

## Hypoxaemia and liver cirrhosis: a new argument in favour of a "diffusion-perfusion defect"

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*Hypoxaemia and liver cirrhosis: a new argument in favour of a "diffusion-perfusion defect". J.-B. Thorens, A.F. Junod.*

**ABSTRACT:** Liver cirrhosis is sometimes associated with very severe hypoxaemia, which is thought to be the result of intrapulmonary vascular dilatations (IPVDs). These vascular abnormalities, although close to the gas exchange units, are so dilated that diffusion of oxygen molecules to their centre is impaired, causing an increase in alveolar-arterial oxygen tension difference ( $P(A-a)O_2$ ). On the other hand, administration of 100% oxygen provides enough driving pressure to overcome this relative diffusion defect and rules out a true intrapulmonary shunt.

We report a case in which, in spite of a normal increase in arterial oxygen tension ( $P_{aO_2}$ ) under 100% oxygen, exercising results in a marked impairment of oxygen exchange and a large intrapulmonary shunt. This is probably due to the increased cardiac output and preferential blood flow through these low resistance IPVDs.

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The association of liver cirrhosis with cyanosis and arterial oxygen desaturation has been recognized for many years [1]. It has been reported to occur in the absence of pleural effusion, pulmonary hypertension or pulmonary disorders [2]. Some of these patients show a severe hypoxaemia with a marked increase in alveolar-arterial oxygen tension difference ( $P(A-a)O_2$ ).

The mechanism used to explain the hypoxaemia of these patients has been called "alveolar-capillary oxygen disequilibrium" or, more appropriately, "diffusion-perfusion defect" on the basis of the presence of intrapulmonary vascular dilatations (IPVDs), especially in the lower lobes [3, 4]. The association of a marked increase in  $P(A-a)O_2$  whilst breathing room air, together with the measurement of a small shunt effect whilst breathing a fractional inspiratory oxygen ( $F_{IO_2}$ ) of 1.0 is the functional hallmark of this anomaly. These vascular abnormalities, although close to the gas exchange units, are so dilated that diffusion of oxygen molecules to their centre is impaired. However, an increase in  $F_{IO_2}$  provides enough driving pressure to overcome this relative diffusion defect. In the sitting position, it is hypothesized that redistribution of blood flow in these dilated, low resistance vessels, is the origin of a further increase in  $P(A-a)O_2$ , called orthodeoxia [4].

As an extension of this concept of "diffusion-perfusion defect", we postulated that exercise testing under a  $F_{IO_2}$  of 1.0 should result in the appearance of a venous admixture effect. The shorter transit time of red blood cells in the pulmonary capillaries that accompanies physical exercise should partially offset

the beneficial effect of the high  $F_{IO_2}$  and result in a substantial true shunt effect. Moreover, because of the low resistance of these dilated vessels, there should be a preferential increase in blood flow through these units and, as a consequence, further deterioration in oxygen exchange.

### Case report

A 45 yr old civil servant, was admitted because of platypnoea and dyspnoea on exertion. Two years previously, he had been admitted to the hospital for bleeding from oesophageal varices, and percutaneous liver biopsy confirmed the diagnosis of liver cirrhosis.

On physical examination, the patient appeared cyanotic and slightly jaundiced. Spider naevi were numerous on the trunk and upper limbs. Bilateral gynaecomastia was present. Heart sounds were normal. Pulse rate was 80 pulses·min<sup>-1</sup> and arterial blood pressure 120/70 mmHg. Respiratory rate was 12 breaths·min<sup>-1</sup>. No rales were heard. Liver was palpable 6 cm below the costal margin. The haematocrit was 43% and reticulocyte count 1.8%. The white blood cell count was  $5.4 \times 10^9 \cdot l^{-1}$  and the platelet count  $138 \times 10^9 \cdot l^{-1}$ . Prothrombin time was 70% of control and activated partial thromboplastin time 31 s. Bilirubin was  $31 \mu\text{mol} \cdot l^{-1}$ , the  $\gamma$ -glutamyl transferase ( $\gamma\text{GT}$ ) 186 U·l<sup>-1</sup>. Alkaline phosphatase, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were normal. A chest radiograph was normal.

Results of lung function tests are shown in table 1.



Table 1. - Lung function tests

	Result (% pred)	Predicted value
FEV <sub>1</sub> l	3.26 (94)	3.47
FVC l	4.56 (104)	4.40
FEV <sub>1</sub> /FVC %	71 (90)	79
MMEF l·s <sup>-1</sup>	2.2 (54)	4.04
<b>Oxygen single-breath test</b>		
Closing volume/VC %	7	17±7
Phase 3 % N <sub>2</sub> ·l <sup>-1</sup>	1.33	1.16±0.7
<b>Diffusion test</b>		
DLCO mmol·min <sup>-1</sup> ·kPa <sup>-1</sup>	3.33 (34)	9.78
Kco mmol·min <sup>-1</sup> ·kPa <sup>-1</sup> ·l <sup>-1</sup>	0.52	1.94±0.44

Normal values were taken from [5]. FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity; MMEF: maximal mid-expiratory flow rate; VC: vital capacity; DLCO: single-breath diffusing capacity for carbon monoxide; Kco: carbon monoxide transfer coefficient (DLCO/alveolar volume).

