ERJ Express. Published on March 30, 2016 as doi: 10.1183/13993003.01678-2015

Diagnostic concordance of different criteria for exercise pulmonary hypertension in subjects with normal resting pulmonary artery pressure

To the Editor:

Pulmonary hypertension is defined by a resting mean pulmonary artery pressure (mPAP) ⩾25 mmHg [1]. Despite a better understanding of the biology of pulmonary hypertension and new therapeutic advances, pulmonary hypertension remains diagnosed late in its natural history and is largely a non-curable condition [2]. Recently, there has been renewed interest in stress-testing of the pulmonary circulation since the early stages of pulmonary vascular disease (PVD) or left heart disease (LHD) can be associated with normal resting mPAP but an abnormal haemodynamic response that is unmasked by exercise [3–5].

Although no consensus definition currently exists for the diagnosis of exercise pulmonary hypertension, any criteria for exercise pulmonary hypertension should incorporate an assessment of mPAP–cardiac output (mPAP–CO) relationship from a physiological perspective, since mPAP is a flow-dependent variable. Current evidence suggests that in health, mPAP should not exceed 30 mmHg at a cardiac output of <10 $L \cdot min^{-1}$ [3]. However, multiple methods of mPAP–CO assessment have been proposed in the literature for exercise stress-testing of the pulmonary circulation, and it is unknown whether these differing methods necessarily produce concordant results.

A recent clinical study by our group has favoured the criteria for exercise pulmonary hypertension using the combined haemodynamic parameters of peak mPAP ($mPAP_{max}$) >30 mmHg and peak total pulmonary resistance (TPR_{max}) >3 WU during exercise [5]. TPR_{max} uses a single-point mPAP–CO ratio at peak exercise. This combined criterion has been shown to significantly reduce the number of healthy controls who are misclassified as having exercise pulmonary hypertension compared with the previous definition of exercise pulmonary hypertension (mPAP >30 mmHg) [6]. An alternative method of mPAP–CO assessment for the diagnosis of exercise pulmonary hypertension uses the slope of multipoint mPAP–CO relationships taken at multiple levels of exercise (generally 4–5 data points), and an mPAP–CO slope >3 WU is used to define exercise pulmonary hypertension [4]. Finally, a method that uses a two-point measurement of the mPAP–CO slope from resting and peak exercise haemodynamics has also been proposed [7, 8]. Although these different methods of assessing the mPAP–CO relationship appear "similar", they are not synonymous when one considers carefully the behaviour of the mPAP–CO relationship during exercise. The aim of our study was to evaluate the diagnostic concordance of the different methods that have been proposed for the assessment of the mPAP–CO relationship for the diagnosis of exercise pulmonary hypertension.

A total of 169 subjects (n=68 controls; n=49 PVD; n=52 LHD) with normal resting mPAP ⩽20 mmHg underwent exercise haemodynamic evaluation with lower limb cycle ergometry. The detailed exercise protocol has been reported previously [9]. This retrospective study was approved by the ethics board of the Université Paris-Sud (approval no. 9708) and informed consent was obtained from all patients.

Patients were defined as displaying exercise pulmonary hypertension according to each of the following three diagnostic criteria: 1) exercise $mPAP_{max}$ >30 mmHg plus exercise TPR_{max} >3 WU ($mPAP_{max}$ >30 mmHg +TPR_{max} >3 WU); 2) linearised slope of multiple mPAP–CO relationships >3 WU ($mPAP–CO_{slope}$ >3 WU); and 3) the ratio of $mPAP_{max}$ minus resting mPAP over peak cardiac output minus resting cardiac output >3 WU ($\Delta mPAP/\Delta CO$ >3 WU). Diagnostic concordance was then assessed based on the percentage of cases with concordant classification and the kappa statistic. Statistical analyses were performed using SPSS v22 (IBM, Chicago, IL, USA).

Detailed demographics of the study population, including resting and exercise haemodynamic results, have been reported elsewhere [5]. The average number of mPAP–CO points available from rest to peak exercise was (5.4±1.7). For the $mPAP–CO_{slope}$ method, the median R^2 of the linear regression fit of mPAP–CO points was 0.86 (range 0.32–0.99).

All three criteria were associated with high diagnostic accuracy for the discrimination of controls from patients with PVD and LHD, with respective area under the curve (AUC) on ROC analysis as follows:

$mPAP_{max}+TPR_{max}$=0.99, $mPAP–CO_{slope}$=0.94, and ΔmPAP/ΔCO=0.96. Table 1 summarises the respective sensitivities and specificities of the three different haemodynamic criteria for the discriminaton of controls *versus* patients with LHD and PVD.

When the three different criteria with their respective cut-off values were used to classify patients into the presence or absence of exercise pulmonary hypertension, concordant classification was found in 80.5% of cases for $mPAP_{max}+TPR_{max}$ *versus* $mPAP–CO_{slope}$ (κ=0.61); 85.8% for $mPAP+TPR_{max}$ *versus* ΔmPAP/ΔCO (κ=0.71); and 84.0% for $mPAP–CO_{slope}$ *versus* ΔmPAP/ΔCO (κ=0.68).

