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The relationship between pulmonary artery wedge pressure and pulmonary blood volume derived from contrast-echocardiography: a proof-of-concept study

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Abstract

Background—Pulmonary transit time (PTT) obtained from contrast-echocardiography is a marker of global cardiopulmonary function. Pulmonary blood volume (PBV), derived from PTT, may be a non-invasive surrogate for left-sided filling pressures, such as pulmonary artery wedge pressure (PAWP). We sought to assess the relationship between PBV obtained from contrast-echocardiography and PAWP.

Methods—Participants were adult survivors of childhood cancer that had contrast-echocardiography performed nearly simultaneously with right-heart catheterization. PTT was derived from time-intensity curves of contrast passage through the right-ventricle (RV) and left atrium (LA). PBV relative to overall stroke volume (rPBV) was estimated from the product of PTT and heart rate during RV-LA transit. PAWP was obtained during standard right-heart catheterization. The Spearman correlation coefficient was used to assess the relationship between rPBV and PAWP.

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KM: concept/design, data analysis/interpretation, drafting article, critical revision of article, approval of article, statistics, secured funding

DL: concept/design of study, critical revision of article, approval of article

ELB: concept/design, critical revision of article, approval of article

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Results—The study population consisted of 7 individuals who had contrast-echocardiography and right-heart catheterization within 3 hours of each other. There was a wide range of right atrial (1–17 mmHg), mean pulmonary artery (18–42 mmHg), and PAW pressures (4–26 mmHg) as well as pulmonary vascular resistance (< 1 to 6 Wood Units). We observed a statistically significant correlation between rPBV and PAWP ($r = 0.85$; $p = 0.02$).

Conclusion—Relative PBV derived from contrast-echocardiography correlates with PAWP. If validated in larger studies, rPBV could potentially be used as an alternative to invasively determined left-sided filling pressure.

Keywords

contrast echocardiography; pulmonary transit time; pulmonary arterial wedge pressure

INTRODUCTION

Non-invasively determined pulmonary transit time (PTT) predicts mortality in pulmonary arterial hypertension (1) and can potentially serve as a global marker of cardiac performance (2). PTT is readily obtained during contrast echocardiography, has been shown to be reproducible, and the necessary data can be acquired autonomously by a sonographer within the workflow of a high-volume echocardiography laboratory (3).

The relationship between PTT and pulmonary blood volume (PBV) suggests the potential for non-invasive determination of PBV as well. Prior studies have compared echocardiographically-derived and invasively determined PBV *in vitro* (4) and in patients undergoing cardiac surgery (5). PBV is related to left atrial (LA) pressure (6). Pulmonary artery wedge pressure (PAWP) is a more readily available estimate of LA pressure that is commonly used in clinical practice. If shown to be a reasonable surrogate for PAWP, non-invasively obtained PBV could be useful in the determination of volume status, categorization of pulmonary hypertension sub-types, and in assessing response to therapy (i.e. volume administration or diuresis).

Therefore, in a proof-of-concept pilot study, we aimed to assess the relationship between PBV determined by contrast-echocardiography and invasively obtained PAWP.

THEORY

PBV and PTT are related by the cardiac output (CO), the product of stroke volume (SV) and heart rate (HR):

$$PBV = PTT * CO = PTT * [SV * HR] \quad (1)$$

PTT can be normalized by the HR, which produces the normalized PTT (nPTT), a parameter that reports on the number of ‘beats’ (cardiac cycles) needed for the PBV to traverse the pulmonary circulation, rather than the amount of time needed to do so.

$$nPTT = PTT * HR \quad (2)$$

Combining equations (1) and (2) and re-arranging terms yields the following:

$$nPTT = PBV/SV \quad (3)$$

The normalized PTT gives the PBV relative to the overall stroke volume (rPBV) and can facilitate serial measurements within a given patient (assessing for changes over time or with an intervention) and could be used for comparisons between patients as well.

Stroke volume can be estimated via standard trans-thoracic echocardiography (TTE) using the product of the left-ventricular outflow tract velocity-time integral (LVOT VTI) and the LVOT area (7). Therefore, an estimate of absolute PBV can be obtained from rPBV as well. This capability would be particularly useful when performing serial measurements, as it allows determination of which component of rPBV (or both) changed over time or in response to an intervention.

METHODS

Study population

This study was approved by the Vanderbilt Medical Center IRB.

The study population consisted of adult survivors of childhood cancer exposed to chest radiation (St Jude Lifetime Cohort) who underwent comprehensive right-heart catheterization at our institution as part of a definitive evaluation for pulmonary hypertension (8). The study protocol called for those individuals to undergo a standard TTE with echocardiographic contrast on the same day, prior to the catheterization procedure.

