REVIEW ARTICLE

CURRENT CONCEPTS

Hepatopulmonary Syndrome — A Liver-Induced Lung Vascular Disorder

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THE HEPATOPULMONARY SYNDROME IS CHARACTERIZED BY A DEFECT IN arterial oxygenation induced by pulmonary vascular dilatation in the setting of liver disease[1]; patients of all ages can be affected. This clinical syndrome has three components: liver disease, pulmonary vascular dilatation, and a defect in oxygenation. A classification of the severity of the hepatopulmonary syndrome based on abnormalities in oxygenation is vital because severity influences survival and is useful in determining the timing and risks of liver transplantation (Table 1). The vascular component includes diffuse or localized dilated pulmonary capillaries and, less commonly, pleural and pulmonary arteriovenous communications. Arterial hypoxemia is common in the context of hepatic disease; its cause is often multifactorial (e.g., ascites, hepatic hydrothorax, and chronic obstructive pulmonary disease in patients with alcoholism), and in the particular case of the hepatopulmonary syndrome, the pathophysiological features are unique. The definition of arterial hypoxemia associated with the hepatopulmonary syndrome is based on measurements of the partial pressure of oxygen that are performed with the patient in a standardized position, preferably sitting and at rest. The use of the more sensitive alveolar–arterial oxygen gradient is important because it can increase abnormally before the partial pressure of oxygen itself becomes abnormally low as the gradient measure compensates for the reduced levels of arterial carbon dioxide and hyperventilation, along with respiratory alkalosis, that are common in cirrhosis (Table 1).[2]

Contrast-enhanced transthoracic echocardiography with saline (shaken to produce microbubbles >10 μm in diameter) is the most practical method to detect pulmonary vascular dilatation (Fig. 1).[3,4] After the administration of agitated saline in a peripheral vein in the arm, microbubble opacification of the left atrium within three to six cardiac cycles after right-atrial opacification indicates microbubble passage through an abnormally dilated vascular bed; microbubbles do not pass through normal capillaries (normal range of the capillary diameter, <8 to 15 μm). This qualitative approach is more sensitive and less invasive than the injection of technetium-99m–labeled macroaggregated albumin in the peripheral vein for lung scanning[4,5] with quantitative uptake in the brain (Fig. 2). However, neither method can be used to discern discrete arteriovenous communications from diffuse precapillary and capillary dilatations or intracardiac shunt. The former distinction can be made by means of pulmonary angiography. The latter distinction can be made by means of transesophageal contrast-enhanced echocardiography that directly reveals the intraatrial septum, identifies the existence of an intraatrial right-to-left shunt, and shows the passage of microbubbles entering the left atrium through the atrial septal abnormality or pulmonary veins. In patients with the hepatopulmonary syndrome, pulmonary angiography should be performed only when the hypoxemia is severe (i.e., the partial pressure of oxygen is <60 mm Hg [8.0 kPa]), poorly responsive to administration of 100% oxygen, and when there is a strong suspicion (on the basis of a chest com-

Table 1. Diagnostic Criteria for the Hepatopulmonary Syndrome.*

Variable	Criterion
Oxygenation defect	Partial pressure of oxygen <80 mm Hg or alveolar–arterial oxygen gradient ≥15 mm Hg while breathing ambient air
Pulmonary vascular dilatation	Positive findings on contrast-enhanced echocardiography or abnormal uptake in the brain (>6%) with radioactive lung-perfusion scanning
Liver disease	Portal hypertension (most common) with or without cirrhosis
Degree of severity†	
Mild	Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen ≥80 mm Hg
Moderate	Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen ≥60 to <80 mm Hg
Severe	Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen ≥50 to <60 mm Hg
Very severe	Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen <50 mm Hg (<300 mm Hg while the patient is breathing 100% oxygen)

