DOI: 10.1002/pul2.12128

RESEARCH ARTICLE

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

Comparison between thermodilution and Fick methods for resting and exercise-induced cardiac output measurement in patients with chronic dyspnea

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Funding information
None

Abstract

Studies comparing thermodilution (TD) and the direct Fick method (dFM) for cardiac output (CO) measurement are rare. We compared CO measurements between TD (2–5 cold water injections), the dFM, and indirect Fick method (iFM) at rest and during exercise, and assessed the effect of averaging different numbers of TD measurements during exercise. This retrospective study included 300 patients (52.3% women, mean age 66 ± 11 years) having pulmonary hypertension (76.0%) or unexplained dyspnea. Invasive hemodynamic and gas exchange parameters were measured at rest (supine; $n = 300$) and during unloaded cycling (semi-supine; $n = 275$) and 25-W exercise (semi-supine; $n = 240$). All three methods showed significant differences in CO measurement (ΔCO) at rest ($p \leq 0.001$; ΔCO > 1 L/min: 45.0% [iFM vs. dFM], 42.0% [iFM vs. TD], and 45.7% [TD vs. dFM]). ΔCO (TD vs. dFM) was significant during unloaded cycling ($p < 0.001$; ΔCO > 1 L/min: 56.6%) but not during 25-W exercise ($p = 0.137$; ΔCO > 1 L/min: 52.8%). ΔCO (TD vs. dFM) during 25-W exercise was significant when using one or two ($p \leq 0.01$) but not three ($p = 0.06$) TD measurements. Mean ΔCO (TD [≥3 measurements] vs. dFM) was −0.43 ± 1.98 and −0.06 ± 2.29 L/min during unloaded and 25-W exercise, respectively. Thus, TD and dFM CO measurements are comparable during 25-W exercise (averaging ≥3 TD measurements), but not during unloaded cycling or at rest. Individual ΔCOs vary substantially and require critical interpretation to avoid CO misclassification.

Abbreviations: CO, cardiac output; CPET, cardiopulmonary exercise testing; dFM, direct Fick method; FM, Fick method; iFM, indirect Fick method; LOA, limits of agreement; PAH, pulmonary arterial hypertension; PAPm, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; peakVO_2, maximum oxygen uptake per minute at exercise; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; SD, standard deviation; TD, thermodilution; TR, tricuspid regurgitation; VO_2, oxygen uptake per minutewas no significant difference; WU, Wood units.

KEYWORDS
cardiac output, dyspnea, exercise, Fick method, thermodilution

INTRODUCTION

Despite the progress in the use of noninvasive diagnostic modalities in patients with cardiovascular diseases, especially echocardiography and cardiopulmonary exercise testing (CPET), right heart catheterization (RHC) is still of great clinical importance. In patients with suspected pulmonary hypertension (PH), an invasive measurement of pulmonary hemodynamic parameters is the decisive diagnostic procedure.

Apart from determining indications for RHC, it is crucial to standardize the RHC procedure, which was thoroughly outlined in a German guideline on the performance of RHC in patients with PH.[1] For the measurement of cardiac output (CO), both gas analytical (Fick) and thermodilution (TD) methods are widely applied in clinical practice. The authors of the German guideline[1] state that a reliable CO calculation using the Fick method (FM) requires actual measurement of oxygen uptake (direct Fick method, dFM), and estimation of oxygen uptake from tables (indirect Fick method, iFM) is not supported. Data should be collected repeatedly, especially if TD is used, to allow for the monitoring of variations in measured values and the calculation of the means of these values. A CO difference of <10% is considered to be the quality standard.[1] Repeated TD is particularly difficult under exercise conditions, requiring trained and well-cooperating staff. In the case of intracardiac or intrapulmonary shunts, CO measurement by the dFM is clearly preferred. The application of the dFM under exercise conditions requires an equilibrium of oxygen uptake per minute (VO_2) at each measurement time. In some patients, the setting and stabilization of this equilibrium can last for a few minutes at every exercise step, depending on the disease severity. Consequently, the European Guideline on RHC during exercise[2] states that the dFM is "the gold standard for the determination of CO," whereas TD serves as a "reliable alternative method." Rapidly changing hemodynamic parameters with increasing workload make it difficult to obtain multiple measurements using TD, "but it seems reasonable to obtain at least two measurements at each step."[2]

Studies comparing CO measurements obtained by TD and FM are rare; moreover, the few published studies used small patient sample sizes. Therefore, it is unclear if these methods can be used interchangeably to measure CO. To address this, we performed a retrospective analysis of our data using the dFM as a reference. First, we analyzed and compared CO at rest calculated using the dFM, TD, and the iFM. Second, we sought to demonstrate the effect of averaging multiple TD measurements during exercise (as recommended by Kovacs et al.[2]) on the comparability of TD and dFM measurements.

METHODS

Patients

Between 2005 and 2020, 1062 RHCs were performed at the University Hospital Greifswald; within this data set, we identified 367 patients who underwent their first RHC under exercise conditions using the dFM. Of the 367 patients, 300 had both TD and dFM measurements at rest in a supine position and were therefore included in the study population. The remaining 67 patients were excluded owing to missing data from either TD or the dFM. A complete flow chart of the analysis is shown in Figure 1.

