



Measurement of pulmonary transit time and estimation of pulmonary blood volume after exercise using contrast echocardiography

Ken Monahan¹ · Evan Brittain¹ · James J. Tolle²

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Abstract

Background Pulmonary transit time (PTT) and pulmonary blood volume (PBV) derived from non-invasive imaging correlate with pulmonary artery wedge pressure. The response of PBV to exercise may be useful in the evaluation of cardiopulmonary disease but whether PBV can be obtained reliably following exercise is unknown. We therefore aimed to assess the technical feasibility of measuring PTT and PBV after exercise using contrast echocardiography.

Methods In healthy volunteers, PTT was calculated from time-intensity curves generated as contrast traversed the cardiac chambers before and immediately after participants performed sub-maximal exercise on the Standard Bruce Protocol. From the product of PTT and heart rate (HR) during contrast passage through the pulmonary circulation, PBV relative to systemic stroke volume (rPBV) was calculated.

Results The cohort consisted of 14 individuals (age: 46 ± 8 years; 2 female) without cardiopulmonary disease. Exercise time was $8 \frac{3}{4} \pm 1 \frac{3}{4}$ minutes and participants reached $85 \pm 9\%$ of age-predicted maximal HR, which corresponded to a near-doubling of resting HR at the time of post-exercise contrast injection. Data sufficient to derive PTT and rPBV were obtained for all participants. With exercise, the change in PBV from baseline ranged from 56 to 138% of systemic stroke volume, consistent with rPBV and absolute PBV values obtained in prior studies.

Conclusions Acquisition of PTT and rPBV using contrast echocardiography after exercise is achievable and the results are physiologically plausible. As the next step towards clinical implementation, validation of this technique against hemodynamic exercise studies appears reasonable.

Keywords Contrast echocardiography · Pulmonary transit time · Exercise echocardiography

Background

Pulmonary transit time (PTT) derived from contrast-enhanced imaging has recently been demonstrated to correlate with invasively measured left-sided filling pressures [1, 2]. Given this association, PTT-based metrics may be of use in identifying and gauging the response to treatment of cardiopulmonary disorders such as heart failure with preserved ejection fraction (HFpEF), which remains challenging to diagnose and manage despite its high prevalence and morbidity [3].

The hallmark of HFpEF is exertional intolerance coupled with a prominent increase in left-sided filling pressures during exercise [4]. Echocardiographic diastolic stress tests have been developed to assess non-invasively the change in filling pressures with exercise [5, 6], but a key parameter (E/e' ; the ratio of mitral valve inflow velocity to mitral annular velocity by tissue Doppler imaging) may not be obtainable in a substantive portion of individuals and the association of E/e' with invasively measured filling pressures is not entirely consistent [7]. If validated against invasive hemodynamics, comparison of PTT at rest and following exercise may complement the current evaluation of HFpEF. However, whether satisfactory measurement of PTT following exercise is possible remains unknown.

Therefore, as a preliminary step towards comparing post-exercise PTT from contrast-echocardiography to invasive filling pressures, we conducted a proof-of-concept study

✉ Ken Monahan
ken.monahan@vumc.org

¹ Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

² Division of Allergy, Pulmonary, and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

to assess the technical feasibility of obtaining PTT after exercise.

Theory

As previously described [1], the normalized PTT (nPTT) quantifies the number of cardiac cycles (‘beats’) necessary for the pulmonary blood volume (PBV) to traverse the pulmonary circulation. This term is equivalent to the PBV relative to the systemic stroke volume (SV), termed relative PBV (rPBV).

$$\begin{aligned} \text{PBV} &= \text{Cardiac output} \times \text{PTT} = (\text{SV} \times \text{HR}) \times \text{PTT} \\ &= \text{SV} \times \text{nPTT} \Rightarrow \frac{\text{PBV}}{\text{SV}} = \text{nPTT} = \text{rPBV} \end{aligned} \quad (1)$$

The ratio of rPBV after exercise to rPBV at baseline then takes the form:

$$\frac{\text{rPBV}_{\text{EXERCISE}}}{\text{rPBV}_{\text{BASELINE}}} = \frac{\frac{\text{PBV}_{\text{EXERCISE}}}{\text{SV}_{\text{EXERCISE}}}}{\frac{\text{PBV}_{\text{BASELINE}}}{\text{SV}_{\text{BASELINE}}}} \quad (2)$$

