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Impedance Cardiography Is a Potent Non-Invasive Method in Cardiac Output Measurement and Pulmonary Arterial Hypertension Risk Assessment

ABSTRACT

Background: Impedance cardiography (ICG) offers a potential alternative for hemodynamic assessment in pulmonary arterial hypertension (PAH) as a non-invasive technique.

Methods: A total of 132 patients who underwent right heart catheterization (RHC) were included. Cardiac output (CO) and stroke volume (SV) measured by thermodilution during RHC (CO_{TD}) and ICG (CO_{ICG}) were compared. The capacity of ICG in PAH risk stratification and clinical deterioration prediction was also analyzed.

Results: Ninety-three pre-capillary pulmonary hypertension patients were enrolled, 54 (58.06%) patients belong to Group 1 PAH, and 39 (41.94%) patients were diagnosed with chronic thromboembolic pulmonary hypertension. The mean CO_{TD} was 4.93 ± 1.06 L/min, while the CO_{ICG} was 4.41 ± 1.23 L/min, showing a moderate correlation (r = 0.49, P < .001). In Group 1 PAH patients, the CO_{TD} was 5.13 ± 1.10 L/min, and CO_{ICG} was 4.57 ± 1.22 L/min (r = 0.52, P < .001). Bland–Altman analysis indicated a mean difference of 0.52 L/min and limits of agreement from −1.76 to 2.80 L/min. The mean SV_{TD} was 64.63 ± 17.10 mL, and the SV_{ICG} was 60.94 ± 18.03 mL (r = 0.53, P < .001) with a mean difference of 3.69 mL. After a 1-year follow-up, the CI_{ICG} and SVI_{ICG} showed potential power in predicting clinical deterioration in PAH patients, with area under the curves of 0.76 and 0.81, respectively.

Conclusion: Impedance cardiography measured CO and SV presented an acceptable correlation with RHC in PAH patients. Stroke volume index and cardiac index measured by ICG is potent to identify the low-risk status and predict clinical deterioration in PAH patients.

Keywords: Impedance cardiography, pulmonary arterial hypertension, cardiac output, stroke volume

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by an increase in mean pulmonary arterial pressure and pulmonary vascular resistance (PVR), which lead to a decrease in cardiac output (CO) and death.[1] Until now, although there are a dozen target drugs for PAH treatment, the pulmonary arterial pressure is hardly reversed to normal.[2] The primary goal for PAH treatment is to maintain a low-risk status with normal CO and cardiac index (CI).[3] Thermodilution (TD) during right heart catheterization (RHC) is the reference standard for CO measurement in PAH patients. However, TD is invasive, and equipment and PAH expertise are in demand, constraining its use in the routine risk assessment of PAH patients.

The technique of impedance cardiography (ICG), initially introduced by Kubicek et al[4] in 1966, has garnered widespread recognition over the past half-century in cardiovascular diseases. Impedance cardiography operates on the principles of Ohm's law, assuming that the impedance of thoracic tissue is parallel to the blood in the thorax. Four pairs of electrodes are symmetrically attached to the root of the neck and the bilateral midaxillary line at the level of the xiphoid. The stroke volume (SV) is measured by monitoring impedance changes during each cardiac

ORIGINAL INVESTIGATION

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cycle.[5] Owing to its convenience and non-invasive characteristics, ICG is predominantly employed in the hemodynamic assessment during cardiopulmonary exercise testing as well as in the management of heart failure and hypertension.[6-9] Previously, several studies discussed the correlation and agreement between CO measured by ICG (CO_{ICG}) and TD during RHC (CO_{TD}) in heart diseases and PH patients; unfortunately, the conclusions were controversial.[10-13] The difference may be attributed to very small study populations and mixed types of PH patients. Moreover, previous studies were carried out based on the old PH definition that mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg, which has been changed to mPAP > 20 mm Hg according to the latest PAH guideline. The agreement between CO_{ICG} and CO_{TD} under the new PH diagnostic criteria is unclear.

Cardiac index derived from CO is a traditional hemodynamic factor involved in PAH risk stratification with cut-off value of ≥2.5 L/min/m^2 and <2.0 L/min/m^2 to determine low-risk and high-risk, respectively. Meanwhile, the new guideline, for the first time, recommends stroke volume index (SVI) in PAH risk stratification with cut-off value of >38 mL/m^2 and <31 mL/m^2 to determine low-risk and high-risk separately.[3] Both CI and SVI can be acquired during an ICG examination. Whether CI_{ICG}/SVI_{ICG} can be used for PAH risk stratification has not been reported.

In the present study, the CO_{ICG} and CO_{TD} were compared under the new PH diagnostic criteria and further explored the possibility of using CI_{ICG} and SVI_{ICG} for PAH risk stratification in a retrospective PAH cohort.

METHODS

Subjects

Suspected PH patients who underwent RHC from September 2018 to December 2022 were screened. Group 1 and Group 4 pre-capillary PH patients diagnosed by RHC were included. Pulmonary arterial hypertension was diagnosed according to the new hemodynamic definition that mean pulmonary arterial pressures (mPAP) > 20 mm Hg and pulmonary arterial wedge pressure (PAWP) ≤ 15 mm Hg. The exclusion criteria were: (1) patients with an unstable condition; (2) patients with severe generalized edema and sepsis; (3) PH secondary to left heart diseases and chronic respiratory diseases; (4) sustained tachyarrhythmia; (5) patients with uncorrected congenital heart disease (with intracardiac shunts); and (6) patients refused to participate or sign an informed consent form. This study was reviewed and approved by the Institutional Ethics Committee.

Data Collection

The clinical characteristics including age, gender, body mass index (BMI), type of PH, six-minute walking distance (6MWD), World Health Organization functional class (WHO-FC), and N-terminal-prohormone B-type natriuretic peptide (NT-proBNP) were collected. Factors that have been previously reported to affect ICG accuracy were also collected, including arrhythmia (atrial flutter, atrial fibrillation, frequent atrial/ventricular premature beats), extremity edema, and pericardial effusion.

