EDITORIAL

The hepatopulmonary syndrome: NO way out?

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"How diseases of the liver affect lung function?" is one of those puzzling questions that can turn obsessive for those who want to understand how two seemingly distinctive organs can interact and eventually lead to severe disorders [1, 2]. The most common respiratory consequence of liver disease is hypoxaemia, which is often mild to moderate [3]. Seldom severe hypoxaemia occurs when the arterial pressure of oxygen (Pa,O$_2$) falls below 8 kPa (60 mmHg), heralding the occurrence of a condition known as the "hepatopulmonary syndrome" (HPS). HPS is characterised by a triad of conditions, namely: 1) advanced liver disease (with or without liver cirrhosis); 2) widespread intrapulmonary vasodilatation; and 3) alveolar-arterial oxygen gradient (PA-a,O$_2$) >2.6 kPa (20 mmHg) whilst breathing room air [2, 3]. Clinical symptoms typically include shortness of breath, which may either worsen on standing (platypnoea) and/or be accompanied by a 10% fall in Pa,O$_2$ (orthodeoxia). As with other lung disorders, hypoxaemia results from impaired gas exchange, which, in HPS, is particularly perturbed by excessive and widespread dilatation of intrapulmonary vessels. After decades of careful investigations, the underlying mechanisms linking altered gas exchange and pulmonary vasodilatation are now well delineated [2–4]. Reduced tone causing vascular relaxation occurs at both ends of the capillary bed, *i.e.* affecting pre-capillary and post-capillary vessels. This allows mixed venous blood to speed through, or even bypass, gas exchange units. It is believed that hypoxaemia occurs as a result of one (or the combination of several) of these following mechanisms: 1) ventilation-perfusion mismatching (reflecting excess perfusion for a given ventilation); 2) true intrapulmonary anatomical shunts; and 3) diffusion-perfusion impairment (due to increased oxygen diffusion distance from alveoli to haemoglobin across the dilated vessels) [5–9]. Vascular dilatation can be observed using contrast-enhanced echocardiography or fractional brain uptake after lung perfusion of technetium-99m macroaggregated albumin lung scanning [10].

As pulmonary vasodilatation is the main culprit, hunting endogenous vasodilators that reduce pulmonary vascular tone logically became a sound strategy for those whose quest was to unravel the missing "molecular" link between the diseased liver and the affected lung. Nitric oxide (NO), one of the most potent and prominent endogenous pulmonary vasodilators [11], soon appeared as a very likely candidate, not only for the hyperdynamic circulatory syndrome in cirrhosis [12], but also for HPS [13]. This hypothesis has been further consolidated in the light of clinical and experimental results from several recent studies [2]. First, pulmonary endogenous production of NO, which can be assessed by measuring exhaled NO [14], is increased in patients with HPS [15–18] and returns to normal values 3–12 months after orthotopic liver transplantation [17, 18]. Interestingly, normalisation of exhaled NO concentrations was observed either whilst the patient achieved normoxaemia again [17] or correlated with reduced PA-a,O$_2$ [18] after liver transplantation. This is consistent with the hypothesis of a major contributory role of endogenous NO in causing inadequate pulmonary vasodilatation, hence ventilation-perfusion mismatching and hypoxaemia, in HPS. The second question that naturally arises from these observations is "what is (are) the origin(s) of the increased NO production in HPS?". Early studies from our group have provided evidence of vascular hyporeactivity, which resulted from increased NO production in both systemic and pulmonary vascular beds of animals with experimental cirrhosis [19, 20]. Applying the technique of multiple flow analysis, which allows to differentiate alveolar from bronchial origins of exhaled NO, DELCLAUX *et al.* [21] have elegantly zoomed in on the alveoli as the major source of increased NO production in cirrhotic patients. "What are the cellular types, and the NO synthases (NOS) subtypes, which are involved in this overproduction of NO?" came naturally as the question to ask at this stage. In experimental cirrhosis, overexpression of both inducible (NOS-2) and constitutive (NOS-3) isoforms are seen in alveolar macrophages and pulmonary endothelial cells, respectively [22, 23]. Although the same pattern of lung NOS overexpression has not yet been documented in patients with HPS, this probably occurs in most cases, at least in patients who have been successfully treated with synthesis inhibitors of either NO or its target, namely the second messenger cyclic guanosine monophosphate (cGMP). Two reports recently described successful use of this therapeutic strategy in HPS patients, who were improved by either nebulisation of the NOS inhibitor, N^G-nitro-L-arginine methyl ester [24], or intravenous administration of methylene blue, an inhibitor of the main molecular target of NO, the cGMP-synthesising enzyme soluble guanylyl cyclase [25] (fig. 1).