A routine perfusion lung scan was normal. Pulmonary angiography was normal and no arteriovenous fistula was visible. The pulmonary artery pressure, measured during pulmonary angiography was 25/9 mmHg (mean 15 mmHg). Two-dimensional echocardiography with Doppler was normal but contrast-enhanced echocardiography revealed a transient and delayed echogenicity of the left heart chambers, four cardiac cycles after its detection in the right heart chambers. With a normal pulmonary angiography, this is indicative of IPVDs [6].

Arterial blood gas measurements supine, sitting, at rest and during exercise at 40 Watt, are reported in table 2. Under 100% oxygen, arterial oxygen tension (Pao<sub>2</sub>) is dramatically reduced during exercise and the magnitude of the right-to-left shunt fraction increases markedly. The table also shows that the right-to-left shunt fraction decreases when supine. An exercise study was not performed whilst breathing room air because of shortness of breath.

## Discussion

This case of liver cirrhosis with marked hypoxaemia is probably due to intrapulmonary vascular dilations resulting in a diffusion-perfusion defect. This diagnosis can be made on the basis of the following features: 1) two-dimensional contrast-enhanced echocardiography reveals echogenicity of the left atrium four cardiac cycles after the right heart chambers have been opacified, in the absence of visible arteriovenous shunt on pulmonary angiography [6]; 2) the Pao<sub>2</sub> worsens when the patient is sitting (orthodeoxia) and his dyspnoea is relieved by recumbency (platypnoea); and 3) the Pao<sub>2</sub> increases markedly following administration of 100% inspired oxygen [4].

These IPVDs are thought to be the extreme expression of a disorder due to an abnormal vascular reactivity with loss of hypoxic pulmonary vasoconstriction. Mild hypoxaemia develops first, leading to ventilation-perfusion inequality. Then, regions with very low ventilation/perfusion ratio and a shunt-like mechanism develop, resulting in profound hypoxaemia [7, 8].

The redistribution of blood flow in the low resistance vessels is more obvious during the exercise study whilst breathing 100% oxygen with a fall in Pao<sub>2</sub> to 9.85 kPa, compatible with a large intrapulmonary shunt effect. When the calculation of this effect was made with the assumption of an arteriovenous oxygen content difference of 5 and 9 volume percent, a shunt effect of 39 and 26%, respectively, was obtained. Because patients with liver cirrhosis tend to have a high cardiac output [7], an arteriovenous difference of 5 volume percent during a 40 W exercise may be more likely. These results support the concept of a "diffusion-perfusion defect" in which O<sub>2</sub> transfer should be very rapidly limited as a result of the increased cardiac output during exercise and of the increased velocity of blood through the IPVDs. The fall in Pao<sub>2</sub> appears to be out of proportion with the low level of exercise and would be consistent with a preferential flow through these low resistance, dilated capillaries with further impairment of oxygenation.

The precise cause of these IPVDs remain hypothetical, but includes poor metabolism of vasodilators, such as vasoactive intestinal peptide, or inhibition of

Table 2. - Arterial blood gas measurements

	Room air		100% O <sub>2</sub>		
	Supine	Sitting	Supine	Sitting	Sitting 40 W
pH	7.45	7.41	7.44	7.39	7.34
Pao <sub>2</sub> kPa	6.7	6.0	69.9	58.1	9.9
Sao <sub>2</sub> %	87.0	81.4	99.9	99.9	93.6
Paco <sub>2</sub> kPa	3.4	3.2	3.8	3.6	3.9
Qs/Qt* %	-	-	8.1	12	26-39**

\*: Cao<sub>2</sub>-Cv̄o<sub>2</sub> was assumed to be 5 vol% at rest; \*\*: Qs/Qt of 39% corresponds to a Cao<sub>2</sub>-Cv̄o<sub>2</sub> of 5 vol% and Qs/Qt of 26% corresponds to a Cao<sub>2</sub>-Cv̄o<sub>2</sub> of 9 vol%. Qs/Qt: intrapulmonary right-to-left shunt fraction; Pao<sub>2</sub>: arterial oxygen tension; Sao<sub>2</sub>: arterial oxygen saturation; Paco<sub>2</sub>: arterial carbon dioxide tension; Cao<sub>2</sub> and Cv̄o<sub>2</sub>: arterial and mean venous oxygen content, respectively.



vasoconstrictors such as endothelin [4]. Pharmacological attempts to improve hypoxaemia have been numerous (beta-blockers to reduce cardiac output, cyclooxygenase inhibitors, plasma exchange, almitrine bismesylate, somatostatine) but largely unsuccessful [4, 5, 9]. The reports of recovery from severe hypoxaemia following liver transplantation appear to be more promising [10-12].

In summary, the mechanism of "diffusion-perfusion defect" specifically induces severe hypoxaemia in patients with liver cirrhosis. It is the result of preferential blood flow through dilated vessels located, preferentially, at the base of the lungs. The functional abnormalities are: low  $P_{aO_2}$  at rest in room air, worsening of hypoxaemia in the sitting position (orthodeoxia), with a normal increase in  $P_{aO_2}$  on 100% oxygen. However, exercising results in further impairment of oxygen exchange and in the development of a large intrapulmonary shunt effect, because it substantially shortens the transit time of blood in the pulmonary capillaries, especially in these low resistance dilated vessels.

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