A Case of Unexplained Hypoxemia

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We present a patient with acute-onset dyspnea and unexplained severe hypoxemia. No signs of severe cardiopulmonary disease, pulmonary arterial hypertension, or pulmonary embolism were present. The patient was diagnosed with hepatopulmonary syndrome, since liver disease of alcoholic origin was present, markedly increased alveolar-arterial oxygen difference existed, and intrapulmonary vascular dilations were demonstrated. The condition of the patient did not improve and he was referred for liver transplantation, which is the only treatment option with documented efficacy. The case highlights the importance of thinking outside the thorax when evaluating patients with dyspnea. *Key words: hepatopulmonary syndrome; hypoxemia; echocardiography; respiratory insufficiency; dyspnea.* [Respir Care 2012;57(11):1963–1966. © 2012 Daedalus Enterprises]

Introduction

Insufficient oxygenation of the blood is termed hypoxemia, whereas hypoxia refers to the situation in which oxygen delivery does not meet the demands of the organism. Oxygenation of the blood is often expressed as oxygen saturation and measured by either pulse oximetry or arterial blood gas analysis, by which the P_{O_2} can also be determined. Oxygen saturation is normally 96–98% in younger adults.[1]

The alveolar-arterial oxygen difference ($P_{(A\text{-}a)O_2}$) is the difference between the P_{O_2} in the alveoli and arterial blood, and can be used to distinguish between different causes of hypoxemia. Generally, hypoxemia associated with a normal $P_{(A\text{-}a)O_2}$ is caused by pure hypercapnic (type II) respiratory failure (eg, from obesity), and hypoxemia associated with widened $P_{(A\text{-}a)O_2}$ is caused by non-hypercapnic (type I) respiratory failure. This is seen in many respiratory disorders with ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch, such as COPD, various interstitial lung diseases, and pulmonary vascular diseases, including pulmonary embolism and the hepatopulmonary syndrome.[2]

Patients with dyspnea and unexplained hypoxemia are often referred to the respiratory specialist for evaluation. Most often these patients are evaluated for various cardiopulmonary and primary pulmonary vascular diseases (pulmonary arterial hypertension and pulmonary embolism). In some cases, however, the clinician is faced with no specific diagnosis, although severe hypoxemia obviously exists. In these cases, thorough history taking and evaluation for hypoxemia mediated by extrathoracic diseases with pulmonary involvement must be performed.

Case Report

A 52-year-old male was admitted to the Department of Acute Medicine at our hospital, with monosymptomatic, acute-onset dyspnea, with a duration of 4 days. Otherwise he was well. He did not have any family history of cardiopulmonary diseases, except for a son with asthma. Each day he consumed 10 bottles of beer, but did not use any medications, illegal drugs, or tobacco. He had no exposures to lung toxic drugs or substances.

On examination the patient appeared in no distress. The blood pressure was 122/68 mm Hg, pulse 98 beats/min, temperature 37.1°C, oxygen saturation in the supine position was 90% while breathing ambient air, and respiratory rate was 16 breaths/min. Besides a discrete and transient systolic murmur with predominance over the apex, no abnormalities (including crackles, clubbing or cirrhotic stigmata) were noted on physical examination. Electrocardio-

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Table 1. Biochemical Analyses

	Reference Value at This Institution	Initial Visit	Follow-up
Venous Blood Sample			
Hemoglobin, mmol/L	8.0–11.0	7.2	7.0
Leucocytes, $\times 10^9$ cells/L	3.0–10.0	6.1	4.0
Platelets, $\times 10^9$ cells/L	120–400	66	60
Sodium, mmol/L	136–146	140	137
Potassium, mmol/L	3.3–4.7	3.5	3.9
Albumin, g/L	37–48	32	29
Urea, mmol/L	3.0–7.8	3.5	3.4
Creatinine, μmol/L	30–105	69	71
Coagulation factors II, VII, X, units/L	0.7–1.3	0.37	0.38
D-dimer, mg/L	< 0.5	0.45	ND
Troponin I, μg/L	0.00–0.03	0.00	ND
Alanine aminotransferase, U/L	10–70	40	30
Alkaline phosphatase, U/L	35–105	86	86
Bilirubin, μmol/L	< 20	57	50
C-reactive protein, mg/L	< 10	3	2
Arterial Blood Sample			
pH	7.35–7.45	7.47	ND
P_{aO_2}, mm Hg	72–103	56	ND
P_{aCO_2}, mm Hg	34–43	3.6	ND
Base excess, mmol/L	–3.0 to 3.0	–3.1	ND
Bicarbonate, mmol/L	21–27	22	ND
Lactate, mmol/L	0.5–2.1	2.3	ND
Alveolar-arterial oxygen difference, mm Hg	15	54	61

