Heart, Lung and Circulation (2019) **28,** 289–294
1443-9506/04/$36.00
https://doi.org/10.1016/j.hlc.2017.10.019

ORIGINAL ARTICLE

Diagnostic Performance of Pulmonary Capacitance at Rest and During Exercise in Idiopathic Pulmonary Arterial Hypertension

Pankaj Jain, MBBS *, Sriram Rao, MBBS, Peter Macdonald, MD, PhD, Eugene Kotlyar, MD, Andrew Jabbour, MBBS, PhD, Christopher Hayward, MD, Anne Keogh, MD

St Vincent's Hospital, Sydney, NSW, Australia

Received 28 July 2017; received in revised form 24 October 2017; accepted 29 October 2017; online published-ahead-of-print 8 November 2017

Background Reliable markers of early disease are needed in pulmonary arterial hypertension (PAH). As measures of the contribution of abnormal vascular compliance to overall vascular resistance, resting and exercise pulmonary capacitance—defined as the stroke volume divided by the change in pulmonary pulse pressure—may be sensitive markers of early disease.

Methods We examined all patients in our pulmonary hypertension database with idiopathic PAH, who had undergone rest and exercise right heart catheterisation in one sitting. Standard haemodynamic measurements were obtained, including pulmonary capacitance. These results were compared to age- and sex-matched normal controls.

Results We analysed 27 right heart catheterisations in idiopathic PAH patients and 23 in controls. Mean pulmonary artery pressure (MPAP), mean pulmonary capillary wedge pressure (mPCWP), pulmonary vascular resistance (PVR) and right ventricular stroke work index (RVSWI) were significantly higher at baseline in diseased patients, while Cardiac Index (CI) and pulmonary capacitance were significantly lower. MPAP, mPCWP, cardiac index and RVSWI increased significantly in both groups with exercise. Pulmonary capacitance decreased significantly in both groups. Pulmonary vascular resistance decreased with exercise in the control group only. Capacitance and PVR were inversely correlated at rest (time-constant of 0.79 s) and with exercise (time-constant of 0.56 s). The receiver operating characteristic (ROC) curve for capacitance as a diagnostic marker demonstrated an AUC of 0.96 at rest and 0.95 with exercise.

Conclusions In idiopathic pulmonary arterial hypertension (IPAH) there is a reduction in pulmonary capacitance at baseline and left-shift of the inverse capacitance-PVR relationship with exercise. Both resting and exercise pulmonary capacitance have potential as diagnostic markers in early disease.

Keywords Pulmonary arterial hypertension • Haemodynamics • Exercise • Pulmonary vascular resistance • Pulmonary capacitance

*Corresponding author at: Cardiology Department Level 4, Xavier Building, Victoria St Darlinghurst, NSW 2024, Australia. Fax: +61 2 8382 3898. Email: pankaj.jain@svha.org.au

Introduction

It has been established that a rise in resting pulmonary arterial pressure—upon which diagnosis of pulmonary arterial hypertension is predicated [1]—is a relatively late event in the pathogenesis of pulmonary hypertension, occurring after the majority of the microcirculation has been lost [2]. Meanwhile, current guidelines emphasise the importance of the timely institution of specific disease-modifying therapy in appropriate patients [3]. These factors highlight the importance of identifying reliable markers of early disease [4].

Despite its omission from diagnostic criteria, pulmonary vascular resistance (PVR) remains an important measurement in that it directly reflects the underlying pathophysiology of pulmonary hypertension as primarily a vascular disorder [5]. However, obtaining PVR requires invasive measurement and involves multiple potential sources of error. Furthermore, vascular resistance itself has multiple components—including vasoconstriction, obliteration and remodelling, and vascular compliance—with different mediators driving each component [5]. As a measure of mean resistance over the entirety of the cardiac cycle, PVR ignores the pulsatile nature of pulmonary flow, and cannot delineate to what degree these various components contribute to changes in pulmonary pressure through the cardiac cycle [5,6]. In contrast, pulmonary capacitance—defined as the stroke volume divided by the change in pulmonary pulse pressure—is a specific measure of the contribution of abnormal vascular compliance to overall vascular resistance. Abnormal capacitance may manifest before vascular obliteration drives the dramatic increases in PVR seen in late disease and therefore may be a more sensitive marker of early disease.