Re-arranging terms yields the following:

$$\frac{\text{rPBV}_{\text{EXERCISE}}}{\text{rPBV}_{\text{BASELINE}}} = \frac{\frac{\text{PBV}_{\text{EXERCISE}}}{\text{PBV}_{\text{BASELINE}}}}{\frac{\text{SV}_{\text{EXERCISE}}}{\text{SV}_{\text{BASELINE}}}} \quad (3)$$

Thus, the ratio described in Eq. (3) provides an assessment of the impact of exercise on PBV relative to, or ‘correcting for’, the change in systemic SV under the same conditions. Analogous to the general expression in Eq. (1), no direct estimation of systemic SV is required to obtain this ratio; only the PTT and contemporaneous HR are needed.

Methods

This study was approved by the Vanderbilt Medical Center Institutional Review Board and all participants gave written informed consent.

Study population

Healthy individuals that reported engaging in regular exercise were recruited to participate in the study. No participant reported an allergy or prior adverse reaction to DEFINITY® contrast. One participant reported a history of obstructive sleep apnea. No other significant co-morbidities were present in any member of the cohort.

Demographics, basic anthropomorphic data, pregnancy status (where applicable), resting blood pressure and resting

HR were obtained on the day of the study visit. Hemodynamics were determined to be in a range conducive to exercise for all participants. Blood pressure and HR were again recorded at the end of the study.

All components of study data acquisition were conducted at our institution’s Clinical Research Center, a dedicated research environment within Vanderbilt Medical Center through which qualified nursing, sonographer, and exercise supervisory support was provided. A standard peripheral intravenous catheter (20 or 22 gauge) was inserted into the right antecubital vein by an experienced research nurse.

The participants and all study personnel were masked throughout the protocol (including during and recovering from exercise) in accordance with our institution’s policies during the COVID pandemic.

Echocardiography

For all participants, a limited echocardiogram was performed at rest on an EPIQ7C cardiac ultrasound instrument (Philips, Amsterdam, The Netherlands) by a single experienced sonographer. Assessment of left ventricular ejection fraction (LVEF), left ventricular outflow tract (LVOT) diameter, LVOT velocity–time integral (VTI), mitral valve inflow velocity (E); mitral valve tissue Doppler velocity (e'), tricuspid annular plane systolic excursion (TAPSE), and an estimate of right atrial pressure using the inferior vena cava size and response to deep inspiration were obtained according to American Society of Echocardiography guidelines. With the exception of LVOT diameter, these measurements were repeated after the post-exercise contrast injection. The LVOT VTI measurement was recorded as soon as possible following opacification of the left heart.

After exclusion of inter-atrial shunt with agitated saline contrast studies at rest and with Valsalva, DEFINITY® (Perflutren lipid microsphere, Lantheus Medical Imaging Inc, Billerica Massachusetts) was used for ultrasound contrast administration as previously described [1, 8]. To minimize delays in contrast arrival to the right heart due to pooling in the great veins of the right upper extremity, for both baseline and post-exercise injections contrast was injected with participants lying in the left lateral decubitus position with the right arm extended vertically. The entry of contrast into the right heart and subsequent appearance in the left heart was recorded in the apical 4-chamber view during normal respiration. Each participant received approximately 0.5 mL of DEFINITY® under each study condition (baseline and post-exercise) with contemporaneous image acquisition to record the passage of contrast through the cardiac chambers.

Exercise protocol

Prior to initiating the exercise protocol, additional echocardiographic images were obtained to confirm clearance from the cardiac chambers of the DEFINITY[®] administered during the baseline injection as to not confound the post-exercise determination of PTT.

The exercise apparatus consisted of a treadmill (Trackmaster RS232, Full Vision Inc, Newton KS), EKG lead/tracking device (Mortara X12 + XScribe, Mortara Instrument Inc, Milwaukee WI), and an integrated software platform (Ultima CPX with PF and Cardio2, MGC Diagnostics Corporation, St Paul MN).

Electrocardiographic leads were attached to participants in the standard configuration with allowances made such that lead placement did not interfere with the optimal echocardiographic window as determined by the sonographer. The EKG signal from the exercise apparatus was synched to the ultrasound instrument such that the latter used a standard lead from the former as its telemetry signal. Therefore, the single lead EKG signal and HR recorded by the ultrasound machine were identical to that recorded by the exercise software. A standard 12-lead EKG was recorded every minute of exercise, at peak exercise, and at each minute for the first several minutes of recovery. HR was recorded in a similar fashion.

