Eur Respir J, 1994, 7, 839–842
DOI: 10.1183/09031936.94.07050839

European Respiratory Journal
ISSN 0903 - 1936

EDITORIAL

Is severe arterial hypoxaemia due to hepatic disease an indication for liver transplantation? A new therapeutic approach

R. Rodriguez-Roisin*, M.J. Krowka**

The term hepatopulmonary syndrome (HPS) can be defined by a clinical triad of chronic liver disease (most commonly, all types of hepatic cirrhosis and chronic active hepatitis), pulmonary gas exchange abnormalities, resulting ultimately in arterial hypoxaemia, and intrapulmonary vascular dilatations, in the absence of intrinsic cardiopulmonary disease [1, 2]. Additional features, such as platypnoea and orthodeoxia with or without shortness of breath, low transfer factor (diffusing capacity for carbon monoxide, D_{LCO}) and haemodynamic abnormalities (systemic and pulmonary vasodilatation), can be also present, but their prevalence varies between patients [2]. It is not intended, however, that HPS encompasses all cardiorespiratory disorders which may be associated with chronic liver disorders. Although it is estimated that arterial hypoxaemia may be present in one-third of patients with hepatic cirrhosis, the actual prevalence of HPS remains unknown.

All postmortem lung studies exclusively refer to a common structural derangement of the pulmonary circulation, namely a generalized vasodilatation of the pulmonary vascular bed at the precapillary level, near to the gas exchange zone. Although larger arteriovenous communications and pleural spider naevi may be seen, they are uncommon. These intrapulmonary vascular deformities (15–500 μm in diameter, instead of the normal-sized capillary range, 8–15 μm in diameter) may facilitate more direct passage of mixed venous blood to the arterial side of the pulmonary circulation, hence jeopardizing the mechanisms of normal arterial oxygenation.

Clinical findings

Platypnoea (dyspnoea induced by the upright position) and orthodeoxia (arterial hypoxaemia enhanced by the upright position; decrease in arterial oxygen tension, Pa_{O_2}, ≥10% from supine) (prevalence 88%), finger clubbing (83%), varying signs and symptoms of chronic liver disorder (82%), and shortness of breath (18%), constitute the most conspicuous clinical markers of HPS at initial presentation [3]. Although chest radiographic abnormalities are unusual, both increased basal pulmonary vascularity and interstitial markings may be visible.

Pulmonary gas exchange disturbances in HPS result in a wide spectrum of oxygenation abnormalities: from the subclinical increased alveolar to arterial O_2 tension gradient ($P_{A}\text{-}a_{O_2}$) (≥15 mmHg or 2.0 kPa) to the presence of severe arterial hypoxaemia (<60 mmHg (8.0 kPa) at rest and lying supine whilst breathing room air), requiring long-term oxygen therapy [2–4]. Both an increased $P_{A}\text{-}a_{O_2}$ (mean ≥20 mmHg (2.7 kPa)) and a reduced arterial carbon dioxide tension (Pa_{CO_2}) (mean, ≤32 mmHg (4.3 kPa)), reflecting mild-to-moderate chronic increased minute ventilation, appeared to be the most common abnormal lung function tests in patients with various chronic hepatic diseases, who were candidates for liver transplantation [4]. $P_{A}\text{-}a_{O_2}$ was abnormally increased in all but two patients with HPS diagnosed by echocardiographic evidence of intrapulmonary vascular dilatations, severe arterial hypoxaemia was noted in nearly 60% and low transfer factor in 83% [3]. In contrast, spirometric abnormalities were unusual, averaging normal values.

Systemic hypotension, low pulmonary vascular pressures, a reduced sensitivity to vasoconstrictors and an inordinately high cardiac output are the haemodynamic characteristics in HPS. Hypoxaemia appears to be associated with both more severe liver disease and low pulmonary vascular resistance [5], suggesting defective hypoxic pulmonary vasoconstriction, and supporting the view of little or no hypoxic vascular response in approximately one-third of these patients [2].