RHC

Indications for RHC were exclusion or proof of PH in the context of complete clinical diagnosis or proof of PH as a differential diagnosis in patients with chronic dyspnea. All catheterization procedures were performed in hospitalized patients who gave written informed consent before the procedure. An exercise RHC with a simultaneous measurement of oxygen uptake was performed in patients with a suspected multifactorial etiology of dyspnea, based on the findings of the preceding noninvasive examinations (echocardiography, CPET, and body plethysmography). We previously published a detailed description of the exercise RHC procedure.[3] Briefly, the procedure began with the measurement of hemodynamic parameters at rest with the patient in the supine position (0°); a second measurement of hemodynamic parameters was performed at rest with the patient in a semi-supine position (45°). CO was next measured during unloaded cycling in a semi-supine position for 3–5 min (45° at 0 W), and finally during 25-W exercise in a semi-supine position for 5 min; in some cases, patients underwent exercise with intensity exceeding 50 W. The level of exercise in the final step corresponded to 58 ± 19% of the maximum oxygen

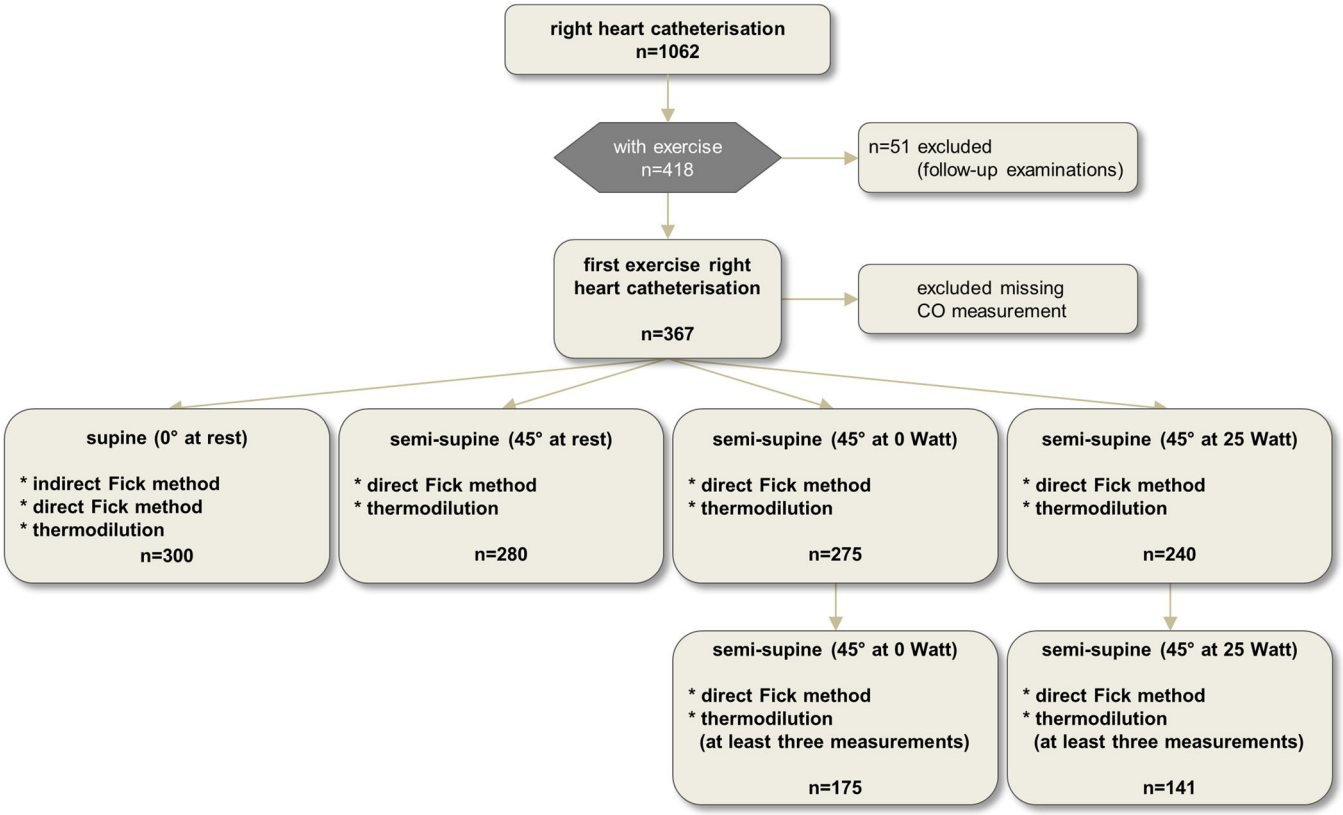

FIGURE 1 Flow chart of the study design. CO, cardiac output.

uptake (peakVO_2) achieved by the patient during cycle ergometry in the sitting position, performed on average 12 days beforehand.

At rest, CO was measured via TD (based on 3–5 cold water injections), the dFM, and the iFM using the table of LaFarge.[4] During exercise, CO was measured via TD and the dFM. For TD during exercise, a mean of 3 (range: 2–5) cold water injections was used with a verification of the visualized temperature curve. The dFM was used after reaching a steady state (mostly after 3–5 min) of oxygen uptake per minute (VO_2) at the respective exercise intensity levels. VO_2 was measured with a 10 s average using a CPET system (SentrySuite; Viasys Healthcare GmbH) via a face mask at room temperature.

CO measured by TD was calculated as the mean of all available TD measurements in each patient, unless otherwise specified. Outliers (defined as measurements not within 20% of the other measurements) were excluded. In the subset of patients with at least three TD measurements during exercise, we assessed the effect of averaging different numbers of TD measurements. Within this subset, we recalculated CO during exercise based on only the first TD measurement or the mean of the first two or three TD measurements. PH was defined as mean pulmonary artery pressure (PAPm) >20 mmHg.

