



# Echocardiographic determination of pulmonary arterial capacitance

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## Abstract

A growing body of evidence has demonstrated that pulmonary arterial capacitance (PAC) is the strongest hemodynamic predictor of clinical outcomes across a wide spectrum of cardiovascular disease, including pulmonary hypertension and heart failure. We hypothesized that a ratio of right ventricular stroke volume (RVOT VTI) to the associated peak arterial systolic pressure (PASP) could function as a reliable non-invasive surrogate for PAC. We performed a prospective study of patients undergoing simultaneous transthoracic echocardiography and right heart catheterization (RHC) for various clinical indications. Measurements of the RVOT VTI/PASP ratio from echocardiographic measurements were compared against PAC calculated from RHC measurements. Correlation coefficients and Bland–Altman analysis compared the RVOT VTI/PASP ratio with PAC. Forty-five subjects were enrolled, 38% were female and mean age was 54 years (SD 13 years). The reason for referral to RHC was most commonly post-heart transplant surveillance (40%), followed by heart failure (22%), and pulmonary hypertension (18%). Pre-capillary pulmonary hypertension was present in 18%, isolated post-capillary pulmonary hypertension was present in 13%, and combined pre-and post-capillary pulmonary hypertension was present in 29%. The RVOT VTI/PASP ratio was obtainable in the majority of patients (78%), and Pearson's correlation demonstrated moderately-strong association between PAC and the RVOT VTI/PASP ratio,  $r=0.75$  ( $P<0.001$ ). Bland–Altman analysis demonstrated good agreement between measurements without suggestion of systematic bias and a mean difference in standardized units of  $-0.133$ . In a diverse population of patients and hemodynamic profiles, we validated that the ratio of RVOT VTI/PASP to be a reliably-obtained non-invasive marker associated with PAC.

**Keywords** Pulmonary hypertension · Heart failure · Echocardiography · Imaging and diagnostics

## Introduction

Heart failure and pulmonary hypertension together affect more than 26 million people worldwide, each portending a poor prognosis, reduced quality of life, and significant economic burden [1, 2]. Both are associated with hemodynamic derangement and the development of pathologic pulmonary vascular remodeling resulting in increased arterial stiffness [3]. There is a growing body of evidence demonstrating that

pulmonary arterial capacitance (PAC) is the strongest hemodynamic predictor of clinical outcomes, and that its predictive ability persists across a wide spectrum of cardiovascular diseases, including pulmonary arterial hypertension, heart failure with reduced ejection fraction (HFrEF), and heart failure with preserved ejection fraction (HFpEF) [3–7].

The pulmonary arterial vasculature is intrinsically elastic in nature, which is a mechanically favorable adaptation that minimizes right ventricular work by reducing ventricular afterload and dampening pulse-wave reflection [3]. Pathologic pulmonary vascular remodeling common to many disease states uncouples the right ventricle from this mechano-energetically beneficial relationship with the pulmonary vasculature. PAC is an expression of this pulmonary vascular remodeling, and is easily calculated at right heart catheterization (RHC) by dividing the right ventricular stroke volume by the pulmonary arterial pulse pressure (systolic – diastolic pressure) [8]. Though a non-invasive method

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for estimating PAC by echocardiography has previously been developed, its use is limited by its need for a sufficient pulmonary regurgitation signal, which is not obtainable in nearly half of patients [5].

Given the importance of PAC to predict clinical outcomes, we aimed to identify a more reliably obtained, non-invasive method to estimate PAC by standard imaging techniques. In principle PAC describes the relationship between volume displacement into the pulmonary arterial system and the resulting pressure generated (capacitance =  $\Delta\text{Volume}/\Delta\text{Pressure}$ ). Conceptually, the right ventricular outflow track velocity time integral (RVOT VTI) and pulmonary arterial systolic pressure (PASP) are the most intuitive measures of right ventricular displacement and peak pressure obtained in standard practice. Therefore, we hypothesized that a ratio of the RVOT VTI to the associated PASP could function as a reliable non-invasive surrogate for PAC. We compared the ratio of RVOT VTI to PASP against the gold-standard of PAC measured by RHC. In a similar fashion, we evaluated other measures of right ventricular displacement with respect to PASP to examine correlation with invasive PAC (tricuspid annular plane systolic excursion (TAPSE), right ventricular fractional area of change (FAC), and right ventricular Doppler tissue velocity (RV S')).