The most sensitive noninvasive tools to identify intrapulmonary vascular deformities are either a positive two-dimensional contrast-enhanced echocardiography or the extrathoracic appearance of intravenous radiolabelled microspheres. Normally, microbubbles of agitated saline or indocyanine green (60–90 μm in diameter), identified as echoes, or isotopic albumin particles (20–60 μm in diameter) are trapped in the pulmonary capillary network. Instead, these microbubbles or macroaggregates pass directly through dilated pulmonary capillaries in patients with HPS, to be detected either in the left cardiac cavities or in the systemic circulation, respectively.

*Servei de Pneumologia i Al.lèrgia Respiratòria, Hospital Clínic, Facultat de Medicina, Universitat de Barcelona, Barcelona, Spain, and **Mayo Medical School, Division of Thoracic Diseases, Mayo Clinic, Jacksonville, FL, USA. Correspondence: R. Rodriguez-Roisin, Servei de Pneumologia i Al.lèrgia Respiratòria, Hospital Clínic, Villarroel 170, Barcelona - 08036, Spain. RR-R is supported by Grant 93/306 from the Fondo de Investigación Sanitaria (FIS) de la Seguridad Social (Spain).

It is of note that the more severe the hepatic failure, the greater the severity of the HPS; however, some of the most critical pulmonary manifestations may sometimes precede the liver dysfunction. The presence of spider naevi has been suggested as one the most sensitive clinical markers [2]. Patients with spider naevi may have an increased level of liver dysfunction, systemic and pulmonary haemodynamic disturbance and gas exchange abnormalities.

Pathophysiology

For many years, arterial hypoxaemia in patients with HPS has been related to the presence of one, or the coexistence of several, of the following mechanisms of abnormal gas exchange: intrapulmonary and portopulmonary shunts, alveolar to end-capillary diffusion limitation to O_2 and/or ventilation-perfusion ($\dot{V}_A/\dot{Q}$) mismatching. In contrast, alveolar hypoventilation has not been shown. Over the last decade, studies using state-of-the-art techniques have pointed to mild to moderate $\dot{V}_A/\dot{Q}$ abnormalities as the most common mechanism of altered Pa_{O_2} [2]. This suggests the presence of alveoli with low $\dot{V}_A/\dot{Q}$ units, in which ventilation is maintained but perfusion is greatly increased. In the most severe cases of hepatic failure, however, severe intrapulmonary shunt plays a pivotal role as an intrapulmonary factor determining the degree of arterial hypoxaemia in addition to $\dot{V}_A/\dot{Q}$ inequality. Although diffusion limitation to O_2 may coexist, its influence may be negligible if hypoxaemia is not severe enough; similarly, portopulmonary shunt is considered of little impact. The concept of diffusion-perfusion defect, shown in other pulmonary vascular malformations, such as haemorrhagic hereditary telangiectasia (Rendu-Osler-Weber syndrome), is viewed primarily as a mechanism of $\dot{V}_A/\dot{Q}$ mismatch, with the potential coexistence of some diffusion limitation to O_2, probably enhanced by the increased cardiac output [2].

It must be remembered that, in the presence of an increased cardiac output, Pa_{O_2} may still reach high values whilst breathing 100% O_2 (≥450 mmHg or 60 kPa), with high levels of shunt, determined by the inert gas technique, in the order of 20%.

The role of increased cardiac output in influencing the levels of hypoxaemia is of paramount importance to the understanding of many of the clinical findings of HPS. Enhancement of arterial hypoxaemia by the upright position (*i.e.*, orthodeoxia) has been shown to be associated with higher arterial to venous O_2 content difference and lower mixed venous oxygen tension *(i.e.,* a lower cardiac output) than when lying supine [6]. Conceivably, gravitational blood flow differences are maximized in the upright position. This may induce further deterioration in $\dot{V}_A/Q$ mismatch, possibly reinforced by a lower pulmonary vascular tone.

In brief, a wide spectrum of gas exchange abnormalities can be found in patients with HPS. At one extreme, patients with severe liver failure may have a marked circulatory hyperdynamic state, with varying degrees of loss of hypoxic pulmonary vasconconstriction and moderate to severe arterial hypoxaemia, partly offset by the high levels both of cardiac output and minute ventilation. In patients with HPS, the latter two factors represent the major extrapulmonary mechanisms for adjustment of gas exchange. At the other extreme, patients may have very little abnormality in respiratory gases, with little or no haemodynamic change. In between would be the majority of patients, with varying degrees of arterial blood gas abnormalities and haemodynamic disturbances.

