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Noninvasive and Simple Assessment of Cardiac Output and Pulmonary Vascular Resistance With Whole-Body Impedance Cardiography Is Useful for Monitoring Patients With Pulmonary Hypertension

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Background: Right heart catheterization (RHC) is the gold standard for the diagnosis of pulmonary hypertension (PH) and a useful tool for monitoring PH. However, there are some disadvantages in the regular use of RHC because it is invasive. Noninvasive methods for monitoring hemodynamics are needed to manage patients with PH. In this study, we aimed to evaluate the reliability of noninvasive hemodynamic assessment with whole-body impedance cardiography (Non-Invasive Cardiac System [NICaS]) for PH.

Methods and Results: We investigated 65 consecutive patients undergoing RHC. Two-thirds of them had pulmonary arterial hypertension and one-third had chronic thromboembolic PH; 25% of the patients were receiving medical therapy. Cardiac output (CO) was estimated by NICaS (NI-CO), thermodilution (TD-CO), and the Fick method (Fick-CO). There was a strong correlation between NI-CO and TD-CO ($r=0.715$, $P<0.0001$) and Fick-CO ($r=0.653$, $P<0.0001$). Noninvasive pulmonary vascular resistance (PVR) was estimated using a conventional invasive equation with NI-CO, mean pulmonary arterial pressure was calculated by echocardiographic measurement, and pulmonary capillary wedge pressure was estimated at 10 mmHg in all cases. NICaS-derived PVR was very strongly correlated with invasive PVR (TD-PVR: $r=0.704$, $P<0.0001$; Fick-PVR: $r=0.702$, $P<0.0001$).

Conclusions: Noninvasive measurement of CO and PVR using NICaS and echocardiography is a useful tool for the assessment of PH.

Key Words: Cardiac output; Noninvasive assessment; Pulmonary hypertension; Pulmonary vascular resistance; Whole-body impedance cardiography

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by elevated pulmonary vascular resistance (PVR) because of pulmonary vascular remodeling. This leads to a decrease in cardiac output (CO) and ultimately death. Recently, targeted medical therapy for PAH patients with endothelin-receptor antagonists, phosphodiesterase-5 inhibitors, and prostacyclin analogs has been established,[1] and the prognosis of PAH has improved.[2] However, there is no universally accepted consensus on the treatment goals or follow-up strategy for PAH patients. Right heart catheterization (RHC) is not only the gold standard for the diagnosis of PAH, but is also a useful tool for monitoring PAH, and is recommended 3–6 months after new treatments and in the case of clinical worsening.[1] Hemodynamic monitoring with RHC is predictive of survival and effective in a goal-oriented treatment strategy,[3,4] and has been recommended by a recent guideline;[1] however, there are some disadvantages in the regular use of RHC as a follow-up procedure, especially with regard to invasiveness. Noninvasive and less complicated methods for monitoring hemodynamics are needed to manage patients with pulmonary hypertension (PH). Less invasive hemodynamic monitoring has recently been suggested as feasible in some situations.[5] The Non-Invasive Cardiac System (NICaS; NI Medical, Hod-Hasharon, Israel) is a device for calculating CO noninvasively with whole-body impedance cardiography (ICG_{WB}). The NICaS-derived CO (NI-CO) has been shown to be as reliable as the RHC-derived CO and is applicable for the noninvasive assessment of cardiac function

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Table 1. Clinical Characteristics of All Patients at Initial Hospitalization

Age (years)	62±14
Female (%)	39 (65)
Diagnosis (%)	
PAH	38 (63)
IPAH	12 (20)
CTD-PAH	24 (40)
Po-PAH	2 (3)
PH associated with respiratory disorders	3 (5)
CTPH	20 (33)
WHO-fc (%)	
1	1 (1.7)
2	22 (37.3)
3	32 (54.2)
4	4 (6.8)
Treatment (%)	25 (24)
Bosentan	13 (22)
Sildenafil	14 (23)
Beraprost	10 (17)
Hemodynamic variables	
sPAP (mmHg)	53.9±21.3
mPAP (mmHg)	31.7±12.0
RAP (mmHg)	3.7±4.2
PCWP (mmHg)	7.0±4.3
CO (TD) (L/min)	4.90±1.62
CO (Fick) (L/min)	3.92±2.08
PVR (TD) (dyn·s^{-1}·cm^{-5})	433±244
PVR (Fick) (dyn·s^{-1}·cm^{-5})	581±344
HR (beats/min)	73±11

CO, cardiac output; CTD-PAH, collagen tissue disease associated PAH; CTEPH, chronic thromboembolic pulmonary hypertension; HR, heart rate; IPAH, idiopathic PAH; mPAP, mean PAP; PAH, pulmonary arterial hypertension; Po-PAH, portal PAH; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; TD, thermodilution; WHO-fc, World Health Organization functional class.

in patients with left-sided chronic heart failure,[6,7] but its feasibility in patients with PH has not been evaluated. The purpose of this study was to evaluate the reliability of noninvasive measurement of CO and PVR with ICGWB in patients with PH.