* All criteria were determined by means of positive contrast-enhanced echocardiography (i.e., microbubble opacification of the left heart chambers three to six cycles after right atrial passage). The abbreviated formula for the alveolar–arterial gradient is as follows:

$$P_AO_2 - PaO_2 = (F_IO_2 [P_{atm} - PH_2O] - [PaCO_2/0.8]) - PaO_2,$$

where P_AO_2 denotes partial pressure of alveolar oxygen, PaO_2 partial pressure of arterial oxygen, F_IO_2 fraction of inspired oxygen, P_{atm} atmospheric pressure, PH_2O partial pressure of water vapor at body temperature, and $PaCO_2$ partial pressure of arterial carbon dioxide (0.8 corresponds to the standard gas-exchange respiratory ratio at rest); the normal range is 4 to 8 mm Hg (0.5 to 1.1 kPa). The normal range for the partial pressure of oxygen is 80 to 100 mm Hg (10.7 to 13.3 kPa) at sea level, while the patient is at rest and breathing ambient air. For patients older than 64 years of age, a value of ≤70 mm Hg (9.3 kPa) for PaO_2 or ≥20 mm Hg for the alveolar-arterial gradient is often used. Ambient air is the respired gas unless otherwise indicated. To convert millimeters of mercury to kilopascals, multiply by 0.133.
† Data are from Rodríguez-Roisin et al.[1]

puted tomographic scan) of direct arteriovenous communications that would be amenable to embolization.[6]

CLINICAL MANIFESTATIONS

Dyspnea on exertion, at rest, or both is the predominant presenting symptom, usually after years of liver disease. However, dyspnea is a nonspecific finding that is common in patients with advanced liver diseases because of the range of hepatic complications such as anemia, ascites and fluid retention, and muscle wasting. There are no signs, symptoms, or hallmarks of the hepatopulmonary syndrome on physical examination. However, the presence of spider nevi, digital clubbing, cyanosis, and severe hypoxemia (partial pressure of oxygen, <60 mm Hg) strongly suggests hepatopulmonary syndrome (Fig. 3).[1] If the partial pressure of oxygen in arterial blood decreases by 5% or more or by 4 mm Hg (0.5 kPa) or more when the patient moves from a supine to an upright position (called orthodeoxia), he or she may describe worsening dyspnea (platypnea) related to further ventilation–

perfusion mismatch.[7] The chest radiograph is frequently nonspecific, perhaps suggesting a mild interstitial pattern in the lower lung that may reflect the existence of diffuse pulmonary vascular dilatation. Portopulmonary hypertension, which is sometimes associated with mild hypoxemia but rarely with severe hypoxemia, is frequently confused with the hepatopulmonary syndrome.[8] In portopulmonary hypertension, obstruction of flow to the pulmonary arterial bed is caused by vasoconstriction, as well as proliferation of the endothelium and smooth muscle, in situ thrombosis, and plexogenic arteriopathy. Increasing pulmonary vascular resistance to flow leads to right heart failure and death.[1] The diagnosis is made by means of right heart catheterization and according to pulmonary hemodynamic criteria (Table 2).

A decrease in the single-breath diffusing capacity for carbon monoxide is the only routine pulmonary-function test that is consistently abnormal result in patients with the hepatopulmonary syndrome.[9] However, low diffusing capacity is not specific[10] and may not normalize (as do other gas-exchange indexes) after liver transplantation,[11,12]
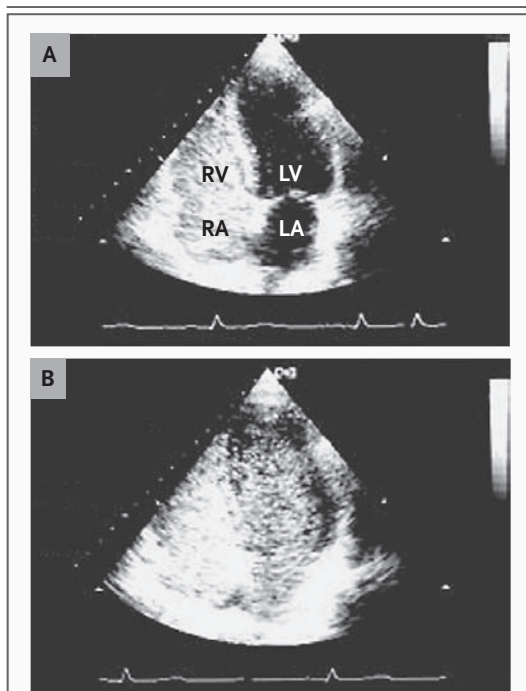
Figure 1. Transthoracic Echocardiographic Features of the Hepatopulmonary Syndrome.