Mechanism

The precise mechanism underlying these haemodynamic changes remains unknown, despite numerous investigations aimed to assess the potential role of vasodilator agents. An increased synthesis and release of nitric oxide (NO), a potent vasodilator with ubiquitous biological activity, has been postulated as the key factor modulating the hyperkinetic systemic and pulmonary circulatory abnormalities [7]. If this hypothesis is true, the use of competitive inhibitors of NO synthesis should restore the sensitivity of the hypoxic vascular response, reversing the haemodynamic changes of HPS and ultimately re-establishing pulmonary oxygenation.

Medical therapeutical options

Data describing the natural history of the HPS are scarce. In patients with deteriorating arterial oxygenation and HPS, 4 out of 7 died within 4 yrs [3]. Therapeutic interventions must, therefore, address improvement of symptoms and effect on overall survival. Long-term oxygen therapy is the simplest approach to improving symptoms in these patients. Most individuals have a substantial response to supplemental oxygen. Whilst spontaneous resolution of HPS in patients with reversible aspects of liver disease has been reported, such reversibility has yet to be described in patients with chronic liver disease [8]. At the present time, there have been no reports indicating improvement in pulmonary oxygenation following plasmapheresis or plasma exchange techniques [1].

Single case reports have documented improvement in deteriorating arterial oxygenation due to HPS with medications such as prostaglandin-$F_{2\alpha}$ [9], steroids and cytoxan [2], and garlic preparations [10]. Small series studies, utilizing propranolol [2], indomethacin [6], somatostatin analogue [3] and almitrine bismesylate [2] have also been described in patients with HPS; limited improvements have been noted in patients using almitrine, and further studies in patients with severe hypoxaemia are in progress.

Interventional radiology

Well-documented improvement in pulmonary oxygenation has been accomplished following serial coil embolotherapy in carefully selected patients with HPS [11, 12]. Ideally, these patients should have discrete

arteriovenous communications as opposed to diffuse lesions. The effect of transjugular intrahepatic portosystemic shunting procedures on patients with HPS is unknown.

Liver transplantation

Once considered to be an absolute contraindication to transplantation, severe hypoxaemia due to HPS is currently a relative contraindication in many centres. Do clinical situations arise when severe hypoxaemia or deteriorating arterial oxygenation may be an indication for liver transplantation? We think so. Firstly, patients with severe hypoxaemia due to HPS have been safely transplanted. Not only do they survive the transplantation process, but the hypoxaemia can resolve over time (usually within months) (table 1). However, some failures do occur, and it is unclear what the prognostic factors may be. Although it has been suggested that restoration of normal gas exchange may take longer after transplantation when the principal mechanism of hypoxaemia is intrapulmonary shunt, this observation has been neither confirmed nor refuted [2]. Those who respond poorly to 100% supplemental oxygenation (Pa_{O_2} <150 mmHg or 20 kPa) probably have the greatest perioperative survival risk. Indeed, perioperative volume overload may have further deleterious effects on gas exchange which can be reversible.

Data from DIMAND *et al.* [18], LABERGE *et al.* [19], the Mayo Clinic [3] and other teams suggest that a subset of patients with severe hypoxaemia or deteriorating pulmonary oxygenation due to HPS in the setting of clinically stable hepatic dysfunction can be transplanted safely with complete resolution of severe hypoxaemia. These patients would not necessarily have been transplanted due to the severity of their liver disease alone.

One final point concerns the importance of identifying the aetiology of abnormal Pa_{O_2} in patients with liver disease. Some individuals may have deteriorating oxygenation due to significant pulmonary hypertension as opposed to HPS. It is crucial to distinguish these patients, because if the pulmonary hypertension is severe (mean pulmonary artery pressure >50 mmHg (6.7 kPa)), the prognosis may be very poor, with intraoperative and immediate perioperative deaths having been reported [24]. In short, distinction between hypoxaemia due to HPS and pulmonary hypertension is extremely important if transplantation is to be considered.