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Methods

This study was approved by Kobe University Hospital Institutional Review Board and the patients provided written informed consent to participate.

Patients

We enrolled 65 consecutive patients with known or suspected pulmonary hypertension hospitalized in Kobe University Hospital from April 2010 to August 2011. All patients who were scheduled for RHC without fulfilling one of the exclusion criteria were eligible for the study. The exclusion criteria included restlessness and/or unstable patient condition, severe aortic valve regurgitation and/or aortic stenosis, aortic aneurysm, heart rate >130 beats/min, intra- and extracardiac shunts, severe peripheral vascular disease, severe pitting edema, sepsis, and dialysis, all of which interfere with the accurate measurement of impedance-derived CO with NICaS, as previously described.[6] Patients with elevated pulmonary capillary wedge pressure (PCWP >15 mmHg) on RHC were also excluded; 5 patients were excluded because of the presence of an intra-cardiac shunt; 29 patients were reevaluated 3–6 months after new treatments or at clinical worsening.

Table 2. Hemodynamic Measurements

Parameter	Value
TD-CO (L/min)	4.92±1.56
Fick-CO (L/min)	3.87±1.24
Echo-CO (L/min)	4.34±1.11
NI-CO (L/min)	4.40±1.32
TD-PVR (dyn·s^{-1}·cm^{-5})	446±249
Fick-PVR (dyn·s^{-1}·cm^{-5})	583±362
Echo-PVR (dyn·s^{-1}·cm^{-5})	660±363
NI-PVR (dyn·s^{-1}·cm^{-5})	544±316

Echo-CO, echocardiography-derived cardiac output; Echo-PVR, echocardiography-derived PVR; Fick-CO, cardiac output derived by the modified Fick method; Fick-PVR, PVR derived by modified Fick method; NI-CO, NICaS-derived cardiac output; NI-PVR, NICaS with echocardiography-derived PVR; PVR, pulmonary vascular resistance; TD-CO, thermodilution-derived cardiac output; TD-PVR, thermodilution-derived PVR.

Hemodynamics

Hemodynamic data were derived from standard RHC in all patients using a 6Fr Swan-Ganz catheter (Baxter Healthcare, Irvine, CA, USA). The catheter was introduced into the pulmonary artery under fluoroscopic guidance. Mean pulmonary arterial pressure (mPAP), systolic and end-diastolic pulmonary arterial pressure (sPAP and dPAP), mean right atrial pressure, and PCWP were measured. CO was measured using the following techniques.

Thermodilution-Derived CO (TD-CO) A 5-ml bolus of iced 5% glucose solution was injected 5 times at the same rate. The results of 3 injections within 15% of their extreme disparity were averaged to derive the TD-CO value.

Modified Fick method (Fick-CO) Blood samples were obtained from systemic and pulmonary arteries. All samples were measured for oxygen saturation with the same device (Radiometer ABL 715, Copenhagen, Denmark).

NI-CO These measurements were performed simultaneously with the measurement of TD-CO and Fick-CO during RHC. The measurement of NI-CO followed the method as previously reported:[6] an alternating electrical current of 1.4 mA with a 30-kHz frequency is passed through the patient via 2 pairs of tetrapolar electrodes – 1 pair placed on the wrist above the radial pulse, and the other pair placed on the contralateral ankle above the posterior tibialis arterial pulse. If the arterial pulses in the legs are either absent or of poor quality, the second pair of electrodes is placed on the contralateral wrist.