Understanding the complex effects of exercise on the pulmonary vasculature carries further potential for identifying early diagnostic markers. In normal individuals, exercise induces progressive recruitment [4] and distensibility [7] of the vascular system, resulting in an overall decrease in pulmonary vascular resistance in the face of increased cardiac output [8]. It is known that these processes are progressively lost in pulmonary arterial hypertension, as obliteration of the microcirculation results in an inability to recruit vasculature in response to increased pulmonary blood flow. However, due to a lack of prospective validation data, exercise haemodynamics are excluded entirely from current diagnostic guidelines [3].

Methods

In our study we aimed to evaluate the diagnostic performance of invasively measured pulmonary arterial capacitance at rest and during exercise in a group of patients with idiopathic pulmonary arterial hypertension. We retrospectively examined all patients in our pulmonary hypertension database with pulmonary hypertension due to idiopathic disease, who had undergone rest and exercise right heart catheterisation in one sitting. The diagnosis of pulmonary hypertension could have been made prior to, or as a result of, the index right heart study. Patients with an established diagnosis whose pulmonary pressures had dropped below the diagnostic cut-off as a result of treatment were included in the study. Patients with elevated pulmonary capillary wedge pressure greater than 18 mmHg were excluded. Patients with a pulmonary capillary wedge pressure between 15 mmHg and 18 mmHg who had nonetheless previously been diagnosed with idiopathic pulmonary arterial hypertension were included in the disease cohort.

From our database, we identified a cohort of age and sex-matched control patients who had normal right heart catheterisation parameters at rest, and no prior or subsequent diagnosis of heart failure, valvular disease or pulmonary hypertension. Patient consent for use of clinical and right heart catheterisation data had been obtained at the time of enrolment in the database.

Standard measurements taken at rest and during exercise in both the disease and control groups included measurement of heart rate (HR), right atrial pressure (RAP), systolic (sPAP) and diastolic (dPAP) pulmonary arterial pressure, mean pulmonary artery pressure (mPAP), mean pulmonary capillary wedge pressure (mPCWP) and cardiac output (CO) by the thermodilution method. MPCWP was measured as the visual estimate of the mean over the respiratory cycle. Thermodilution was performed between 3 and 5 times in each case, with outliers excluded prior to calculating the average CO. Stroke volume (SV) was calculated as CO divided by HR. Cardiac index (CI) was calculated as cardiac output divided by body surface area (BSA). Transpulmonary gradient (TPG) was calculated as the mPAP minus mPCWP. Pulmonary vascular resistance was determined as the TPG divided by CO. Pulmonary arterial capacitance was calculated as the SV divided by the pulmonary arterial pulse pressure (sPAP-dPAP).

Right heart catheterisation was performed in the supine position via the right internal jugular approach. Exercise testing was performed using either supine cycle ergometer or active straight leg raise, at the discretion of the supervising clinician. Exercise using the supine cycle ergometer was performed at a uniform cadence of 50 rpm, with increasing resistance allowing for increasing increments of 20 watts every 3 minutes until submaximal workload was achieved.

Data were analysed using Microsoft Excel. Continuous variables were assessed for statistical significance using repeated measures analysis of variance (ANOVA). Variables demonstrating overall statistical significance (defined as $p < 0.05$) were then assessed in a post-hoc manner to determine differences in resting and exercise values within both the control and diseased groups, as well as differences between the two groups at baseline using the two-tailed student's t-test. The relationship between capacitance and PVR was assessed using linear regression analysis.

Results

Baseline Characteristics

Twenty-seven right heart catheterisations were analysed in patients with idiopathic disease. Age- and sex-matched

Table 1 Baseline characteristics (data presented as mean +/− standard deviation unless otherwise specified).

Baseline characteristics	IPAH cohort (n = 27)	Controls (n = 23)
Age (years)	52.6 +/− 19.8	50.7 +/− 17.8
Male (%)	26	21
pHTN specific therapy (%)	48	0
Median WHO functional class	3	N/A
BSA (m^2)	1.80 +/− 0.22	1.82 +/− 0.20
BMI (kg/m^2)	26.9 +/− 4.5	26.1 +/− 4.8
Exercise type		
Bike (%)	22	61
SLR (%)	78	39
Median follow-up (years)	3.5 +/− 2.7	N/A
Alive at follow-up (%)	81	N/A
Timing of study		
Baseline study (%)	48	100
Follow-up study (%)	52	0

Abbreviations: BMI = body mass index; BSA = body surface area.

controls could not be found for four patients, resulting in a control group consisting of 23 patients. There was, nevertheless, no significant difference between the two cohorts in terms of age, sex, body mass index (BMI) or body surface area (BSA). Controls were more likely to have undergone cycle ergometer testing than patients with IPAH. Baseline characteristics in the two groups are outlined in Table 1.