The contrast-enhanced echocardiograms in Panels A and B show opacification of the right atrium (RA) and right ventricle (RV) with microbubbles and delayed opacification of the left atrium (LA) and left ventricle (LV), respectively. These findings are the standard for the diagnosis of the hepatopulmonary syndrome. A video showing the appearance of microbubbles in the right heart, followed by a delayed appearance of microbubbles (approximately five cardiac cycles later) in the left cardiac chambers, is available with the full text of this article at www.nejm.org.

suggesting structural remodeling of the pulmonary vasculature.[13]

Any acute or chronic form of liver disease can coexist with hypoxemia due to pulmonary vascular dilatation; thus, portal hypertension is not required for the syndrome to be manifested. Most cases of the hepatopulmonary syndrome are associated with clinical evidence of cirrhotic and noncirrhotic portal hypertension (e.g., gastroesophageal varices, splenomegaly, or ascites). Less appreciated is the fact that the criteria for the hepatopulmonary syndrome have been met in patients with acute liver failure and ischemic hepatitis.[14] There is no relationship between the presence or severity of the hepatopulmonary syndrome and the severity of liver disease as assessed on the basis of the Child–Turcotte–Pugh classification or the Model for End-Stage Liver Disease (MELD).[15]

Advanced liver disease associated with several pulmonary complications, pleural complications, or both (Table 3) is part of the differential diagnosis of the hepatopulmonary syndrome. Fortunately, the use of qualitative echocardiography, lung-scanning quantification with uptake in the brain, or both can distinguish hypoxemia induced by the hepatopulmonary syndrome from all other causes of hypoxemia.[5] Clinical judgment may still be necessary, however, to unravel the severity of hypoxemia in the hepatopulmonary syndrome and in coexisting pulmonary conditions such as chronic obstructive pulmonary disease or pulmonary fibrosis; these conditions occur in up to 30% of patients with the hepatopulmonary syndrome.[16]

The Rendu–Osler–Weber syndrome (also called hereditary hemorrhagic telangiectasia) and consequences of cavopulmonary anastomoses after operations for various congenital heart conditions[17] also resemble the hepatopulmonary syndrome (Table 2). Both can be associated with severe hypoxemia caused by pulmonary vascular dilatation, which may be diffuse or discrete in nature.

PREVALENCE AND NATURAL HISTORY

The term "hepatopulmonary syndrome," which was probably coined in 1977,[18] was preceded by compelling descriptions based on autopsy and clinical findings.[19-21] An autopsy study in patients with liver cirrhosis, reported in 1966 by Berthelot et al.,[21] first suggested that marked pulmonary vascular dilatation may play a role in this condition.[1]

Data from liver-transplantation centers indicate that the prevalence of the hepatopulmonary syndrome, including that involving mild stages (Table 1), ranges from 5 to 32%.[22] No prospective, multicenter prevalence studies have been reported to date. The range in prevalence is primarily a function of varying cutoffs for the abnormal alveolar–arterial gradient and partial pressure of oxygen that are used to define gas-exchange abnormalities.[22] A task force has recommended criteria that are reasonable from a clinical perspective for the alveolar–arterial gradient and the partial pressure of oxygen in patients of all ages (Table 1).[1]