Overall, 78% of cases were fully concordant across all three criteria. Diagnostic disagreement were very uncommon for cases with either very flat mPAP–CO response (TPR_{max} <2 WU) (0%) or steep mPAP–CO response (TPR_{max} >4 WU) (6%). The value of the zero-flow pressure intercept for cases that were fully concordant for all three criteria was not significantly different compared with cases with diagnostic disagreement (median (interquartile range), 1.5(−3.4–5.6) *versus* 1.3 (−8.8–6.4) mmHg; p=0.44).

The present study highlights that the different criteria that have been recently proposed for the diagnosis of exercise pulmonary hypertension are not interchangeable. Although all of these criteria incorporate an assessment of mPAP–CO relationship during exercise (in contrast to the old definition which contained only a pressure parameter), the differing methodologies of each criteria may result in significant disagreement for the diagnosis of exercise pulmonary hypertension.

Pulmonary pressure-flow relationship is usually well described by linear relationships over physiological flow ranges but this is only an approximation. In health, the mPAP–CO relationship when left atrial pressure is held unchanged may actually display a slight curvilinearity [10], owing to the natural distensibility of the pulmonary circulation. Other non-linear patterns of mPAP–CO relationship have also been described in disease states such as pulmonary arterial hypertension [11].

Using a simple linear model, the mPAP–CO relationship can be expressed as $y=ax+b$, where y is mPAP, x is CO and b is the extrapolated pressure intercept at zero flow. It can be easily appreciated that for all of the criteria to be fully consistent, the following conditions must be met: 1) the zero-flow pressure intercept must cross origin, and 2) the mPAP–CO relationship must be strictly linear over the measured flow ranges. Given that these assumptions are not always met, it is not surprising that diagnostic disagreement is present amongst the different criteria for exercise pulmonary hypertension. Furthermore, haemodynamic measurements at maximal exercise may be more sensitive at detecting late-exercise surge in pulmonary artery pressure induced by low mixed venous oxygen content and sympathetic nervous system activation [12], or excessive late-exercise rise in left atrial pressure. Accordingly, both the $mPAP_{max}+TPR_{max}$ and the ΔPAP/ΔCO methods place greater emphasis on the single measurement obtained at peak exercise, whereas the $mPAP–CO_{slope}$ method characterises mPAP–CO response across all exercise stages. The different criteria also have practical implications for exercise haemodynamic testing since linear regression analysis of multipoint measurements at many different workloads ($mPAP–CO_{slope}$) is more complex, in comparison to the more simple approach in which exercise pulmonary hypertension is diagnosed whenever mPAP exceeds 30 mmHg at an equivalent cardiac output of <10 $L·min^{-1}$ ($mPAP_{max}+TPR_{max}$). However, it must be acknowledged that this is simply a practical observation and detailed mPAP–CO plots (with >4–5 points) afford a more detailed description of vascular resistance during exercise.

For the majority of healthy subjects who have very flat pressure–flow relationships, all three criteria will allow correct classification as normal response. Conversely, for many patients with exercise pulmonary hypertension and very steep pressure–flow response, they will also exceed the threshold set by all three criteria. However,

TABLE 1 Diagnostic performance of various criteria for discriminating controls *versus* patients with PVD and LHD

	Patients n	$mPAP_{max}+TPR_{max}$ [#]		$mPAP–CO_{slope}$ [¶]		ΔmPAP/ΔCO [+]	
		Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
All	169	0.93 (0.86–0.96)	1.0 (0.95–1.0)	0.72 (0.62–0.81)	0.88 (0.78–0.95)	0.94 (0.88–0.98)	0.87 (0.76–0.94)
Diagnosis							
PVD	49	0.94 (0.84–0.98)	1.0 (0.95–1.0)	0.67 (0.52–0.80)	0.88 (0.78–0.95)	0.88 (0.75–0.95)	0.87 (0.76–0.94)
LHD	52	0.92 (0.82–0.97)	1.0 (0.95–1.0)	0.77 (0.63–0.87)	0.88 (0.78–0.95)	1.0 (0.93–1.0)	0.87 (0.76–0.94)

[#]: sensitivity and specificity values based on peak mean pulmonary arterial pressure ($mPAP_{max}$) >30 mmHg and peak total pulmonary resistance (TPR_{max}) >3 WU; [¶]: sensitivity and specificity values based on the mPAP–cardiac output slope ($mPAP–CO_{slope}$) >3 WU; [+]: sensitivity and specificity values based on the ratio of $mPAP_{max}$ minus resting mPAP over peak cardiac output minus resting cardiac output (ΔmPAP/ΔCO) >3 WU. PVD: pulmonary vascular disease; LHD: left heart disease.

there will remain a significant number of subjects who will have discrepant classification, as demonstrated by our results. Imprecise pressure and cardiac output measurements in clinical practice may also contribute to our findings. Limitations of the current study include a small number of subjects above the age of 70 years, patients with a diagnosis of PVD were over-represented by chronic thromboembolic disease, and the majority of subjects were women.

