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EDITORIAL

Do Late Bubbles Correspond to Early Hepatopulmonary Syndrome?

Hilary M. DuBrock,* Michael J. Krowka**

* Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, United States.
** Transplant Research Center, Mayo Clinic, Charlton Building, Rochester, United States.

The study by Mendizabal, *et al*. in this issue of *Annals of Hepatology* describes the natural history of isolated intrapulmonary vascular dilatation (IPVD) (with normal oxygenation) in liver transplant candidates and compares the survival of patients with isolated IPVD to patients with hepatopulmonary syndrome (HPS) and controls without IPVD. In portopulmonary hypertension, IPVD was unexpectedly documented and noted to be associated with worse survival.[1] Despite being commonly encountered in liver transplant candidates,[2] the natural history and outcomes of IPVD and its relationship to HPS have not been previously described. This study provides a valuable contribution to our understanding of clinical outcomes of IPVD, but still leaves many questions unanswered.

In this prospective cohort study, 35% (7/20) of patients with isolated IPVD and serial arterial blood gases went on to meet criteria for HPS with a subsequent increase in Alveolar-arterial (A-a) gradient and decline in Partial pressure of oxygen in arterial blood (PaO_2) over a mean duration of 21 months of follow-up. Although comparisons could be limited by the small sample size, it would be important to know if there were any differences between the 7 patients who developed HPS and the 13 who did not. For example, did the patients who develop HPS just have longer follow-up periods? Would all patients have developed HPS over time if they were followed for a longer duration? What was the PaO_2 decline over time in HPS? Additionally, it would be valuable to know if patients with IPVD remain stable for a period of time and then suddenly develop abnormal gas exchange or if there is a slow, steady decline in oxygenation over time. This information would be helpful to elucidate whether IPVD is a distinct precursor to HPS or whether IPVD, mild, moderate and severe HPS just represent a spectrum of the same disease. Lastly, if isolated IPVD is truly a precursor of HPS, is progression to HPS preventable?

We were surprised that controls without significant cardiopulmonary disease also had abnormal gas exchange (median A-a gradient 17.2, IQR 7.6-26.8). The reasons for this are not known, but could be due to inclusion of patients with subclinical cardiopulmonary disease. Alternatively, discordant positioning with upright, seated arterial blood gases and supine contrast-enhanced echocardiograms may have misclassified some patients with true HPS as controls. The authors did not comment on the positioning for contrast-enhanced echocardiography, but supine, as opposed to upright, positioning may limit detection of IPVD.[3] Although repeat arterial blood gases were not performed at a time of clinical deterioration, it would be also be important to know whether a repeat evaluation for cardiopulmonary disease, such as development of a new pleural effusion, was performed at the time of follow-up testing.

The low prevalence of patients with severe HPS in the study and the region is quite interesting. As the authors state, this may be related to differences in genetic risk factors for HPS as described by Roberts, *et al*.[4] It is also possible that differences in altitude contribute to the low prevalence of severe HPS in Argentina. As previously suggested by Valley, *et al*.,[5] hypoxic pulmonary vasoconstriction at higher altitude may mitigate pulmonary vasodilatation and hypoxemia. If anything, this could result in an underestimation of the risk of progression to HPS in patients with IPVD residing at lower altitude.

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Lastly, HPS patients in this cohort did not have statistically significant differences in survival compared to the IPVD patients or controls. The appearance of the survival curves and the overall increase, albeit non-significant, in death rates suggest that HPS may still be associated with worse survival, but the ability to detect a significant difference in this single center study may have been limited by the smaller sample size compared to PVCLD2.[2] Regardless, as the authors mention, most published literature in HPS is based on North American and European cohorts, and publication of outcomes in this well-characterized cohort of patients with IPVD and HPS adds significantly to the field.

In summary, 35% of liver transplant candidates in Argentina with IPVD develop abnormal arterial oxygenation over time, thus meeting diagnostic criteria for HPS. Future studies to identify risk factors for progression to HPS, to further explore the relationship between altitude and HPS and to identify the cause(s) of abnormal gas exchange in controls without significant cardiopulmonary disease or IPVD are warranted.

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Correspondence and reprint request:
Michael J. Krowka, M.D.
Transplant Research Center, Mayo Clinic, Charlton Building, 10th Floor, 200 First St. SW, Rochester, MN 55905, United States.
E-mail: krowka.michael@mayo.edu