The NICaS apparatus calculates the stroke volume (SV) by Frinerman's formula:[8]

$$SV = dR/R \times \rho \times L2/Ri \times (\alpha+\beta)/\beta \times KW \times HF$$

where dR is the impedance change; R is the basal resistance; ρ is the blood electrical resistivity; L is the patient's height; Ri is the corrected basal resistance according to sex and age; KW is a correction factor for weight according to ideal values; HF is the hydration factor, which takes into account the body water composition. $\alpha+\beta$ is equal to the ECG R-R wave interval

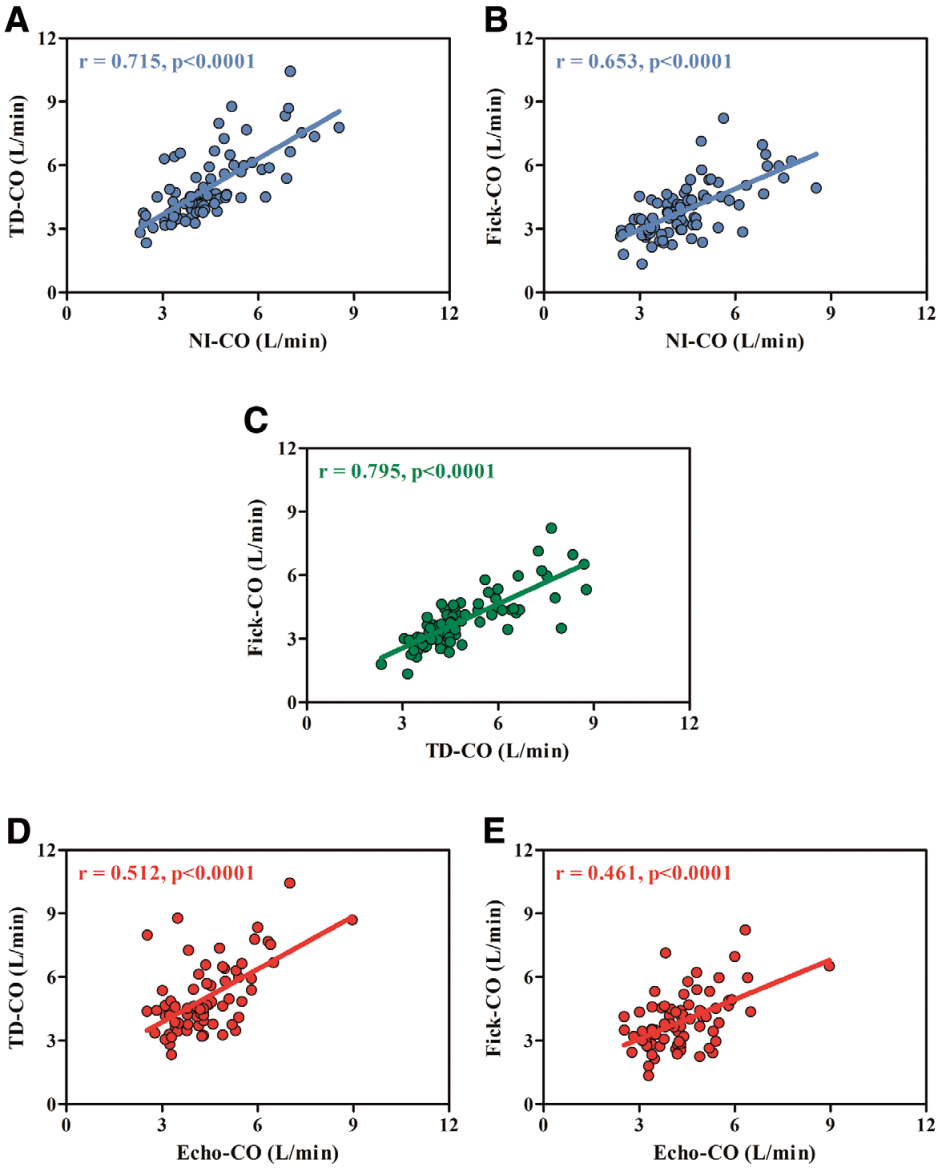

Figure 1. Linear correlation analysis between TD-CO and NI-CO (**A**), Fick-CO and NI-CO (**B**), TD-CO and Fick-CO (**C**), TD-CO and Echo-CO (**D**), and Fick-CO and Echo-CO (**E**). TD-CO, thermodilution-derived cardiac output; NI-CO, NICaS-derived cardiac output; Fick-CO, cardiac output derived by the modified Fick method; Echo-CO, echocardiography-derived cardiac output.

and β is the diastolic time interval. To calculate the CO, SV is multiplied by the heart rate. Because the NI-CO values are calculated every 20 s, the average of 3 measurements obtained consecutively during 60 s of monitoring is considered to be the NI-CO value for each individual case.