Statistical analysis

Continuous variables are presented as median (25th, 75th percentile) or mean ± standard deviation. Nominal variables are presented as absolute numbers and percentages. Differences between patient groups and paired measurements were examined using the nonparametric Mann–Whitney*U* test or Kruskal–Wallis test and the Wilcoxon signed-rank test, respectively. For CO measurement comparison, we used Bland–Altman plots (to calculate the mean bias and limits of agreement [LOA]). A $p < 0.05$ was considered statistically significant. All analyses were performed using SAS software (version 9.4; SAS Institute Inc.).

RESULTS

Patients

Baseline demographic data and functional parameters of the study population ($n = 300$) are shown in Table 1. Overall, 52.3% of patients were women, and the mean patient age was 66 ± 11 years. The proportion of patients with concomitant diseases corresponded to the mean age and indication of RHC: 65.3%, 28.0%, 27.3%, 26.0%, 21.3%, and 21.3% of patients had arterial hypertension, atrial fibrillation,

TABLE 1 Clinical and demographic characteristics of the study population

Parameter	*N*	%	Median (25th; 75th)	Mean (±SD)
Age (years)	300		67 (58; 75)	66 (±11)
Females	157	52.3		
Height (cm)	300		169 (163; 176)	169 (±9)
Weight (kg)	300		81 (70; 94)	83 (±19)
BMI (kg/m^2)	300		28 (25; 32)	29 (±6)
BSA (m^2, Dubois)	300		1.91 (1.77; 2.08)	1.93 (±0.24)
Comorbidities[a]				
Diabetes mellitus	78	26.0		
Arterial hypertension	196	65.3		
Atrial fibrillation	84	28.0		
Peripheral artery disease	14	4.7		
Chronic kidney failure	57	19.0		
Cancer	51	17.0		
Coronary heart disease	82	27.3		
COPD/Asthma	64	21.3		
Venous thromboembolism	64	21.3		
Cerebrovascular disease	11	3.7		
Interstitial lung disease	20	6.7		
Echocardiography	282			
LVEF				
LVEF < 45%	4	1.4		
Diastolic dysfunction	90	31.9		
TAPSE	226		21 (18; 25)	21 (±6)
Verified tricuspid valve insufficiency	159	56.4		
Estimated systolic PAP	182		46 (35; 63)	50 (±20)
Right heart catheter (supine [0° at rest])				
RAPmean (mmHg)	296		7 (4; 10)	8 (±6)
PAPmean (mmHg)	300		29 (20; 40)	31 (±13)
PAPmean >20 mmHg	228	76.0	33 (26; 45)	36 (±11)
PAWP (mmHg)	295		13 (9; 18)	14 (±7)
PAWP > 15 mmHg	104	35.3	19 (17; 25)	21 (±5)
PVR (WU)/thermodilution	298		2.70 (1.50; 4.59)	3.62 (±3.02)
CO (l/min)/thermodilution	300		5.03 (4.25; 6.07)	5.18 (±1.42)
CI (l/min/m^2)/thermodilution	300		2.59 (2.22; 3.06)	2.70 (±0.70)
PVR (WU)/indirect Fick	294		3.16 (1.76; 5.57)	4.32 (±3.79)
CO (l/min)/indirect Fick	300		4.32 (3.69; 4.96)	4.38 (±1.09)
CI (l/min/m^2)/indirect Fick	296		2.26 (1.95; 2.54)	2.28 (±0.51)
PVR (WU)/direct Fick	296		2.58 (1.37; 4.68)	3.59 (±3.21)

TABLE 1 (Continued)

Parameter	*N*	%	Median (25th; 75th)	Mean (±SD)
CO (l/min)/direct Fick	300		5.29 (4.24; 6.31)	5.48 (±1.79)
CI (l/min/m^2)/direct Fick	298		2.69 (2.20; 3.36)	2.85 (±0.91)
Lung function				
TLC (% predicted)	179		91.80 (81.90; 102.80)	92.75 (±18.80)
Reduced (<80%)	43	24.0		
VC (% predicted)	180		84.15 (70.10; 96.35)	82.32 (±20.42)
Reduced (<80%)	80	44.4		
FVC (% predicted)	180		87.20 (70.30; 99.60)	85.46 (±21.20)
Reduced (<80%)	68	37.8		
FEV1 (% predicted)	180		82.90 (64.75; 94.60)	79.70 (±20.96)
FEV1/FVC (%)	180		76.49 (69.74; 82.34)	75.48 (±10.40)
Reduced (<70%)	47	26.1		
RV (% predicted)	179		106.90 (87.20; 125.90)	110.42 (±41.77)
RV/TLC (%)	179		46.37 (39.51; 53.51)	47.89 (±16.32)
DLCOc (% predicted)	155		54.80 (41.50; 68.10)	55.67 (±19.55)
Reduced (<60% pp)	92	5.9		
KCOc (% predicted)	156		74.05 (55.80; 89.10)	73.39 (±24.33)
Reduced (<60%)	47	30.1		
Cardiopulmonary exercise testing (CPET)				
Maximal workload (W)	233		84 (52; 100)	77 (±39)
Maximal workload (% predicted)	233		54.70 (40.76; 67.62)	53.42 (±23.58)
Exercise duration (s)	232		270 (200; 333)	279 (±108)
Heart rate (at rest)	233		77 (68; 88)	78 (±15)
Heart rate (maximal)	232		113 (99; 131)	116 (±24)
peakVO_2 (ml/min)	233		1189 (903; 1424)	1218 (±427)
peakVO_2 (% predicted)	233		65.02 (54.45; 77.12)	66.17 (±18.45)
Reduced (<80% predicted)	185	79.4		
VO_2@ AT (ml/min)	223		797 (658; 945)	829 (±260)
VO_2@AT (% of peakVO_2 predicted)	223		44.81 (37.21; 53.13)	45.08 (±11.05)
<40% of peakVO_2 predicted	77	34.5		
VO_2/HR max.	232		10.18 (8.14; 13.22)	10.67 (±3.42)
VE/VCO_2 slope	231		36 (30; 45)	39 (±13)
pathological values (> 34)	138	59.7		
VE/VCO_2 @ rest	225		39.0 (34.2; 46.0)	40.4 (±8.9)
VE/VCO_2 @ AT	223		35.5 (31.4; 43.4)	38.1 (±10.0)
petCO_2 @ rest (mmHg)	232		28.80 (24.54; 32.38)	28.42 (±5.99)
petCO_2 @ AT (mmHg)	224		30.76 (25.57; 34.94)	30.35 (±6.73)
$AaDO_2$ max (mmHg)	208		42.01 (30.91; 59.82)	45.36 (±19.72)