For this study, the goal of the exercise was to augment the HR sufficiently while still maintaining the ability to control respiration well enough to facilitate post-exercise imaging, with special attention to recording adequately the path of contrast through the right and left-sided cardiac chambers. Thus, the exercise level obtained was intentionally sub-maximal for all participants. Participants exercised on a Standard Bruce Protocol [9] until their HR reached 2.5 times the baseline level, their HR reached a plateau in stage 3 or higher, or they indicated the onset of subjective inability to control respiration. At the cessation of exercise, the sonographer started a timer on the ultrasound instrument (i.e. the timer began at peak exercise) and the participant returned to the echocardiography table (located approximately 3 feet from the treadmill). The sonographer obtained a stable apical 4-chamber view and contrast was injected during suspended respiration at end-expiration.

PTT, rPBV, and PBV determination

The recorded images of contrast traveling from the right heart to left heart were analyzed offline using QLab 10.7 software (Philips, Amsterdam, The Netherlands).

Regions of interest (ROI; 5 mm square) were placed in the RV, LA, and LV adhering to the following guidelines as closely as possible. 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. Analogous to the RV, the LV ROI was placed approximately 1 cm distal to the mitral valve leaflet tips equidistant from the interventricular septum and LV-free wall. The LV ROI was used in the entrance of contrast to the LA was not optimally visualized, a scenario encountered in several post-exercise images. Our prior work has demonstrated that ROI location has minimal impact on the value of PTT [10]. After placement of ROIs, time-intensity curves of contrast passage through the RV, LA and LV were generated by the QLab software. These curves served as the inputs to our previously described inflection point algorithm, from which PTT is calculated [11].

As described in the Theory section, rPBV was estimated as the product of PTT and average HR during the passage of contrast from the RV to the LA or LV. All participants were in sinus rhythm during both contrast injections. Absolute PBV was estimated as the product of rPBV and echocardiographically derived SV, the latter calculated as the product of LVOT VTI and LVOT area [12].

Results

Cohort characteristics and exercise performance

Table 1 displays basic demographic, echocardiographic, and exercise characteristics. The cohort consisted of 14 healthy individuals (2 women, 12 men) primarily in their fifth decade (youngest: 34.9 years, oldest: 58.7 years) with a low prevalence of obesity (two individuals had a body mass index of ≥ 30 kg/m²). All had normal left ventricular ejection fraction, normal left-sided filling pressure estimate (by E/e'), and normal right ventricular systolic function. All exercised for at least 6 $\frac{3}{4}$ minutes and the average participant nearly completed stage III of the Bruce Protocol. Despite not being a maximal exercise test, all participants reached at least 70% of age-predicted maximum HR (APMHR) and the average participant achieved 85% APMHR, the typical goal of exercise tests obtained for clinical reasons. At peak exercise, the average HR was more than twice that at rest, with only 1 participant not achieving this level of HR augmentation. Average HR recovery at 1-min was nearly 50 beats per minute and comprised nearly 60% of the difference between baseline and peak-exercise HRs, suggesting participants had an overall good level of fitness.

To quantify the inherent delay between exercise and obtaining the primary data needed to derive PTT and PBV, the intervals between peak exercise, contrast injection, and subsequent LVOT VTI measurement were recorded. The HR

Table 1 Cohort characteristics

Parameter	Exercise cohort (<i>n</i> = 14)
Demographic/anthropomorphic	
Age (years)	46 ± 8
Gender (F/M)	2/12
Height (cm)	174 ± 9
Weight (kg)	76 ± 11
BMI (kg/m ²)	25 ± 3
BSA (m ²)	1.9 ± 0.2
Echocardiographic	
Biplane Simpson's LVEF (%)	63 ± 4
LVOT diameter (cm)	2.1 ± 0.1
E/e'	8 ± 2
TAPSE (cm)	2.4 ± 0.3
Exercise	
Bruce Protocol time (min:sec)	8:47 ± 1:52
Peak exercise HR (bpm)	147 ± 16
Peak exercise HR/Resting HR	2.3 ± 0.3
Peak exercise HR (% APMHR)	85 ± 9
HR recovery at 1 min (bpm, %)	48 ± 13, 59 ± 18

