver may trigger neural reflexes or altered hormone production, secretion or metabolism leading to worsening of the IPVD (241). Such mechanisms are believed to effect changes in renal perfusion (hepatorenal reflex) and splanchnic vasodilatation, and may initiate abnormal sodium and water retention leading to the development of ascites (243-247). Of course, if the major mechanism of IPVD development were related to increased shunting of vasoactive gastrointestinal peptides around the liver, TIPS or portocaval/spleno-renal shunting might be expected to worsen the intrapulmonary microcirculatory derangement. No evidence exists however, to suggest that HPS is more common or more severe in patients with portosystemic shunts.

Orthotopic Liver Transplantation for the Hepatopulmonary Syndrome

As recently as the mid 1980's, severe hypoxemia (PaO_2<50 mm Hg) due to intrapulmonary shunting was considered to be an absolute contraindication to liver transplantation (248-252). A variety of insults may conspire to cause oxygenation problems in the early postoperative period: large fluid shifts, renal dysfunction, capillary leak syndromes (including ARDS), bacterial infections, pleural effusions and atelectasis. While it had been previously demonstrated that the shunts due to IPVD will often resolve after transplantation, the time course to recovery is highly variable ranging from a few days to several weeks or even months. It was feared that inability to oxygenate these patients postoperatively would lead to more postoperative complications including graft dysfunction and a higher mortality. In 1994, Hobeika and coworkers reported their experience with nine HPS children (253). By three months post-op, five had a normal PaO_2 and demonstrated closure of intrapulmonary shunts by radionuclide scanning. The other four patients, three of which had pre-op arterial O_2 tensions less than 50 mm Hg, died: three from respiratory failure and one from primary graft nonfunction. Preoperative response to 100% O_2 did not predict outcome in this small series. The

early transplant experience in patients with HPS was frought with other complications including cerebral infarction due to air emboli from the donor liver passing through intrapulmonary shunts (254). This problem was rectified by modification of the original surgical technique.

Reports then began appearing in the literature indicating that even severely hypoxemic patients could be successfully transplanted (42, 58, 255). In one patient with a preoperative PaO_2 of 34 mm Hg (57 mm Hg on 100% O_2), no improvement in oxygenation was seen for three months after his transplant and this probably contributed to the development of a variety of postoperative complications including gastrointestinal bleeding, infections and renal failure (42). By 14 months, however, room air PaO_2 was 116 mm Hg (561 mm Hg on 100% O_2). Gradually, severe hypoxemia due to HPS became recognized as only a relative contraindication to OLT and patients with arterial O_2 tensions less than 70 mm Hg were accepted as long as they could be easily oxygenated on high inspired fractions of O_2 (70, 256).

In 1990, Gunnarson and colleagues indicated that the number of major complications associated with OLT and mortality (at three months) were not different in hypoxemic patients ($PaO_2 \leq 75$ mm Hg, n = 6) compared to normoxemic patients (n = 11). The median time on mechanical ventilation was three times longer in the hypoxemic group but this failed to reach statistical significance (257). Multiple reports and small series are now available which clearly support improvement in intrapulmonary shunting and oxygenation after transplantation (41, 43, 44, 58, 111, 253, 255, 258-261). Indeed, for some patients, transplantation has been performed primarily **because** of worsening hypoxemia (41-43, 58, 253, 255, 261). Advanced HPS, once an absolute contraindication to OLT, has itself become an occasional **indication** for transplant even in the presence of otherwise stable hepatocellular function. While it is true that not all patients improve after OLT (6, 68, 108, 252, 253, 262, 263), if those with type II angiograms and those that died in the early postoperative period (less than one month) are excluded, very few "nonresponders" remain. It must be remembered that even in patients who have a favorable response, several weeks may pass before significant improvement in oxygenation occurs. To call the reported early failures **true** failures may therefore be unjustified. Even patients without evidence of HPS may suffer profound oxygenation problems in the early period following OLT.