## Methods

### Study subjects

The University of California San Francisco (UCSF) Institutional Review Board approved this study. Eligible subjects included those over the age of 18 who were being referred for right heart catheterization by their respective cardiologists. Written, informed consent was obtained from all subjects who agreed to participate in this prospective, observational study. Baseline demographics were collected on enrollment including age, sex, New York Heart Association classification of heart failure, cardiovascular comorbidities, left ventricular ejection fraction, B-type natriuretic peptide, and primary condition prompting referral for right heart catheterization.

### Right heart catheterization

Standard cardiac catheterization laboratory protocol for performing a right heart catheterization via brachial or internal jugular vein was followed for all enrolled subjects. Pulmonary arterial pulse pressure was defined as the difference in systolic and diastolic pressure. Stroke volume was calculated by dividing the Fick cardiac output by the heart rate. PAC

was determined by dividing stroke volume by the pulmonary arterial pulse pressure.

Patients were categorized into the following hemodynamic profiles based on RHC data: no pulmonary hypertension (mean pulmonary artery pressure (mPAP) < 25 mmHg, pulmonary vascular resistance (PVR) < 3 Wood units, pulmonary capillary wedge pressure (PCWP) < 15 mmHg); pre-capillary pulmonary hypertension (mPAP > 25 mmHg, PVR > 3 Wood units, PCWP < 15 mmHg); post-capillary pulmonary hypertension (mPAP > 25 mmHg, PVR < 3 Wood units, PCWP > 15 mmHg); or combined pre and post-capillary pulmonary hypertension (mPAP > 25 mmHg, PVR > 3 Wood units, PCWP > 15 mmHg).

### Echocardiography

Transthoracic echocardiography was performed using a commercially available ultrasound system within 4 h of right heart catheterization (Philips Epiq, Phillips Medical Systems, Andover, MA, USA), and all measurements were performed by a single echo-trained investigator for standardization. The RVOT VTI was measured using the pulse wave Doppler signal obtained from RVOT in the parasternal short axis view. TAPSE was measured using M-mode to determine the maximal systolic excursion of the lateral tricuspid annulus obtained in the apical four chamber view. FAC was defined as the percent area change between right ventricular end-diastole and end-systole obtained in the apical four chamber view. RV S' was defined as peak systolic lateral tricuspid annular velocity obtained via Doppler tissue imaging from the apical four chamber view.

PASP was calculated using the modified Bernoulli equation; four times the peak tricuspid regurgitation jet velocity squared, plus the right atrial pressure determined by size and collapsibility of the inferior vena cava [9]. The tricuspid regurgitation jet velocity was measured by continuous-wave Doppler in all standard views, and the highest possible value with a well delineated Doppler envelope was used.

The non-invasive surrogates for PAC were defined as the ratio of the RVOT VTI to PASP, TAPSE to PASP, FAC to PASP, and RV S' to PASP.

### Statistical analysis

Normally distributed continuous variables are presented as means  $\pm$  standard deviations (SD). Correlations between continuous variables are described using Pearson's correlation coefficients and are graphed with a fitted regression line. For Bland–Altman analysis, variables were standardized and paired differences are plotted against the pairwise means; plots are fitted with a regression line [10, 11]. Statistical analyses were performed using STATA 13 (College Station, TX).