Echocardiography

Echocardiography was performed using a Vivid 5 system and a 3.5-MHz transducer (GE Vingmed Ultrasound AS, Horten, Norway). Two-dimensional Doppler examinations were performed in the usual manner. CO was measured by tracing the left ventricular ejection flow (Echo-CO). Echo-sPAP was estimated from the peak velocity of the tricuspid regurgitation jet plus estimated right atrial pressure (Echo-RAP).[9]

Measurement of PVR

PVR (dyn·s^{-1}·cm^{-5}) was calculated using RHC from the equation:

$$PVR = 80 \times (mPAP - PCWP)/CO_{TD,\,Fick}\ (TD\text{-}PVR,\ Fick\text{-}PVR).$$

PVR was also estimated noninvasively using a combination of NICaS and echocardiography, and by echocardiography alone.[10] Echo-mPAP was calculated as Echo-sPAP×0.61+2 mmHg, as previously described,[11] and noninvasive PVR was calculated as 80×(Echo-mPAP–PCWP)/$CO_{Echo,\,NI}$ (Echo-PVR, NI-PVR). PCWP for the calculation of noninvasive PVR was estimated at 10 mmHg in all cases.[10]

Statistical Analysis

Quantitative data are presented as mean±SD. The correlations

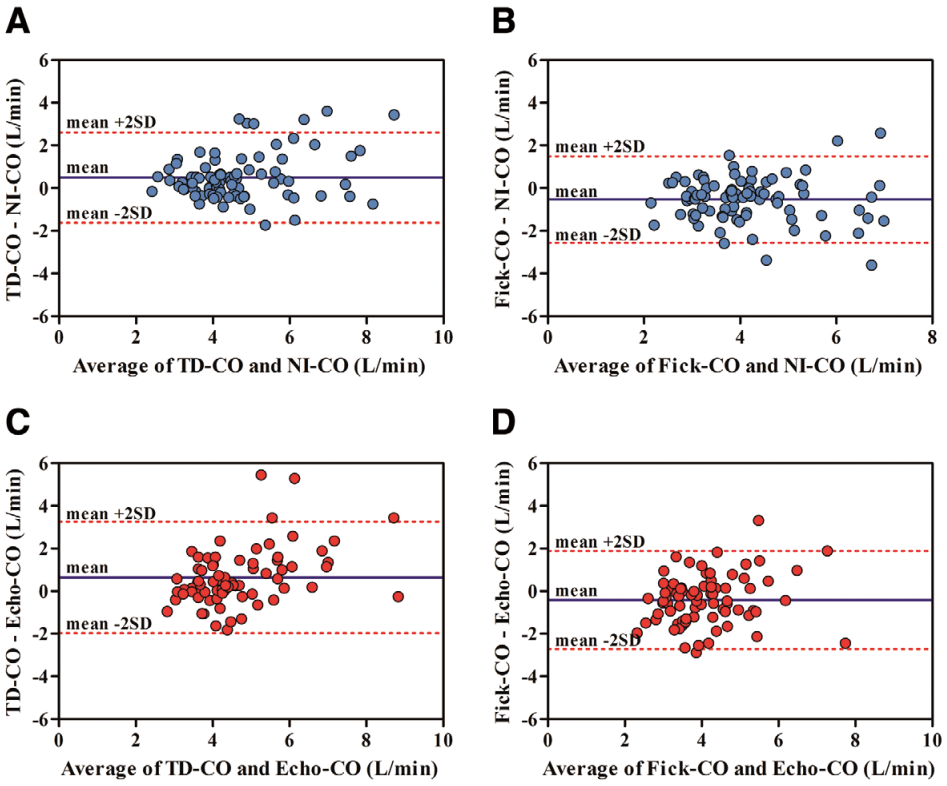

Figure 2. Bland-Altman plots with mean difference (solid line) ±2SD (dotted line) comparing TD-CO and NI-CO (**A**), Fick-CO and NI-CO (**B**), TD-CO and Echo-CO (**C**), and Fick-CO and Echo-CO (**D**). TD-CO, thermodilution-derived cardiac output; NI-CO, NICaS-derived cardiac output; Fick-CO, cardiac output derived by the modified Fick method; Echo-CO, echocardiography-derived cardiac output; SD, standard deviation.

among TD-CO, Fick-CO, Echo-CO, and NI-CO and between Echo-mPAP and mPAP measured by RHC (RHC-mPAP) were determined by calculating the Spearman's rank correlation coefficient. P<0.05 was considered to be significant. Agreement between methods was analyzed by the Bland-Altman method.[12] The limits of the agreement were expressed as the mean±SD. The 95% confidence intervals (CIs) of the bias were also calculated. Receiver-operating characteristic (ROC) curves were generated for the detection of elevated PVR defined as > 240 dyn·s^{-1}·cm^{-5} (3 Wood units [WU]). The area under the curve (AUC), cut-off value, sensitivity, and specificity were estimated by the ROC curves. All statistical analyses were performed using GraphPad Prism version 5 (GraphPad Software, La Jolla, CA, USA).

