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How to Measure Peripheral Pulmonary Vascular Mechanics

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Abstract

Pulmonary hypertension (PH) is initially a disease of the small, peripheral resistance arteries. Changes in these vessels are best assessed by measurement of pulmonary artery pressure at several levels of flow to generate multi-point pressure-flow curves. This approach is superior to the traditional single-point measurement of pulmonary vascular resistance (PVR) because it allows a flow-independent definition of the resistive properties of that portion of the pulmonary vascular bed and also provides information on its distensibility. In animal models, multi-point pressure-flow curves can be obtained using an isolated, ventilated, perfused lung system. Clinically, cardiopulmonary exercise testing (CPET) with non-invasive echocardiography is feasible and provides realistic values of the resistance and peripheral compliance. Together, these values can be used to better understand and screen for PH and exercise-induced PH.

I. Introduction

Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (mPAP) greater than 25 mmHg at rest [1]. In the early stages of the disease, dramatic decreases in cross-sectional area available for flow in the small, peripheral pulmonary arteries occur. These transform the normally low resistance pulmonary circulation into a high resistance circuit. Later, the highly compliant nature of the pulmonary vascular bed is also lost, which has profound consequences for right ventricular function.

Typically, PH is diagnosed on the basis of an invasive right heart catheterization in which mPAP, pulmonary capillary wedge pressure (PCW) and cardiac output (Q) are measured. Pulmonary vascular resistance (PVR) is then calculated at this single functional state as (mPAP-PCW)/Q. However, this measurement fails to take into account either normal or abnormal changes in pressure that occur with changes in flow. For example, PVR decreases with exercise in response to recruitment and pressure-induced dilation of small, peripheral

arteries [2]. The failure of PVR to decrease with exercise has recently been described as a clinical entity: exercise-induced pulmonary hypertension [3]. This abnormal functional aspect of the peripheral pulmonary circulation cannot be recognized from single-point calculations of PVR. In addition, when assessing the effects of drugs with the single-point PVR, one can confuse the effect of a drop in pressure (lower mPAP-PCW) with an increase in cardiac output (higher Q) [4].

When PVR is computed from multi-point pressure-flow curves, the result is flow rate-independent and thus a more reliable measure of pulmonary vascular functional state. In addition, the multi-point pressure-flow curves can be used to estimate the distensibility of the small, peripheral arteries [5], which determines their ability to dilate in response to increasing pressure. Pressure-flow curves can be obtained clinically with hemodynamic measurements during cardiopulmonary exercise testing (CPET) [4] or in animal models with isolated, ventilated, perfused lung systems [6]. Like the failure of PVR to decrease with exercise, decreased distensibility may be a clinical entity or risk factor for development of PH.

The development and progression of PH largely depends on the small, peripheral arteries. Thus, accurate techniques for measuring peripheral pulmonary vascular mechanics in patients and animal models are worthy of discussion. Here, we present techniques for measuring peripheral pulmonary artery mechanics from multi-point pressure-flow curves and results from studies in animals and healthy human subjects.

II. Methods

A. Normal and diseased mouse lungs

To demonstrate methods for measuring peripheral pulmonary vascular mechanics in animals, we used male C57BL6/J mice with normal (control: CTL) and diseased (hypoxia-induced PH: HPH) lungs. To create HPH, mice were exposed to 10 days of hypobaric hypoxia such that the partial pressure of oxygen was reduced by half, as previously described [6]. Mice were euthanized with an intraperitoneal injection of 150 mg/kg pentobarbital solution. All protocols and procedures were approved by the University of Wisconsin Institutional Animal Care and Use Committee.

Following euthanasia, the trachea, pulmonary artery and left atrium were cannulated for ventilation, perfusate inflow and perfusate outflow, respectively. The lungs were ventilated with room air and perfused with heated RPMI 1640 cell culture medium with 3.5% Ficoll (an oncotic agent). A syringe pump was used to create steady pulmonary vascular flow of perfusate. In parallel, a high frequency oscillatory pump superimposed an oscillatory component on the pulmonary vascular flow. Pressure transducers measured the instantaneous PAP and LAP. Flow rate (Q) was measured with an in-line flow meter. Details on this isolated, ventilated perfused lung setup are available in [6].