**Table 1** Cohort description

	N/%
Age, years (SD)	54 ± 13
Female	17 (38%)
HFpEF	15 (33%)
HFrEF	10 (22%)
Ischemic	3 (7%)
Non-ischemic	20 (44%)
NYHA class	
1	5 (14%)
2	12 (34%)
3	17 (49%)
4	1 (3%)
Cardiovascular related comorbidities	
CAD	4 (9%)
HTN	34 (75%)
HLD	7 (16%)
CKD	21 (31%)
DM	13 (29%)
AF	7 (16%)
Obesity	14 (31%)
Smoker	20 (44%)
COPD	4 (9%)
OSA	5 (11%)
Physical exam	
Systolic blood pressure (mmHg) (SD)	123 ± 27
Diastolic blood pressure (mmHg) (SD)	72 ± 13
Heart rate (BPM) (SD)	80 ± 14
LVEF	54%
BNP (pg/ml) (range)	809 (0–4090)
Echocardiographic variables	
RVOT VTI (cm) (SD)	13.1 ± 3.9
PASP (mmHg) (SD)	46.6 ± 20.6
TAPSE (cm) (SD)	1.6 ± 0.5
FAC (%) (SD)	41 ± 8
RV S' (cm/s) (SD)	10.5 ± 2.8
Reason for right heart catheterization	
Heart failure	10 (22%)
Valvular disease	6 (13%)
Pulmonary hypertension	8 (18%)
Post-heart transplant	18 (40%)
Other	3 (7%)
Hemodynamics	
Right atrial pressure (mmHg) (SD)	8 ± 5.4
Pulmonary arterial systolic pressure (mmHg) (SD)	46 ± 21
Pulmonary arterial diastolic pressure (mmHg) (SD)	19 ± 10.1
Mean pulmonary artery pressure (mmHg) (SD)	30 ± 13.6
Pulmonary capillary wedge pressure (mmHg) (SD)	15 ± 8.3
Fick cardiac index (L/min/m <sup>2</sup> ) (SD)	2.7 ± 1.0
Pulmonary vascular resistance (Wood units) (SD)	3.7 ± 4.5
Pulmonary arterial capacitance (mL/mmHg) (SD)	2.94 ± 1.54

**Table 1** (continued)

	N/%
Pulmonary hypertension	
No pulmonary hypertension (mPAP < 25 mmHg, PVR < 3 Wood units, PCWP < 15 mmHg)	18 (40%)
Pre-capillary pulmonary hypertension (mPAP > 25 mmHg, PVR > 3 Wood units, PCWP < 15 mmHg)	8 (18%)
Post-capillary pulmonary hypertension (mPAP > 25 mmHg, PVR < 3 Wood units, PCWP > 15 mmHg)	6 (13%)
Combined pre and post-capillary pulmonary hypertension (MPAP > 25 mmHg, PVR > 3 Wood units, PCWP > 15 mmHg)	13 (29%)

SD Standard deviation, *HFpEF* Heart failure preserved ejection function, *HFrEF* Heart failure reduced ejection function, *NYHA* New York Heart Association, *CAD* Coronary artery disease, *HLD* Hyperlipidemia, *CKD* Chronic kidney disease, *DM* Diabetes mellitus, *AF* Atrial fibrillation, *COPD* Chronic obstructive pulmonary disease, *LVEF* Left ventricle ejection fraction, *BNP* Brain natriuretic peptide, *PVR* Pulmonary vascular resistance, *mPAP* Mean pulmonary artery pressure, *PCWP* Pulmonary capillary wedge pressure

**Table 2** Correlation between non-invasive and invasive PAC measurements

	R	p Value
RVOT VTI/PASP	0.75	<0.001
FAC/PASP	0.68	<0.001
RV S'/PASP	0.65	<0.001
TAPSE/PASP	0.62	<0.001

*RVOT VTI* Right ventricular outflow track velocity time integral, *FAC* Fractional area of change, *PASP* Pulmonary arterial systolic pressure, *RV S'* right ventricular Doppler tissue velocity, *TAPSE* Tricuspid annular plane systolic excursion

## Results

Forty-five subjects were enrolled, 38% were female and mean age was 54 years (SD 13 years) (Table 1). The reason for referral to right heart catheterization was most commonly post-heart transplant surveillance 40%, followed by heart failure 22%, and pulmonary hypertension 18%. Pre-capillary pulmonary hypertension was present in 18%, isolated post-capillary pulmonary hypertension was present in 13%, and combined pre-and post-capillary pulmonary hypertension was present in 29%.