Demographic characteristics, anthropomorphic measurements, and medical history were abstracted from the electronic medical record. For consistency, the participant ID numbers from the prior study (8) are maintained (Tables 1–3).

Echocardiography, contrast administration, and PTT measurement

For all participants, a comprehensive echocardiogram was performed in our Intersocietal Accreditation Commission for Echocardiography-certified laboratory on an iE33 ultrasound instrument (Philips, Amsterdam, The Netherlands) by the same sonographer (LS). Assessment of LVOT VTI, mitral valve inflow velocity (E), mitral valve tissue Doppler velocity (e'), and right ventricular (RV) fractional area change (FAC) were performed according to American Society of Echocardiography guidelines; as LVOT diameter was challenging to measure in most individuals, a nominal value of 2 cm was used for women and 2.3 cm was used for men (9–11). DEFINITY® (Perflutren lipid microsphere, Lantheus Medical Imaging, Inc., Billerica, Massachusetts) was used for ultrasound contrast administration, as previously described, after exclusion of intra-cardiac shunting by agitated saline injection (3). The entry of contrast into the right-heart and subsequent appearance in

the left-heart were recorded in the apical 4-chamber view. These images were analyzed offline using QLab 9.1 software (Philips, Amsterdam, The Netherlands). Regions of interest (ROI; 5 mm square) were placed in the RV and LA. The RV ROI was placed approximately 1 cm distal to the tricuspid valve leaflet tips equidistant from the interventricular septum and RV free wall. The LA ROI was placed approximately 1 cm from the posterior wall of the LA equidistant from the interatrial septum and LA free wall. After placement of ROIs, time-intensity curves of contrast passage through the RV and LA were generated by the QLab software. These curves served as the inputs to our previously described inflection point algorithm, from which PTT is calculated (12).

Invasive hemodynamics via right-heart catheterization

Under sterile conditions, a Swan-Ganz catheter was floated through an introducer placed in the right internal-jugular vein using the modified Seldinger technique. Pressure tracings were obtained in the standard fashion from the right-atrium (RA), main pulmonary artery (mPA), and pulmonary artery wedge (PAW) position and cardiac outputs/indices were determined using the thermodilution and Fick methods. All pressures were measured at end-expiration. The wedge position was verified by waveform analysis, although not by oxygen saturation. All participants had their catheterization performed by the same proceduralist (RNP).

Normalized PTT and rPBV determination

As described in the Theory section, rPBV (equivalent to nPTT) was estimated as the product of PTT and average HR during the passage of contrast from the RV to the LA. All participants were in sinus rhythm during their echocardiographic studies. Absolute PBV was estimated as the product of rPBV and echocardiographically derived SV, taken as the product of LVOT VTI and LVOT area. The latter assumes a circular geometry of the LVOT and is the product of $\pi/4$ and the LVOT diameter squared. Using the method of disks (i.e. measuring end-diastolic volume and end-systolic volume in the apical-4 chamber and apical 2-chamber views) yielded similar values for SV (Table 1). Given that E/e' is commonly used as an echocardiographic surrogate for PAWP (13), the ratio of mitral inflow velocity to tissue Doppler velocity was calculated for each participant as well.

Statistical analysis

Correlation of echocardiographically-determined rPBV with invasively determined PAWP was determined using the Spearman correlation coefficient (GraphPad Prism, La Jolla CA, version 7.02). A similar correlation for E/e' and PAWP was performed as well.

RESULTS

This pilot study consisted of patients who were middle-aged and almost uniformly overweight/obese with a similar distribution of men and women (Table 1). Left ventricular ejection fraction (LVEF) was normal in all participants and RV dysfunction (defined by abnormal RVFAC) was present in 2 participants.

The RA (normal: < 8 mmHg), mPA (normal: < 25 mmHg), and PAW (normal: < 15 mmHg) pressures ranged from normal to significantly elevated (Table 2). The variability was less for cardiac index (Fick method) and mixed venous oxygen saturation. Pulmonary vascular resistance (PVR) varied from < 1 to 6 Wood Units (WU; normal: < 1.5 WU).

PTT, rPBV, and absolute PBV are shown in Table 3, in addition to the elapsed time between the echocardiographic PTT measurement and the beginning of the cardiac catheterization procedure. This interval was < 3 hours for all participants. The Figure shows the relationship between rPBV and PAWP. The correlation coefficient was statistically significant ($r = 0.85$; $p = 0.02$). E/e' and PAWP were not significantly correlated ($r = 0.4$; $p = 0.4$).

DISCUSSION

In this proof-of-concept pilot study, we estimated PBV from contrast-echocardiography and demonstrated a significant correlation with invasively measured left-sided filling pressure. The relationship between non-invasively measured PBV and PAWP in the present study is similar to that found between invasively-acquired PBV and direct left atrial pressure (6). In addition, the absolute values for PBV and PBV indexed to body surface area in the two studies are comparable, particularly among individuals with low filling pressure and low PVR. In the current cohort, E/e' was not an optimal surrogate for PAWP, suggesting that echocardiographically-derived rPBV could potentially serve as an alternative.

