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A feasible method for non-invasive measurement of pulmonary vascular resistance in pulmonary arterial hypertension: Combined use of transthoracic Doppler-echocardiography and cardiac magnetic resonance. Non-invasive estimation of pulmonary vascular resistance

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ABSTRACT

Background: Transthoracic Doppler-echocardiography (TTE) can estimate mean pulmonary arterial pressure (MPAP) and pulmonary capillary wedge pressure (PCWP) reliably, and cardiac magnetic resonance (CMR) is the best modality for non-invasive measurement of cardiac output (CO). We speculated that the combined use of TTE and CMR could provide a feasible method for non-invasive measurement of pulmonary vascular resistance (PVR) in pulmonary arterial hypertension (PAH).

Methods and results: Right heart catheterization (RHC) was undertaken in 77 patients (17M/60F) with PAH, and simultaneous TTE was carried out to evaluate MPAP, PCWP and CO. Within 2 days, CO was measured again with CMR in similar physiological status. Then, PVR was calculated with the integrated non-invasive method: TTE-derived (MPAP–PCWP)/CMR-derived CO and the isolated TTE method: TTE-derived (MPAP–PCWP)/TTE-derived CO, respectively. The PVR calculated with integrated non-invasive method correlated well with RHC-calculated PVR ($r = 0.931$, 95% confidence interval 0.893 to 0.956). Between the integrated non-invasive PVR and RHC-calculated PVR, the Bland–Altman analysis showed the satisfactory limits of agreement (mean value: -0.89 ± 2.59). In comparison, the limits of agreement were less satisfactory between TTE-calculated PVR and RHC-calculated PVR (mean value: -1.80 ± 3.33). Furthermore, there were excellent intra- and inter-observer correlations for the measurements of TTE and CMR ($P < 0.001$ for all).

Conclusions: The combined use of TTE and CMR provides a clinically reliable method to determine PVR non-invasively. In comparison with RHC, the integrated method shows good accuracy and repeatability, which suggests the potential for the evaluation and serial follow-up in patients with PAH.

Translational perspective: In PAH, the non-invasive measurement of PVR is very important in clinical practice. Up to now, however, the widely accepted non-invasive method is still unavailable. Since TTE can estimate (MPAP–PCWP) reliably and CMR is the best image modality for the measurement of CO, the combined use of two modalities has the potential to determine PVR non-invasively. In this research, the integrated non-invasive method showed good diagnostic accuracy and repeatability compared with RHC. Therefore, it might be a feasible method for non-invasive measurement of PVR in patients with PAH.

1. Introduction

The measurement of pulmonary vascular resistance (PVR) is crucial in the diagnosis and management of pulmonary arterial hypertension (PAH). Right heart catheterization (RHC) is widely considered the "gold standard" to determine PVR, however, it is limited by the associated disadvantages [1]. Therefore, it is necessary to develop a feasible method for the non-invasive measurement of PVR. Recent reports have investigated the applicability of transthoracic Doppler-echocardiography (TTE) or cardiac magnetic resonance (CMR), and some novel methods have been proposed [2–13]. However, the intrinsic limitations of each image modality compromised the accuracy and

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reproducibility in these methods. Up to now, with the isolated use of TTE or CMR, there was no widely accepted method for non-invasive evaluation of PVR.

Previous studies have demonstrated that TTE and CMR had complementary advantages. TTE had the potential to estimate mean pulmonary arterial pressure (MPAP) and pulmonary capillary wedge pressure (PCWP) reliably [14–23]. In the non-invasive measurement of cardiac output (CO), however, CMR had more accuracy and reproducibility than TTE [24–26]. Based on the formula (MPAP–PCWP)/CO, it became possible to calculate PVR directly with TTE-derived (MPAP–PCWP) and CMR-derived CO. Therefore, we hypothesized that the combined use of TTE and CMR might have the potential to estimate PVR non-invasively. This study was performed to determine whether the integrated modality formed a reliable non-invasive method to measure PVR in PAH.