Right Heart Catheterization and Impedance Cardiography

Seven-Fr Swan-Ganz catheter (Edwards Lifesciences, California) was used for RHC. Mean right atrial pressure (mRAP), mean pulmonary arterial pressure (mPAP), PAWP, mixed venous oxygen saturation (SvO_2) and cardiac output (CO_{TD}) by thermodilution technique were recorded.[14] Pulmonary vascular resistance was calculated as (mPAP-PAWP)/CO_{TD}. CI_{TD} was calculated as CO_{TD}/body surface area. SV_{TD} was calculated as CO_{TD}/heart rate and SVI_{TD} was calculated as SV_{TD}/body surface area.

The ICG examination was conducted by the same physician using CSM3100 (Shenzhen Qianfan Electronics Co. Ltd, China). There were two electrodes positioned bilaterally at the base of the neck, and another two pairs of electrodes located at the intersection of the xiphoid process level and mid-axillary level. The essential information, including sex, age, height, weight, systolic blood pressure, and diastolic blood pressure, was entered in the software. CO_{ICG}, CI_{ICG}, SV_{ICG}, and SVI_{ICG} were calculated automatically.

Patients Follow-up and Risk Stratification

Clinically deteriorated patients were assessed by an experienced PH expert if they exhibited a decline in exercise tolerance, required hospitalization due to symptom aggravation, or experienced death within 1 year of follow-up. Risk stratification was carried out according to the 2022 ESC/ERS guidelines of PAH. The cut-off values for CI_{TD} were >2.5 L/min/m^2 to determine low-risk status and <2.0 L/min/m^2 to determine high-risk status. The cut-off values for SVI_{TD} were >38 mL/m^2 to determine low-risk status and <31 mL/m^2 to determine high-risk status.

Statistical Analysis

The normality of continuous data was assessed using the Shapiro-Wilk test. Continuous variables were expressed as the mean with the SD (M ± SD) for normally distributed data, or otherwise as the median with the interquartile range (IQR). Categorical variables were described as counts and percentages. For normally distributed data, when comparing the means of continuous variables between two independent groups, an independent samples t-test was employed; for comparisons involving three or more independent groups, a one-way analysis of variance (ANOVA) was utilized. The linear relationship between two variables was assessed using Pearson's correlation coefficient. Conversely,

HIGHLIGHTS

- Impedance cardiography measuring cardiac output and stroke volume presented an acceptable correlation with right heart catheterization in pulmonary arterial hypertension (PAH) patients.
- Stroke volume index and cardiac index measured by impedance cardiography is potent to identify the low-risk status in PAH patients.
- Stroke volume index and cardiac index measured by impedance cardiography is potent to predict clinical deterioration in PAH patients.

for non-normally distributed data, the Mann-Whitney U test was used to compare the median of variables between two groups, while the Kruskal-Wallis H test was employed for comparisons involving more than two groups. The relationship between two variables was assessed using Spearman's rank correlation coefficient. If there was a significant difference between groups, a post-hoc test was used to compare groups (Tukey HSD test for one-way ANOVA and Bonferroni adjusted Dunn test for Kruskal–Wallis H test). When comparing categorical variables, Pearson's chi-square test was used when all expected frequencies were ≥5. If any expected frequency was <5, Fisher's exact test was employed. The Bland–Altman method was used to assess the agreement between TD and ICG, with the mean difference and limits of agreement (LoA) calculated. The acceptability of the new method was evaluated by calculating the percentage error, which was obtained by dividing twice the SD by the mean of the 2 methods.[18] The receiver operator characteristic (ROC) curve was employed to elucidate the efficacy of CI_{ICG} and SVI_{ICG} in clinical deterioration prediction. A *P*-value < .05 was considered significant. Statistical analysis was performed using GraphPad Prism (v. 8.0.2, GraphPad Software, San Diego, CA, USA) and OriginPro (v. 2024 SR1, OriginLab Corp., Northampton, MA, USA).

Statement

We have not used artificial intelligence (AI)-assisted technologies in the production of submitted work.

RESULTS

Patient Characteristics

A total of 132 patients were screened, and 21 patients were excluded with PH after RHC. There were 14 patients with uncorrected intracardiac shunts and 4 patients with left heart disease excluded. Finally, 93 pre-capillary PH patients were enrolled in the study. Fifty-four (58.06%) patients belong to Group 1 PAH, of which 31 (57.41%) patients were IPAH, 10 (18.52%) patients were CTD-PAH, and 13 (24.07%) patients were repaired CHD-PAH. The other 39 (41.94%) patients were diagnosed with chronic thromboembolic pulmonary hypertension (CTEPH). Fifty-nine (63.44%) patients were female with an average age of 47.38 ± 16.08 years. Baseline hemodynamic parameters measured by RHC and ICG were shown in Table 1.

Cardiac Output Comparison Between Thermodilution and Impedance Cardiography

The CO measured by TD and ICG were 4.93 ± 1.06 L/min and 4.41 ± 1.23 L/min, respectively. Correlation between CO_{TD} and CO_{ICG} was moderate ($r = 0.49$, $P < .001$) (Figure 1A). Among patients with Group 1 PAH, the mean CO_{TD} and CO_{ICG} were 5.13 ± 1.10 L/min and 4.57 ± 1.22 L/min, respectively. The correlation slightly stronger compared to the whole cohort ($r = 0.52$, $P < .001$) (Figure 1B). The Bland-Altman method was used to analyze the agreement of the two methods. The bias was 0.52 L/min, with LoA ranging from –1.76 to 2.80 L/min and a percentage error of 49.89% (Figure 2A). For Group 1 PAH patients, the bias was 0.55 L/min and the LoA was –1.70 to 2.80 L/min, with a percentage error (Figure 2B).