The natural history of the hepatopulmonary syndrome can be described by the assessment of
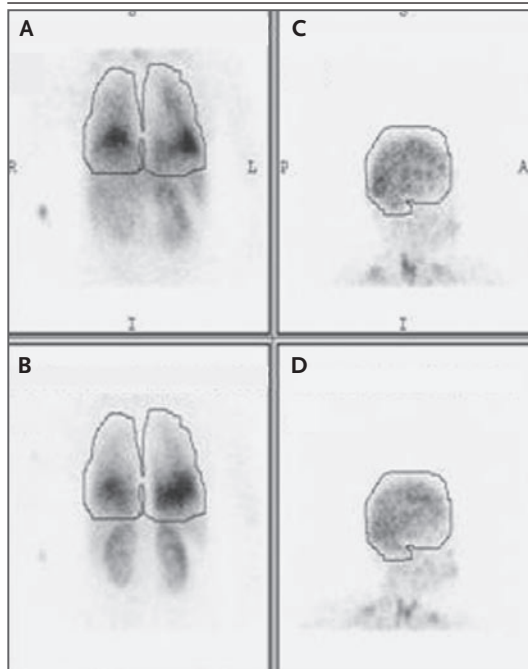
Figure 2. Findings of Hepatopulmonary Syndrome on Lung and Brain Scans.

An alternative to echocardiographic studies for the diagnosis of the hepatopulmonary syndrome is the use of technetium-99m–labeled macroaggregated albumin for lung scanning with uptake in the brain. Panel A shows radioactivity in the anterior lungs, and Panel B radioactivity in the posterior lungs, as well as the kidneys. Panel C shows radioactivity in the right side of the cerebrum, and Panel D radioactivity in the left side of the cerebrum (uptake in the brain, 62%; normal uptake, <6%).[5]

Figure 3. Clinical Features of Severe Hepatopulmonary Syndrome in a 38-Year-Old Man.

This patient has physical traits of cirrhosis and characteristic pulmonary signs and symptoms of the hepatopulmonary syndrome, including cyanosis, finger clubbing, and severe hypoxemia with orthodeoxia (i.e., increased hypoxemia when the patient moves from a supine to an upright position). He requires continuous oxygen therapy through a transtracheal catheter.

survival among patients in two distinct cohorts: patients being considered for liver transplantation and those who are not candidates for this approach because of age or coexisting conditions.[23] Studies have shown a median survival of 24 months and a 5-year survival rate of 23% among 37 patients who were not candidates for liver transplantation; in contrast, a control group of patients without the hepatopulmonary syndrome who did not undergo transplantation and who were matched for the cause and severity of liver disease according to the Child classification, age, and MELD score, had a median survival of 87 months, with a 5-year survival rate of 63%.[15] Survival was significantly worse among patients with a partial pressure of oxygen of less than 50 mm Hg (6.7 kPa) at the time of diagnosis. These data are consistent with findings from a recent study indicating that the coexistence of the hepatopulmonary syndrome worsened the prognosis for patients with cirrhosis, even after adjustment for the Child classification of liver disease.[24] The causes of death associated with the hepatopulmonary syndrome are usually multifactorial and related primarily to the complications of hepatic disease. It is rare for severe hypoxemic respiratory failure to be the primary cause of death.

PATHOBIOLOGY

The unique striking pathological feature of hepatopulmonary syndrome is gross dilatation of the pulmonary precapillary and capillary vessels (to 15 to 100 μm in diameter when the patient is at rest), coupled with an absolute increase in the number of dilated vessels visualized by means of injection at autopsy. In addition, a few pleural and pulmonary arteriovenous communications (shunts) and portopulmonary venous anastomoses can be seen.[21] The increased wall thickness of small veins and capillary walls has also been observed.[13] However, before the current definition of the syndrome and the availability of imaging techniques to identify pulmonary vascular dilatation, these findings were documented after death in patients with liver cirrhosis and various degrees of hypoxemia. Furthermore, the pulmonary vasculature in hepatic