2. Methods

2.1. Study patients

From January 2009 to July 2014, a total of 77 patients (age 32.42 ± 11.01 years, 17M/60F) with PAH were enrolled. Among these patients, there were 70 patients with idiopathic PAH and 7 patients with post-operative persistent PAH after surgical closure of ventricular septal defect (n = 4), patent ductus arteriosus (n = 2) and atrial septal defect (n = 1). All patients were in sinus rhythm. Patients (n = 16) with unstable clinical condition, inadequate image quality, arrhythmia (such as atrial fibrillation, frequent premature beats and so on), significant mitral or aortic regurgitation, variations of heart rate and blood pressure ≥10% (between RHC/TTE and CMR), and contraindications of CMR examination were all excluded from the study. For the patients aged ≥45 years (n = 11), coronary artery disease was excluded with selective coronary angiography (defined as ≥50% reduction in lumen diameter). The study was approved by our hospital research ethics committee, and informed consent was obtained from each patient.

2.2. Study design

In this study, PAH was defined as MPAP >25 mm Hg and PCWP ≤ 15 mm Hg at rest (RHC) [27]. During RHC, simultaneous TTE examination was performed in patients with PAH. The invasive hemodynamic data, TTE-derived (MPAP–PCWP) and TTE-derived CO were obtained at rest. Within 2 days after RHC/TTE, CMR was performed without intervening therapy and the resting CO was calculated non-invasively in similar physiological status (variations of heart rate and blood pressure <10%). According to the formula TTE-derived (MPAP–PCWP)/CMR-derived CO and TTE-derived (MPAP–PCWP)/TTE-derived CO, the non-invasive PVR was calculated, respectively. Furthermore, the results were compared with RHC-calculated PVR using the Bland–Altman analysis. Individuals in whom RHC, TTE and CMR variables were obtained were blinded to each other's calculations. Furthermore, thirty-eight patients were randomly selected to validate the intra-observer and inter-observer variability, respectively. For intra-observer reproducibility, the examination was repeated twice by the same observer in a consecutive manner. For inter-observer reproducibility, CMR was validated by two independent observers based on the same imaging result (without any communication). And for TEE, two independent observers conducted the examination in turn also without communication.

2.3. RHC

Our procedure for cardiac catheterization has been described previously [28]. In brief, all patients underwent routine RHC (Swan-Ganz, Edwards Lifesciences) under local anesthesia. The complete hemodynamic data and blood samples were obtained at rest. The measurements included mean right atrial pressure, right ventricular pressure, systolic pulmonary arterial pressure (SPAP), diastolic pulmonary arterial pressure (DPAP), MPAP and PCWP. According to the oxymetric principle of Fick, CO and PVR [PVR = (MPAP–PCWP) / CO] were calculated.

2.4. TTE

In patients undergoing RHC, simultaneous TTE (Philips IE33, instrument equipped with a 3–5 MHz transducer) was performed. TTE-derived MPAP was calculated as TTE-derived SPAP × 0.61 + 2 mm Hg, according to Chemla et al. [16]. SPAP was estimated by TTE from the systolic right ventricular-to-right atrial pressure gradient using the modified Bernoulli equation, and the assessment of right atrial pressure was performed in accordance with previously described methods. Furthermore, isovolumic relaxation time (IVRT) and color M-mode Doppler flow propagation velocity (FPV) were measured. According to the equation: $4.5\ (10^3 / [2 \cdot VRT] + FPV) - 9$, PCWP was estimated non-invasively [18]. Based on TTE-derived MPAP and PCWP, the transpulmonary pressure gradient (MPAP–PCWP) was calculated non-invasively. According to the recommendations in guideline, the measurements of stroke volume (SV) and CO (SV × heart rate) were made at the level of the left ventricular (LV) outflow tract [29].

2.5. CMR

All examinations were performed on a 1.5 Tesla MR scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) at rest, and the protocol has been described previously [30–31]. In brief, scout images acquired by using half-Fourier acquisition single-shot turbo spin-echo (HASTE) sequence were used to analyze the morphology and structure of the heart. Retrospective electrocardiographic-gating cine images were acquired using a true fast imaging with steady-state precession (TrueFisp) sequence. For the volumetric and functional measurements, contiguous short-axis images through the entire ventricle (from base to apex, no gap) were obtained. The following parameters were used: FOV, 250 mm × 188 mm; slice thickness, 8 mm; matrix, 156 mm × 192 mm; TR, 2.8 ms; TE, 1.39 ms; flip angle, 70°; number of signal averages, 2–4. LV end-diastolic and end-systolic volumes, LV ejection fraction (LVEF), SV, and CO (SV × heart rate) were calculated. In addition, right ventricular (RV) end-diastolic and end-systolic volumes, RVEF were also calculated (the endocardial borders of all short-axis images at end-diastole and end-systole were manually traced with the inclusion of RV outflow to the pulmonary valve and the trabeculae in the RV volume).