Results

The baseline characteristics of all patients at initial hospitalization are summarized in **Table 1**. Approximately two-thirds of the patients had PAH (World Health Organization [WHO] classification of PH group 1) and the other one-third of the patients had chronic thromboembolic PH (CTEPH: WHO group 4); 5% of the patients were classified as WHO group 3. At enrollment, 24% of the patients were receiving medical therapy.

Relationships Among Parameters

The mean CO values from all measurements in these subjects for TD-CO, Fick-CO, Echo-CO, and NI-CO were 4.92±1.56 L/min, 3.87±1.24 L/min, 4.34±1.11 L/min, and 4.40±1.32 L/min, respectively (**Table 2**). A significant and very strong correlation was observed between TD-CO and NI-CO (r=0.715, P<0.0001) and between TD-CO and Fick-CO (r=0.795, P<0.0001) by 2-tailed Spearman's rank correlation test (**Figure 1**). There was a strong correlation between Fick-CO and NI-CO (r=0.653, P<0.0001). However, the correlation between Echo-CO and TD-CO or Fick-CO was significant but not strong (r=0.512 or 0.461, P<0.0001, respectively). The differences between 2 measurements were plotted according to the Bland-Altman method (**Figure 2**). The mean bias and limits of agreement between TD-CO and NI-CO, Fick-CO and NI-CO, and TD-CO and Fick-CO were 0.50±1.08 (–1.61 to 2.61) L/min, and –0.54±1.04 (–2.57 to 1.49) L/min, and 1.02±0.86 (–0.68 to 2.71) L/min, respectively. The limits of agreement between TD-CO and Echo-CO, and Fick-CO and Echo-CO were 0.64±1.33 (–1.97 to 3.26) L/min and –0.42±1.18 (–2.73 to 1.88) L/min, respectively. There was no clear difference in the measurements of CO among the patients with idiopathic PAH, collagen tissue disease associated PAH or CTEPH (**Figure S1**).

Comparison of Invasive and Noninvasive Measurement of mPAP and PVR

The mean values of all measurements of invasive mPAP and Echo-mPAP were 32.9±1.28 mmHg and 43.0±1.59 mmHg, respectively. There was a very strong correlation between inva-

sive mPAP and Echo-mPAP (r=0.703, P<0.0001; Figure 3A). The limits of agreement between invasive mPAP and Echo-mPAP were –9.63±10.2 (–29.6 to 10.4) mmHg (Figure 3B).

The mean values of all measurements of TD-PVR, Fick-PVR, Echo-PVR, and NI-PVR were 446±249 dyn·s^{-1}·cm^{-5}, 583±362 dyn·s^{-1}·cm^{-5}, 660±363 dyn·s^{-1}·cm^{-5}, and 644±316 dyn·s^{-1}·cm^{-5}, respectively (Table 2). There were significant and very strong correlations between TD-PVR and NI-PVR (r=0.704, P<0.0001), between Fick-PVR and NI-PVR (r=0.702, P<0.0001), and between TD-PVR and Fick-PVR (r=0.942, P<0.0001) (Figures 4A,D). However, the correlation between PVR measured by invasive methods and Echo-PVR was not as strong (r=0.602 or 0.603, P<0.0001, respectively; Figures 4G,J) as that between invasive methods and NI-PVR. Figure 4B and dyn·s^{-1}·cm^{-5} shows the Bland-Altman plots of the differences between TD-PVR, Fick-PVR, and NI-PVR. The limits of agreement between TD-PVR and NI-PVR, Fick-PVR and NI-PVR, and TD-PVR and Fick-PVR were –195±265 (–715 to 326) dyn·s^{-1}·cm^{-5}, –35±325 (–673 to 603) dyn·s^{-1}·cm^{-5}, and –135±164 (–457 to 187) dyn·s^{-1}·cm^{-5}, respectively. The limits of agreement between TD-PVR and Echo-PVR, and Fick-PVR and Echo-PVR were –191±266 (–713 to 330) dyn·s^{-1}·cm^{-5}, and –33±341 (–703 to 635) dyn·s^{-1}·cm^{-5}, respectively (Figures 4H,K). The AUC for NI-PVR to detect increased PVR >240 dyn·s^{-1}·cm^{-5} (3 WU) against TD and Fick-PVR were 0.84 (95% CI, 0.72–0.96) and 0.92 (95% CI, 0.84–0.99), respectively (Figures 3C,F), and optimal cut-off values were 411 dyn·s^{-1}·cm^{-5} (sensitivity: 81.3%, specificity: 75%) and 400 dyn·s^{-1}·cm^{-5} (sensitivity: 80.3%, specificity: 100%), respectively. The AUC for Echo-PVR against TD and Fick-PVR were lower: 0.75 (95% CI, 0.57–0.92) and 0.83 (95% CI, 0.66–0.99) (Figures 4I,L) compared with that for NI-PVR against TD and Fick-PVR.