The time course to resolution of the HPS may depend on the nature of the principal gas exchange abnormality. Some speculate that those with high true shunt fractions (i.e., by MIGET) may take months for the hypoxemia to correct vs. days or weeks in the case of predominant ventilation-perfusion mismatching (264, 265). Of course, correction of IPVD is not the only variable. Liver transplantation usually is associated with a rapid rise in systemic vascular resistance and fall in cardiac output without much change in blood pressure (262, 266), but reversal of the hyperdynamic circulatory state of cirrhosis is not universal. Henderson and colleagues found that the mean cardiac output remained elevated and unchanged from pre-operative levels at one and two years post-OLT (267). It is notable, though, that pre-transplant hemodynamics were assessed by pulmonary artery catheterization with thermodilution

in this study, while at follow-up, radionuclide angiocardiography was utilized. In their 1996 review, Lange and Stoller discuss some possible predictors of reversibility for HPS after OLT including younger age, less severe preoperative hypoxemia, good response to breathing 100% oxygen and a type I pattern on angiography (264). Unfortunately, the data do not currently exist to validate the positive predictive value of any of these characteristics.

Krowka and colleagues recently published a comprehensive review of 81 patients with HPS who underwent liver transplantation **(See addendum 1)** (261). This included their own recent experience with three severely hypoxemic individuals who were successfully transplanted. The analysis was somewhat hindered by the lack of standardized testing preoperatively among different investigators with regard to the gas exchange deficits in these patients (i.e., arterial blood gas determinations in supine vs. upright positions, variable techniques for administering 100% O_2 and calculating shunt fraction, and absent preoperative room air PaO_2 measurements in 32 of 81 patients transplanted). Nevertheless, the analysis of available data by these authors has provided some valuable insights regarding the prognosis of patients who are candidates for OLT and the appropriate timing of the procedure. Seven of 23 patients (30%) with a room air $PaO_2 \leq$ 50 mm Hg expired within three months of OLT. The other 26 patients with reported preoperative arterial oxygen tensions had levels above 50 mm Hg, and only one (4%) died. This result was statistically significant ($p < 0.02$). Also, the mean PaO_2 for survivors was significantly higher than that of patients who died (54.2 ± 13.2 vs. 44.7 ± 7.7 mm Hg, $p < 0.03$). Overall, 66 of 81 patients (82%) demonstrated improvement in or resolution of the syndrome within 15 months of OLT. Although their mortality was higher, 70% of the patients with documented oxygen tensions below 50 mm Hg also recovered, and patients who demonstrated a supine $PaO_2 \geq 400$ mm Hg on 100% O_2 generally had limited morbidity. At this time, it is recommended that transplantation be offered to patients with deteriorating oxygenation before the room air PaO_2 decreases below 50 mm Hg (261).

Summary

The hepatopulmonary syndrome is caused by dilatation of the pulmonary microvasculature in advanced liver disease leading to hypoxemia. The phenomenon is most common and severe in patients with chronic hepatic disorders, especially cirrhosis, where perhaps one third of subjects are affected. Dyspnea, platypnea, digital clubbing, cutaneous spider nevi, a reduced DLCO and orthodeoxia are common clinical features. The diagnosis is confirmed when a liver patient with hypoxemia has intrapulmonary shunting identified by contrast-enhanced echocardiography or radionuclide perfusion scanning **(See addendum 2 for diagnostic algorithm)**. The structural alterations in the pulmonary vessels are probably induced by an excess of circulating or locally produced vasodilators, and possibly by neurohumoral reflexes triggered by portal and hepatic sinusoidal hypertension. Thus far, medical therapy has been disappointing, but the changes in HPS are known to be reversible. Additional studies focusing on the role of nitric oxide and vasodilating purine nucleotides may lead to more efficacious treatments in the future. The effect of corticosteroids and other

specific inhibitors of the inducible form of nitric oxide synthase should be evaluated for safety and efficacy (first in the rat model of HPS). Cyclooxygenase inhibitors also deserve additional study. Our one patient with severe hypoxemia experienced a reduction in A-aDO_2 of 40 mm Hg after just two weeks of therapy with indomethacin, suggesting a pathogenic role for excess vasodilating prostaglandins in this patient. It is also possible that decreasing prostacyclin levels by cyclooxygenase blockade lowered this patient's portal pressure. If portal and hepatic sinusoidal hypertension do trigger some sort of neurohumoral reflex affecting IPVD, this could be another reason for the successful outcome which was observed. For now, liver transplantation remains the only validated option for severely affected patients. Prospective, controlled trials of TIPS in patients with the hepatopulmonary syndrome will be required before this can be recommended as a viable alternative in severely affected patients who have no other immediate indication for transplantation.

