The hepatopulmonary syndrome: NO way out?

To the Editors:

The hepatopulmonary syndrome (HPS) is defined by the triad of chronic liver disease, abnormal pulmonary gas exchange (low arterial oxygen tension \( P_{a,O_2} \) and transfer factor of the lung for carbon monoxide), and intrapulmonary vascular dilatation [1]. The recent editorial on HPS [2] suggests that “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”. But, is this strategy actually so logical? The key feature of the intrapulmonary vascular dilatation in HPS is the intrapulmonary shunt shown physiologically by a low \( P_{a,O_2} \) after 100% oxygen breathing, and anatomically by the passage of radiolabelled albumin macroaggregates (20–60 \( \mu \)m in diameter), or echobubbles, through the pulmonary capillary bed [3]. The striking feature pathologically is gross dilatation of capillaries in the alveolar septum, diameters of 100 \( \mu \)m being described [4]. Is it likely that endogenous vasodilators are responsible for “relaxing” alveolar capillaries to such an extent? Of course, endogenous vasodilators may play a part in “remodelling” these capillaries.

With regard to pulmonary gas exchange, two factors seem to operate in severe hepatopulmonary syndrome: 1) a

REFERENCES


From the author:

Teramoto and colleagues have completely misunderstood the purpose of the ERS Task Force on diagnosis and management of chronic cough [1]. The document deals with patients who have had a cough for >8 weeks. It is not about patients who can’t cough. To suggest in their opening paragraph that we neglect cough in the elderly is simply disingenuous. We deliberately separated chronic cough in children from that in adults since the aetiology is different. However, in adults the causes and treatment of chronic cough are not age related and the elderly were frequent attendees in the 13 studies quoted in table 1 which presents the accumulated experience of specialist cough clinics [1].

Decreased cough and aspiration are important clinical problems but they were not the subject of our discussions. Clearly neurological illness [2, 3] and anatomical abnormality [4] can increase the likelihood of aspiration but this is neither age specific nor relevant to clinicians dealing with patients who present with isolated chronic cough.

Finally, an important function of documents such as the Task Force report is to provide a balanced overview of the literature. Teramoto and colleagues seem to have concentrated largely on their own work, which perhaps goes some way to explain the current debate.

A.H. Morice
Division of Academic Medicine, University of Hull, Castle Hill Hospital, Cottingham, UK.

REFERENCES

The finely tuned balance would be disrupted in favour of processes of growth, repair, senescence and apoptosis. In HPS, and capillary network [4, 5]. Capillaries and arterioles are not directly connected to the pulmonary circulation following surgical treatment of congenital heart defects [4–6]. These patients develop pulmonary vascular dilatations and pulmonary shunting, much like that observed in the HPS, and these abnormalities resolve after redirection of hepatic veins to the cavopulmonary connection [6].

J.M.B. Hughes points out that after liver transplantation, pulmonary vascular resistance increases and arterial oxygen tension improves, but the carbon monoxide transfer factor remains low, suggesting a return to normal of arteriolar tone with restoration of pulmonary vasoreactivity to improve the matching of perfusion to ventilation, but persistently dilated pulmonary capillaries. Whether this is really the case remains uncertain. The carbon monoxide transfer factor cannot be anything but a very imperfect measure of pulmonary capillary calibre, and there are many causes of abnormally low carbon monoxide transfer factor in liver-transplanted patients. The pulmonary vascular dilatations after liver transplantation have been shown to reverse over time, although slowly and not always completely in the case of gross dilatations [4, 5, 7]. Here also, we agree with J.M.B. Hughes that a return to normal of endogenous nitric oxide production is unlikely to be the sole determinant of the reversal of pulmonary vascular structure and function to normal equilibrium state.

REFERENCES


From the authors:

Our recent editorial [1] argued that increased nitric oxide (NO) production is an important factor underlying the molecular mechanisms that cause pulmonary vascular dilatations in the hepatopulmonary syndrome (HPS). J.M.B. Hughes rightly points out that there is likely to be more to it than just the vasodilatory effects of NO to account for gross capillary dilatations typically found in the HPS. Indeed, there is little smooth muscle to relax in normal capillaries, and increased capillary diameters by a factor of 10 would be an unlikely consequence of vasorelaxation. We agree that other vasodilatating mediators, such as carbon monoxide and the vasoactive intestinal peptide, along with an overexpression of the endothelin B receptor [2, 3], are likely to be involved in a complex reversal of angiogenesis at the pulmonary arterioles and capillary network [4, 5]. Capillaries and arterioles are not fixed structures, but are the net result of dynamic antagonistic processes of growth, repair, senescence and apoptosis. In HPS, this finely tuned balance would be disrupted in favour of dominant apoptosis and senescence, while pulmonary hypertension is the opposite situation of excessive uncontrolled angiogenesis. That the liver controls the constant remodelling of the pulmonary circulation is illustrated by the fact that pulmonary vascular dilatations occur when systemic veins are directly connected to the pulmonary circulation following surgical treatment of congenital heart defects [4–6]. These patients develop pulmonary vascular dilatations and pulmonary shunting, much like that observed in the HPS, and these abnormalities resolve after redirection of hepatic veins to the cavopulmonary connection [6].

R. Naeije* and A.T. Dinh-Xuan*

Service de Physiologie-Explorations Fonctionnelles, Centre Hospitalier Universitaire Cochin, Université Paris V, Paris, France.

REFERENCES