Table 2. Differential Diagnosis and Treatment of Pulmonary Vascular Disorders Associated with Hepatic Abnormalities.*

Variable	Hepato-pulmonary Syndrome	Hereditary Hemorrhagic Telangiectasia	Cavo-pulmonary Anastomosis	Porto-pulmonary Hypertension
Type of disorder				
Inherited	No	Yes	No	No
Acquired	Yes	No	Yes	Yes
Presentation				
Pediatric	Yes	Yes	Yes	Yes
Adult	Yes	Yes	No	Yes
Documented genetic predisposition (familial with genetic polymorphisms)	No	Yes	No	No
Vascular dilatation				
Diffuse	Yes	In rare cases	Yes	In rare cases
Discrete	In rare cases	Yes	Yes	No
Detection of lung abnormalities on contrast-enhanced echocardiography	Yes	Yes	Yes	Yes
Severe hypoxemia (PaO$_2$ <50 mm Hg [6.7 kPa])	Yes	Yes	Yes	In rare cases
Normalization of hypoxemia on breathing 100% oxygen	Yes	No	No	Yes
Right heart catheterization and pulmonary angiography usually necessary				
Diagnosis	In highly selected cases	Yes	Yes	Yes
Management	No	Yes	Rare	Yes
Treatment				
Embolotherapy	In rare cases	Yes	Yes	No
Liver transplantation	Yes	In highly selected cases	No	In highly selected cases
Redirection of hepatic-vein flow	No	No	Yes	No
Pulmonary vasodilator therapy	No	No	No	Yes

* PaO$_2$ denotes partial pressure of arterial oxygen.

cirrhosis is characterized by the paradoxical combination of reduced or absent tone and some degree of inhibition of hypoxic pulmonary vasoconstriction.[25]

The prerequisite of pulmonary vascular dilatation facilitates the passage of mixed venous blood either rapidly or even directly, through intrapulmonary shunt, into the pulmonary veins. The defect in oxygenation is due to a ventilation–perfusion mismatch characterized by increased blood flow while alveolar ventilation is uniformly preserved (Fig. 4), and in 30% of patients with cirrhosis, this blood flow is enhanced by the absence or impairment of hypoxic pulmonary vasoconstric-

tion.[25] The severity of hypoxemia appears to be directly related to the extent of intrapulmonary shunt, diffusion–perfusion impairment, or both; in contrast, the role of portopulmonary vascular communications is marginal.[9,26-28] Ventilation–perfusion mismatch and shunt worsening constitute the key mechanisms of orthodeoxia in the hepatopulmonary syndrome, probably because of a more rigid and fixed pulmonary vascular tone, which is less liable to proportionately accommodate gravitational blood-flow changes to ventilation in dependent alveolar units.[7] An increase in the partial pressure of oxygen to the breathing of 100% oxygen (≥300 mm Hg [40.0 kPa])

Table 3. Major Pulmonary Consequences in Patients with Advanced, Nonmalignant Liver Disorders.

Location of Disorder	Consequences
Parenchyma	Lymphocytic or organizing pneumonitis (especially primary biliary cirrhosis), or both; panacinar emphysema (severe alpha$_1$-antitrypsin deficiency); aspiration pneumonitis (due to hepatic encephalopathy)
Pleura or diaphragm	Hepatic hydrothorax (with or without ascites), chylothorax, pulmonary-function effect of massive ascites
Pulmonary vasculature	Hepatopulmonary syndrome, portopulmonary hypertension

often occurs in the hepatopulmonary syndrome.[29] This response may be increased by an elevated cardiac output, indicating the complexity of gas-exchange abnormalities. An alveolar–capillary diffusion limitation to oxygen, essentially reflecting a diffusion–perfusion defect,[30] predominates in advanced stages of the syndrome. These advanced stages aggravated by a high cardiac output resulting in a shorter transit time of red cells, are akin to a low diffusing capacity associated with hepatic dysfunction in general[10] and with the hepatopulmonary syndrome in particular.[9] The diffusing capacity may be reduced because the alveolar–capillary interface is too wide to allow for complete equilibration of carbon monoxide with hemoglobin.