Even in the context of a proof-of-concept assessment, this study has several notable limitations. Clearly, the sample size is small and larger studies are needed to validate these findings. The spectrum of cardiopulmonary disorders represented in this study is relatively narrow, as most participants had pulmonary hypertension, although the range of hemodynamics represented is reasonably broad. The generalizability of these findings to populations without pulmonary hypertension needs to be established. To further assess whether rPBV adds value to established echocardiographic metrics, this technique should be examined in conditions where E/e' is challenging to interpret (i.e. atrial fibrillation, prosthetic mitral valves, constrictive pericarditis, infarction affecting myocardium near the medial or lateral annulus of the mitral valve). Use of the apical 4-chamber view to derive rPBV confounds the measurement due to the inclusion of the RV into the flow pathway. Theoretically, this variability could be reduced by using the parasternal long-axis view or apical 3-chamber view (i.e. the RVOT could be used as the right-sided chamber) or the parasternal short-axis view at the level of the aortic valve (where the mPA could be used, thus eliminating any portion of the RV), although these options were not tested in the present study.

In conclusion, we provide preliminary evidence that PTT obtained from contrast echocardiography can be used to derive rPBV, which correlates with invasive PAWP. If confirmed in subsequent studies, this parameter could be useful in the non-invasive assessment of volume status, distinguishing pre-capillary from post-capillary pulmonary hypertension, and gauging response to interventions.

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Figure. Relationship between relative pulmonary blood volume (rPBV) derived from contrast-echocardiography and pulmonary arterial wedge pressure (PAWP)

There is a strong correlation between rPBV and PAWP over a wide range of PAWP.

Table 1

Demographic and standard echocardiographic characteristics of study participants

ID *	Age (years)	Gender (F/M)	BMI (kg/m ²)	BSA (m ²)	LVEF (%)	RVFAC (%)	LVOT VTI (cm)	SV – VTI (mL)	SV – BPS (mL)	E/e'
2	44.7	M	26.8	1.96	50	41	15.1	63	56	
3	52.5	F	18.7	1.68	55	40	19.9	63	60	21
5	53.0	F	29.3	1.76	55	16	14.0	44	50	22
6	50.9	F	36.3	2.07	60	38	17.2	54	52	14
7	44.4	M	27.0	1.83	58	19	19.8	82	69	27
8	49.0	M	31.0	2.12	69		22.5	93	102	8
9	48.7	M	41.2	2.03	61	46	25	104	90	12

BMI body mass index

BPS Biplane Simpson's method

BSA body surface area

E mitral inflow velocity

E' mitral annulus tissue Doppler velocity

LVEF left ventricular ejection fraction

LVOT left ventricular outflow tract

RVFAC right-ventricular fractional area change

SV stroke volume

VTI velocity-time integral (method)

* participant ID numbers from the prior study (8) are maintained here

Table II

Invasive hemodynamics from right heart catheterization

ID *	CI (L/min/m ²)	MvO ₂ (%)	RAP (mmHg)	mPAP (mmHg)	PAWP (mmHg)	PVR (WU)
2	2.2	61	17	32	24	1.8
3	2.6	70	1	19	4	3.5
5	2.1	61	13	41	26	4.0
6	3.1 [†]	76	6	23	9	2.2
7	2.7	77	10	30	18	2.4
8	2.7	72	7	21	16	0.9
9	3.3	72	4	18	9	1.3

CI cardiac index (Fick method)

mPAP mean pulmonary arterial pressure

MvO₂ mixed venous oxygen saturation

PAWP pulmonary arterial wedge pressure

PVR pulmonary vascular resistance

RAP right atrial pressure

WU Wood Units

* participant ID numbers from the prior study (8) are maintained here

[†]thermodilution method

Table III
Pulmonary transit time and pulmonary blood volume derived from contrast echocardiography

ID *	TTE-CCL (hrs)	PTT (sec)	HR (bpm)	rPBV (beats)	PBV index (mL/m ²)
2	2.3	4.58	95	7.25	232
3	2.2	3.13	94	4.90	182
5	2.9	4.92	85	6.97	174
6	1.4	3.49	94	5.47	143
7	2.1	5.84	68	6.62	298
8	1.9	4.24	97	6.85	229
9	1.4	4.80	60	4.80	186

HR heart rate

PBV pulmonary blood volume

PTT pulmonary transit time

rPBV pulmonary blood volume relative to stroke volume

TTE-CCL interval between echocardiogram and cardiac catheterization

* participant ID numbers from the prior study (8) are maintained here