2.6. Statistical analysis

Categorical variables were presented as counts with percentages and compared by Chi-square test or Fisher's exact test. Continuous variables were presented as mean ± SD or median with IQR and compared by grouped t-test or Wilcoxon rank sum test. Pearson or spearman correlation coefficients were calculated first and linear regression models were constructed. Furthermore, Bland–Altman analysis was carried out for agreement assessments, the lower and upper limits of agreement were estimated, as the mean ± 2SDs with 95% confidence interval (CI). Pearson's or Spearman's correlation and Bland–Altman analysis were also used to assess the intra-observer and inter-observer reproducibility. A two-sided $P < 0.05$ was considered statistically significant. Statistical software used in this study was SPSS 16.0 and MedCalc 9.5.

3. Results

Clinical and demographic characteristics of the patients were listed in Table 1. The TTE-derived (MPAP–PCWP) and RHC-derived (MPAP–PCWP) were comparable (55.06 ± 17.67 mm Hg vs 58.45 ± 18.76 mm Hg, $P = 0.25$). The linear regression analysis revealed a good correlation (r = 0.934, 95% CI: 0.897–0.957) for all patients

Table 1
Clinical and hemodynamic characteristics of patients with PAH (n = 77).

Sex, M/F	17/60
Age, years	32.42 ± 11.01
BSA, m^2	1.48 ± 0.14
Diagnosis, n	77
Idiopathic PAH, n (%)	70 (90.9%)
Post-operative persistent PAH, n (%)	7 (9.1%)
RHC	
SPAP, mm Hg	103.64 ± 31.38
DPAP, mm Hg	39.97 ± 16.31
MPAP, mm Hg	68.00 ± 19.28
PCWP, mm Hg	9.55 ± 1.96
MPAP–PCWP, mm Hg	58.45 ± 18.76
CO, L/min	4.83 ± 1.91
Heart rate, bpm	79.23 ± 10.05
Invasive PVR, Wood	13.86 ± 7.05
TTE	
MPAP, mm Hg	64.56 ± 18.05
PCWP, mm Hg	9.49 ± 1.99
MPAP–PCWP, mm Hg	55.06 ± 17.67
CO, L/min	3.76 ± 1.45
TTE-calculated PVR, Wood	16.55 ± 8.27
Mild tricuspid regurgitation, n (%)	42(54.5%)
Moderate tricuspid regurgitation, n (%)	31(40.3%)
Severe tricuspid regurgitation, n (%)	4(5.2%)
CMR	
LVEDV, ml	88.90 ± 50.78
LVESV, ml	40.65 ± 32.09
LVEF, %	55.92 ± 9.91
Heart rate, bpm	77.97 ± 11.64
CO, L/min	4.18 ± 1.72
RVEF, %	25.15 ± 9.6
Integrated non-invasive PVR, Wood	14.75 ± 6.83

Notes: BSA, body surface area; Invasive PVR, PVR calculated with RHC; Integrated non-invasive PVR, PVR calculated with TTE-derived (MPAP–PCWP)/CMR-derived CO.

(Supplemental Fig. 1). Using the Bland–Altman analysis (Supplemental Fig. 2), TTE-derived (MPAP–PCWP) showed satisfactory limits of agreement with RHC-derived (MPAP–PCWP). The mean value was 3.39 ± 6.73 (SD), and TTE-derived (MPAP–PCWP) and RHC-derived (MPAP–PCWP) values were well within one standard deviation (17.67 and 18.76, respectively).

The CO from CMR and RHC were 4.18 ± 1.72 L/min and 4.83 ± 1.91 L/min, respectively. The linear regression analysis also showed a good correlation (r = 0.805, 95% CI: 0.709–0.872) (Supplemental Fig. 3). Using the Bland–Altman analysis (Supplemental Fig. 4), CMR-derived CO demonstrated the good limits of agreement with RHC-derived CO. The mean value was −0.65 ± 0.85 (SD), and CMR-derived CO and RHC-derived CO values were well within one standard deviation (1.73 and 1.92, respectively).