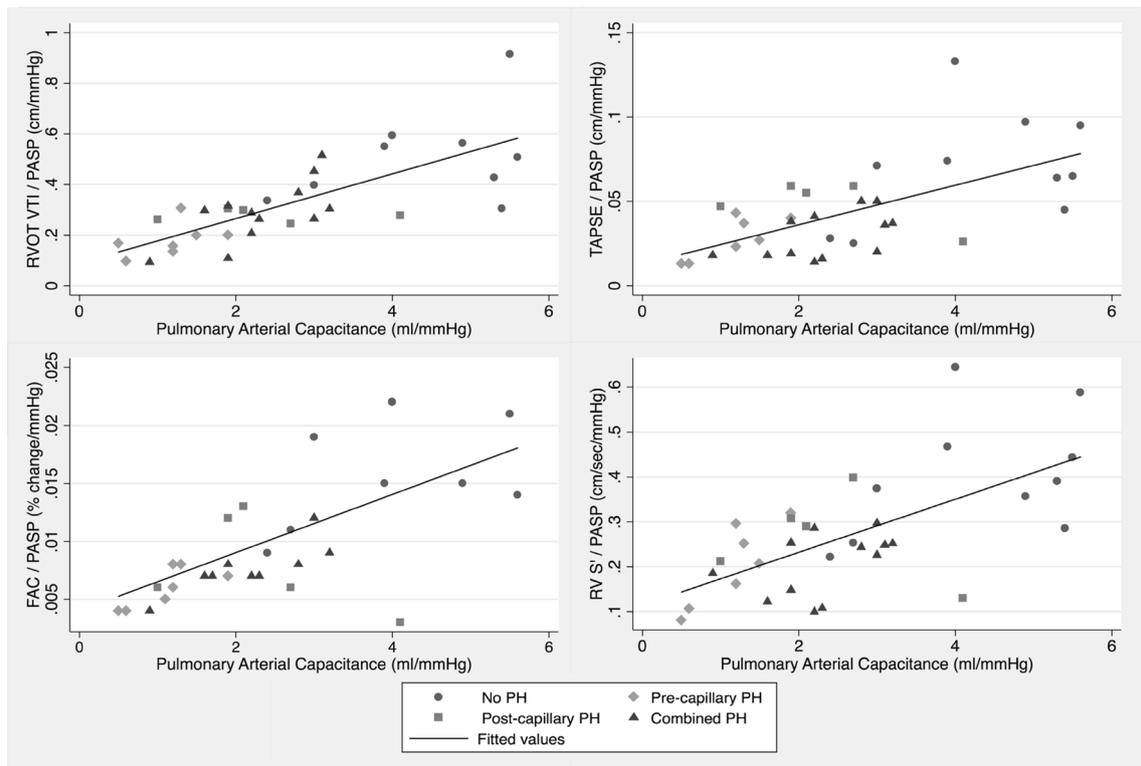
An adequate tricuspid regurgitation signal required for PASP estimation was obtained in 35 of the 45 patients enrolled (78%). Echocardiographic measures of right ventricular function were technically obtainable in the vast majority of the sample: RVOT VTI 96% (n = 43/45), FAC 87% (n = 39/45), RV S' 100% (n = 45/45), and TAPSE 100% (n = 45/45). All four of our hypothesized non-invasive surrogates for PAC correlated with invasively measured PAC (Table 2). The RVOT VTI/PASP ratio had the strongest correlation coefficient of  $r = 0.75$  ( $P < 0.001$ ,  $n = 33/45$ ). Correlations for other metrics were FAC/PASP  $r = 0.68$  ( $P < 0.001$ ,  $n = 30/45$ ), RV S'/PASP  $r = 0.65$  ( $P < 0.001$ ,  $n = 35/45$ ), and TAPSE/PASP  $r = 0.62$  ( $P < 0.001$ ,  $n = 35/45$ ) (Fig. 1).

A Bland–Altman plot of RVOT VTI/PASP ratio and PAC found good agreement without suggestion of systematic bias and a mean difference in standardized units of  $-0.133$  (Fig. 2).

## Discussion

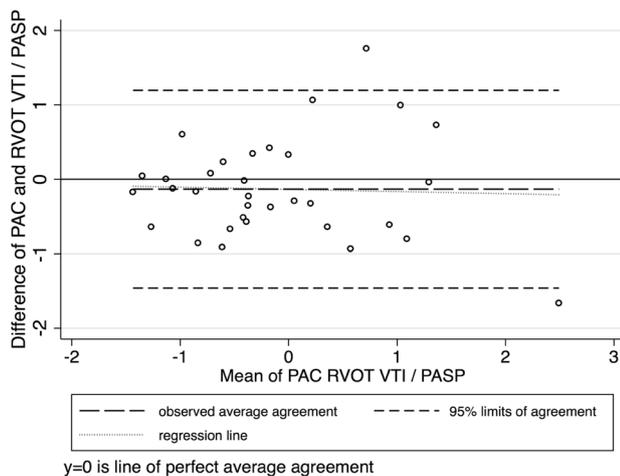
In this study we found that the ratio of RVOT VTI/PASP is a non-invasive hemodynamic surrogate for PAC in a diverse population of patients, including those with HFpEF, HFrEF, pulmonary hypertension, and post-heart transplantation. The literature has consistently called for the adoption of PAC in clinical practice, and there is increasing data that support its use over conventional metrics [3, 4, 7]. Our validation of the RVOT VTI/PASP ratio as an echocardiographic index of PAC enables estimation of PAC from routinely reported echocardiographic measurements that are obtainable in most patients.