To obtain multi-point pressure-flow curves, lungs were lungs perfused with steady flow at flow rates of 1 to 5 ml/min. Lungs were preconditioned with pulsatile flow from 1 to 5 ml/min at physiological frequencies. Normal ventilation (2 to 10 cm H_2O at 90 breaths/min) occurred whenever data were not being collected.

B. Healthy human subjects

After approval by the Ethical Committee of the Erasme University Hospital, healthy volunteers gave a written informed consent to participate in exercise stress tests with echocardiography. Each subject underwent an echocardiographic examination at rest and as workload was increased by 20 W every 2 min until the maximum tolerated. The

echocardiography was performed on a semi-recumbent cycle ergometer as previously described [7]. Systolic PAP (sPAP) was estimated from the maximum velocity (V) of continuous Doppler tricuspid regurgitation according to $sPAP = 4 \times V^2 + 5$ mmHg where 5 mmHg was the pressure assumed in the right atrium [8]. Mean PAP was calculated as $0.6 \times sPpa + 2$ [9] and left atrial pressure (LAP) was estimated from the ratio of mitral flow E and tissue Doppler mitral annulus E′ waves [10]. LAP was used as an approximation of PCW. Finally, cardiac output was estimated from left ventricular outflow tract cross sectional area and pulsed Doppler velocity-time integral [11].

C. Data analysis

Multipoint mPAP-Q curves were created for each subject and linear regression was used to determine best fit slope and intercept minimizing the sum of least square error. To compute the distensibility α of the small resistance arteries, each multipoint mPAP-Q plot was fit to the equation

$$mPAP = \frac{\left[(1+\alpha LAP)^5 + 5\alpha R_0 Q\right]^{\frac{1}{5}} - 1}{\alpha} \quad (1)$$

where R_0 is the total PVR at rest [5].

All results shown here are presented as mean ± SD. The statistical analysis consisted of a repeated measures analysis of variance. When the F ratio of the analysis of variance reached a $P < 0.05$ critical value, paired or unpaired modified Student's t-tests were applied as indicated to compare specific situations [12].

III. Results

A. Normal and diseased mouse lungs

In normal and diseased mouse lungs, multi-point pressure-flow curves are reasonably well fit by either straight lines or (1). By best-fit to a linear equation, we found that in CTL lungs, the average slope was 1.88 ± 0.23 mmHg min/ml, and the intercept 7.2 ± 0.8 mmHg, with a correlation coefficient R^2 of 0.99 ± 0.01 ($P = 0.00039 \pm 0.00064$). In HPH lungs, the average slope was similar: 1.71 ± 0.22 mmHg min/ml whereas the intercept was significantly higher: 11.8 ± 0.7 mmHg ($P<0.05$). In HPH lungs the fit to a linear equation was also excellent ($R^2 = 0.99 \pm 0.002$; $P = 0.00019 \pm 0.00010$).

Multi-point pressure-flow curves also were well fit by the distensibility equation, at all but the lowest flow rate (Fig. 1). The average distensibility coefficient α was significantly lower in HPH compared to CTL lungs (4.1 ± 0.5% CTL vs. 3.1 ± 0.5% $mmHg^{-1}$ HPH; $p<0.05$). The overall fitting was excellent in both groups ($R^2 = 0.99 \pm 0.009$ in CTL and 0.99 ± 0.002 in HPH lungs).

B. Healthy human subjects

In human subjects, good quality signals were recovered at all levels of exercise. As shown in Table 1, exercise was accompanied by a four-fold increase in Q, and an increase in sPAP that exceeded 40 mmHg in 19 of 25 subjects. Exercise did not affect LAP or PVR at rest.

Each mPAP-Q relationship was well described by a linear approximation. The average slope was 1.37 ± 0.65 mmHg min/L, and the intercept 8.2 ± 3.6 mmHg, with a correlation coefficient R^2 of 0.92 ± 0.06 ($P = 0.0018 \pm 0.005$). The mPAP-Q relationships also were

well fit by the distensibility equation. The average distensibility coefficient α for all subjects was of 0.017 ± 0.018 $mmHg^{-1}$. The average R2 for the fit to (1) was 0.92 ± 0.06 (P = 0.0020 ± 0.006). Representative multi-point pressure-flow curves with linear and curvilinear fits to (1) are shown in Fig. 2.