The heart rates were comparable between RHC/TTE and CMR (79.23 ± 10.05 bmp vs 77.97 ± 11.64 bmp, $P = 0.474$), and variation of heart rate was 1.26 ± 4.61. The integrated non-invasive PVR was 14.75 ± 6.83 Woods and invasive PVR was 13.86 ± 7.05 Woods. The good correlation (r = 0.931, 95% CI: 0.893–0.956) was confirmed with linear regression analysis (Fig. 1A). The Bland–Altman analysis showed the satisfactory limits of agreement between integrated non-invasive PVR and invasive PVR (Fig. 1B). The mean value was −0.89 ± 2.59 (SD), and integrated non-invasive PVR and invasive PVR values were well within one standard deviation (6.84 and 7.06, respectively). While between TTE-calculated PVR and invasive PVR, linear regression analysis (Supplemental Fig. 5) showed the good correlation (r = 0.912, 95% CI: 0.865–0.943), and the Bland–Altman analysis (Supplemental Fig. 6) showed the less satisfactory limits of agreement (mean value: −1.80 ± 3.33).

Furthermore, the difference between TTE-calculated PVR and invasive PVR was significantly larger than the difference between integrated non-invasive PVR and invasive PVR (Fig. 2, t = −4.78, $P < 0.001$ by the paired t-test analysis). The mean value of the difference between them was −1.79 ± 3.33 (SD). Based on the formula ABS ((X PVR - invasive PVR)/invasive PVR) for measuring the relative error, sd1 and sd2 were produced by non-invasive PVR and TTE-calculated PVR, respectively. And they all were divided into 4 categories by 0 to 0.1, 0.1 to 0.3, 0.3 to 0.5, and 0.5 to 1 (Table 2), respectively. Statistically significant difference was found between sd1 and sd2 for these categories by McNemar test ($\chi^2 = -19.371$, $P = 0.004$).

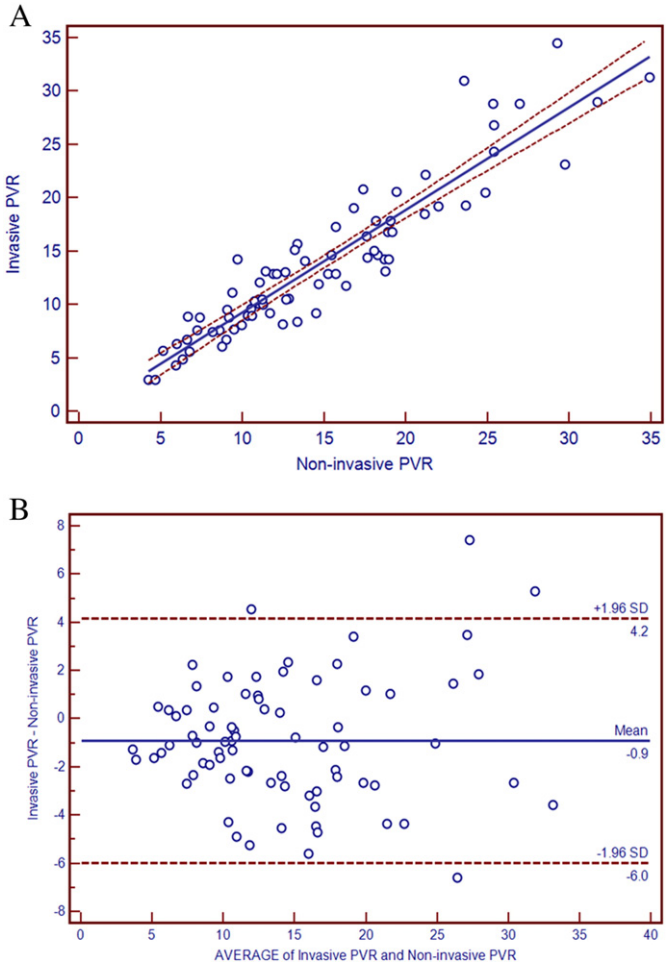

Fig. 1. A, Scatter diagram and regression line between integrated non-invasive PVR and invasive PVR (r = 0.931, 95% CI: 0.893–0.956) in all patients. B, Bland–Altman plot of the difference between integrated non-invasive PVR and invasive PVR against the mean of the non-invasive PVR and invasive PVR.