There is a growing body of evidence demonstrating that PAC is the strongest hemodynamic predictor of mortality in heart failure and pulmonary hypertension. In patients with HFrEF, low PAC was found to be a better predictor of cardiac death, urgent cardiac transplantation, and ventricular fibrillation than conventional invasive parameters, including pulmonary capillary wedge pressure, mean pulmonary arterial pressure, pulmonary vascular resistance (PVR), and cardiac index [4]. Notably, in this population, PAC retained its prognostic ability in subgroup analysis after dichotomizing patients by normal and elevated PVR, further supporting that it is a highly sensitive marker of disease. Similarly, invasive PAC in patients with pre-capillary pulmonary hypertension was shown to be a superior predictor of mortality than PVR, cardiac index, mean pulmonary arterial pressure, and right atrial pressure [12]. Not only is PAC a powerful prognostic tool, but there is data to suggest that it is a better therapeutic target for the titration of WHO Group-I pulmonary arterial hypertension



**Fig. 1** Scatter Plot of Right Ventricular Displacement to PASP ratio versus Pulmonary Artery Capacitance. *PAC* Pulmonary artery capacitance (ml/mmHg), *PASP* Peak arterial systolic pressure (mmHg), *RVOT VTI* Right ventricular outflow track velocity time integral (cm), *TAPSE* Tricuspid annular plane systolic excursion (cm), *FAC* Right ventricular fractional area of change (% change), *RV S'* Right ventricular Doppler tissue velocity (cm/s), *No PH* no pulmonary hypertension (mPAP < 25 mmHg, PVR < 3

Wood units, PCWP < 15 mmHg), *Pre-capillary PH* Pre-capillary pulmonary hypertension (mPAP > 25 mmHg, PVR > 3 Wood units, PCWP < 15 mmHg), *Post capillary PH* Post-capillary pulmonary hypertension (mPAP > 25 mmHg, PVR < 3 Wood units, PCWP > 15 mmHg), *Combined PH* Combined pre and post-capillary pulmonary hypertension (mPAP > 25 mmHg, PVR > 3 Wood units, PCWP > 15 mmHg)



**Fig. 2** Bland–Altman plot of RVOT VTI/PASP and PAC. *PAC* Pulmonary artery capacitance (ml/mmHg), *PASP* Peak arterial systolic pressure (mmHg), *RVOT VTI* Right ventricular outflow track velocity time integral (cm)

medications than PVR, cardiac index, or right ventricular stroke work index [13].

In an eloquent series of studies, Guazzi et al. demonstrated that the TAPSE/PASP ratio correlates to PAC by RHC and serves as an index of right ventricular function and its coupling to the pulmonary circulation. They demonstrated that this measurement had the ability to stratify disease severity and predict clinical outcomes within a cohort of patients with HFpEF [6, 14]. Assuming their findings were largely mediated by the relationship between the TAPSE/PASP ratio and PAC, the stronger correlation between the RVOT VTI/PASP ratio and PAC in our study may suggest that the RVOT VTI/PASP ratio could provide a better noninvasive index of right ventricular—pulmonary arterial coupling.

The ratio RVOT VTI/PASP is similar to the widely accepted Abbas formula for calculating echo-based PVR [15]. This likeness is a result of the inverse hyperbolic relationship between PVR and PAC [8]. The primary distinction between the two formulae is that the RVOT VTI/PASP ratio

utilizes the modified Bernoulli equation and accounts for right atrial pressure to derive an estimated pressure (PASP) rather than the tricuspid regurgitation velocity alone.

Similar to the invasive determination of PAC, we did not observe that the RVOT VTI/PASP ratio differentiated between the three pulmonary hypertension hemodynamic profile subgroups (pre-capillary, post-capillary, or combined). Interestingly however, all of the patients who did not have pulmonary hypertension had an RVOT VTI/PASP ratio greater than 0.3 cm/mmHg ( $n=9$ ). This finding suggests that the RVOT VTI/PASP ratio may provide incremental value to echocardiographic screening of pulmonary hypertension beyond the current standard of using the PASP in isolation.