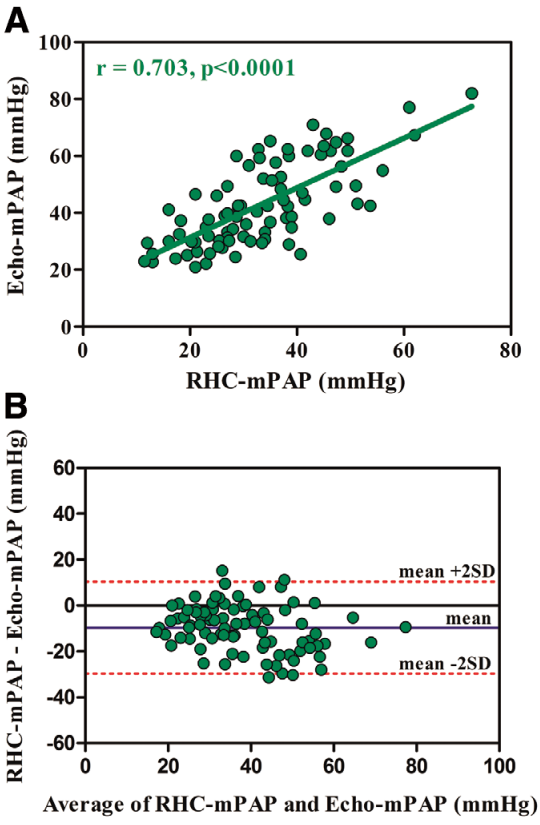

Figure 3. Linear correlation analysis between RHC-mPAP and Echo-mPAP (**A**). Bland-Altman plots with mean difference (solid line) ±2SD (dotted line) comparing RHC-mPAP and Echo-mPAP (**B**). RHC, right heart catheterization; mPAP, mean pulmonary arterial pressure; Echo-mPAP, mPAP calculated by echocardiography; SD, standard deviation.

Discussion

We report on the reliability of a noninvasive and simple method of assessing CO and PVR using ICG$_{WB}$ in patients with PH. Previous reports have indicated the feasibility of hemodynamic assessment using various methods in comparison with RHC in a range of clinical settings;[13] however, a reliable method for the assessment of PH has not yet been established. In particular, there are few studies that have addressed the noninvasive assessment of hemodynamics in PH. Hemodynamic assessment using cardiac magnetic resonance or echocardiography have been shown to be reliable,[10,14–17] but these methods require expensive equipment and trained operators. Thoracic impedance cardiography has been used for the measurement of CO noninvasively in PAH,[18] and its reliability was shown to be compromised in cardiac patients in a meta-analysis.[19]

We demonstrated strong correlations among the NICaS, TD, and the Fick methods for the measurement of CO. Although the limits of agreement between NI-CO and TD-CO or Fick-CO estimated by the Bland-Altman approach were not small, they were acceptable when compared with previous reports.[13] Therefore, we believe that NICaS can be a reliable tool for the noninvasive assessment of CO in PH. However, compared with NI-CO, the correlation between Echo-CO and TD-CO or Fick-CO was weaker and the limits of agreements were larger. The relative inaccuracy of CO measured by echocardiography was consistent with a previous report,[20] and may be a consequence of using the Doppler method, severe tricuspid regurgitation, and operator-dependency.