Early, mild stages of the hepatopulmonary syndrome, characterized by an elevated alveolar–arterial gradient alone or a partial pressure of oxygen between 60 mm Hg and 80 mm Hg (10.7 kPa) while the patient is respiring ambient air are caused by ventilation–perfusion mismatch with or without modest shunt (<10%), whereas later, severe hepatopulmonary syndrome (partial pressure of oxygen, <60 mm Hg) may encompass all intrapulmonary determinants of abnormal gas exchange (Table 1).[1] Arterial deoxygenation may also be reduced by hyperventilation, which increases the alveolar partial pressure of oxygen, and high cardiac output, which raises the mixed venous partial pressure of oxygen.

The correlation between the degree of hepatic dysfunction and portal hypertension and the prevalence and severity of the hepatopulmonary syndrome remains controversial. Rare congenital cardiac disorders without liver injury in which either

hepatic venous blood flow does not reach the lung[31] or portal venous blood reaches the inferior vena cava without passing through the liver (i.e., the type 1 Abernethy malformation)[32] have clinical similarities to the hepatopulmonary syndrome; this provides support for the hypothesis that blood from the gut must cross the liver to prevent pulmonary vascular dilatation.

Enhanced pulmonary production of nitric oxide has been implicated as a key priming factor for the development of pulmonary vascular dilatation,[33] but its relationship to the presence of portal hypertension, the hyperdynamic circulatory state, and the degree of liver injury remains unsettled. Although the levels of nitric oxide in exhaled air are increased, which is consistent with pulmonary overproduction, in the hepatopulmonary syndrome, there is normalization after liver transplantation.