(Continues)

TABLE 1 (Continued)

Parameter	*N*	%	Median (25th; 75th)	Mean (±SD)
Pathological values (>35)	139	66.8		
$PaetCO_2$ @ rest (mmHg)	212		5.76 (3.62; 8.85)	6.64 (±4.93)
$PaetCO_2$ peak (mmHg)	208		6.21 (3.47; 9.92)	7.22 (±6.22)
Pathological values (>6)	104	50.0		
VE/MVV (%)	227		61.90 (49.24; 72.87)	61.38 (±16.12)
Pathological values (>80%)	23	10.1		

Abbreviations: $AaDO_2$, alveolar-arterial oxygen difference at peak exercise; BMI, body mass index; BSA, body surface area; CI, cardiac index; CO, cardiac output; DLCOc, diffusing capacity of the lungs for carbon monoxide corrected to hemoglobin value; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; HR heart rate; KCOc, transfer coefficient of the lung for carbon monoxide corrected to hemoglobin value; LVEF, left ventricular ejection fraction; $PaetCO_2$, end-tidal partial pressure of carbon dioxide; PAP, pulmonary artery pressure; PAPmean, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; $peakVO_2$, maximum oxygen uptake per minute at exercise; $petCO_2$, end-tidal partial pressure of carbon dioxide; PVR, pulmonary vascular resistance; RAPmean, mean right atrial pressure; RV, residual volume; TAPSE, tricuspid annular plane systolic excursion; TLC, total lung capacity; VC, vital capacity; VO_2@AT, oxygen uptake at anaerobic threshold; VO_2, oxygen uptake per minute; VE/VCO_2slope, slope of minute ventilation to carbon dioxide output; VE/VCO_2, carbon dioxide equivalent at anaerobic threshold; VE/MVV, breathing reserve.

[a]Multiple mentions possible.

coronary heart disease, diabetes mellitus, chronic obstructive pulmonary disease, and chronic thromboembolic disease, respectively. Right ventricular function, measured using tricuspid annular plane systolic excursion, was normal on average (21 ± 6 mm). Of 282 patients who were evaluated by echocardiography, 159 patients (56.4%) had tricuspid regurgitation (TR) Grade II or higher. Based on the measurement of hemodynamic parameters, 76.0% of patients had PH. Pulmonary function tests revealed that 24.0% and 26.1% of patients had restrictive and obstructive pulmonary diseases, respectively. $PeakVO_2$ during exercise (initial CPET) was below 80% of the predicted level in 79.4% of patients. The aerobic capacity was severely impaired, as 77 of 233 patients (34.5%) had a VO_2 at anaerobic threshold below 40% of the predicted $peakVO_2$.

CO was measured by TD, the iFM, and the dFM during supine rest in all 300 patients. TD and dFM measurements were also taken during semi-supine rest in 280 of the patients, during semi-supine unloaded cycling in 275 of the patients (with at least three TD measurements in 175 patients), and during semi-supine 25-W exercise in 240 of the patients (with at least three TD measurements in 141 patients) (Figure 1). Data obtained during >50-W exercise ($n = 75$ [53 with at least three TD measurements]) were not analyzed because they came from a relatively small, potentially nonrepresentative subset of the overall study population.

Methods of CO measurement at rest

There were significant differences between the three methods in CO measurements taken at rest in the supine position ($p \leq 0.001$; $n = 300$; Figure 2a). The proportion of patients with a difference in CO (ΔCO) > 1 L/min when comparing iFM versus dFM, iFM versus TD, and TD versus dFM was 45.0%, 42.0%, and 45.7%, respectively; the corresponding proportion of patients with $\Delta CO > 2$ L/min was 21.7%, 11.0%, and 14.3% respectively. CO measurements taken at rest in the semi-supine position showed a significant difference between TD and the dFM ($p = 0.002$; $n = 280$; Figure 2b). $\Delta CO > 1$ L/min and $\Delta CO > 2$ L/min were observed 48.2% and 17.1% of patients, respectively.

The mean ΔCO values at rest in the supine position were as follows: iFM versus dFM, -1.1 ± 1.23 L/min (LOA: ± 2.41 L/min); iFM versus TD, -0.8 ± 1.05 L/min (LOA: ± 2.05 L/min); and TD versus dFM, -0.3 ± 1.37 L/min (LOA: ± 2.69 L/min). At rest in the semi-supine position, the mean ΔCO between TD and the dFM was -0.33 ± 1.53 L/min (LOA: ± 2.99 L/min) (Supporting Information: Figure S1).

