Pulmonary Circulation

Understanding exercise hemodynamics

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The current definition of pulmonary hypertension as a resting mean pulmonary arterial pressure (mPAP) $\geq$25 mmHg is not based on scientific evidence but on expert opinion. It has been shown that below 25 mmHg, PAP may have an impact on survival and morbidity in patients with scleroderma and in lung disease such as chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis. Recently, the same has been shown in a large cohort of unselected patients.[1] The PAP increase during exercise may predict physical capacity[2] and morbidity/mortality events.[3]

Exercise causes PAP to increase significantly;[4] in young healthy individuals, the main driver for the increase in PAP is the increase in cardiac output (CO), but in elderly patients and patients with heart and lung disease, increasing filling pressures of the left ventricle and air trapping during exercise may become increasingly important.[5] As demonstrated in Fig. 1, there are three different prototypes of a pathologic PAP/CO relationship but unfortunately, combinations of all these patterns are common. Importantly, the PAP/CO slope and the PAP/CO relationship in general may vary considerably between individuals. Because the equation for pulmonary vascular resistance (PVR) can be rearranged as

$$\mathrm{PAP/CO} = \mathrm{PVR} + \mathrm{PAWP/CO} = \mathrm{TPR}$$

one component contributing to the PAP/CO relationship is the PVR, indicating pulmonary vascular function, and the other component is the pulmonary artery wedge pressure (PAWP)/CO ratio, indicating left ventricular function. The third component is only relevant in obstructive lung disease. It is the exercise-induced increase in intrathoracic pressure due to trapped air. TPR stands for ''total pulmonary resistance'' and is calculated as PAP/CO.

Exercise hemodynamics represent a great tool to get insight into the individual pathologic mechanisms limiting exercise capacity. On the other hand, making a precise diagnosis is quite difficult because there are no generally accepted limits of normal. It has been shown that relating PAP to CO during exercise avoids misclassification of patients.[6,7] However, there is not even general consensus where to place the zero level in the non-supine individual and how to read the pressures: during breath-hold, during continued breathing at end-expiration, or during continued breathing using an average over three or more breathing cycles.[8]

In the current issue of *Pulmonary Circulation*, Oliveira et al. analyze a large number of 723 right heart catheter investigations in patients with dyspnea on exertion from a single expert center. More than half of these investigations were characterized by resting PAP $<$ 25 mmHg and PAWP $\leq$ 15 mmHg (n = 452) and the other 271 patients by either PAP $>$ 25 mmHg or PAWP $>$ 15 mmHg. After exclusion of patients with severe heart or lung disease, anemia, and premature exercise cessation, this resulted in just 16 patients who were labelled as ''resting PH'' (rPH). Among the patients with PAP $<$ 25 mmHg, the same exclusion process resulted in the remaining 259 patients who were assigned to four ranges of resting supine PAP and classified according to their PAP and PVR during peak upright exercise.

Oliveira et al. investigated the question if ''exercise PH'' (ePH) has a functional consequence for these patients. They defined ePH as a significant increase in PAP $>$ 33 mmHg combined with a sustained PVR elevation $>$2.1 WU during peak exercise. For patients aged $<$50 years, they used thresholds of 30 mmHg for PAP and 1.34 WU for PVR. This definition of ePH was derived from PAP- and PVR-responses from individuals who were investigated due to dyspnea on exertion.[9] These individuals were classified as ''normal'' because they all reached at least the lower limit of normal peak VO2. Among the 259 patients, there were 35 fulfilling the ePH criteria and 224 who did not. The patients without ePH had a well-preserved peak VO2 while ePH patients presented with substantially decreased peak VO2, similar to rPH patients. ePH was also associated with older age (59 years vs. 53 years), more co-morbidities, and significantly higher PAP/CO slopes. Thus, all these factors seem to be very much correlated to each other.

As expected, resting PAP was a significant predictor of ePH. The higher the resting pressure, the higher the likelihood for of ePH. Interestingly, among the ''borderline PAP group'' with resting PAP in the range of 21–24 mmHg, only 27% fulfilled the criteria for ePH. This is in contrast to Lau et al.[10] who found that, in their borderline patients,

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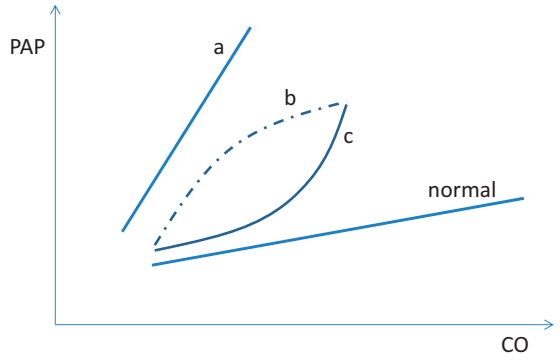

Figure 1. Prototypes of pathologic PAP/CO relationship.
a, pulmonary vascular disease with severely elevated PVR; b, LV disease with early PAWP increase during exercise; c, obstructive lung disease with late air trapping during exercise.

86% fulfilled their ePH criteria. The ePH definition of Lau et al. was in agreement with the recent suggestion by Hervé et al.[6] using the criteria of peak PAP > 30 mmHg and peak TPR > 3WU. Using TPR instead of PVR for the ePH definition causes inclusion of all the patients with heart and/or lung disease that would not fulfil the PVR criteria of the other ePH definition. This may be the main reason for the large difference in the rate of ePH between the studies.

Oliveira et al. are to be commended for their valuable contributions to a better understanding of exercise hemodynamics. They used PVR as a criterion for ePH. This makes a lot of sense, particularly when we think of identifying patients with exercise-limiting pulmonary vasculopathy, because an elevated PVR is quite sensitive and specific for pulmonary arterial remodeling. However, we should also acknowledge that the majority of people with unexplained dyspnea are the complicated multimorbid patients with significant dysfunction of both heart and lung. For this purpose, TPR at peak exercise would be the better general marker of a life-threatening disease.

Cardiopulmonary exercise test with simultaneous right heart catheter investigation represents the gold standard for the analysis of unexplained dyspnea. As specialized clinicians, we should be able to find a consensus how to categorize all the investigated patients with abnormal pulmonary hemodynamics on exercise. We are still searching for a consensus on most basic questions like the posture and how to read the pressures and we need an international approach for the establishment of more advanced techniques. There are many steps to go before we can clearly state which features in exercise hemodynamics identify the best candidates for targeted pulmonary vascular therapies.

Conflict of interest

The authors declare that there is no conflict of interest.

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