[33] The use of nitric oxide inhibitors to treat the condition has had discrepant results. Methylene blue, an inhibitor of the soluble guanylate cyclase and cyclic guanosine monophosphate pathway, transiently improved arterial oxygenation,[34] whereas N^G-nitro-L-arginine methyl ester, through inhibition of nitric oxide synthase by competition with substrate, did not influence gas-exchange abnormalities in a wide spectrum of patients with the hepatopulmonary syndrome.[35] In studies of the hepatopulmonary syndrome, pulmonary microvascular endothelial changes appeared to be induced by increased endothelial nitric oxide synthase–derived nitric oxide production as well as by enhanced expression of inducible nitric oxide synthase and activity in intravascular macrophages.[36] Likewise, increased biliary production and the release of endothelin-1 and the enhanced expression of pulmonary vascular endothelin-B receptors, leading to endothelin-1–mediated endothelial nitric oxide synthase–derived nitric oxide overproduction, have been reported.[37] In this context, norfloxacin decreased macrophage accumulation and normalized inducible nitric oxide synthase,[38] a finding that supports the role of bacterial translocation in pulmonary macrophage accumulation and its contribution to pulmonary vascular dilatation. Similarly, experimental studies in which development of the hepatopulmonary syndrome was prevented by pentoxifylline, an inhibitor of the production of tumor necrosis factor α,[39,40] suggest a pathogenetic role of this mediator in the hepatopulmonary syndrome. Other molecular vasodilating effects through nitric
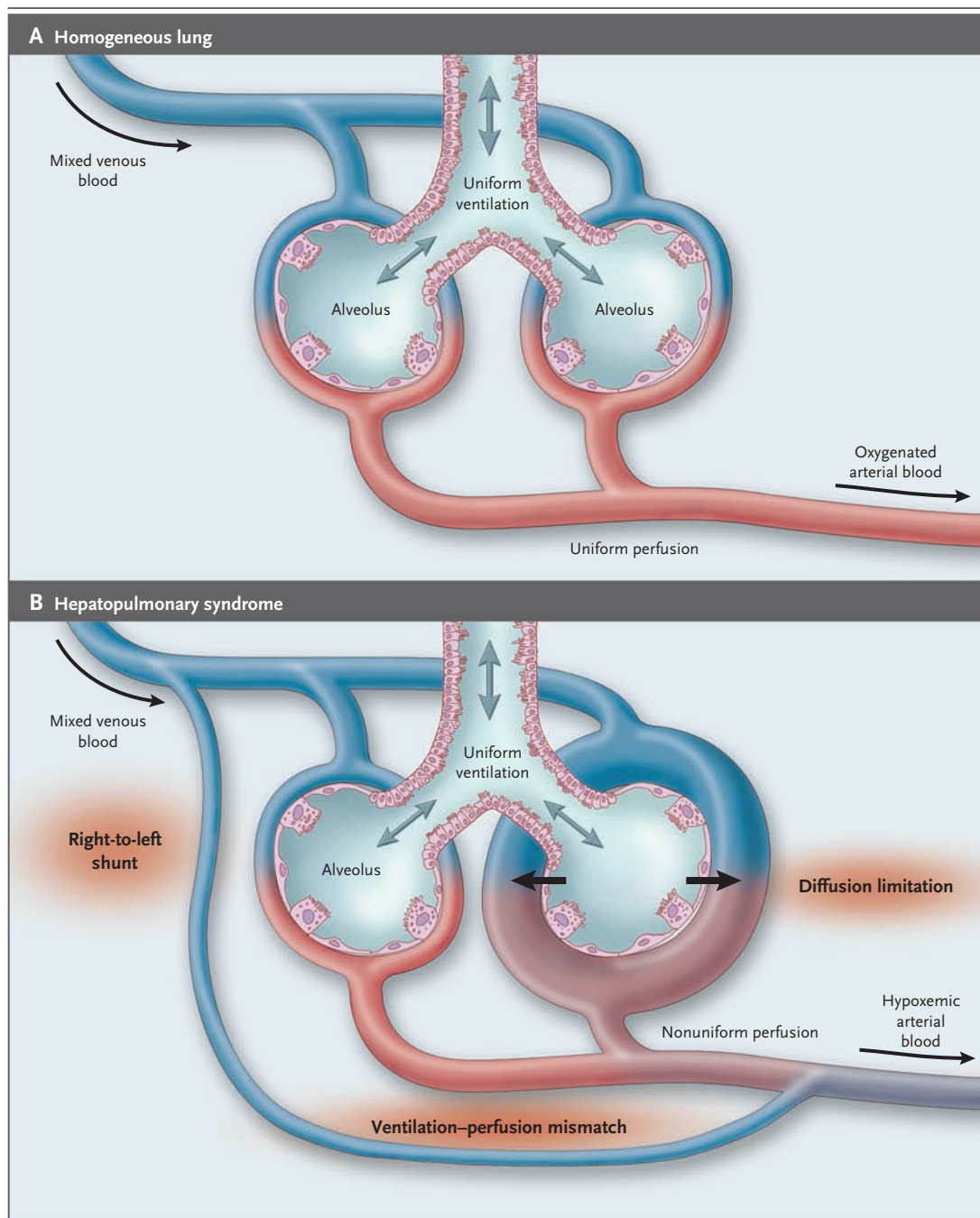
Figure 4. Mechanisms of Arterial Hypoxemia in the Hepatopulmonary Syndrome in a Two-Compartment Model of Gas Exchange in the Lung.