ND = no data collected

gram and chest x-ray were interpreted as normal. Biochemical analyses revealed a marked elevation of liver enzymes, with coagulation deficiency and hypoalbuminemia (Table 1). Arterial blood gas analysis demonstrated hypoxemia and partly compensated respiratory alkalosis (see Table 1). The $P_{(A\text{-}a)O_2}$ was elevated and calculated to be 54 mm Hg (expected 15 mm Hg).

Transthoracic echocardiography undertaken by a cardiologist and performed without the administration of agitated saline was normal. As the patient was not in distress, he was discharged without treatment. Further evaluation as an out-patient was scheduled.

One month later he was seen in the out-patient respiratory clinic. No changes in symptoms were noted. Oxygen saturation while seated was 88% when breathing ambient air, and showed marked decline to 58% while climbing stairs to the first floor. Physical activity resulted in marked cyanosis. Spirometry showed FVC of 4.14 L (83% of predicted), FEV_1 of 3.4 L (85% of predicted), and FEV_1/FVC of 0.81. Body plethysmography revealed a total lung capacity of 5.4 L (71% of predicted). Single breath diffusion capacity for carbon monoxide (D_{LCO}) was 35% of predicted, and 58% of predicted when corrected for hemoglobin and alveolar volume (D_{LCOc}/V_A). Ten minutes after inhalation of oxygen at 15 L/min administered via nonrebreathing mask with reservoir bag, the oxygen saturation rose from 88% to 92%. Oxygen saturation was 88% in both the supine and the upright position. The $P_{(A\text{-}a)O_2}$ at this time was 61 mm Hg (expected 15 mm Hg). A lung $\dot{V}/\dot{Q}$ scintigraphy (Fig. 1) was normal, excluding pulmonary embolism as the cause of hypoxemia. Additional static scinti-

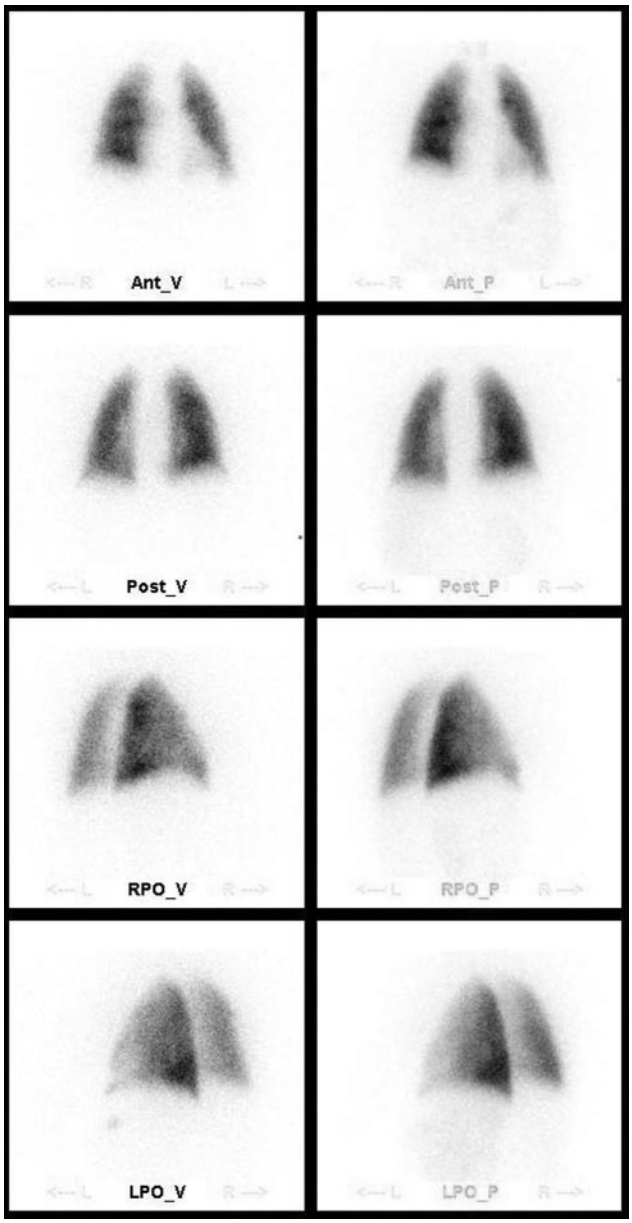

Fig. 1. Normal ventilation-perfusion scintigraphy. Left column: Ventilation images showing normal distribution of radioactive technetium-99m aerosol (99m-Tc Technegas) in both lungs. Right column: Perfusion images showing normal distribution of radioactive macroaggregated albumin particles (99m-Tc-MAA) in the vasculature of both lungs.