Stroke Volume Comparison Between Thermodilution and Impedance Cardiography

Generally, SV measured by TD and ICG were 64.63 ± 17.10 mL and 60.94 ± 18.03 mL, respectively, with a moderate correlation ($r = 0.53$, $P < .001$) (Figure 3A). For patients with Group 1 PAH, SV_{TD} and SV_{ICG} were 67.54 ± 19.04 mL and 61.88 ± 17.94 mL, respectively, with a moderate correlation ($r = 0.51$, $P < .001$) (Figure 3B).

Bland–Altman analysis showed the bias was 3.69 mL, with LoA ranging from –29.78 to 37.14 mL, and a percentage error of 54.38% (Figure 4A). For Group 1 PAH patients, the bias was 5.66 mL, LoA was –30.16 to 41.48 mL with a percentage error of 56.50% (Figure 4B).

The analysis of CO and SV among CTEPH patients revealed a poorer correlation and agreement between TD and ICG compared to the PAH patients, especially concerning agreement (Supplementary Figures 1 and 2).

Factors Which May Influence the Correlation Between the Different Methods

To further study the confounding factors which may influence CO_{ICG} accuracy, the patients were divided into comparable and non-comparable groups depending on whether the difference between CO_{TD} and CO_{ICG} ≥ 20%. As shown in Table 2, body weight index (BMI), heart rate, hemodynamic parameters, pericardial effusion, peripheral edema, arrhythmia, and PAH etiology do not affect ICG CO accuracy.

Impedance Cardiography in Predicting Clinical Deterioration and Classify Risk Status

Sankey diagrams were generated to visually represent the overlap of CI and SVI across the two methods for baseline risk stratification in Group 1 PAH patients. Fifty-four patients finished 1-year follow-up. Figure 5A displayed movement of PAH patients between risk categories based on CI_{ICG} and CI_{TD}. CI_{ICG} classified 30 (55.5%) patients as low-risk; 48.1% moved into the low-risk category of CI_{TD} and 7.4% low-risk moved into intermediate-risk by CI_{TD} risk stratification. Risk stratification between SVI_{ICG} and SVI_{TD} showed less consistence (Figure 5B). In order to determine the cut-off value of CI_{ICG} and SVI_{ICG} in predicting low-risk status, ROC curve analysis was further carried out based on follow-up data.

After a 1-year follow-up, clinical deterioration was observed in 8 out of 54 patients with Group 1 PAH. An ROC curve was constructed to study the ability of CI_{ICG} and SVI_{ICG} in predicting clinical worsening events in Group 1 PAH patients. For CI_{ICG}, the area under the curve (AUC) was 0.76 (95% CI 0.59-0.94), the CI_{ICG} cut-off value was 2.45 L/min/m^2, the sensitivity was 70%, and the specificity was 81.80%, respectively (Figure 6A). The AUC for SVI_{ICG} was 0.81 (95% CI 0.63-0.98), the cut-off value was 32.25 mL/m^2, the sensitivity was 76%, and the specificity was 81.80% (Figure 6B).

DISCUSSION

Several studies have already compared ICG against TD in CO measurement in PH patients since 2004.[10,11,13,15,16] The current study has several major differences from the previous ones. Firstly, CO_{TD} and CO_{ICG} were compared according to the