For TTE-derived (MPAP–PCWP), the intra-observer and inter-observer reproducibility was high, and the average differences were −1.13 and −1.87, respectively. The Pearson correlation coefficient was 0.977 and 0.955, respectively ($P < 0.001$ for both). For CMR-derived CO, the intra-observer and inter-observer variability were −0.076 and −0.186, respectively. The Pearson correlation coefficient was 0.995 and 0.993, respectively ($P < 0.001$ for both). Both the intra-observer (Supplemental Fig. 7) and inter-observer (Supplemental Fig. 8) have the respectively satisfactory reproducibility for TTE-derived (MPAP–PCWP) by using the Bland–Altman analysis, and the intra-observer (Supplemental Fig. 9) and inter-observer (Supplemental Fig. 10) for CMR-derived CO do the same as it.

4. Discussions

In this research, PVR was calculated directly with the combined use of TTE-derived (MPAP–PCWP) and CMR-derived CO. In comparison to RHC, PVR from this integrated non-invasive method showed the good accuracy and reproducibility in patients with PAH. To our knowledge, it is the first report to determine PVR with the combined use of TTE

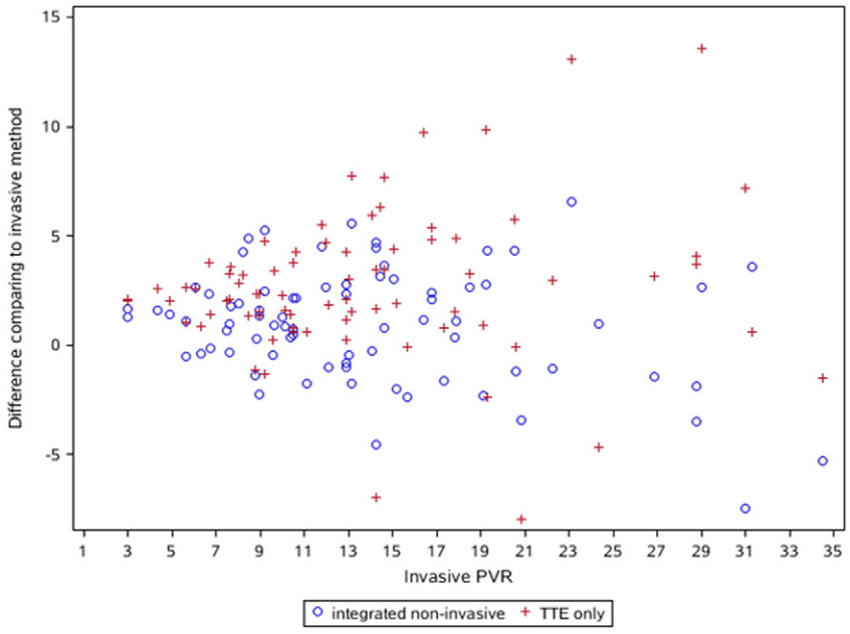

Fig. 2. Scatter of the difference between integrated non-invasive PVR and invasive PVR and the difference between TTE–PVR and invasive PVR against the invasive PVR. The latter was significantly larger than the former ($t = -4.78$, $P < 0.001$) by the paired t-test analysis.

and CMR, and our findings suggested that this integrated method was clinically feasible for non-invasive calculation of PVR in PAH.

In patients with PAH, PVR is an important prognostic factor and is frequently repeated for serial follow-up. Though RHC is the "gold standard" for the evaluation of PVR, its invasive nature makes it unsuitable for frequent and repeated use [1,27]. In addition, the cost and ionizing radiation also become the important disadvantages of RHC. Therefore, it is urgent to develop the reliable and accurate methods for non-invasive estimation of PVR. In preliminary studies, the significant relationships have been identified between some parameters of TTE/CMR and PVR, and several composite numerical models have been established to evaluate PVR non-invasively [2–13]. Limited by the intrinsic nature of each image modality, these methods were usually indirect, and the widely accepted method was still unavailable.