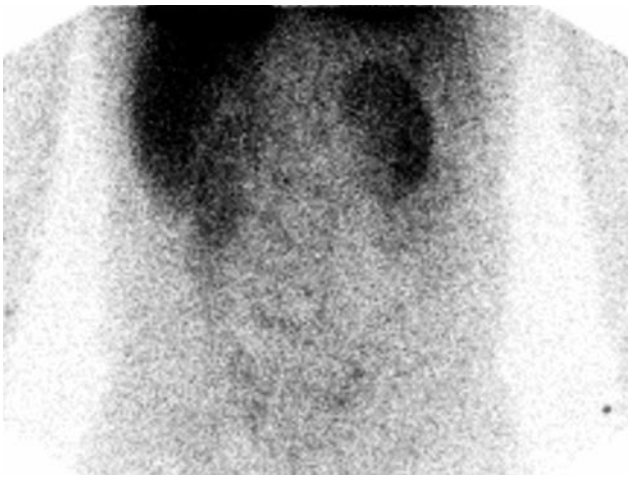

Fig. 2. Pulmonary shunt imaging. Static image of the abdomen in posterior projection after injection of technetium-99m macroaggregated albumin particles (99m-Tc-MAA), showing marked pathologic extra-pulmonary tracer uptake in kidneys and liver, compatible with severe pulmonary shunt. The patient underwent subsequent control scintigraphy, with additional imaging of the brain, allowing for shunt quantification according to the following formula: (GMBC/0.13)/((GMBC/0.13) + GMLC), where GMBC is the count rate over the brain (geometric mean), GMLC is the count rate over the lungs (geometric mean), and 0.13 represents an assumption of the brain receiving 13% of the cardiac output. This patient's shunt fraction was calculated as 25%.

graphic images showed marked tracer uptake in the brain, liver, and kidneys (Fig. 2). High-resolution computed tomography of the lungs showed enlargement of the pulmonary vasculature and a nonspecific reticular pattern in the subpleural area. These imaging studies suggested shunting as the main explanation of the patient's hypoxemia and diffusion problems.

Simultaneously, the patient was evaluated at the out-patient gastroenterology clinic, because of his liver failure. Ultrasonography of the liver showed hyperechoic tissue, with no focal abnormalities. The biochemical analyses are presented in Table 1. The conclusion was liver dysfunction induced by alcohol. He was advised to stop drinking.

At a follow-up visit to the out-patient respiratory clinic after 3 months, the resting oxygen saturation had fallen to 74%. After mild exercise the oxygen saturation immediately fell to 40%. D_{LCO} and D_{LCO_c}/V_A had fallen to 19% of predicted and 32% of predicted, respectively. As previously noted, there was a slight increase in oxygen saturation with oxygen at 15 L/min via non-rebreathing mask with reservoir bag. Despite his severe hypoxemia he was able to maintain some activities of daily living and was not interested in supplemental oxygen therapy.

According to the discussion below, the clinical diagnosis was hepatopulmonary syndrome. Because of rapid worsening of respiratory function the patient was referred for liver transplantation, which was performed 10 months after the initial presentation.

Discussion

Dyspnea and mild hypoxemia are common findings in patients with hepatic dysfunction. The reasons for these are many (eg, diminished total lung capacity from ascites, hepatic hydrothorax, portopulmonary hypertension, coexisting cardiopulmonary diseases, and alpha-1 antitrypsin deficiency).[3] However, severe diffusion problems and hypoxemia are uncommon findings in patients with liver disease, and the hepatopulmonary syndrome should be suspected in this setting, especially if no evidence of severe cardiopulmonary disease exists.

Above we have described a patient with alcoholic liver disease who presented with dyspnea, hypoxemia, and signs of right-to-left shunting on lung scintigraphy.

No evidence of heart disease nor pulmonary hypertension was found on electrocardiogram and echocardiography. Pulmonary embolism was excluded by lung scintigraphy, and severe pulmonary parenchymal disease was unlikely, due to normal spirometry, near normal total lung capacity, and only discrete subpleural reticular abnormalities on high-resolution computed tomography.