Table 1. Clinical characteristics of all subjects

	Total (n = 93)	IPAH (n = 31)	Repaired CHD-PAH (n = 13)	CTD-PAH (n = 10)	CTEPH (n = 39)	*P*
Age, years	47.38 ± 16.08	34.77 ± 10.21	40.54 ± 12.65	37.50 ± 12.97	62.21 ± 7.53▲■●	<.001
Female	59 (63.4%)	24 (77.4%)	8 (57.1%)	10 (100%)■	17 (43.6%)▲●	.002
Height, cm	163.81 ± 6.96	163.03 ± 5.72	162.92 ± 9.15	162.40 ± 3.33	165.10 ± 7.70	.509
Weight, Kg	61.56 ± 9.07	60.44 ± 7.61	57.62 ± 12.22	59.65 ± 11.02	64.26 ± 7.93	.075
BMI, kg/m^2	22.93 ± 2.98	22.72 ± 2.55	21.58 ± 3.43	22.63 ± 4.09	23.62 ± 2.74	.168
WHO FC III/IV	45 (48.4%)	13 (41.9%)	3 (23.1%)	3 (30.0%)	26 (66.7%)▲■	.032
6MWD, m	434.53 ± 80.98	471.48 ± 78.55	449.77 ± 88.13	455.30 ± 51.55	394.74 ± 70.66▲	<.001
Pericardial effusion	16 (17.2%)	4 (12.9%)	1 (7.7%)	1 (10.0%)	10 (25.6%)	.315
Peripheral edema	15 (16.1%)	1 (3.2%)	3 (23.1%)	1 (10.0%)	10 (25.6%)	.060
Arrhythmia	5 (5.4%)	1 (3.2%)	1 (7.7%)	0 (0)	3 (7.7%)	.695
HGB, g/L	135.80 ± 21.27	136.16 ± 19.80	140.15 ± 25.07	145.80 ± 17.73	131.51 ± 21.47	.228
NT-proBNP, pg/mL	225.30 (96.50, 1430.00)	259.00 (94.00, 892.00)	154.00 (76.50, 460.00)	115.00 (70.00, 184.25)	315.00 (101.00, 2170.00)	.053
RHC parameters						
mRAP, mm Hg	5.00 (3.00, 7.00)	4.00 (3.00, 6.00)	5.00 (3.50, 8.00)	3.50 (3.00, 5.25)	6.00 (4.00, 8.20)	.108
mPAP, mm Hg	43.69 ± 16.95	47.03 ± 16.02	43.92 ± 22.34	32.80 ± 8.83	43.74 ± 16.63	.148
PVR, Wood Units	6.81 (4.00, 10.07)	7.74 (4.80, 12.20)	6.30 (3.02, 10.22)	4.38 (2.87, 5.45)	7.80 (4.00, 8.97)	.069
PAWP, mm Hg	8.60 ± 3.22	7.97 ± 2.71	8.61 ± 3.18	9.50 ± 3.78	8.87 ± 3.48	.528
CO, L/min	4.93 ± 1.06	5.07 ± 1.23	5.28 ± 1.05	5.10 ± 0.78	4.67 ± 0.95	.201
CI, L/min/m^2	2.97 ± 0.69	3.01± 0.76	3.29 ± 0.67	3.20 ± 0.66	2.77 ± 0.61	.059
SvO_2, %	66.81 ± 7.29	69.60 ± 7.04	67.92 ± 8.28	70.14 ± 3.31	63.37 ± 6.59▲●	<.001
SV, mL	64.63 ± 17.10	67.86 ± 22.36	69.24 ± 16.69	64.35 ± 9.06	60.59 ± 13.17	.239
SVI, mL/m^2	38.80 ± 10.53	40.22 ± 13.19	43.09 ± 10.72	40.31 ± 8.03	35.84 ± 7.88	.110
ICG parameters						
CO, L/min	4.41 ± 1.23	4.65 ± 1.36	4.24 ± 1.21	4.76 ± 0.66	4.19 ± 1.23	.329
CI, L/min/m^2	2.65 ± 0.70	2.81 ± 0.80	2.62 ± 0.91	2.96 ± 0.42	2.46 ± 0.66	.081
SV, mL	60.94 ± 18.03	61.50 ± 18.57	61.54 ± 19.76	63.50 ± 14.94	59.64 ± 18.30	.932
SVI, mL/m^2	36.79 ± 10.25	37.30 ± 10.44	38.23 ± 11.34	39.35 ± 10.46	35.26 ± 9.83	.615
PAH specific target therapy	78 (83.87%)	31 (100.00%)	10 (76.92%)	8 (80.00%)	29 (74.36%)	
Therapy type†						
Monotherapy*	33 (42.31%)	9 (29.04%)	2 (20.00%)	5 (62.50%)	17 (58.61%)▲■	.012
PDE5I	11 (14.10%)	1 (3.23%)	0	0	10 (34.48%)	
ERA	17 (21.79%)	7 (22.58%)	2 (20.00%)	5 (62.50%)	3 (10.34%)	
PA	1 (1.28%)	0	0	0	1 (3.45%)	
sGCS	3 (3.85%)	0	0	0	3 (10.34%)	
CCB	1 (1.28%)	1 (3.23%)	0	0	0	
Dual combination‡	36 (46.15%)	18 (58.07%)	6 (60.00%)	3 (37.5%)	9 (31.03%)▲	.017
ERA+PDE5I	27 (34.62%)	15 (48.39%)	5 (50.00%)	3 (37.50%)	4 (13.79%)	
ERA+sGCS	1 (1.28%)	0	1 (10.00%)	0	0	
ERA+CCB	2 (2.56%)	2 (6.45%)	0	0	0	
ERA+PA	2 (2.56%)	1 (3.23%)	0	0	1 (3.45%)	
PDE5I+PA	4 (5.13%)	0	0	0	4 (13.79%)	
Triple combination⁂	9 (11.54%)	4 (12.9%)	2 (20.00%)	0	3 (10.34%)	.352
PCA+ ERA+PDE5I	3 (3.85%)	2 (6.45%)	1 (10.00%)	0	0	
ERA+PDE5I+PA	6 (7.69%)	2 (6.45%)	1 (10.00%)	0	3 (10.34%)	
Interventional treatment						
BPA	N/A	N/A	N/A	N/A	28 (71.79%)	N/A

▲< 0.05 vs. IPAH; ■ < 0.05 vs. Repaired CHD-PAH; ● < 0.05 vs. CTD-PAH

6MWD, 6-minute walk distance; BMI, body weight index; CO, cardiac output; CI, cardiac index; CHD-PAH, congenital heart disease associated pulmonary arterial hypertension; CTD-PAH, connective tissue disease associated pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; HGB, hemoglobin; HR, heart rate; ICG, impedance cardiography; IPAH, idiopathic pulmonary arterial hypertension; mRAP, mean right atrial pressure; mPAP, mean pulmonary arterial pressure; NT-proBNP, *N*-terminal pro B-type natriuretic peptide; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; SV, stroke volume; SVI, stroke volume index; SvO_2, mixed venous oxygen saturation; RHC, right heart catheterization; WHO-FC, World Health Organization functional class.

†Among those who received PAH therapy.

*Among those who received single therapy.

‡Among those who received dual therapy.

⁂Among those who received triple therapy.

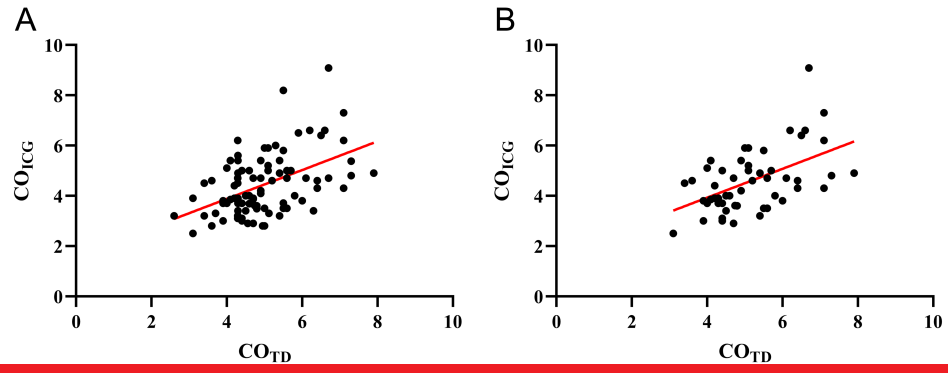

Figure 1. Scatter plot for cardiac output measured by thermodilution and impedance cardiography. (A) CO_{TD} and CO_{ICG} of all patients. The red line represents the regression equation: $CO_{ICG} = 1.59 + 0.57*CO_{TD}$, $R^2 = 0.24$, $P < 0.001$. (B) Scatter plot for CO_{TD} and CO_{ICG} of patients with Group 1 PAH. The red line represents the regression equation: $CO_{ICG} = 1.635 + 0.57*CO_{TD}$, $R^2 = 0.27$, $P < .001$.