In a homogeneous lung with uniform alveolar ventilation and pulmonary blood flow in a healthy person (Panel A), the diameter of the capillary ranges between 8 and 15 μm, oxygen diffuses properly into the vessel, and ventilation–perfusion is well balanced. In patients with the hepatopulmonary syndrome (Panel B), many capillaries are dilated, and blood flow is not uniform. Ventilation–perfusion mismatch emerges as the predominant mechanism, irrespective of the degree of clinical severity, either with or without intrapulmonary shunt, and coexists with restricted oxygen diffusion into the center of the dilated capillaries in the most advanced stages (bold arrows).

oxide–independent molecular mechanisms have also been described; these include enzymatic carbon monoxide production by increased expression of heme oxygenase-1[41,42] and stimulation of calcium-activated potassium channels by endothelial-derived hyperpolarizing factor.[43] The correlation between the partial pressure of oxygen and carboxyhemoglobin in patients with the hepatopulmonary syndrome points to the potential influence of increased carbon monoxide production in abnormal gas exchange.[44]

TREATMENT

Currently, no effective medical therapies for the hepatopulmonary syndrome exist, and liver transplantation is the only successful treatment.[45] However, both postoperative mortality and the interval between transplantation and the resolution of arterial hypoxemia have been shown to be increased in patients with severe pretransplantation hypoxemia due to this syndrome.[46] In the largest single-institution series, patients with the hepatopulmonary syndrome had a 5-year survival rate of 76% after liver transplantation, a rate not significantly different from that among patients without the hepatopulmonary syndrome who underwent transplantation.[15] The strongest predictor of death was a preoperative partial pressure of oxygen of 50 mm Hg or less and a lung scan with brain uptake of 20% or more.[47] Because of the poor outcome without liver transplantation, the diagnosis of the hepatopulmonary syndrome associated with a partial pressure of oxygen of less than 60 mm Hg is considered to be an indication for liver transplantation, and patients with this syndrome are given a higher priority for transplantation than patients with other disorders.[48]

Spontaneous resolution of the hepatopulmonary syndrome and the development of portopulmonary hypertension before or after liver transplantation for the hepatopulmonary syndrome is uncommon.[1] In contrast, data from several uncontrolled trials and anecdotal evidence indicate that treatment with almitrine, antibiotics, beta-blockers, cyclooxygenase inhibitors, garlic preparation, systemic glucocorticoids and cyclophosphamide, inhaled nitric oxide, nitric oxide inhibitors, and somatostatin has been uniformly unsuccessful.[1] Long-term oxygen therapy remains the most frequently recommended therapy for symptoms in patients with severe hypoxemia, although compliance with this treatment and its efficacy and cost–benefit value remain unsettled.

A few additional unproven therapeutic alternatives with uncertain results have been recommended. The use of a transjugular intrahepatic portosystemic shunt[49] has been proposed to reduce portal pressure in patients with the hepatopulmonary syndrome. However, the limited available data, along with the risk of exacerbating the hyperkinetic circulatory state, thereby enhancing pulmonary vasodilatation and increasing the severity of the hepatopulmonary syndrome, do not provide support for its use as a palliative strategy. Cavoplasty has been shown to be an effective treatment for the hepatopulmonary syndrome when it is associated with the Budd–Chiari syndrome.[50] In a single case report, coil embolization (embolotherapy) in the rare context of angiographic arteriovenous communications has been shown to improve arterial oxygenation temporarily.[6]

In summary, screening for the hepatopulmonary syndrome with the use of arterial blood gases is recommended in patients with chronic liver disease who report dyspnea or who are candidates for liver transplantation. Future research should address the genetic polymorphisms associated with the hepatopulmonary syndrome, circulating factors emanating from the hepatic veins that may affect the pulmonary vascular tone, and angiogenic factors (including, among the most relevant factors, endothelin-1, vascular endothelial growth factor, and platelet-derived growth factor). Hepatic explants from patients with the hepatopulmonary syndrome who undergo liver transplantation should be examined for biomarker sentinel clinical correlates that could lead to effective medical interventions. Finally, the question of which patients with the hepatopulmonary syndrome should receive a high priority for liver transplantation should be answered on the basis of long-term outcomes of transplantation in patients with various degrees of severity of the syndrome and various causes of liver disease.

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