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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: $4.5\ (10^3\ /\ [2 \cdot \text{VRT}] + \text{FPV}) - 9$, PCWP was estimated non-invasively [18]. Based on TTE-derived MPAP and PCWP, the trans-pulmonary 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