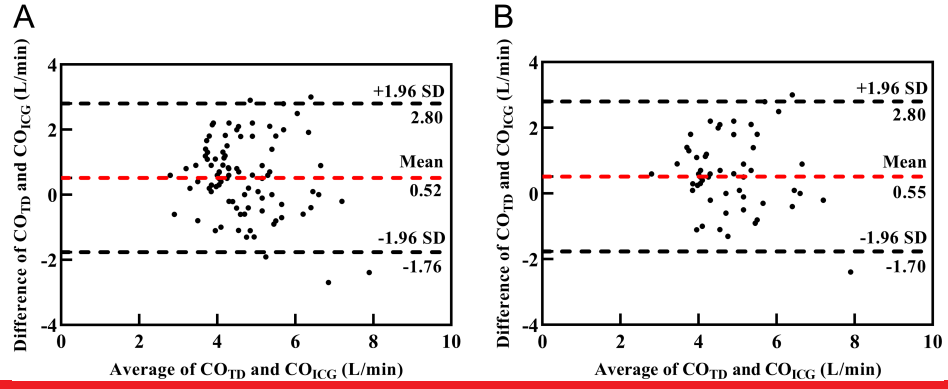

Figure 2. Bland-Altman analysis comparing CO_{TD} and CO_{ICG}. The black broken lines represent the 95% limit of agreement and red broken line represents the mean difference. (A) CO_{TD} and CO_{ICG} of all patients. Mean = 0.52 L/min, SD = 1.17 L/min, and the LoA = −1.76 to 2.80 L/min. (B) CO_{TD} and CO_{ICG} of patients with Group 1 PAH. Mean = 0.55 L/min, SD = 1.15 L/min, and the LoA = −1.70 to 2.80 L/min.

latest PH definition with mPAP > 20 mm Hg, published in the 2022 ESC/ERS PH guideline, while previous studies were carried out based on the old PH definition with mPAP ≥ 25 mm Hg. Secondly, the focus was on PAH, especially those belonging to Group 1 PAH. PH patients secondary to left heart diseases (Group 2), unrepaired congenital heart disease, or lung diseases and/or hypoxia (Group 3), were excluded, because these patients exhibited different heart and lung geometry, which may be a confounding factor for ICG measurement. Thirdly, the potential of ICG-measured CI and SVI in PAH risk assessment was investigated.

Pulmonary arterial hypertension is a devastating, occultly progressive disease resulting in death. The treatment

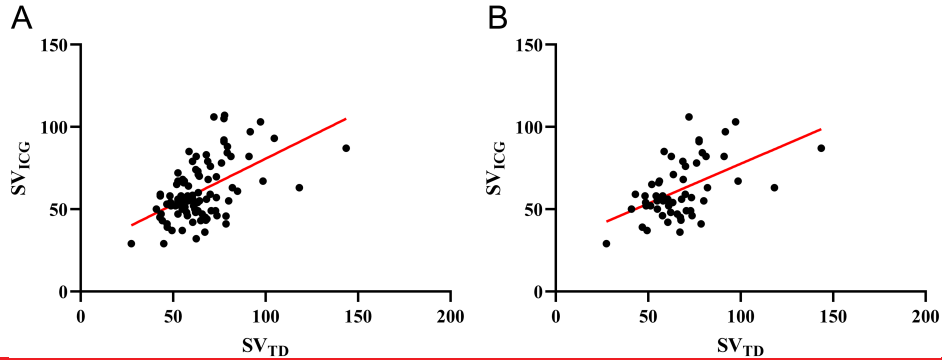

Figure 3. Scatter plot for stroke volume measured by thermodilution and impedance cardiography. (A) SV_{TD} and SV_{ICG} of all patients. The red line represents the regression equation: $SV_{ICG} = 24.90 + 0.56*SV_{TD}$, $R^2 = 0.28$, $P < .001$. (B) SV_{TD} and SV_{ICG} of patients with Group 1 PAH patients. The red line represents the regression equation: $SV_{ICG} = 29.23 + 0.48*SV_{TD}$, $R^2 = 0.26$, $P < .001$.

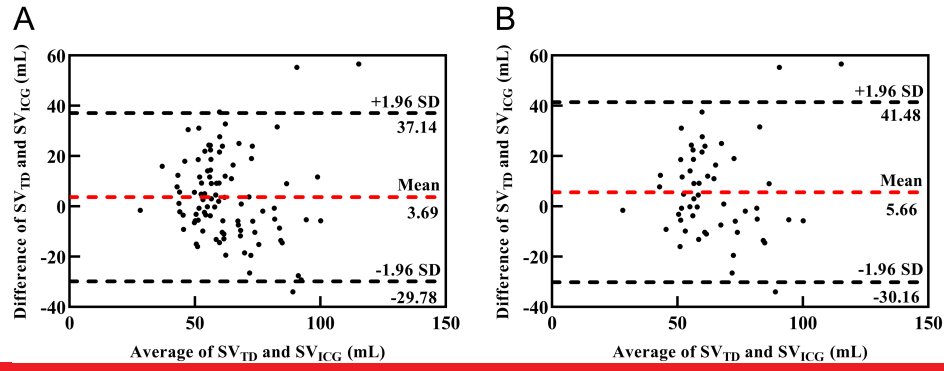

Figure 4. Bland–Altman analysis comparing SV_{TD} and SV_{ICG}. The black broken lines represent the 95% limit of agreement and red broken line represents the mean difference. (A) SV_{TD} and SV_{ICG} of all patients. Mean = 3.69 mL, SD = 17.07 mL, and the LoA = −29.78 to 37.14 mL. (B) SV_{TD} and SV_{ICG} of patients with Group 1 PAH. Mean = 5.66 mL, SD = 18.28 mL, and the LoA = −30.16 to 41.48 mL.