In the current issue of the *European Respiratory Journal*, SZTRYMF *et al.* [26] have taken us a step further down the path exploring intracellular signalisation of NO with their study on the effect of pentoxifylline, a nonspecific inhibitor of synthesis of the pro-inflammatory cytokine tumour necrosis factor (TNF)-α [26]. It is known that synthesis of NO by the inducible enzyme NOS-2 is regulated at a transcriptional level, mainly through activation of transcription factors, *e.g.* nuclear factor-κB or activator protein-1, both of which are stimulated by TNF-α [27] (fig. 1). Thus, targeting TNF-α would be a logical approach, especially after the recent finding of increased production of this cytokine in experimental HPS [28]. The paper by SZTRYMF *et al.* [26], demonstrating that pretreatment with pentoxifylline prevented HPS and the hyperdynamic circulatory syndrome, presumably through inhibition of TNF-α synthesis and NOS-2 induction, elegantly adds a new piece of information to our knowledge on the

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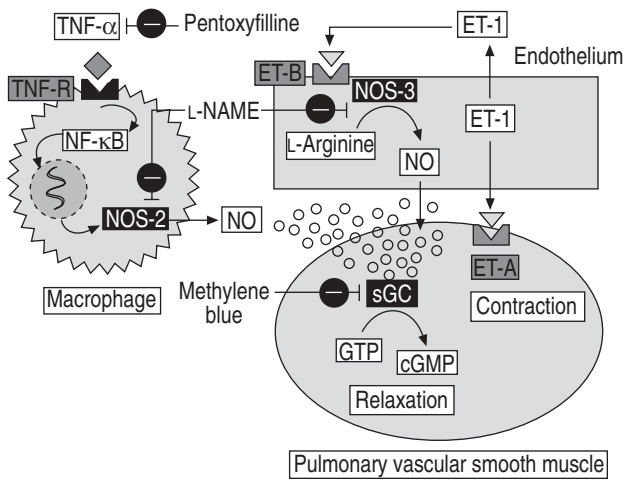
Fig. 1. – Possible interactions between nitric oxide (NO), endothelin (ET)-1 and tumour necrosis factor (TNF)-α in the pathogenesis of hepatopulmonary syndrome. cGMP: cyclic guanosine monophosphate; ET-A and ET-B: endothelin receptors A and B; GTP: guanosine triphosphate; L-NAME: N^G-nitro-L-arginine methyl ester; NF-κB: nuclear factor-κB; NOS: nitric oxide synthase; sGC: soluble guanylyl; TNF-R: TNF-α receptors.

pathophysiology of HPS. This further supports the central role of excess NO synthesis as a major molecular mechanism. The recent suggestion of a possible implication of endothelin (ET)-1 in HPS may further complicate an already complex scheme [28]. However, as overexpression of pulmonary ET-B receptors, which provides another mechanism for the stimulation of NO release (fig. 1), is seen in experimental HPS [29, 30], NO is likely to keep on focussing our interest for a while yet.

Therefore, the spotlight is pinpointing down on nitric oxide. But we all know the interest and pitfall of this approach. Too much focus certainly allows greater scrutiny for a given factor, but also favours the risk of overlooking the others. Let′s keep both nitric oxide in mind and our mind open for other forthcoming players in hepatopulmonary syndrome pathogenesis.