APMHR age-predicted maximum heart rate, *bpm* beats per minute, *BMI* body mass index, *BSA* body surface area, *E* mitral valve inflow velocity, *e'* medial mitral valve annulus tissue Doppler velocity, *HR* heart rate, *LVEF* left ventricular ejection fraction, *LVOT* left ventricular outflow tract, *TAPSE* tricuspid annular plane systolic excursion

at each of these time points was recorded as well. Echocardiographic contrast was injected 30 ± 8 s following peak exercise and the LVOT VTI was measured 47 ± 12 s after the injection. The corresponding HRs were as follows: peak exercise: 147 ± 16 bpm; post-exercise contrast injection: 123 ± 24 bpm; LVOT VTI measurement: 89 ± 15 bpm.

Pulmonary transit time and pulmonary blood volume metrics

A time-intensity curve at baseline and post-exercise for a representative participant is shown in Fig. 1. Baseline and post-exercise data for HR, PTT, rPBV, and stroke volume are presented in Table 2. The reported HRs reflect the conditions at the time contrast was injected. Therefore, the 'exercise-HR' is not indicative of HR at peak-exercise, but after some degree of HR recovery during the interval between peak-exercise and injection, as noted above. The ratio of exercise-HR to baseline HR was 1.9 ± 0.3 indicating that participants' HR at the time of the post-exercise contrast injection was nearly double their baseline.

From a technical standpoint, the data necessary to derive PTT following the exercise were able to be obtained in all participants.

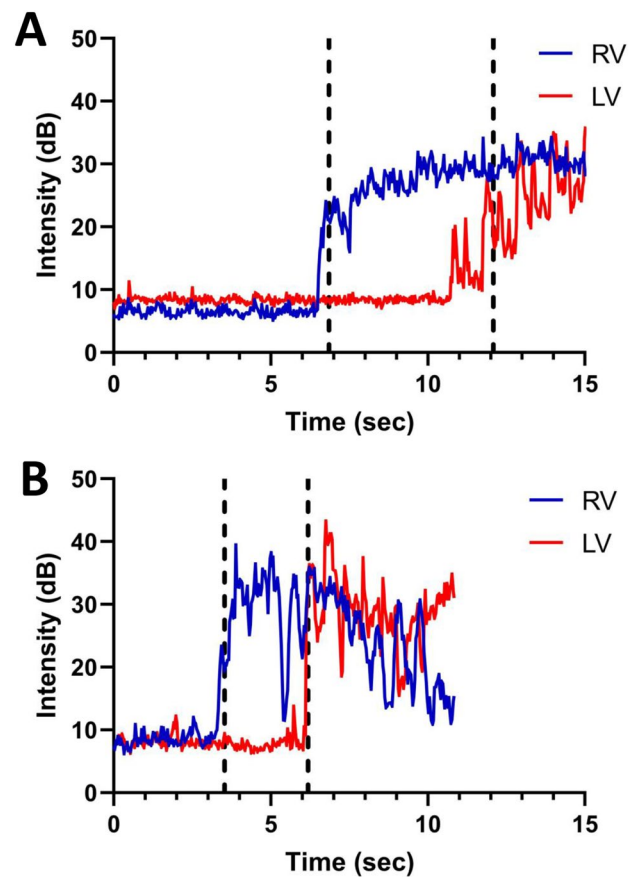


Fig. 1 Representative time-intensity curve. The intensity of the contrast passing through the regions of interest (RV and LV in this example) as a function of time are depicted for the same participant **A** at rest; and **B** post-exercise. The dashed vertical lines represent the inflection points in each curve as identified by our algorithm. The interval between the RV and LV inflection points is the PTT. The post-exercise PTT is shorter than the baseline PTT in this example (2.66 s post-exercise vs 5.24 s at baseline). *LV* left ventricle, *RV* right ventricle, *PTT* pulmonary transit time

As expected, for most participants (13/14), PTT decreased following exercise relative to baseline. For slightly less than half of the participants ($n=6$), rPBV decreased with exercise and rPBV increased for the remainder of the cohort (Fig. 2). Correspondingly, the mean rPBV ratio ($rPBV_{EXERCISE}/rPBV_{REST}$) was near unity (1.02 ± 0.23). The range of rPBV indicates that with exercise, PBV increased between 56 and 138% relative to the change in systemic stroke volume. In one individual, both rPBV and systemic stroke volume decreased modestly with exercise. Interestingly, that participant had relatively low HR recovery indicating, at least within our relatively fit cohort, a lower degree of overall fitness.