In conclusion, our study demonstrates that the different methods used to define mPAP–CO relationship for the diagnosis of exercise pulmonary hypertension suffer from lack of diagnostic concordance in a substantial number of cases. This is particularly relevant for patients who have exercise mPAP–CO response close to the current threshold of 3 WU proposed in the current literature. Significant advancement has already been made to incorporate the assessment of flow and not merely pressure for the diagnosis of exercise pulmonary hypertension. The scientific community must now come to an agreement on a practical and robust definition of exercise pulmonary hypertension in order for progress to occur in this field.

@ERSpublications
Methodology of pressure–flow assessment needs to be standardized for the diagnosis of exercise pulmonary hypertension http://ow.ly/YMgZw

Laurent Godinas[1,2,3,4], Edmund M Lau[1,2,3,5], Denis Chemla[1,3,6], Frédéric Lador[7], Laurent Savale[1,2,3], David Montani[1,2,3], Xavier Jaïs[1,2,3], Olivier Sitbon[1,2,3], Gérald Simonneau[1,2,3], Marc Humbert[1,2,3] and Philippe Hervé[1,3,8]
[1]Faculté de Médecine, Université Paris-Sud, Université Paris-Saclay, Le Kremlin-Bicêtre, France. [2]Service de Pneumologie, AP-HP, Le Kremlin-Bicetre, France. [3]INSERM UMR_S999, Hôpital Marie Lannelongue, Le Plessis Robinson, France. [4]Service de Pneumologie, CHU UcL Namur, Yvoir, Belgium. [5]Sydney Medical School, University of Sydney, Camperdown, Australia. [6]Département de Physiologie, AP-HP, Le Kremlin-Bicetre, France. [7]Service de Pneumologie – Programme Hypertension Pulmonaire, Hôpitaux Universitaires de Genève, Geneva, Switzerland. [8]Département de Chirurgie Thoracique, Vasculaire et de Transplantation Pulmonaire, Hôpital Marie Lannelongue, Le Plessis Robinson, France.

Correspondence: Edmund Lau, Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, University of Sydney, Missenden Rd, Camperdown NSW 2050, Australia. E-mail: edmund.lau@sydney.edu.au

Received: Oct 10 2015 | Accepted after revision: Feb 18 2016

Support statement: Funding for this manuscript was provided by Fondation Mont-Godinne.

Conflict of interest: Disclosures can be found alongside the online version of this article at erj.ersjournals.com

References

1 Hoeper MM, Bogaard HJ, Condliffe R, *et al.* Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62: Suppl. 25, D42–D50.
2 Lau EMT, Humbert M, Celermajer DS. Early detection of pulmonary arterial hypertension. *Nat Rev Cardiol* 2014; 12: 143–155.
3 Naeije R, Vanderpool R, Dhakal BP, *et al.* Exercise-induced pulmonary hypertension: physiological basis and methodological concerns. *Am J Respir Crit Care Med* 2013; 187: 576–583.
4 Lewis GD, Bossone E, Naeije R, *et al.* Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. *Circulation* 2013; 128: 1470–1479.
5 Herve P, Lau EM, Sitbon O, *et al.* Criteria for diagnosis of exercise pulmonary hypertension. *Eur Respir J* 2015; 46: 728–737.
6 Kovacs G, Avian A, Olschewski H. Proposed new definition of exercise pulmonary hypertension decreases false positive cases. *Eur Respir J* 2016 [In press DOI: 10.1183/13993003.01394-2015].
7 Portillo K, Torralba Y, Blanco I, *et al.* Pulmonary hemodynamic profile in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2015; 10: 1313–1320.
8 Kovacs G, Avian A, Tscherner M, *et al.* Characterization of patients with borderline pulmonary arterial pressure. *Chest* 2014; 146: 1486–1493.
9 Lau EM, Chemla D, Godinas L, *et al.* Loss of vascular distensibility during exercise is an early hemodynamic marker of pulmonary vascular disease. *Chest* 2015 [In press DOI: 10.1378/chest.15-0125].
10 Naeije R, Chesler N. Pulmonary circulation at exercise. *In*: Terjung R, ed. Comprehensive Physiology. Hoboken, John Wiley & Sons, Inc., 2012.
11 Tolle JJ, Waxman AB, Van Horn TL, *et al.* Exercise-induced pulmonary arterial hypertension. *Circulation* 2008; 118: 2183–2189.
12 Kafi SA, Mélot C, Vachiéry JL, *et al.* Partitioning of pulmonary vascular resistance in primary pulmonary hypertension. *J Am Coll Cardiol* 1998; 31: 1372–1376.