IV. Discussion

The mechanical properties of the small, peripheral vessels in the pulmonary circulation are important to pulmonary vascular function. In animal models, these can be measured with isolated vessel tests [13], microcomputed tomography imaging at various pressures [14] and estimated from multi-point pressure-flow relationships [5]. Of these, only multi-point pressure-flow curves can be generated in patients and so only this technique is currently clinically useful.

Measurements of resistance and distensibility in normal and diseased mouse lungs indicate that significant functional changes occur in peripheral pulmonary arteries with PH that can be detected via the multi-point pressure-flow curves.

In healthy human subjects, a previous analysis of invasive hemodynamic measurements at exercise showed a mPAP-Q slope of 0.94 ± 9.4 mmHg min L^{-1} with an extrapolated pressure intercept of 8.2 ± 7.9 mmHg in 63 young adults, and a slope of 2.54 ± 0.77 mmHg min L^{-1} with a pressure intercept of 2.3 ± 5.4 mmHg in 14 older subjects [2]. The average slope of mPAP-Q of 1.37 mmHg min L^{-1} in the present study agrees with these previous invasive measurements. This is especially important because non-invasively obtained estimates of mPAP eliminate the need for right heart catheterization, which is associated with morbidity and mortality, especially in PH patients.

The present calculations of α also agree with prior in vitro studies in which a value of 0.02 $mmHg^{-1}$ was obtained in several species, including humans [3]. We expect that with PH, distensibility will decrease significantly, indicating peripheral vascular stiffening. Calculations of α from single point measurements of Ppa and Q support this conjecture [15] but neither invasive nor non-invasive multi-point Ppa-Q data in patients with PH are currently available.

In spite of previously reported excellent correlations between echocardiographic and invasive measurements of pulmonary artery pressures [16–19], and recent progress in ultrasound technology, poor agreement between the two techniques has also been reported [20], which is a potential limitation to our findings. Nevertheless, we believe that the excellent agreement between our non-invasive estimates of both mPAP-Q slope and α with previous invasive and also in vitro studies is unlikely to have occurred by chance, despite increased noise in the non-invasively obtained data, which causes relatively large standard deviations.

V. Summary

In animal models, multiple techniques are available for measuring peripheral pulmonary vascular mechanics. In humans, non-destructive and preferably non-invasive techniques such as CPET with echocardiography are required. Here we describe robust techniques for the measurement of peripheral pulmonary vascular mechanics in animals and humans and provide representative data in healthy and diseased populations.

The development and progression of PH largely depends on the small, peripheral arteries. More consistent and accurate measurement of peripheral pulmonary vascular mechanics

may improve our understanding of PH progression and ultimately lead to better management and treatment of this disease.

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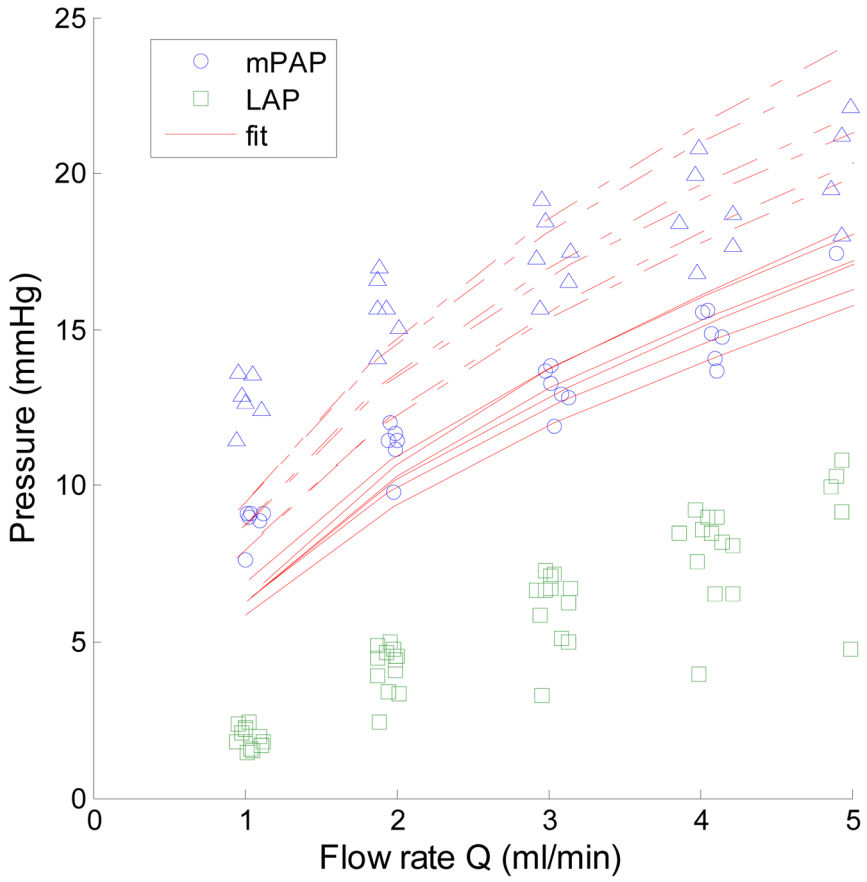