Methods of CO measurement during exercise (unloaded cycling and 25-W exercise)

There was a significant difference between TD and the dFM in CO measurements taken during unloaded cycling ($p < 0.001$; $n = 275$; Figure 2c); $\Delta CO > 1$ L/min and $\Delta CO > 2$ L/min were observed in 56.6% and 23.4% of patients, respectively. During 25-W exercise, there was no significant difference in CO values between TD and the dFM ($p = 0.137$; $n = 240$; Figure 2d); $\Delta CO >$

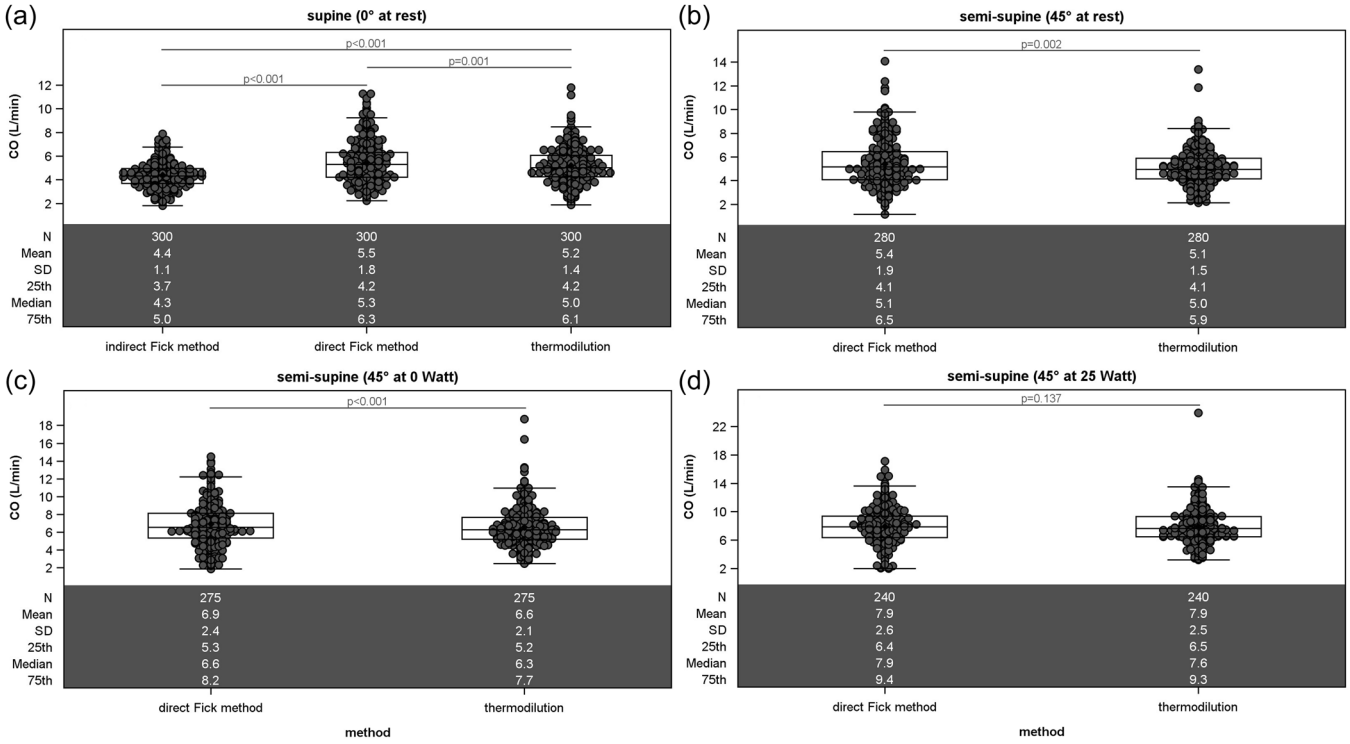

FIGURE 2 Comparison of the different methods of CO measurement. Measurements were taken (a) at rest, supine (0°), (b) at rest, semi-supine (45°), (c) during unloaded cycling (0 W), semi-supine (45°), and (d) during 25-W exercise, semi-supine (45°). CO, cardiac output; SD, standard deviation.

1 L/min and ΔCO > 2 L/min were observed in 52.8% and 25.6% of patients, respectively. The mean ΔCO between TD and the dFM was −0.38 ± 1.93 L/min (LOA: ± 3.78 L/min) during unloaded cycling and 0 ± 2.31 L/min (LOA: ± 4.52 L/min) during 25-W exercise (Supporting Information: Figure S1).

Averaging different numbers of TD measurements during exercise (unloaded cycling and 25-W exercise)

In patients with at least three TD measurements during unloaded cycling ($n = 175$), ΔCO between TD and the dFM remained significant regardless of the number of TD measurements that were included in the calculation (all TD measurements, the first measurement alone, or the first two or three measurements ($p < 0.001$; Figure 3a). In patients with at least three TD measurements during 25-W exercise ($n = 141$), ΔCO between TD and the dFM was not significant when the mean of all TD measurements ($p = 0.076$) or the mean of the first three TD measurements ($p = 0.061$) was used (Figure 3b). A significant difference was observed between the two methods if only the first TD measurement ($p = 0.001$) or the mean of the first two TD measurements ($p = 0.012$) was used.

In patients with at least three TD measurements during exercise, the mean ΔCO between TD (mean of all measurements) and the dFM was −0.43 ± 1.98 L/min (LOA: ± 3.88 L/min) during unloaded cycling and −0.06 ± 2.29 L/min (LOA: ± 4.49 L/min) during 25-W exercise (Figure 4).