Our study has several limitations, including its modest sample size and lack of clinical outcome data. Additionally, we were unable to test the effects of significant tricuspid or pulmonic regurgitation on the accuracy of the RVOT VTI/PASP ratio in estimating PAC. Though we have no reason to suspect that it would be invalidated in these cases, further investigation is needed. Future directions also include prospective examination of this noninvasive measurement in a diverse cohort of patients with associated clinical outcomes data.

## Conclusions

This study demonstrates that the ratio of RVOT VTI/PASP is a reliably obtained non-invasive marker strongly associated with pulmonary arterial capacitance.

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**Conflict of interest** All authors report no conflicts of interest to disclose.

## References

- Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, Jaarsma T, Krum H, Rastogi V, Rohde LE, Samal UC, Shimokawa H, Budi Siswanto B, Sliwa K, Filippatos G (2014) Heart failure: preventing disease and death worldwide. *ESC Heart Fail* 1:4–25
- Prins KW, Thenappan T (2016) World Health Organization Group I pulmonary hypertension: epidemiology and pathophysiology. *Cardiol Clin* 34:363–374
- Thenappan T, Prins KW, Pritzker MR, Scandurra J, Volmers K, Weir EK (2016) The critical role of pulmonary arterial compliance in pulmonary hypertension. *Ann Am Thorac Soc* 13:276–284
- Pellegrini P, Rossi A, Pasotti M, Raineri C, Ciccoira M, Bonapace S, Dini FL, Temporelli PL, Vassanelli C, Vanderpool R, Naeije R, Ghio S (2014) Prognostic relevance of pulmonary arterial compliance in patients with chronic heart failure. *Chest* 145:1064–1070
- Mahapatra S, Nishimura RA, Oh JK, McGoon MD (2006) The prognostic value of pulmonary vascular capacitance determined by Doppler echocardiography in patients with pulmonary arterial hypertension. *J Am Soc Echocardiogr* 19:1045–1050
- Guazzi M, Dixon D, Labate V, Beussink-Nelson L, Bandera F, Cuttica MJ, Shah SJ (2017) RV contractile function and its coupling to pulmonary circulation in heart failure with preserved ejection fraction: stratification of clinical phenotypes and outcomes. *JACC Cardiovasc Imaging* 10:1211–1221
- Al-Naamani N, Preston IR, Paulus JK, Hill NS, Roberts KE (2015) Pulmonary arterial capacitance is an important predictor of mortality in heart failure with a preserved ejection fraction. *JACC Heart Fail* 3:467–474
- Tedford RJ (2014) Determinants of right ventricular afterload (2013 Grover conference series). *Pulm Circ* 4:211–219
- Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB (2010) Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 23:685–713 (786-8)
- Martin Bland J, Altman D (1986) Statistical methods for assessing agreement between two methods of clinical measurement. *The Lancet* 327:307–310
- Nicholas J. Cox TS (2000) CONCORD: Stata module for concordance correlation. Statistical Software Components S404501, Boston College Department of Economics, Accessed 09 Aug 2007
- Mahapatra S, Nishimura RA, Sorajja P, Cha S, McGoon MD (2006) Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. *J Am Coll Cardiol* 47:799–803
- Medrek SK, Kloefkorn C, Nguyen DTM, Graviss EA, Frost AE, Safdar Z (2017) Longitudinal change in pulmonary arterial capacitance as an indicator of prognosis and response to therapy and in pulmonary arterial hypertension. *Pulm Circ* 7:399–408
- Guazzi M, Bandera F, Pelissero G, Castelvechchio S, Menicanti L, Ghio S, Temporelli PL, Arena R (2013) Tricuspid annular plane systolic excursion and pulmonary arterial systolic pressure relationship in heart failure: an index of right ventricular contractile function and prognosis. *Am J Physiol Heart Circ Physiol* 305:H1373–H1381
- Abbas AE, Franey LM, Marwick T, Maeder MT, Kaye DM, Vlahos AP, Serra W, Al-Azizi K, Schiller NB, Lester SJ (2013) Non-invasive assessment of pulmonary vascular resistance by Doppler echocardiography. *J Am Soc Echocardiogr* 26:1170–1177

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