Summary

Severe arterial hypoxaemia or deteriorating pulmonary oxygenation due to HPS appears to be reversible within months of orthotopic liver transplantation. Due to the apparently poor prognosis in these patients, such abnormal oxygenation may, indeed, be considered an indication

Table 1. – Liver transplant results in patients with severe HPS (Pa_{O_2} ≤65 mmHg, (8.7. kPa))

Authors [Ref]	Age	Sex	Pretransplant Pa_{O_2}		Liver transplant outcome
	yrs		mmHg	(kPa)	
OH *et al.* [13]	18	F	43	(5.7)	Died/month 3 postop.
STOLLER *et al.* [14]	39	F	62	(8.3)	Success/Pa_{O_2} normal.
ERIKSSON *et al.* [15]	18	F	52	(6.9)	Success/Pa_{O_2} normal.
MEWS *et al.* [16]	12	M	48	(6.4)	Died/day 10 postop.
MCCLOSKEY *et al.* [17]	17	M	40	(5.3)	Success/Pa_{O_2} normal.
DIMAND *et al.* [18]	13	F	44	(5.9)	Success/Pa_{O_2} normal.
	53	M	46	(6.1)	Success/Pa_{O_2} normal.
	17	F	61	(8.1)	Success/Pa_{O_2} normal.
LABERGE *et al.* [19]	12	F	51	(6.8)	Success/Pa_{O_2} normal.
	14	F	53	(7.1)	Success/Pa_{O_2} normal.
ITASAKI *et al.* [20]	13	F	42	(5.6)	Success/Pa_{O_2} normal.
SCHWARZENBERG *et al.* [21]	18	F	35	(4.7)	Success/Pa_{O_2} normal.
SCOTT *et al.* [22]	38	F	35	(4.7)	Success/Pa_{O_2} normal.
	NR	M	65	(8.7)	Success/Pa_{O_2} normal.
	52	M	51	(6.8)	Success/Pa_{O_2} normal.
	53	F	63	(8.4)	Success/Pa_{O_2} normal.
VAN OBBERGH *et al.* [23]	2	NR	63	(8.4)	Success/Pa_{O_2} normal.
	10	NR	40	(5.3)	Success/Pa_{O_2} normal.
	7	NR	36	(4.8)	Success/Pa_{O_2} normal.
Mayo Clinic (1992–1993) (unpublished)	38	F	63	(8.4)	Success/coil embolotherapy/ Pa_{O_2} normal.
	28	F	49	(6.5)	Success/Pa_{O_2} normal.
Hospital Clinic (1993) (unpublished)	41	M	41	(5.5)	Success/O_2 therapy

HPS: hepatopulmonary syndrome; Pa_{O_2}: arterial oxygen tension; postop.: postoperative; normal.: normalized; NR: not reported. (Conversion to SI units, 1 mmHg = 0.133 kPa).

for liver transplantation in selected clinical situations. The pretransplant distinction between HPS and pulmonary hypertension as a reason for arterial hypoxaemia is essential, however, in that different outcomes appear to exist. Further prospective studies of patients with pulmonary vascular complications of liver disease are desperately needed.