Based on the complementary advantages of TTE and CMR, a new method was proposed for the non-invasive measurement of PVR in this study. Since PVR is directly related to trans-pulmonary pressure gradient (MPAP–PCWP) and inversely related to CO, the non-invasive PVR can be achieved by non-invasive estimation of (MPAP–PCWP) and CO, respectively. It has been previously demonstrated that TTE estimated MPAP and PCWP reliably, but its ability to calculate CO was not as accurate and reproductive as CMR [25–26]. In this study, our findings also proved the flaw of 2D-TTE in the measurement of CO. On the contrary, CMR was the best non-invasive modality to measure CO but its ability to determine MPAP/PCWP was limited [13,32]. Therefore, TTE and CMR can complement each other, and the combined use of two image modalities made it possible to determine PVR non-invasively. In this study, our findings confirmed the potential of this integrated method. Furthermore, the attempt was also made to estimate PVR directly with the isolated use of 2D-TTE in this study. In comparison with RHC, however, TTE-calculated PVR was less satisfactory, which disagreed with recent research [33].

Compared with RHC, TTE can estimate trans-pulmonary pressure gradient (MPAP–PCWP) reliably in this study. In the estimation of MPAP, several studies have identified a strong relationship between TTE and RHC [14–16]. The incremental value of TTE for non-invasive measurement of MPAP has been proven in routine clinical practice [34]. Several TTE methods have been proposed to estimate MPAP, and the simple Chemla' formula ($MPAP = 0.61 \times SPAP + 2$) was adopted in this study [16]. Furthermore, it has previously been demonstrated that PCWP can be estimated reliably with different TTE methods [17–23]. In this study, PCWP was determined non-invasively based on the combined use of pulsed and color M-mode Doppler echocardiography [18]. Therefore, it became possible to estimate trans-pulmonary pressure gradient (MPAP–PCWP) non-invasively with TTE, which was confirmed in this study.

In this research, CO was measured non-invasively with volumetric cine CMR and agreed closely with that from RHC in similar physiological status. There were two methods available in CMR-calculated CO (volumetric cine and velocity-encoded cine), and they had excellent agreement [26]. CMR can overcome the limitations of TTE and provides the best non-invasive method for measurements of SV and CO. Previous reports have showed that CMR-derived CO had good accuracy and reproducibility compared with RHC-derived CO [24–26]. In this study, our findings also showed the reasonable agreement between CMR and RHC, and further corroborated the previous studies.

Table 2
Dividing the difference of integrated non-invasive method comparing to invasive method and the difference of TTE method comparing to invasive method into four categories, respectively (%).

Difference comparing to RHC (integrated non-invasive)	Difference comparing to RHC (TTE only)				Total
	0% to 10%	10% to 30%	30% to 50%	50% to 100%	
0% to 10%	8(10.39)	16(20.78)	3(3.90)	1(1.30)	28(36.36)
10% to 30%	5(6.49)	15(19.48)	12(15.58)	4(5.19)	36(46.75)
30% to 50%	0(0.00)	2(2.60)	3(3.90)	4(5.19)	9(11.69)
50% to 100%	0(0.00)	2(2.60)	1(1.30)	1(1.30)	4(5.19)
Total	13(16.88)	35(45.45)	19(24.68)	10(12.99)	77(100.00)

5. Study limitations

In patients with PAH, both physiologic and imaging factors were contributors to variations in the measurement of PVR. To minimize these influences, the related factors were controlled strictly between RHC/TTE and CMR. In addition, PAH was severe and PVR was high in this study. Therefore, the patients were selected highly in this study. Given the difficulty in the estimation of PAP, the normal controls were absent in this research. CO was measured non-invasively with

volumetric cine CMR in this study. Though there was excellent agreement between volumetric and velocity-encoded cine CMR, the latter was used more frequently and might permit inclusion of more patients. In this research, 30% or greater difference was observed in more than 10% of cases, which added more insight to the influence if the integrated method was used in clinical practice. Compared with the benefit of non-invasive procedure, however, the diagnostic value of integrated method might be acceptable. Furthermore, TTE-derived CO was based on conventional 2D-TTE, not 3D-TTE, in this research. Recent reports suggested that 3D-TTE might be more accurate than 2D-TTE in the measurement of SV [35–36]. Therefore, further research was required to evaluate the possibility of non-invasive PVR based on 3D-TTE.

6. Conclusions

In this study, our findings suggest that PVR can be calculated directly using TTE-derived (MPAP–PCWP) and CMR-derived CO. Furthermore, the results from this integrated non-invasive method showed good diagnostic accuracy and repeatability compared with RHC. Therefore, the combined use of TTE and CMR can provide a clinically feasible method for non-invasive measurement of PVR in patients with PAH.

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Disclosures

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcha.2015.07.008.

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