Comparison between normal and PH subgroups

In this subgroup analysis, patients with at least three TD measurements during exercise were divided into groups with normal and pathological hemodynamics at rest, the latter defined as precapillary PH if the mean pulmonary artery pressure (PAPm) was >20 mmHg and pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and as postcapillary PH if PAPm was >20 mmHg and PAWP > 15 mmHg. There was no significant difference between the normal and PH subgroups in ΔCO (TD vs. dFM) during unloaded cycling ($p = 0.581$; $n = 174$) and during 25-W exercise ($p = 0.961$; $n = 141$; Figure 5).

The mean ΔCO between TD and the dFM during unloaded cycling was as follows: controls, −0.65 ± 2.42 L/min (LOA: ±4.75 L/min); precapillary PH, −0.3 ± 1.73 L/min (LOA: ±3.39 L/min); and postcapillary PH, −0.43 ± 1.81 L/

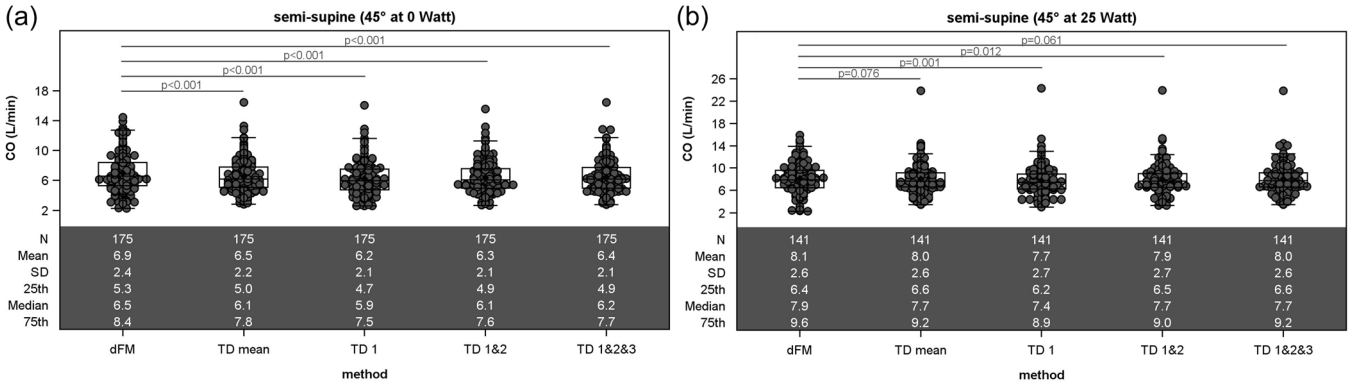

FIGURE 3 Effect of using different numbers of TD measurements to calculate CO during exercise. In patients with at least three TD measurements during exercise, CO for each patient was calculated based on the mean of all available TD measurements (TD mean; outliers not within 20% of the other measurements were excluded), the first TD measurement only (TD 1), and the mean of the first two (TD 1&2) and three (TD 1&2&3) TD measurements. The dFM was used as a reference. Measurements were taken during (a) unloaded cycling (0 W), semi-supine (45°), and (b) 25-W exercise, semi-supine (45°). CO, cardiac output; dFM, direct Fick method; SD, standard deviation; TD, thermodilution.

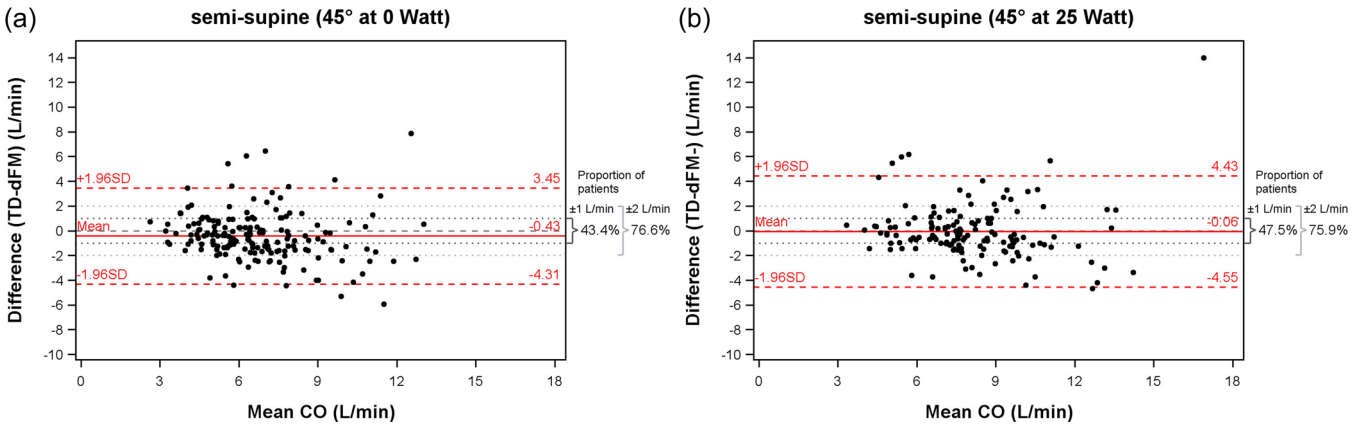

FIGURE 4 Individual differences in CO between TD with at least three measurements and the dFM. Measurements were taken during (a) unloaded cycling (0 W), semi-supine (45°; $n = 175$) and (b) 25-W exercise, semi-supine (45°; $n = 141$). Differences are plotted against the average corresponding values (expressed in liters per minute). The solid line represents the mean (or bias) of the differences, and the dashed lines represent the upper and lower limits of agreement. CO, cardiac output; dFM, direct Fick method; SD, standard deviation; TD, thermodilution.

min (LOA: ±3.54 L/min). The corresponding ΔCO between the methods during 25-W exercise was as follows: controls, 0.1 ± 2.96 L/min (LOA: ±5.8 L/min); precapillary PH, −0.07 ± 1.93 L/min (LOA: ±3.78 L/min); and postcapillary PH, −0.3 ± 1.53 L/min (LOA: ±2.99 L/min) (Supporting Information: Figure S2).