strategy is a risk-based, goal-oriented treatment approach, where achieving and/or maintaining a low-risk status is recommended. Currently, the 2022 ESC/ERS risk stratification tool includes both CI and SVI measured by RHC or cardiac magnetic resonance imaging (cMRI),[17] either invasive or resource-demanding. Guidelines on the diagnosis and treatment of PH have advocated a goal-oriented treatment approach since 2009,[18] not only at baseline but also at follow-up. Patients who reached a low-risk profile at follow-up had similar survival as those who remained low risk from baseline to follow-up. Patients who worsened to an intermediate or high-risk profile during follow-up had as poor survival as those who remained intermediate or high-risk during follow-up.[19] Here, a moderate correlation between CO_{TD} and CO_{ICG} was shown; the ICG method tends to underestimate both CO and SV, with a wide LoA. Another study also proved that ICG accuracy decreases for extreme CO values.[13] Although ICG

Table 2. Possible Confounding Factors of Cardiac Output Values Between Impedance Cardiography and Thermodilution Techniques

	Comparable (n = 49)	Uncomparable (n = 44)	*P*
Age, years	45.49 ± 15.32	49.48 ± 16.82	.235
BMI, kg/m^2	23.15 ± 2.96	22.68 ± 3.02	.454
HR, bpm	77.97 ± 9.86	77.21 ± 9.73	.710
NT-proBNP, pg/mL	174.00 (90.00, 1091.00)	264.50 (99.50, 1657.50)	.392
mRAP, mm Hg	5.00 (3.00, 7.00)	5.00 (4.00, 7.00)	.533
mPAP, mm Hg	45.06 ± 16.43	42.16 ± 17.57	.413
PVR, Wood units	7.74 (4.86, 10.18)	5.59 (3.25, 9.43)	.179
mBP, mm Hg	78.93 ± 13.55	80.39 ± 10.69	.569
Pericardial effusion	8 (16.3%)	8 (18.2%)	1.000
Peripheral edema	10 (20.4%)	3 (11.6%)	.255
Arrhythmia	3 (6.1%)	2 (4.7%)	1.000
ECG low voltage*	2 (4.1%)	3 (7.0%)	.662
Etiology			
IPAH	15 (30.6%)	16 (36.4%)	.557
Repaired CHD-PAH	8 (16.3%)	5 (11.4%)	.491
CTD-PAH	7 (14.3%)	3 (6.8%)	.246
CTEPH	19 (38.8%)	20 (45.5%)	.515

Continuous data are expressed as the mean (SD) and compared using a paired *t*-test. Categorical data are compared using Fisher's exact test. BMI, body weight index; CHD-PAH, congenital heart disease associated pulmonary arterial hypertension; CTD-PAH, connective tissue disease associated pulmonary arterial hypertension; CTEPH, chronic thromboembolic pulmonary hypertension; ECG, electrocardiography; HR, heart rate; IPAH, idiopathic pulmonary arterial hypertension; mBP, mean blood pressure; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; *N*-terminal pro B-type natriuretic peptide; NT-proBNP; PVR, pulmonary vascular resistance.
*$P < .05$ between two groups.

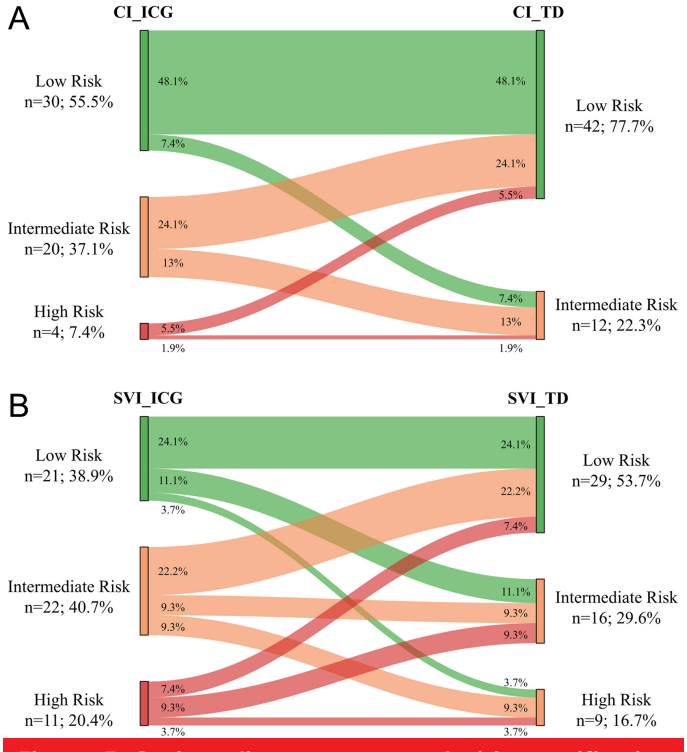

Figure 5. Sankey diagram compared risk stratification differences between impedance cardiography and thermodilution based on (A) cardiac index and (B) stroke volume index, respectively.