Pulmonary Haemodynamics

At rest, patients with IPAH had significantly higher mPAP, mPCWP, PVR and RVSWI compared to controls. Patients with IPAH had significantly lower baseline CI and pulmonary capacitance. Across both cohorts, the mPAP, mPCWP, CI and RVSWI all increased significantly with exercise, while pulmonary capacitance fell significantly. Pulmonary vascular resistance decreased with exercise in the control group but not in the IPAH group. The maximum recorded sPAP during exercise was 150 mmHg. The haemodynamic effects of exercise in cases and controls are summarised in Table 2.

Across the entire cohort at baseline, PVR and pulmonary capacitance exhibited an inverse relationship (Figure 1a and 1 b), with a time constant of 0.79 s (95% confidence interval 0.74–0.85). The inverse relationship between PVR and capacitance was maintained following exercise (Figure 2a and 2 b), with a decreased time constant of 0.56 s (95% confidence interval 0.52–0.60), indicating a left-shift of the rest capacitance-PVR curve. Echocardiographic calculation of pulmonary capacitance was feasible in eight patients with IPAH, with no significant difference between echocardiographically and invasively derived values in these patients (1.59 ml/mmHg vs 1.56 ml/mmHg, p = 0.97), and reasonable linear correlation between the two methods ($r^2 = 0.54$).

Diagnostic Performance

At baseline, PVR had a sensitivity of 87% and a specificity of 95% using a diagnostic cut-off of 2.7 Wood units. The area under the receiver operating characteristic (ROC) curve was 0.98. Capacitance had a sensitivity of 91% and a specificity of 96% using a cut-off of 4.4 ml/mmHg, with an area under the ROC curve of 0.96 (Figure 3a).

With exercise, the area under the ROC curve for PVR increased to 0.99, with an optimal sensitivity and specificity of 95% and 100% respectively at a diagnostic threshold of 2 Wood units. The area under the ROC curve for capacitance was 0.95, with an optimal sensitivity and specificity of 90% and 100% respectively at a diagnostic threshold of 3.2 ml/mmHg (Figure 3b).

Discussion

Our data reveal three key findings. First, pulmonary capacitance is decreased in patients with idiopathic pulmonary hypertension compared to normal controls and decreases

Table 2 Baseline and exercise haemodynamic variables. Data is expressed as mean +/− SD. All variables included in this table demonstrated $p < 0.05$ by repeated measures ANOVA.

	IPAH cohort			Controls			Baseline IPAH vs control
	Baseline	Exercise	p-value	Baseline	Exercise	p-value	p-value
mPAP (mmHg)	41.4 +/− 18.2	54.8 +/− 20.8	<0.001	15.6 +/− 4.2	21.8 +/− 7.8	<0.001	<0.001
mPCWP (mmHg)	10.0 +/− 3.6	14.7 +/− 6.6	0.002	7.7+/− 2.8	10.8 +/− 4.7	0.002	0.01
CI ($L/min/m^2$)	2.5 +/− 0.7	3.7 +/− 1.5	<0.001	3.3 +/− 0.6	5.8 +/− 1.2	<0.001	<0.001
PVR ($dyn.scm^{-5}$)	651 +/− 562	556 +/− 479	0.39	112 +/− 45	82 +/− 35	0.01	<0.001
RVSWI (L/m^2)	1.13 +/− 0.49	1.80 +/− 0.63	<0.001	0.48 +/− 0.15	0.89 +/− 0.34	<0.001	<0.001
Capacitance (ml/mmHg)	2.3 +/− 1.6	1.8 +/− 1.3	0.04	8.3 +/− 3.4	5.5 +/− 1.7	<0.001	<0.001

Abbreviations: IPAH = idiopathic pulmonary arterial hypertension; mPAP = mean pulmonary artery pressure, PVR = pulmonary vascular hypertension, mPCWP = mean pulmonary capillary wedge pressure, CI = cardiac index, RVSWI = right ventricular stroke work index.