The patient was found to have mild anemia, and although a low hemoglobin level in the presence of hypoxemia is known to worsen hypoxia, the degree of anemia was not considered a major problem.[1] The complex of symptoms and findings led to the presumptive diagnosis of hepatopulmonary syndrome. The diagnosis was confirmed when an elevated $P_{(A\text{-}a)O_2}$ and intrapulmonary vascular dilatations (IPVDs) were demonstrated. Orthodeoxia (decrease in oxygen saturation when changing position from supine to upright) was not noted. When orthodeoxia is present, it is sometimes followed by an increase in dyspnea, termed platypnea. This phenomenon is thought to be caused by increased perfusion of IPVDs in the upright position, and is found in most, but not all, patients with the hepatopulmonary syndrome.[4,5]

In clinical practice, IPVDs can be visualized by contrast echocardiography, with microbubbles produced by agitated saline. When injected intravenously, these microbubbles are normally trapped in the pulmonary vasculature and absorbed due to the different sizes of these structures (Table 2). Details of this examination are found elsewhere.[6-9] Alternatively, as in the presented case, shunting via IPVDs can be diagnosed after intravenous injection of technetium-99m macroaggregated albumin, and subsequent demonstration of radioactivity in extra-pulmonary organs. The tracer is normally trapped in the pulmonary vasculature, analogous to the description of microbubbles above.

Other examinations sometimes performed in patients with suspected hepatopulmonary syndrome are transesoph-

Table 2. Diameters of Pulmonary Capillaries and Substances Used in the Diagnostic Workup of the Hepatopulmonary Syndrome

	Diameter, μm
Normal pulmonary capillaries	< 15
Pulmonary capillaries in the hepatopulmonary syndrome	Up to 150
Technetium-99m-macro aggregated albumin	20–90
Agitated saline with microbubbles	60–150

ageal echocardiography when cardiac shunt is suspected, pulmonary angiography when suspicion of true intrapulmonary shunting is a concern, and chest high-resolution computed tomography. In the latter, peripheral, bilateral, and basilar vascular dilations are often found. These findings were present in our patient, and can be mistaken for a reticular pattern, as seen in various interstitial pulmonary diseases.

The hypoxemia observed in hepatopulmonary syndrome is typically due to low $\dot{V}/\dot{Q}$. This $\dot{V}/\dot{Q}$ mismatch is created by IPVDs, which lead to increase in pulmonary blood flow though the parts of the lungs where IPVDs are found. Because the alveolar ventilation is not increased proportionally in these areas, the $\dot{V}/\dot{Q}$ falls and hypoxemia occurs. In severe cases the capillaries are distended to a degree where diffusion of oxygen to the center of the vessel is diminished, further aggravating the hypoxemia. The extent of the IPVDs and the diffusion problems together determines the degree of hypoxemia. This pathophysiology explains the fact that our patient had partial response to oxygen supplementation, which is not seen with anatomic shunting. To a lesser degree, anatomic shunting is seen in some cases of the hepatopulmonary syndrome (eg, because of direct arteriovenous communications).[10] If this is the case, supplemental oxygen will have no or only marginal effect.

The reason for development of IPVDs in hepatopulmonary syndrome is not fully known, but increased production of the vasodilating agent nitric oxide in the lungs is thought to be a main reason. This increased production of nitric oxide is the result of a complex interaction between various mediators and vasoactive agents.[11] Further discussion of this is beyond the scope of this report. Almost all chronic liver diseases, some acute liver conditions, and other diseases with portal hypertension have been reported to cause the hepatopulmonary syndrome.[12-14]

Attempts at pharmacologic treatment of hepatopulmonary syndrome have generally been disappointing, and no vasoactive agent has been shown to improve outcome. The only treatment option with proven efficacy is liver transplantation,[15,16] although severe preoperative hypoxemia ($P_{aO_2} < 50$ mm Hg) is correlated with considerable perioperative mortality.[17]

In conclusion, this case highlights the importance of thinking outside the thorax when evaluating patients with dyspnea and unexplained hypoxemia, especially when no evidence of cardiovascular disease or a primary pulmonary vascular disorder can be established. If hepatopulmonary syndrome is suspected, the most important diagnostic workup is demonstration of IPVDs, by either contrast echocardiography or after intravenous injection of technetium-99m macroaggregated albumin, with subsequent demonstration of radioactivity in extra-pulmonary organs.

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