Table 2 Pulmonary transit time parameters at baseline and post-exercise

ID	HR (bpm)		PTT (sec)		rPBV (beats)		Stroke volume (mL)		PBVi (mL/m ²)		rPBV _{EX} /rPBV _{BL}
	BL	EX	BL	EX	BL	EX	BL	EX	BL	EX	
1	60	115	4.26	2.52	4.26	4.83	84	86	172	200	1.13
2	72	162	4.84	2.2	5.81	5.94	63	67	218	234	1.02
3	72	130	5.18	3.52	6.22	7.63	123	146	412	597	1.23
4	71	140	5.07	1.45	6.00	3.38	86	93	259	157	0.56
5	75	134	5.73	4.24	7.16	9.47	74	117	269	564	1.32
6	57	163	5.01	1.52	4.76	4.13	64	107	155	225	0.87
7	61	135	4.22	2.64	4.29	5.94	67	52	179	192	1.38
8	60	130	4.16	2.06	4.16	4.46	104	140	211	304	1.07
10	61	110	5.24	2.66	5.33	4.88	87	82	253	217	0.92
11	49	86	5.90	3.78	4.82	5.42	104	112	260	316	1.12
12	75	86	5.13	5.34	6.41	7.65	74	89	275	392	1.19
13	55	95	6.01	2.59	5.51	4.10	111	121	290	236	0.74
14	63	122	5.61	2.49	5.89	5.06	69	87	193	209	0.86
15	64	114	6.08	2.9	6.49	5.51	68	89	246	271	0.85

BL baseline, EX exercise, HR heart rate at the time of contrast injection, ID study ID number, PTT pulmonary transit time, PBVi pulmonary blood volume indexed to body surface area, rPBV relative pulmonary blood volume

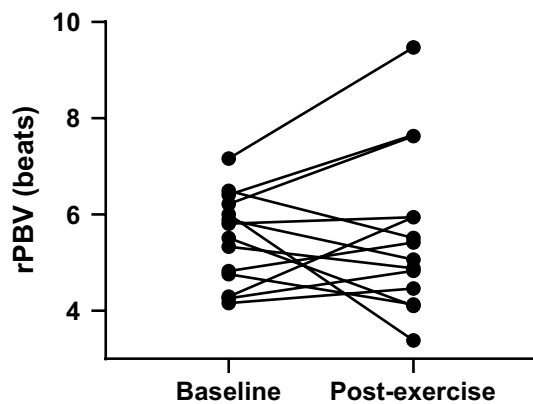


Fig. 2 Comparison of rPBV at rest and following exercise. For most participants, rPBV does not change much between rest and exercise, but rPBV_{EXERCISE}/rPBV_{REST} exhibits an approximate threefold range overall. rPBV relative pulmonary blood volume

Discussion

This proof-of-concept study demonstrates the capability of obtaining PTT by contrast echocardiography following a standard exercise protocol. As this technique requires no additional equipment or personnel beyond what is used clinically in a typical Echocardiography Laboratory, there exists potential to evaluate a variety of symptoms and disease states with this approach.

Our findings are similar to prior investigations that used non-echocardiographic methods to measure the impact

of exercise on PTT and PBV. In a study of patients with mild-moderate heart disease performing supine bicycle ergometry with indwelling pulmonary artery, left atrial, and brachial artery catheters [13], additional analysis of the available individual-level data show a range of rPBV_{EXERCISE}/rPBV_{REST} values comparable to ours (range: 0.9–2; mean: 1.2 ± 0.4 , median: 1.1). A study of young athletes undergoing upright bicycle ergometry and non-invasive first-pass radionuclide angiography [14] showed PBV increased by a factor of 1.5 at maximum exercise with a concurrent doubling of stroke volume, yielding an aggregate rPBV_{EXERCISE}/rPBV_{REST} value of 0.75, also within the range of our findings. In addition, the absolute values of PBVi in the current study are similar to those found in these prior reports as well, allowing for differences in age and general fitness level of the cohorts. Likewise, the overall change in PTT with exercise observed in our study is similar to the trend in these prior reports. For most participants in the invasive-measurement study (8/12 with sufficient data) [13], PTT decreased with exercise. In the radionuclide angiography study [14], only cohort-level data are provided. On that basis, the reported change in PTT with exercise (a decrease of ~68%) is consistent with our findings (a decrease of ~50%).