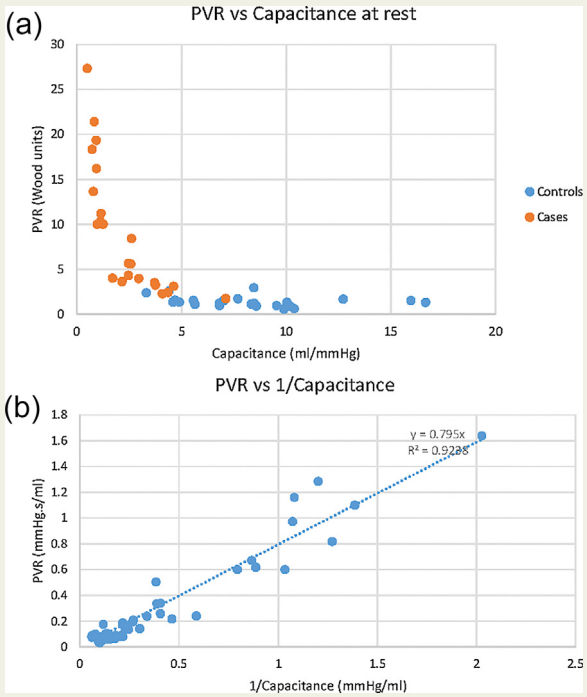

Figure 1 (a) PVR (Wood units) vs Capacitance (ml/mmHg) at rest. (b) PVR (mmHg.s/ml) vs 1/Capacitance (mmHg/ml) at rest, total cohort.
Abbreviation: PVR = pulmonary vascular resistance.

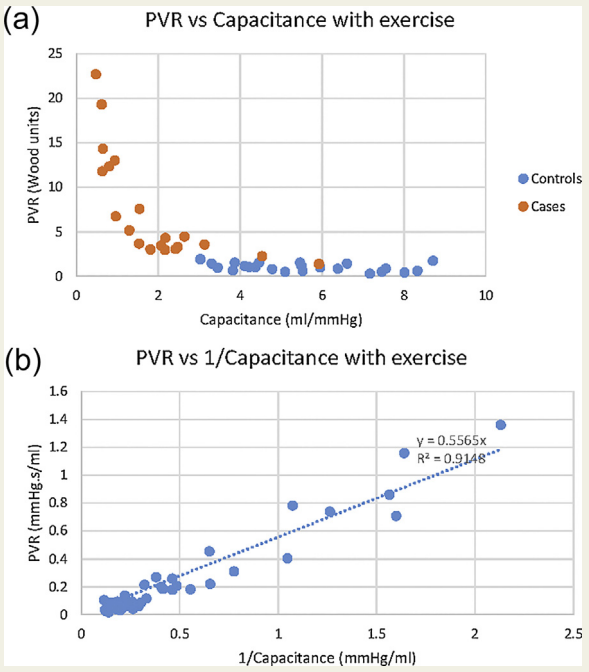

Figure 2 (a) PVR (Wood units) vs Capacitance (ml/mmHg) with exercise. (b) PVR (mmHg.s/ml) vs 1/Capacitance (mmHg/ml) with exercise, total cohort.
Abbreviation: PVR = pulmonary vascular resistance.

further with exercise. Second, there is an inverse relationship between PVR and pulmonary capacitance in health and disease that is maintained—with a reduced time-constant—with exercise. Third, the sensitivity and specificity of pulmonary capacitance in identifying patients with pulmonary hypertension is similar to PVR.

In pulmonary arterial hypertension, increased pulmonary vascular resistance is accompanied by an inversely proportional decrease in pulmonary vascular capacitance [9]. A time constant for this inverse relationship of 0.6 to 0.7 s has been observed in patients with varying disease aetiologies and severities [6]. In our study, the inverse relationship was