Comparison between patients with and without TR

Patients with any number of TD measurements during 25-W exercise who had baseline echocardiographic data available ($n = 199$) were divided into groups with TR (Grade II or higher; $n = 112$) and without TR ($n = 87$). Comparing TD and the dFM at 25-W exercise, ΔCO > 1 L/min was seen in 43.7% of patients with TR and 64.4% of patients without TR, while ΔCO > 2 L/min was seen in 22.3% of patients with TR and 26.4% of patients without TR. There was no significant difference in ΔCO between the groups with and without TR ($p = 0.593$; Figure 6).

The mean ΔCO between TD and the dFM during 25-W exercise was 0.04 ± 1.9 L/min (LOA: ±3.73 L/min) in the group with TR and 0.31 ± 2.56 L/min (LOA: ±5.01 L/min) in the group without TR (Supporting Information: Figure S3).

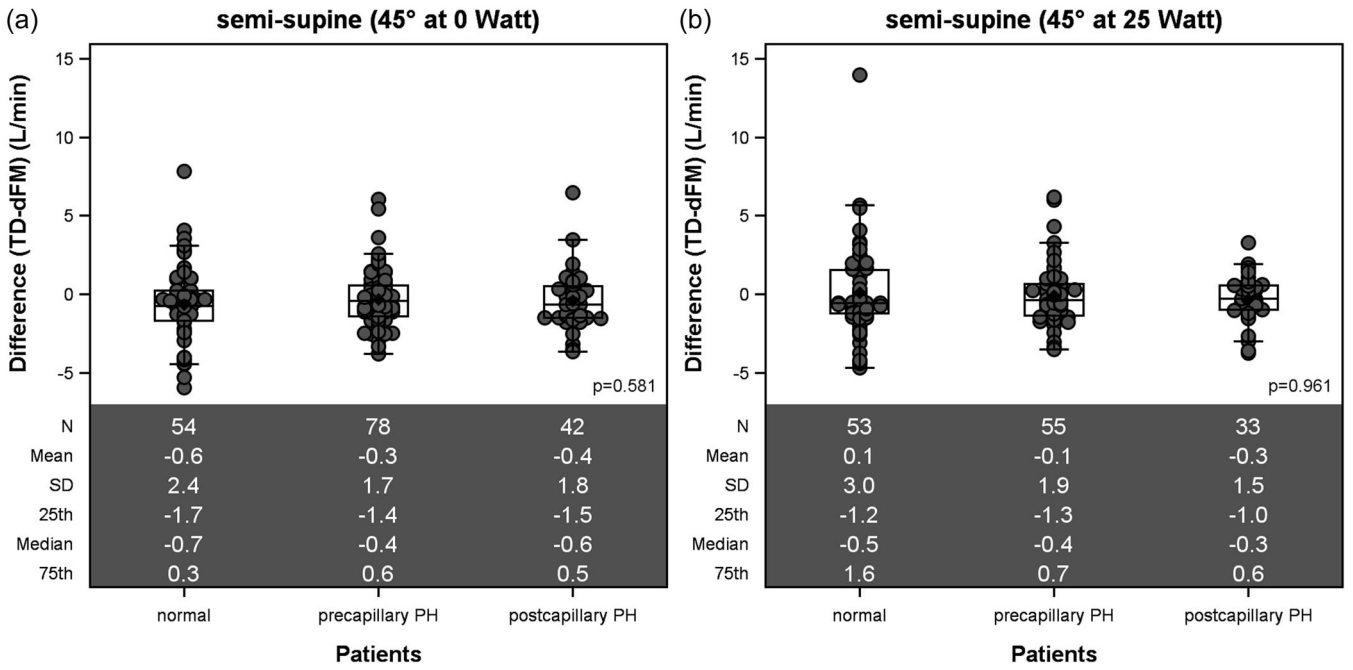

FIGURE 5 The individual differences in cardiac output between TD with at least three measurements and the dFM during exercise in patients with and without PH. Patients were divided into groups with normal (PAPm ≤20 mmHg) and pathological hemodynamics at rest, the latter defined as precapillary PH (PAPm >20 mmHg and PAWP ≤ 15 mmHg) and postcapillary PH (PAPm >20 mmHg and PAWP > 15 mmHg). Measurements were taken during (a) unloaded cycling (0 W), semi-supine (45°; $n = 174$) and (b) 25-W exercise, semi-supine (45°; $n = 141$). dFM, direct Fick method; PAPm, mean pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; SD, standard deviation; TD, thermodilution.