We also demonstrated the feasibility of noninvasive and simple measurement of PVR using a combination of NICaS and echocardiography. Kouzu et al showed that tricuspid regurgitant pressure gradient (TRPG)/right ventricular time-velocity integral (TVI) is reliable for the estimation of PVR.[21] Although TRPG/TVI has been confirmed as a reliable method for estimating PVR,[16] accurate measurement of TVI needs a skilled operator. Lindqvist et al reported the accuracy of a simple Doppler-derived measurement of PVR with the conventional invasive equation in patients with PH;[10] however, their study excluded patients with severe tricuspid regurgitation, which causes inaccuracy in CO measurement using echocardiography. In the present study, we estimated PVR using the conventional invasive equation with the combination of NI-CO and Echo-mPAP. There was very strong correlation not only between invasive mPAP and Echo-mPAP, but also between invasive PVR and NI-PVR. Furthermore, a stronger correlation of PVR was found for the use of NI-CO compared with Echo-CO. The limits of agreements estimated by the Bland-Altman analysis were large, but comparable with previous reports that showed the feasibility of PVR derived by echocardiography against invasive PVR.[21,22] Furthermore, the high AUC, sensitivity, and specificity for NI-PVR to detect increased PVR >240 dyn·s^{-1}·cm^{-5} (3 WU) also indicates the reliability of noninvasive PVR assessment using NICaS.

In our study, the value for TD-CO was significantly higher than the CO values with other methods, including Fick-CO, and therefore, the value of TD-PVR was underestimated. This