Summary of Reported Cases of the Hepatopulmonary Syndrome and the Response to Orthotopic Liver Transplantation

Reference	Age (yr)	Diagnosis	Pao_2 (mm Hg) Room air	Pao_2 (mm Hg) 100% oxygen	Posttransplantation comments
Starzl et al[13]	19 mo	Hepatic carcinoma	Hemoglobin saturation—range, 85-88%	...	All alive at 96, 86, and 49 mo after transplantation; shunt, <15%
	20 mo	BA			
	13 mo	BA			
Sang Oh et al[14]	18	α_1-AT	43	80	No changes in massive shunt after 3 transplantations; died 3 mo after transplantation as a result of intracerebral bleeding
Stoller et al[15]	39	PBC	62	290	Wk 3—Pao_2, 567 on 100% oxygen; wk 52—Pao_2, 84 on room air
Eriksson et al,[16] patient 5	18	TYR	52	...	Mo 2—shunt <1%
Mews et al[17]	12	Wilson's disease	48	95	Sustained, severe hypoxemia with multiorgan failure; MV, 10 days; died 10 days after transplantation
McCloskey et al[18]	16	CRC	40	115	Mo 9—Pao_2, 79 on room air
Dimand et al[19]	13	Cirrhosis	44	194	Wk 12—Pao_2, 70 on room air and 305 on 100% oxygen
	53	Cirrhosis	46	455	Wk 12—Pao_2, 100 on room air
	17	PVT	61	217	Wk 12—Pao_2, 69 on room air and 540 on 100% oxygen
Laberge et al[20]	14	BA	53	340	Mo 9—Pao_2, 96 on room air
	11	BA	51	127	Mo 5—no shunt; saturation, 98% on room air; MV, 17 days
Itasaka et al[21]	13	CRC	42	417	Day 36—transient deterioration; wk 23—hemoglobin saturation, 96%; shunt <1%
Schwarzenberg et al[22]	18	α_1-AT	35	69	Day 5—PVT developed and thus second transplantation was done; 15 days later, intracranial bleeding occurred; MV, 1 mo; Pao_2—no change for 3 mo; mo 14—Pao_2, 114 on room air and 561 on 100% oxygen
Scott et al[23]	38	CRC	35	350	MV, 66 days
	63	CRC	65	389	No oxygen needed after transplantation
	52	CRC	51	446	Shunt improved after transplantation; MV, 27 days
	51	CRC	71	425	No oxygen needed after transplantation
	55	ETOH	63	460	Shunt improved after transplantation; MV, 77 days
	51	ETOH	66	445	No oxygen needed after transplantation
Van Obbergh et al[24]	2	BA	63	186	Wk 6—Pao_2, 89 on room air and 436 on 100% oxygen
	10	BA	40	72	Wk 64—Pao_2, 121 on room air and 535 on 100% oxygen
	7	CRC	36	65	Wk 29—Pao_2, 87 on room air and 443 on 100% oxygen
Caldwell et al[25]	15	Histiocytosis X	55	...	Mo 6—Pao_2, 71 on room air
Hobeika et al[26]	28 mo	BA	48	196	Worsening hypoxemia despite 100% oxygen; died 4 days after transplantation
	...	TYR	58	487	Worsening hypoxemia despite 100% oxygen; died 20 days after transplantation
	...	NHP	56	314	Mo 3—Pao_2, 90 on room air; MV, 7 days
	...	BA	45	...	Worsening hypoxemia despite 100% oxygen; died 35 days after transplantation
	...	AIH	47	400	Primary graft nonfunction; died 10 days after transplantation
	...	PSC	75	300	Mo 8—Pao_2, 100 on room air
	...	BA	65	375	Mo 3—Pao_2, 95 on room air
	...	α_1-AT	78	275	Mo 6—Pao_2, 95 on room air; MV, 19 days
	...	BA	60	197	Mo 3—Pao_2, 90 on room air; MV, 4 days
Fewtrell et al[27]	6 mo	BA	72	...	Alive 3 yr after transplantation
	11	BA	86% saturation	...	Wk 13—shunt 37%
	8.5	BA	60	...	Alive 4 yr after transplantation
	2.5 mo	BA	42	...	Wk 4—shunt, 2.7%; MV, 21 days
	2.5	BA	80% saturation	...	Wk 32—shunt, 6%; MV, 48 days
	9.8	BA	80% saturation	...	Wk 20—shunt, 2%
	9 mo	BA	85% saturation	...	Wk 16—shunt, 2%; MV, 30 days
	3.5	BA	82% saturation	...	MV, 11 days; died 2 days after second transplantation (6 mo after first)