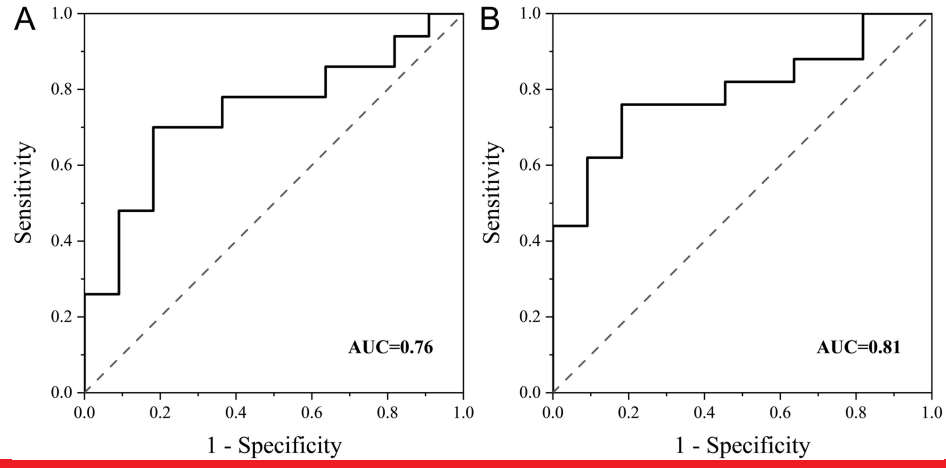

Figure 6. Receiver operator characteristic curve for risk prediction. (A) The receiver operator characteristic (ROC) curve of CI_{ICG} for risk prediction. The area under the curve (AUC) is 0.76. (B) The ROC curve of SVI_{ICG} for risk prediction. The AUC is 0.81.

tends to overestimate the disease severity in risk stratification, it is more accurate in distinguishing patients in low-risk status. The main advantage of ICG over RHC is its non-invasive and reproducible characteristics, which guarantees its utilization during PAH follow-up.

The cut-off value to identify low-risk status varies among different methods. Another guideline-recommended parameter in PAH risk stratification is SVI measured by cMRI (SVI_{cMRI}). The cut-off value was > 40 mL/m^2 for SVI_{cMRI},[20] close to > 38 mL/m^2 for SVI_{TD}. The cut-off value of ICG-measured CI and SVI to distinguish low-risk patients in the follow-up cohort was also verified. The cut-off value was > 2.45 L/min/m^2 for CI_{ICG} and > 32.25 mL/m^2 for SVI_{ICG}, close to the TD method recommended by the guideline.

The correlation between CO_{ICG} and CO_{TD} varies among different studies. Impedance cardiography accuracy may be influenced by various factors, including the skin condition, subcutaneous fat thickness, thoracic morphology, blood resistivity, and tachyarrhythmia.[13,21] However, in the current study with a larger sample size, no valuable indicators to predict CO_{ICG} accuracy were found. The difference between the two methods may be attributed to systematic error. CO_{ICG} is determined by multiplying SV_{ICG} and HR, while SV_{ICG} was influenced by blood resistivity, the distance between the voltage-measuring electrodes, basal thoracic impedance, maximal impedance alteration, and the duration of left ventricular ejection. In patients with PAH, further investigation is necessary to determine whether basal thoracic impedance is affected by increased right heart blood volume or dilation of the dilation pulmonary artery.

Study Limitations

There are several limitations of this study: (1) simultaneous execution of the two methods was not feasible, despite efforts to minimize the time interval between them; (2) the reproducibility of the measurement of CO by ICG in the same patient at different time points at baseline was not tested; (3) clinical worsening events were used to define CI_{ICG} and SVI_{ICG} cut-off values for low-risk status instead of 1-year mortality due to the improved survival rate after PAH treatment, thus extended follow-up is necessary for further convention.

CONCLUSION

Impedance cardiographymeasured CO and SV presented an acceptable correlation with RHC in PAH patients. SVI and CI measured by ICG is potent to identify the low-risk status and predict clinical deterioration in PAH patients.

Ethics Committee Approval: This study was reviewed and approved by the Institutional Ethics Committee, Shandong University, Qilu Hospital, Shandong, China, with the approval number: ER No. 2019 (119), dated 2019.7.4.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors have no conflicts of interest to declare.

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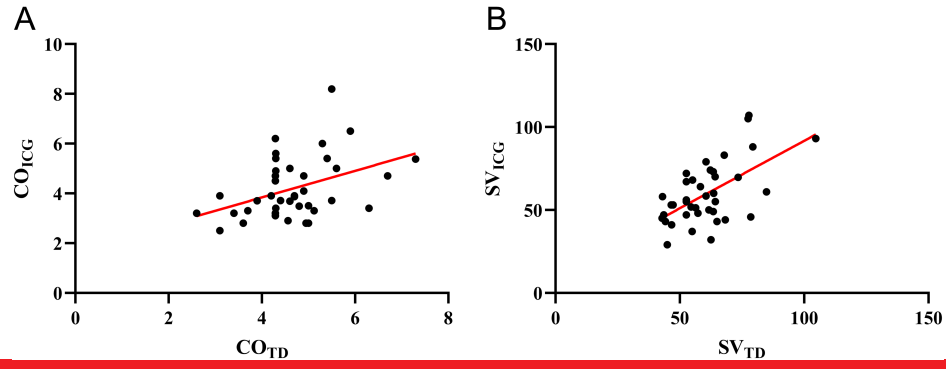
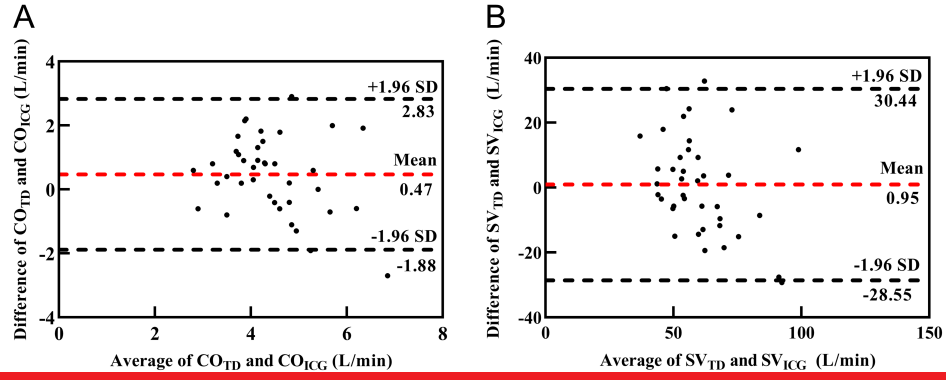
REFERENCES

1. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53(1):1801913. [CrossRef]
2. Leber L, Beaudet A, Muller A. Epidemiology of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: identification of the most accurate estimates

from a systematic literature review. *Pulm Circ*. 2021;11(1): 2045894020977300. [CrossRef]
3. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2023;61(1):2200879. [CrossRef]
4. Kubicek WG, Karnegis JN, Patterson RP, Witsoe DA, Mattson RH. Development and evaluation of an impedance cardiac output system. *Aerosp Med*. 1966;37(12):1208-1212.
5. Woltjer HH, Bogaard HJ, de Vries PM. The technique of impedance cardiography. *Eur Heart J*. 1997;18(9):1396-1403. [CrossRef]
6. Mattavelli I, Vignati C, Farina S, et al. Beyond VO2: the complex cardiopulmonary exercise test. *Eur J Prev Cardiol*. 2023;30(Suppl 2):ii34-ii39. [CrossRef]
7. Delfrate J, Girard-Bock C, Curnier D, et al. Cardiopulmonary response to exercise in adults born very preterm. *Eur Respir J*. 2023;62(5):2300503. [CrossRef]
8. Myers J, Christle JW, Tun A, et al. Cardiopulmonary exercise testing, impedance cardiography, and reclassification of risk in patients referred for heart failure evaluation. *J Card Fail*. 2019;25(12):961-968. [CrossRef]
9. Greco B, Chait Y, Nathanson BH, Germain MJ. A novel hypertension management algorithm guided by hemodynamic data. *Kidney Int Rep*. 2022;7(2):330-333. [CrossRef]
10. Yung GL, Fedullo PF, Kinninger K, Johnson W, Channick RN. Comparison of impedance cardiography to direct Fick and thermodilution cardiac output determination in pulmonary arterial hypertension. *Congest Heart Fail*. 2004;10(2 suppl 2):7-10. [CrossRef]
11. Tonelli AR, Alnuaimat H, Li N, Carrie R, Mubarak KK. Value of impedance cardiography in patients studied for pulmonary hypertension. *Lung*. 2011;189(5):369-375. [CrossRef]
12. Taniguchi Y, Emoto N, Miyagawa K, et al. Noninvasive and simple assessment of cardiac output and pulmonary vascular resistance with whole-body impedance cardiography is useful for monitoring patients with pulmonary hypertension. *Circ J*. 2013;77(9):2383-2389. [CrossRef]
13. Dupuis M, Noel-Savina E, Prévot G, et al. Determination of cardiac output in pulmonary hypertension using impedance cardiography. *Respiration*. 2018;96(6):500-506. [CrossRef]
14. Ganz W, Donoso R, Marcus HS, Forrester JS, Swan HJ. A new technique for measurement of cardiac output by thermodilution in man. *Am J Cardiol*. 1971;27(4):392-396. [CrossRef]
15. Panagiotou M, Vogiatzis I, Jayasekera G, et al. Validation of impedance cardiography in pulmonary arterial hypertension. *Clin Physiol Funct Imaging*. 2018;38(2):254-260. [CrossRef]
16. Yağmur B, Şimşek E, Kayıkçıoğlu M, et al. Could impedance cardiography be a non-invasive alternative method of measuring cardiac output in patients with pulmonary hypertension? *Anatol J Cardiol*. 2023;27(11):650-656. [CrossRef]
17. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3618-3731. [CrossRef]
18. Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC), European Respiratory Society (ERS), International Society of Heart and Lung Transplantation (ISHLT), et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2009;34(6):1219-1263. [CrossRef]
19. Kylhammar D, Kjellström B, Hjalmarsson C, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *Eur Heart J*. 2018;39(47):4175-4181. [CrossRef]
20. van der Bruggen CE, Handoko ML, Bogaard HJ, et al. The value of hemodynamic measurements or cardiac MRI in the follow-up of patients with idiopathic pulmonary arterial hypertension. *Chest*. 2021;159(4):1575-1585. [CrossRef]
21. Charloux A, Lonsdorfer-Wolf E, Richard R, et al. A new impedance cardiograph device for the non-invasive evaluation of cardiac output at rest and during exercise: comparison with the "direct" Fick method. *Eur J Appl Physiol*. 2000;82(4):313-320. [CrossRef]



Supplementary Figure 1. Scatter plot for CO and SV of patients with CTEPH measured by TD and ICG. (A) CO_{TD} and CO_{ICG}. The red line represents the regression equation: $CO_{ICG} = 1.70 + 0.54 * CO_{TD}$, R^2=0.17, P = .009. (B) SV_{TD} and SV_{ICG}. The red line represents the regression equation: $SV_{ICG} = 10.36 + 0.81 * SV_{TD}$, R^2=0.34, P < .001.



Supplementary Figure 2. Bland-Altman analysis comparing CO and SV of patients with CTEPH measured by TD and ICG. The black broken lines represent the 95% limit of agreement and red broken line represents the mean difference. (A) CO_{TD} and CO_{ICG}. Mean = 0.47 mL, SD = 1.20 L/min and the LoA = -1.88 to 2.83 L/min. (B) SV_{TD} and SV_{ICG}. Mean = 0.95 mL, SD = 15.05 mL and the LoA = -28.55 to 30.44 mL.