CHEST

Loss of Vascular Distensibility During Exercise Is an Early Hemodynamic Marker of Pulmonary Vascular Disease

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BACKGROUND: Exercise can distend the normally compliant, thin-walled pulmonary vessels. Loss of distensibility has been suggested as an early marker of pulmonary vascular remodeling. We hypothesized that in mild pulmonary vascular disease (PVD), a reduction in vascular distensibility during exercise occurs prior to the development of overt resting pulmonary hypertension (PH).

METHODS: Distensibility α during exercise (percentage change in vessel diameter per mm Hg increase in transmural pressure) was estimated in 90 subjects using a model of the pulmonary circulation and invasive hemodynamic data. Distensible properties in mild PVD without resting PH (PVD-noPH) (n = 33) were compared with control subjects (n = 26) and PVD with overt resting PH (PVD-PH) (n = 31).

RESULTS: Resting mean pulmonary artery pressure (mPpa) levels were 14 ± 4, 20 ± 3, and 34 ± 10 mm Hg with corresponding exercise mPpa-cardiac output slopes of 1.5 ± 0.6, 3.5 ± 0.9, and 5.7 ± 3.2 mm Hg/L/min for control subjects and the PVD-noPH and PVD-PH groups, respectively. The distensible model produced high accuracy and precision with no mean bias and 95% limits of agreement of −4.5 to 4.5 mm Hg between calculated and measured mPpa. Distensibility α was lowest in the PVD-PH group, intermediate in the PVD-noPH group, and highest in control subjects (0.25 ± 0.14%/mm Hg vs 0.45 ± 0.24%/mm Hg vs 1.40 ± 0.45%/mm Hg, $P < .0001$). Distensibility α discriminated PVD-noPH from control subjects with a sensitivity of 88% and a specificity of 100%. The discriminatory performance of α was similar for the subgroup of PVD-noPH, with a strictly normal resting mPpa ≤ 20 mm Hg.

CONCLUSIONS: Loss of pulmonary vascular distensibility during exercise occurs prior to resting PH in PVD. The usefulness of α as a novel vascular index for the early detection of PVD warrants further validation.

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KEY WORDS: exercise; hemodynamics; pulmonary arterial hypertension; pulmonary hypertension

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ABBREVIATIONS: AUC = area under the curve; Csv/pp = pulmonary artery capacitance; mPpa = mean pulmonary artery pressure; PH = pulmonary hypertension; Ppa = pulmonary artery pressure; Ppw = pulmonary artery wedge pressure; PVD = pulmonary vascular disease; PVD-noPH = pulmonary vascular disease without pulmonary hypertension; PVD-PH = pulmonary vascular disease with pulmonary hypertension; PVR = pulmonary vascular resistance; Q = cardiac output; RHC = right-sided heart catheterization; ROC = receiver-operating characteristic

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Pulmonary vascular disease (PVD) is characterized by progressive remodeling of the pulmonary arteries, resulting in elevation in pulmonary artery pressure (Ppa), right ventricular afterload, and ultimately, right-sided heart failure.[1] At present, the diagnosis of pulmonary hypertension (PH) is defined by a mean Ppa (mPpa) of ≥ 25 mm Hg at rest.[2] Because of the large reserves of the pulmonary circulation, it is recognized that the majority of the pulmonary circulation must be impaired before resting mPpa exceeds 25 mm Hg. Thus, the development of PH is a relatively late hemodynamic event in the evolution of PVD.[3]

The pulmonary circulation is normally thin walled and distensible. During exercise, distension and recruitment of the pulmonary vasculature result in an increase in the total vessel cross-sectional area, resulting in a reduction in pulmonary vascular resistance (PVR).[4] Thus, Ppa-flow relationships in health can display a slight curvilinearity, representing the incremental reduction in PVR at increasing cardiac output (Q).[5,6]

A model of the pulmonary circulation incorporating the index of distensiblity (α, percentage change in diameter per mm Hg increase in distending pressure) can be used to describe pulmonary hemodynamic behavior.[7] In this model, mPpa and pulmonary artery wedge pressure (Ppw) values measured over a range of Q can be used to estimate the distensibility of resistive pulmonary vessels. Calculated values of α using this hemodynamic model have been shown to closely match the true values obtained from in vitro measurements in the normal pulmonary circulation.[8] Pulmonary vascular remodeling may be associated with early changes in vascular distensibility,[9] suggesting that α may serve as a sensitive marker of mild PVD, prior to overt elevation of resting mPpa. Although α has been proposed by investigators as a potentially useful descriptor of the mechanical properties of the pulmonary vasculature,[10,11] it remains unvalidated with respect to its usefulness for the assessment of PVD.

In the current study, we sought to characterize α from invasive exercise hemodynamics in subjects with various severities of PVD. We hypothesized that (1) the α model would provide a valid description of the pulmonary circulation in both health and disease and could accurately predict measured mPpa values over a wide range of distending pressures, and (2) α would be reduced in mild PVD when resting PH has not yet manifested.

Materials and Methods

Patient Population

We reviewed the records of the National Reference Center for Severe Pulmonary Hypertension, Le Kremlin-Bicêtre, France, for exercise right-sided heart catheterizations (RHCs) performed between January 2008 and September 2014. The study was approved by the local ethics review committee (approval no. 9708, Hôpital Bicêtre, Université Paris-Sud). The exercise hemodynamic data of a subset of the study subjects was reported in a previous study.[12] Invasive hemodynamic data required for analysis included mPpa, Ppw, Q (from thermodilution), and heart rate obtained at rest and during exercise. For optimal interpretation of pressure-flow relationships and calculation of α, we included subjects who had at least five complete sets of mPpa-Ppw-Q data points.[10] Subjects were stratified according to three diagnostic groups based on prospectively defined invasive hemodynamic findings and the results of diagnostic investigations (e-Fig 1):

1. Control subjects without PVD included subjects who underwent RHC for investigation of dyspnea of unknown origin or suspected PH who otherwise had no apparent disease affecting the lungs or the heart following diagnostic assessment (n = 26). Subjects had (1) no significant abnormalities on lung function testing, thoracic CT scan, and ventilation-perfusion scintigraphy; (2) no major risk factors for PVD; and (3) normal pulmonary hemodynamics defined by mPpa ≤ 20 mm Hg and Ppw ≤ 15mm Hg at rest,[2,13] and Ppw ≤ 20 mm Hg during maximal exercise.[14] Inclusion of asymptomatic volunteers was not possible for ethical reasons because RHC is invasive.
2. PVD with PH (PVD-PH) included subjects who fulfilled the hemodynamic criteria for the diagnosis of precapillary PH (mPpa ≥ 25 mm Hg and Ppw ≤ 15 mm Hg at rest).[15] These included subjects with pulmonary arterial hypertension (n = 25) and chronic thromboembolic PH (n = 6).
3. PVD without PH (PVD-noPH) included subjects with PVD who did not fulfill the hemodynamic criteria for resting PH (ie, mPpa < 25 mm Hg at rest). The diagnosis of PVD was confirmed by (1) evolution to resting pulmonary arterial hypertension during follow-up (n = 8), (2) lung biopsy consistent with a diagnosis of PVD (n = 4), or (3) thromboembolic disease of the pulmonary circulation documented by positive ventilation-perfusion scintigraphy with obstructive lesions on pulmonary angiography (n = 21). As an a priori, subgroup analyses were also performed for PVD-noPH patients with resting mPpa ≤ 20 mm Hg, because the upper limit of normal mPpa is 20 mm Hg.[13]

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