Summary of Reported Cases of the Hepatopulmonary Syndrome and the Response to Orthotopic Liver Transplantation

Reference	Age (yr)	Diagnosis	Pao_2 (mm Hg) Room air	Pao_2 (mm Hg) 100% oxygen	Posttransplantation comments
Stoller et al[28]	5	CRC	36	...	All improved within 1-8 mo; shunts, 3.5-5.0%
	52	ETOH	43	...	
	39	CAH	45 (on oxygen)	...	
Cremona et al[29]	...	...	64	...	Mo 3—normal oxygenation
Riegler et al[30]	58	HEM	56	442	Pao_2 improved after TIPS; oxygenation normal after transplantation
Rodriguez-Roisin & Krowka[31]	41	...	41	...	Oxygenation improved after transplantation
Scott et al[32]	16 adult patients	...	Range—29-86	...	Duration of hospitalization, 4-120 days; refractory hypoxemia; 1 patient died after transplantation
Bynon et al[33]	6 pediatric patients	...	Range—39-64	...	1 patient died 25 days after transplantation as a result of graft rejection and pulmonary sepsis
Petruff et al[34]	47	ETOH	51	588	Mo 7—Pao_2, 87
Mayo Clinic cases					
Unpublished	47‡	PSC	65, supine	535	Mo 12—Pao_2, 81 while standing
			61, standing	458	
	53‡	ETOH	44, supine	301	Only pretransplantation evaluation at Mayo; multiple intracerebral bleeding sites; oxygenation was satisfactory with tracheostomy; died 28 days after transplantation performed elsewhere
			36, standing	211	
Krowka et al,[11] patient 11	37‡	ETOH	47, supine	431	Only pretransplantation evaluation at Mayo; bilateral pulmonary infiltrates; died 2 mo after transplantation performed elsewhere; no autopsy done
			33, standing	407	
patient 18	27‡	Wilson's disease	93	...	Subclinical HPS; mo 2—Pao_2, 81
Poterucha et al[35]	38‡	AIH	63, supine	313	Mo 7—coil embolotherapy; mo 12—normal Pao_2; MV, 4 days
			45, standing	70	
Current cases	28	CAH	60, supine	550	See text for details
			50, standing	522	
	47	CRC	50, supine	465	
			44, standing	374	
	23	STE	60, supine	481	
			53, standing	346	
			42, exercising	...	