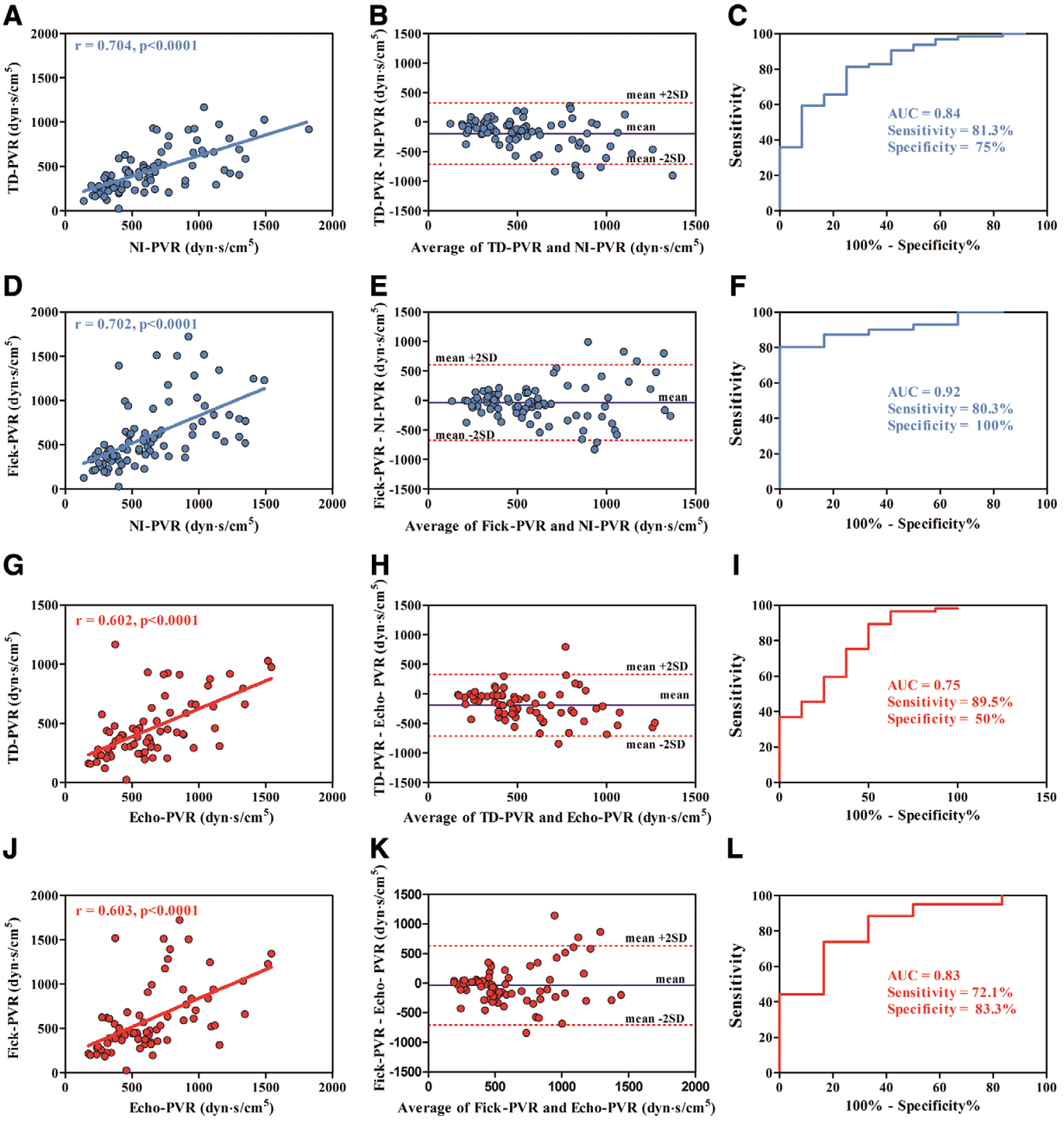

Figure 4. Diagnostic reliability of NI-PVR compared with invasive PVR. Linear correlation analysis between TD-PVR and NI-PVR (**A**), Fick-PVR and NI-PVR (**D**), TD-PVR and Echo-PVR (**G**), and Fick-PVR and Echo-PVR (**J**). Bland-Altman plot with mean difference (solid line) ±2SD (dotted line) comparing TD-PVR and NI-PVR (**B**), Fick-PVR and NI-PVR (**E**), TD-PVR and NI-PVR (**H**), and Fick-PVR and NI-PVR (**K**). Area under the receiver-operating characteristics curve with 95% confidence interval for NI-PVR and Echo-PVR to detect increased PVR (>240 dyn · s^{-1} · cm^{-5} [3 WU]) against TD-PVR (**C**,**I**) and Fick-PVR (**F**,**L**). PVR, pulmonary vascular resistance; NI-PVR, NICaS with echocardiography-derived PVR; TD-PVR, thermodiluyion-derived PVR; Fick-PVR, PVR derived by the modified Fick method; Echo-PVR, echocardiography-derived PVR.

could be caused by overestimation of the value of TD-CO in the presence of low CO, consistent with previous reports.[23]

Study Limitations

The main limitation of this study was the need to measure the Doppler parameter for estimating NI-PVR. Proper alignment of the ultrasound beam is crucial for the Doppler parameter to be determined appropriately. This may have resulted in bias in the measurement of NI-PVR. In our study, the Doppler parameter needed in order to estimate NI-PVR was only TRPG, and there was no patient in whom we were unable to obtain that value. Second, we used the conventional invasive equation for estimating NI-PVR. We had to estimate PCWP at 10 mmHg in all cases as previously reported,[10] which may also have re-

sulted in the measurement of NI-PVR; however, in general, a wide variation in PCWP is not usually observed among patients with PH. Third, because CO measurement using NICaS in patients with cardiac shunts is known to be unreliable,[24] we excluded cases of PAH associated with cardiac shunts. Fourth, noninvasive estimation of CO and PVR with NICaS was feasible; however, there were some patients who had large divergence between NI-CO or NI-PVR and invasive CO or PVR. Further studies are needed to clarify the factors that lead to inaccurate measurements of CO and PVR. Fifth, in our study, the number of patients with WHO functional class 4 was small. Most patients were WHO functional class 2 or 3. The reliability of NICaS in patients with severe PH is to be examined in future studies. Finally, the study sample size was relatively small and originated from a single center. We believe that a larger, multicenter study is needed to appropriately confirm the reliability of the method.

Although recent advances in treatment options and management have improved the outcomes for patients with PH, treatment goals and follow-up strategy are still not well defined. Hemodynamic monitoring with RHC is recommended in a goal-oriented treatment strategy for PH[1] and is the gold standard for the assessment of PAH; however, the invasiveness of RHC is a critical factoring its regular use as a follow-up procedure. A noninvasive, accurate, and simple method is required for the management of patients with PH. We have demonstrated noninvasive measurement of CO and PVR using only simple parameters. Echo-sPAP is needed to estimate PVR, but Echo-sPAP has been established as a simple, reliable screening parameter for PH.[25] This noninvasive, reliable, and simple assessment can be a useful tool for monitoring and managing patients with PH.

Conclusion

Noninvasive measurement of CO and PVR using NICaS is as reliable as invasive RHC. This simple assessment could help physicians to manage their patients with PH.

Disclosures

None.

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Supplementary Files

Supplementary File 1

Figure S1. Linear correlation between NI-CO and TD-CO (A) or Fick-CO (B) in IPAH (●, red line), CTD-PAH (●, blue line) and CTEPH (▲, green line).

Please find supplementary file(s);
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