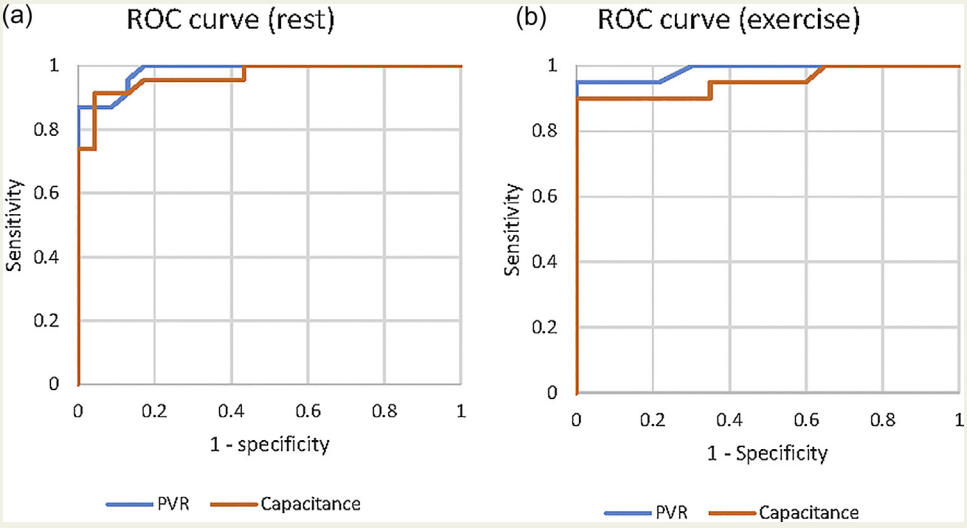

Figure 3 (a) ROC curve for resting PVR and Capacitance in distinguishing cases from controls. (b) ROC curve for exercise PVR and Capacitance in distinguishing cases from controls.
Abbreviations: PVR = pulmonary vascular resistance; ROC = receiver operating characteristic.

present across the entire cohort (time constant 0.79 s). This suggests that, across the continuum from normal patients to those with severe idiopathic disease, increases in pulmonary resistance and, therefore, mean pulmonary pressure are accompanied by a commensurate increase in the spread of systolic and diastolic pressures. In pathophysiological terms, the implication is that progressive loss of microcirculation—manifesting as increased PVR—and loss of distensibility—manifesting as decreased capacitance—occurs in a predictable and parallel manner [10].

During exercise, while the inverse correlation was maintained in the overall cohort, the time constant decreased to 0.56s, indicating a left-shift of the PVR-capacitance curve. This shift is driven by decreases in both PVR and capacitance in healthy controls, and by decreased capacitance alone in diseased patients. The implication is that the relative contribution of arterial stiffness to overall vascular resistance is increased with exercise, in both health and disease. This may be due to a number of factors: it may reflect changes in vascular tone due to local or circulating vasoreactive mediators; it may reflect progressive recruitment of poorly compliant vessels; or it may simply be due to increased left atrial pressure, which is known to decrease pulmonary capacitance [9].

In practice, measurement of pulmonary capacitance is subject to similar deficiencies as those associated with PVR outlined earlier. It is calculated from multiple measurements and is therefore prone to substantial error. Nevertheless, it can provide useful information regarding the specific contribution of pulmonary arterial stiffness to changes in pulmonary pressure through the cardiac cycle. In addition, capacitance can be accurately measured non-invasively using Doppler echocardiography [11], as demonstrated in eight patients with IPAH in this study. In this setting, a major advantage over the non-invasive measurement of PVR lies in the fact that it does not rely on estimation of right atrial pressure, which is a significant potential source of error [12]. It should be noted however, that non-invasive measurement of capacitance does require accurate quantification of the end-diastolic pulmonary regurgitant velocity, the major factor limiting its feasibility in our study.

While capacitance and PVR perform very similarly overall in terms of sensitivity and specificity for the diagnosis of pulmonary arterial hypertension, the inverse capacitance-PVR relationship confers different strengths upon each. Pulmonary vascular resistance rises dramatically in late disease, and therefore maintains a high specificity at a relatively low absolute threshold for positivity. Conversely, capacitance decreases dramatically in early disease, allowing it to remain sensitive at a high absolute threshold. To illustrate this difference, the sensitivity and specificity of resting capacitance with the positive threshold placed at the mean value across the entire cohort (5.3 ml/mmHg) are 95% and 78% respectively, while the sensitivity and specificity of PVR with a similarly placed threshold (5.0 Wood units) are 56% and 100% respectively. Changes in capacitance in early disease may therefore be easier to detect than changes in PVR, at the expense of specificity. For these reasons, we would regard capacitance as complementary measurement to PVR, and particularly suited to non-invasive screening. Baseline capacitance has already been shown to be superior to both cardiac index and PVR in predicting mortality in a cohort of patients with idiopathic disease [13]. Our data suggest that it may have broader potential as a rule-out test in at-risk, asymptomatic cohorts such as those with scleroderma or prior pulmonary emboli.

The selection of patients for case-control studies is inherently problematic. We allocated patients based on clinical diagnosis rather than purely based on numerical diagnostic thresholds, in order to avoid the circular logic of evaluating a diagnostic test against a gold standard from which it is partially derived. We included patients with a clinical diagnosis of idiopathic pulmonary hypertension with mPCWP of between 15 and 18 mmHg, in order to avoid the unnecessary exclusion of patients with small elevation in left atrial pressure that was unlikely to be physiologically relevant. Our method of patient selection based on clinical diagnosis would go some way to explaining the excellent performance of PVR as a diagnostic test in our cohort—it is very likely that in the clinical setting, PVR was used as an adjunct in diagnosis in a large proportion of our diseased cohort, despite current diagnostic guidelines. Nevertheless, the equally robust performance of capacitance remains a valid result, as this measure has not been used for diagnostic purposes at our centre to this point.