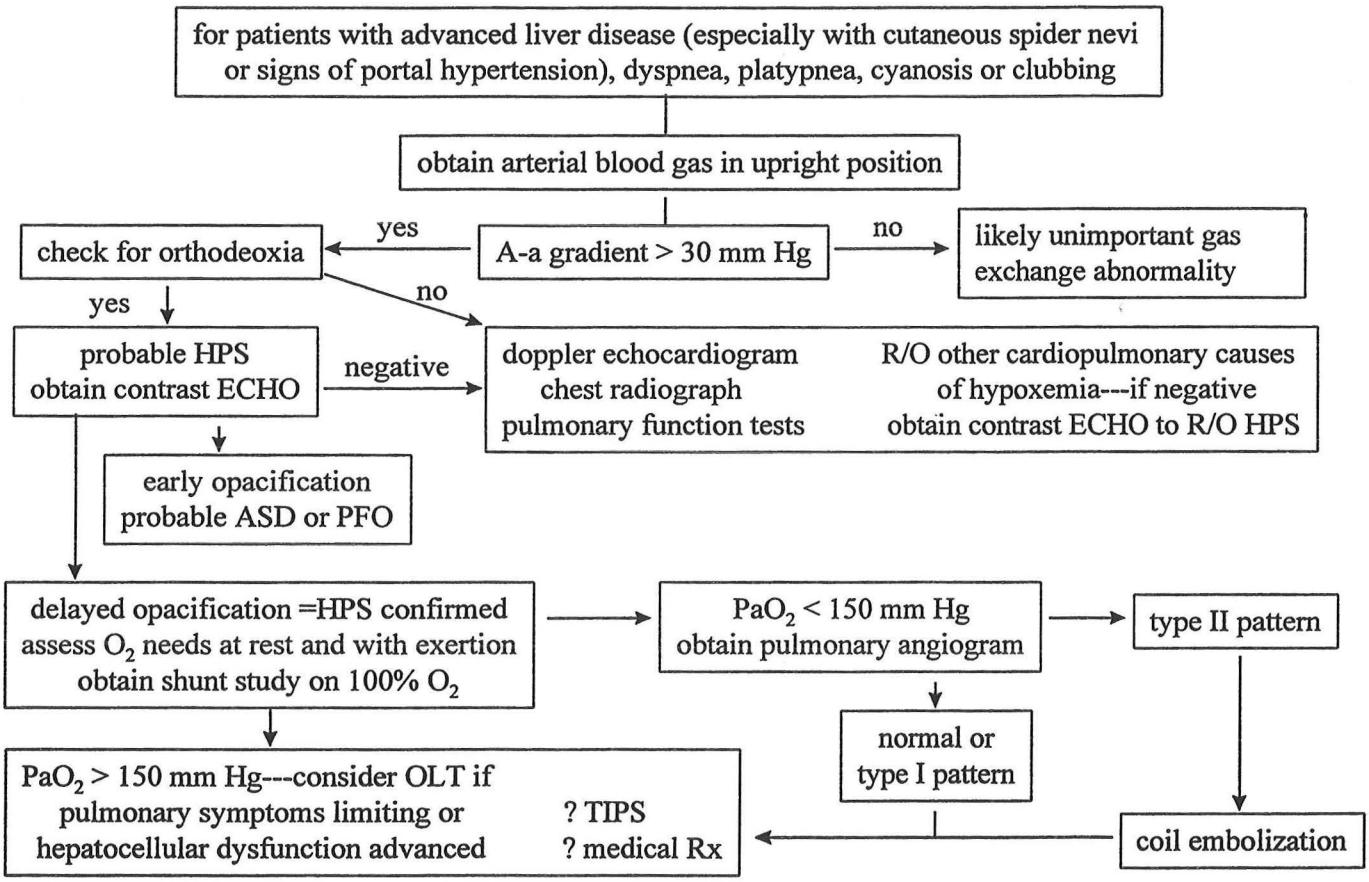
*In addition to these cases, Shaw et al[12] described two patients with refractory hypoxemia who died after transplantation. No other details were provided.

†AIH = autoimmune hepatitis; α_1-AT = α_1-antitrypsin deficiency; BA = biliary atresia; CAH = chronic active hepatitis; CRC = cryptogenic cirrhosis; ETOH = alcoholic cirrhosis; HEM = hemochromatosis; HPS = hepatopulmonary syndrome; MV = mechanical ventilation; NHP = nodular hyperplasia; Pao_2 = arterial oxygen tension; PBC = primary biliary cirrhosis; PSC = primary sclerosing cholangitis; PVT = portal vein thrombosis; STE = steatohepatitis-cirrhosis; TIPS = transjugular intrahepatic portosystemic shunt; TYR = tyrosinemia.

‡Patients underwent liver transplantation because of deteriorating hepatic dysfunction; HPS was not considered a contraindication to transplantation.

ADDENDUM 2

Hypoxemia in Liver Disease
Diagnostic Algorithm



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