Incorporation of echocardiographically based PTT and PBV into studies of pulmonary gas exchange with exercise may provide complementary information to exercise-related changes in pulmonary capillary volume, a key parameter commonly derived from such investigations [15, 16]. It is possible that acquiring contemporaneous estimates of

total PBV against which to compare pulmonary capillary volume at rest and with exercise could lend further insight into the contribution of capillary recruitment or distention to the increased physiologic demands of exercise. Changes in rPBV with activity, with or without accompanying gas-exchange data, may also reflect the effects of elevated left atrial pressure and/or chronotropic incompetence on exercise capacity in suspected or established HFpEF. Generalizing further, a comparison of rPBV under any two conditions (i.e. before and after a volume load or drug administration) can theoretically provide a PBV ratio that takes into account any concurrent change in systemic SV. Although speculative, this metric may be useful in distinguishing non-invasively pre-capillary from post-capillary pulmonary hypertension (PH), which remains a challenge in the absence of invasive hemodynamics. In pre-capillary PH, the hallmark of which is pulmonary vascular obliteration, PBV may be expected to decline relative to SV in response to a volume challenge, whereas in post-capillary PH, if the volume load is distributed passively through the pulmonary and systemic circulations, PBV may change in proportion to SV.

In addition to the small sample size (although comparable to the prior reports cited above) [13, 14], the present study has several limitations. The cohort was not obese, free of significant cardiopulmonary disease and could exercise to reasonable workloads while maintaining the ability to control respiration sufficiently such that interpretable PTT data could be obtained. These characteristics may not be uniformly present in other populations of interest and thus this technique may not be entirely generalizable. Due to the transition time between the treadmill and echocardiography table following exercise, PTT was not measured at true peak exercise. While this scenario is common and not prohibitive in assessments of inducible ischemia with exercise stress echocardiography, the impact of these delays in the evaluation of PTT and PBV remains unclear. Nonetheless, any effects of this transition time could potentially be mitigated by the use of upright or supine bicycle exercise, which could allow PTT acquisition closer to peak exercise. Such equipment was not available for use in this study. Comparisons of rest and exercise PTT necessitate two sequential contrast injections and, as such, there is an obligatory waiting period between the injections to allow the contrast to wash out. In our experience, approximately 15 min of low-level activity (i.e. stage I of the Bruce Protocol) was adequate to remove any residual contrast from the cardiac chambers and great veins of the right upper extremity (the site of the peripheral IV). Following exercise, PTT and LVOT VTI (the key parameter in the determination of SV) are acquired sequentially and therefore represent different physiologic states of recovery. Overcoming this limitation would be technically difficult, if not impractical, as it requires simultaneous acquisition of PTT and LVOT VTI, which would entail separate

ultrasound probes in close proximity to the chest wall each operated by a different sonographer. Nonetheless, although this delay was, on average, less than 20 s in our cohort, the non-simultaneous measurement of rPBV and SV could lead to underestimation of SV and, by extension, underestimation of absolute PBV as well. However, this issue does not impact rPBV or $PBV_{EXERCISE}/rPBV_{REST}$ as these rely only on PTT and the HR during PTT acquisition. Intra-pulmonary shunts induced by exercise [17] could also confound the use of this technique, although this phenomenon was not clearly observed in our small cohort that exercised sub-maximally. However, if this type of shunt were recorded, its magnitude and timing could theoretically be quantified by employing similar principles as used in the present study (i.e. an additional ROI placed in the area of shunt flow).

Conclusion

In summary, estimation of PTT and PBV from contrast-enhanced echocardiography following exercise is technically feasible and yields physiologically plausible results. Proceeding to the comparison of this technique with simultaneous measurement of invasive hemodynamics during exercise appears reasonable.

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Author contributions KM: concept/design, data acquisition/analysis/interpretation, drafting the manuscript, critical revision of the manuscript, approval of article, secured funding, data collection. EB: interpretation of data, critical revision of the article, approval of the article. JJT: interpretation of data, critical revision of the article, approval of the article.

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Declarations

Conflict of interest Ken Monahan declares that he has no conflict of interest relevant to this research. Evan Brittain declares that he has no conflict of interest relevant to this research. James Tolle declares he has no conflict of interest relevant to this research.

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consent was obtained from all patients being included in the study.

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