Our study is hypothesis-generating in nature. Further studies with longitudinal follow-up are required to evaluate the diagnostic performance of capacitance against other potential early markers of disease in borderline or at-risk cohorts.

Conclusion

In patients with idiopathic pulmonary arterial hypertension there is a reduction in pulmonary capacitance and left-shift of the capacitance-PVR relationship with exercise, suggesting an increased relative contribution of pulmonary vascular stiffness to overall resistance. Abnormal capacitance at rest or further reduction with exercise may be an early marker of disease.

Novelty and Significance

In the era of disease-modifying therapy for idiopathic pulmonary arterial hypertension, early diagnosis is critical to patient outcomes. Pulmonary capacitance—a marker of arterial stiffness that is obtainable at right heart catheterisation or non-invasively with echocardiography—is reduced at rest in patients with idiopathic pulmonary arterial hypertension, and reduces further with exercise. These may be sensitive markers of early disease that are complementary to existing diagnostic indices.

The evidence generated in this case-control analysis warrants further prospective study. Confirmation of the role of pulmonary capacitance as a marker of early disease requires longitudinal analysis of patients without established PAH who are nonetheless at high risk, such as those with scleroderma. If it is indeed proven to have predictive value, studies to investigate the effects of early PAH-specific therapy in high-risk patients with reduced pulmonary capacitance would be warranted.

Funding Sources

There were no external funding sources for the conduct of this research.

Declaration of Interest

None of the authors have any conflicts of interest or other relevant disclosures.

References

[1] Hoeper M. The new definition of pulmonary hypertension. Eur Respir J 2009;34:790–1.
[2] Demedts M, Delcroix M, Verhaege R, Verleden G, Peacock A. Prevention and early diagnosis of pulmonary hypertension. In: Pulmonary Vascular Pathology: A Clinical Update. Sheffield: European Respiratory Society Monograph; 2003.
[3] Galie N, Humbert M, Vachiery J, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2015. http://dx.doi.org/10.1093/eurheartj/ehv317.
[4] Lau EM, Manes A, Celermajer DS, Galiè N. Early detection of pulmonary vascular disease in pulmonary arterial hypertension: time to move forward. Eur Heart J 2011;2489–98.
[5] Hunter KS, Lammers SR, Shandas R. Pulmonary Vascular Stiffness: Measurement, Modeling, and Implications in Normal and Hypertensive Pulmonary Circulations. Compr Physiol 2011;1(3):1413–35.
[6] Souza R. Assessment of compliance in pulmonary arterial hypertension. Eur Heart J 2008;29(13):1603–4.
[7] Whyte K. Towards early detection of pulmonary hypertension: a call to arms. Eur Respir J 2014;43(1):16–9.
[8] Lewis GD, Bossone E, Naeijie R, Grunig E, Saggar R, Lancellotti P, et al. Pulmonary Vascular Hemodynamic Response to Exercise in Cardiopulmonary Diseases. Circulation 2013;128:1470–9.
[9] Naeije R, Vachiery J-L, Yerly P, Vanderpool R. The transpulmonary pressure gradient for the diagnosis of pulmonary vascular disease. Eur Respir J 2013;41:217–23.
[10] Naeije R, Vanderpool R, Dhakal B, Saggar R, Saggar R, Vachiery J, Lewis G. Exericise-induced pulmonary hypertension. Am J Respir Crit Care Med 2013;187(6):576–83.
[11] Friedberg M, Feinstein J, Rosenthal M. Noninvasive Assessment of Pulmonary Arterial Capacitance by Echocardiography. J Am Soc Echocardiogr 2007;20(2):186–90.
[12] Brennan J, Blair J, Goonewardena S, Ronan A, Shah D, Vasaiwala S, et al. Reappraisal of the Use of Inferior Vena Cava for Estimating Right Atrial Pressure. J Am Soc Echocardiogr 2007;20(7):857–61.
[13] Mahapatra S, Nishimura R, Sorajja P, Cha S, McGoon M. Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. J Am Coll Cardiol 2006;49(4):799–803.