Fig. 1.

Multi-point pressure-flow curves in isolated, ventilated, perfused lungs from healthy control (○: PAP, □ LAP) and chronically hypoxic (△: PAP, □: LAP) mouse lungs with best fits to (1) shown in solid (CTL) and dashed (HPH) lines. Note that HPH lungs have increased pressure at all flow rates due to remodeling of small, peripheral arteries.

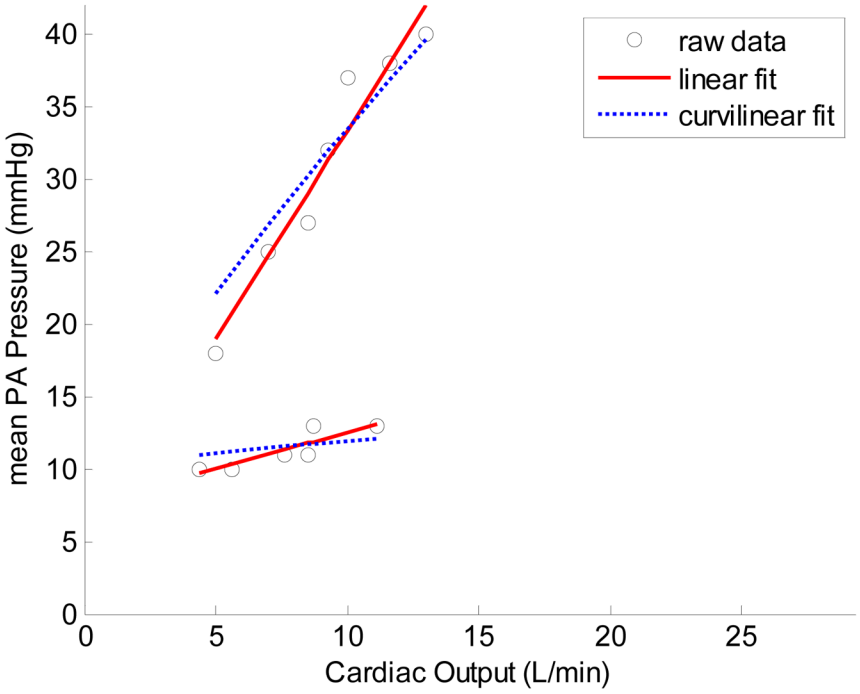

Fig. 2.
Multi-point pressure-flow curves for two representative healthy human subjects during CPET with echocardiography showing a wide range of normal pressure-flow relationships and goodness-of-fit to linear and curvilinear (1) shapes.

Table 1

Hemodynamic measurements at rest and maximum exercise in 25 normal subjects showing the effect of exercise on HR, sBP, sPAP, and Q.

Variables	Baseline	Maximum
HR, bpm	66 ± 10	159 ± 21*
sBP, mmHg	116 ± 9	169 ± 17*
sPAP, mmHg	19 ± 5	46 ± 11*
LAP, mmHg	8 ± 2	9 ± 1
Q, L/min	4.7 ± 1.0	18.0 ± 4.2*
1-pt PVR, WU	1.2 ± 0.6	1.2 ± 0.5

Abbreviation: HR: heart rate; sBP: systolic blood pressure; sPAP: systolic pulmonary artery pressure; Q: cardiac output; 1-pt PVR: single-point pulmonary vascular resistance, WU: Wood units, or mmHg/L/min.

*: $P < 0.05$ compared to baseline