References

1. Rodriguez-Roisin R, Agustí AGN, Roca J. The hepatopulmonary syndrome: new name, old complexities. *Thorax* 1992; 47: 897–902.
2. Hervé P, Lebrec D, Brenot F, et al. Pulmonary vascular disorders in portal hypertension. *Eur Respir J* 1998; 11: 1153–1166.
3. Naeije R. Hepatopulmonary syndrome and portopulmonary hypertension. *Swiss Med Wkly* 2003; 133: 163–169.
4. Wagner PD. Impairment of gas exchange in liver cirrhosis. *Eur Respir J* 1995; 8: 1993–1995.
5. Rodriguez-Roisin R, Roca J, Agustí AGN, Mastai R, Wagner PD, Bosch J. Gas exchange and pulmonary vascular reactivity in patients with liver cirrhosis. *Am Rev Respir Dis* 1987; 135: 1085–1092.
6. Mélot C, Naeije R, Dechamps P, Hallemans R, Lejeune P. Pulmonary and extrapulmonary contributors to hypoxemia in liver cirrhosis. *Am Rev Respir Dis* 1989; 139: 632–640.
7. Hedenstierna G, Söderman C, Eriksson LS, Wahren J. Ventilation-perfusion inequality in patients with non-alcoholic liver cirrhosis. *Eur Respir J* 1991; 4: 711–717.
8. Thorens JB, Junod AF. Hypoxaemia and liver cirrhosis: a new argument in favour of a "diffusion-perfusion defect". *Eur Respir J* 1992; 5: 754–756.
9. Crawford ABH, Regnis J, Laks L, Donnelly P, Engel LA, Young IH. Pulmonary vascular dilatation and diffusion-dependent impairment of gas exchange in liver cirrhosis. *Eur Respir J* 1995; 8: 2015–2021.
10. Krowka MJ, Wiseman GA, Burnett OL, et al. Hepatopulmonary syndrome: a prospective study of relationships between severity of liver disease, PaO$_2$ response to 100% oxygen, and brain uptake after ^{99m}Tc MAA lung scanning. *Chest* 2000; 118: 615–624.
11. Dinh-Xuan AT. Endothelial modulation of pulmonary vascular tone. *Eur Respir J* 1992; 5: 757–762.
12. Vallance P, Moncada S. Hyperdynamic circulation in cirrhosis: a role for nitric oxide? *Lancet* 1991; 337: 776–778.
13. Rolla G. Is nitric oxide the ultimate mediator in hepatopulmonary syndrome? *J Hepatol* 2003; 38: 668–670.
14. Dinh-Xuan AT, Texereau J. Measuring exhaled nitric oxide: not only a matter of how–but also why–should we do it? *Eur Respir J* 1998; 12: 1005–1007.
15. Matsumoto A, Ogura K, Hirata Y, et al. Increased nitric oxide in the exhaled air of patients with decompensated liver cirrhosis. *Ann Intern Med* 1995; 123: 110–113.
16. Sogni P, Garnier P, Gadano A, et al. Endogenous pulmonary nitric oxide production measured from exhaled air is increased in patients with severe cirrhosis. *J Hepatol* 1995; 23: 471–473.
17. Cremona G, Higenbottam TW, Mayoral V, et al. Elevated exhaled nitric oxide in patients with hepatopulmonary syndrome. *Eur Respir J* 1995; 8: 1883–1885.
18. Rolla G, Brussino L, Colagrande P, et al. Exhaled nitric oxide and impaired oxygenation in cirrhotic patients before and after liver transplantation. *Ann Intern Med* 1998; 129: 375–378.
19. Sogni P, Sabry S, Moreau R, Gadano A, Lebrec D, Dinh-Xuan AT. Hyporeactivity of mesenteric resistance arteries in portal hypertensive rats. *J Hepatol* 1996; 24: 487–490.
20. Chabot F, Mestiri H, Sabry S, Dall′Ava-Santucci J, Lockhart A, Dinh-Xuan AT. Role of NO in the pulmonary artery hyporeactivity to phenylephrine in experimental biliary cirrhosis. *Eur Respir J* 1996; 9: 560–564.
21. Delclaux C, Mahut B, Zerah-Lancner F, et al. Increased nitric oxide output from alveolar origin during liver cirrhosis versus bronchial source during asthma. *Am J Respir Crit Care Med* 2002; 165: 332–337.
22. Nunes H, Lebrec D, Mazmanian M, et al. Role of nitric oxide in hepatopulmonary syndrome in cirrhotic rats. *Am J Respir Crit Care Med* 2001; 164: 879–885.
23. Zhang J, Ling Y, Luo B, et al. Analysis of pulmonary heme oxygenase-1 and nitric oxide synthase alterations in experimental hepatopulmonary syndrome. *Gastroenterology* 2003; 125: 1441–1451.
24. Brussino L, Bucca C, Morello M, Scappaticci E, Mauro M, Rolla G. Effect on dyspnoea and hypoxaemia of inhaled N^G-nitro-L-arginine methyl ester in hepatopulmonary syndrome. *Lancet* 2003; 362: 43–44.
25. Schenk P, Madl C, Rezaie-Majd S, Lehr S, Muller C. Methylene blue improves the hepatopulmonary syndrome. *Ann Intern Med* 2000; 133: 701–706.
26. Sztrymf B, Rabiller A, Nunes H, et al. Prevention of hepatopulmonary syndrome and hyperdynamic state by pentoxifylline in cirrhotic rats. *Eur Respir J* 2004; 23: 752–758.
27. Barnes PJ, Adcock IM. Transcription factors and asthma. *Eur Respir J* 1998; 12: 221–234.
28. Luo B, Liu L, Tang L, Zhang J, Ling Y, Fallon MB. ET-1 and TNF-α in HPS: analysis in prehepatic portal hypertension and biliary and nonbiliary cirrhosis in rats. *Am J Physiol Gastrointest Liver Physiol* 2004; 286: G294–G303.
29. Zhang M, Luo B, Chen SJ, Abrams GA, Fallon MB. Endothelin-1 stimulation of endothelial nitric oxide synthase in the pathogenesis of hepatopulmonary syndrome. *Am J Physiol Gastrointest Liver Physiol* 1999; 277: G944–G952.
30. Luo B, Liu L, Tang L, et al. Increased pulmonary vascular endothelin B receptor expression and responsiveness to endothelin-1 in cirrhotic and portal hypertensive rats: a potential mechanism in experimental hepatopulmonary syndrome. *J Hepatol* 2003; 38: 556–563.