References

1. Krowka MJ, Cortese DA. Hepatopulmonary syndrome: an evolving perspective in the era of liver transplantation. *Hepatology* 1990; 11: 138–142.
2. Rodriguez-Roisin R, Agustí AGN, Roca J. The hepatopulmonary syndrome: new name, old complexities. *Thorax* 1992; 47: 897–902.
3. Krowka MJ, Dickson ER, Cortese DA. Hepatopulmonary syndrome: clinical observations and lack of therapeutic response to somatostatin analogue. *Chest* 1993; 104: 515–521.
4. Hourani JM, Bellamy PE, Tashkin DP, Batra P, Simmons MS. Pulmonary dysfunction in advanced liver disease: frequent occurrence of an abnormal diffusion capacity. *Am J Med* 1991 90: 693–700.
5. Vachiéry F, Hadengue A, Moreau R, Gadano A, Soupison T, Lebrec D. Hepatopulmonary syndrome: what relationship with liver failure and hyperkinetic circulation? *Hepatology* 1993; 18: 141A (Abstract).
6. Andrivet P, Cadranel J, Housset B, Herigault R, Harf A, Adenot S. Mechanisms for impaired arterial oxygenation in patients with liver cirrhosis and severe respiratory insufficiency: effects of indomethacin. *Chest* 1993; 103: 500–507.
7. Vallance P, Moncada S. Hyperdynamic circulation in cirrhosis: a role for nitric oxide? *Lancet* 1991; 337: 776–778.
8. Shijo H, Nakayama K, Sasaki H, *et al*. Reversibility of pulmonary telangiectasis in liver cirrhosis evidenced by serial dynamic perfusion imaging. *Clin Nuc Med* 1989; 14: 909–911.
9. Shijo H, Sasaki H, Yuh K, Sakaguchi S, Okumura M. Effects of indomethacin on hepatogenic pulmonary angiodysplasia. *Chest* 1991; 99: 1027–1029.
10. Caldwell SH, Jeffers LJ, Narula OS, Lang LA, Ready KR, Schiff R. Ancient remedies revisited: does *Allium sativum* (garlic) palliate hepatopulmonary syndrome? *J Clin Gastroenterol* 1992; 15: 248–250.
11. Felt RW, Kozak BE, Rosch J, Duell BP, Barker AF. Hepatogenic pulmonary angiodysplasia treated with coil-spring embolization. *Chest* 1987; 91: 920–922.
12. Krowka MJ, Cortese DA. Hepatopulmonary syndrome: current concepts in diagnostic and therapeutic considerations. *Chest* 1994; (in press).
13. Oh KS, Bender TM, Bowen A, Ledesma-Medina J. Plain radiographic, nuclear medicine, and angiographic observations of hepatogenic pulmonary angiodysplasia. *Pediatr Radiol* 1983; 13: 111–115.
14. Stoller JK, Moodie D, Schiavone WA, *et al*. Reduction of intrapulmonary shunt and resolution of digital clubbing associated with primary biliary cirrhosis after liver transplantation. *Hepatology* 1990; 11: 54–58.
15. Eriksson LS, Soderman C, Ericzon BG, Eleborg L, Wahren J, Hedenstierna G. Normalization of ventilation-perfusion relationships after liver transplantation in patients with decompensated cirrhosis: evidence for a hepatopulmonary syndrome. *Hepatology* 1990; 12: 1350–1357.
16. Mews CF, Dorney SF, Shiel AG, Forbes DA, Hill RE. Failure of liver transplantation in Wilson's diseases with pulmonary arteriovenous shunting. *J Pediatr Gastroenterol Nutr* 1990; 10: 230–233.
17. McCloskey JJ, Schlein C, Schwarz K, Klein A, Colombani P. Severe hypoxemia and intrapulmonary shunting resulting from cirrhosis reversed by liver transplantation in a pediatric patients. *J Pediatr* 1991; 118: 902–904.
18. Dimand RJ, Heyman MB, Lavine JE, Bass NM, Lake JR, Ascher NL. Hepatopulmonary syndrome: response to hepatic transplantation. *Hepatology* 1991; 14: 55A (Abstract).
19. Laberge JM, Brandt ML, Lebecque P, *et al*. Reversal of cirrhosis-related pulmonary shunting in two children by orthotopic liver transplantation. *Transplantation* 1992; 53: 1135–1138.
20. Itasaki H, Hershon JJ, Cox KL, *et al*. Transient deterioration of intrapulmonary shunting after pediatric liver transplantation. *Transplantation* 1993; 55: 212–214.
21. Schwarzenberg SJ, Freese DK, Regelmann WE, Gores PF, Boudreau RJ, Payne WD. Resolution of severe intrapulmonary shunting after liver transplantation. *Chest* 1993; 103: 1271–1273.
22. Scott V, Miró A, Kang Y, *et al*. Reversibility of the hepatopulmonary syndrome by orthotopic liver transplantation. *Transplant Proc* 1993; 25: 1787–1788.
23. Van Obbergh L, Carlier M, Clement de Clety S, *et al*. Liver transplantation and pulmonary gas exchanges in hypoxemic children. *Am Rev Respir Dis* 1993; 148: 1408–1410.
24. Prager MD, Cauldwell CA, Ascher NL, Roberts JP, Wolfe CL. Pulmonary hypertension associated with liver disease is not reversible after liver transplantation. *Anesthesiology* 1992; 77: 375–378.