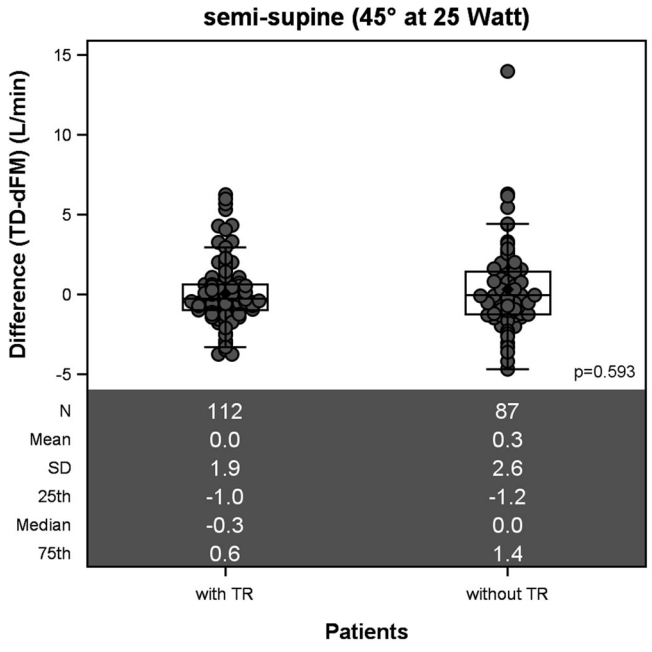

FIGURE 6 The individual differences in cardiac output between TD and the dFM at 25-W (semi-supine) exercise in patients with and without TR. dFM, direct Fick method; SD, standard deviation; TD, thermodilution; TR, tricuspid regurgitation.

Change of PH classification due to exercise data and/or different CO measurement methods

We analyzed all patients at rest and divided them into two groups: the no-PH (PAPm ≤20 mmHg and PAWP ≤ 15 mmHg, $n = 63$) and the PH group. The no-PH group showed the following characteristics during 25-W exercise: 18/63 (28.6%) patients developed exercise-induced PH with PAPm >30 mmHg[5]; further, 7/63 (11.1%) developed postcapillary PH (PAPm >20 mmHg and PAWP > 20 mmHg).

Recent classifications use a pulmonary vascular resistance (PVR) cut-off of 3 Wood units (WU) to differentiate between PAH and other types of PH. Hence, we analyzed the number of patients who would be reclassified if PVR was calculated using the different CO measurement methods. At rest, 148 patients (50.0%) had $PVR_{dFM} \leq 3$ WU and $PVR_{TD} \leq 3$ WU, 21 patients (7.1%) had $PVR_{dFM} \leq 3$ WU and $PVR_{TD} > 3$ WU, 18 patients (6.1%) had $PVR_{dFM} > 3$ WU and $PVR_{TD} \leq 3$ WU, and 109 patients (36.8%) had $PVR_{dFM} > 3$ WU and $PVR_{TD} > 3$ WU. Thus, an identical classification of patients by PVR (≤ 3 WU vs. > 3 WU) was observed in 86.8% of all study patients.

During 25-W exercise, 132 patients (55.7%) had $PVR_{dFM} \leq 3$ WU and $PVR_{TD} \leq 3$ WU, 11 patients (4.6%) had $PVR_{dFM} \leq 3$ WU and $PVR_{TD} > 3$ WU, 10 patients (4.2%) had $PVR_{dFM} > 3$ WU and $PVR_{TD} \leq 3$ WU, and 84 patients (35.4%) had $PVR_{dFM} > 3$ WU and $PVR_{TD} > 3$ WU. Hence, the classification of patients by PVR during exercise (≤3 WU vs. >3 WU) remained unchanged in 91.1% of all study patients.

DISCUSSION

Our data show significant differences between different CO measurement methods at rest and during low-intensity exercise (unloaded cycling) but not during 25-W submaximal exercise. Interestingly, this congruence between TD and the dFM requires an averaging of three or more TD measurements. The individual differences in CO between TD and the dFM (−0.43 L/min during unloaded cycling and −0.06 L/min during a 25-W intensity exercise in patients with at least three TD measurements) seem small, although the considerable LOA (3.9 and 4.5 L/min, respectively) could be decisive in clinical practice, and therefore need a closer examination. However, the classification of PH is based on PVR (less than or greater than 3 WU), and the observed differences in CO measurement methods did not significantly alter the classification. Based on the PVR, 86.8% and 91.1% of patients remained in the same PH class at rest and during exercise, respectively. The importance of exact CO measurement can only be emphasized at this stage.

Previous studies comparing CO measurement methods in healthy participants and patients were conducted at rest only. A previous study of 35 patients with PH found a mean ΔCO between TD and the dFM of +0.01 L/min, with 95% LOA of ±1.1 L/min; this was comparable to our study findings.[6] Another study of 198 patients with and without PH found a mean ΔCO of −0.39 L/min between the aforementioned methods, although the LOA were −4.44 to +3.66 L/min.[7] Concerning comparison of the iFM with TD, a recent, large-scale study analyzed the data of 12,232 patients (mean age 66.4 ± 9.9 years, with only 3.3% women) and confirmed both a minimal mean difference in cardiac index of −0.02 L/min/m^2 or −0.4% and wide 95% LOA between the measurement methods (−1.3 to +1.3 L/min/m^2, or −50.1% to +49.4%).[8] A very recent study compared TD and the iFM in 155 elderly patients (mean age 75.1 ± 6.8 years, 57.7% men) using different standard tables for oxygen uptake in the analysis.[9] This resulted in a mean cardiac index difference between TD and the iFM of +0.22 to −0.42 L/min/m^2, with wide LOAs (−0.64 to +1.09 L/min/m^2 or −1.38 to +0.53 L/min/m^2 depending on the applied standard table). There is a paucity of studies comparing TD and FMs during exercise; the few available studies included a small number of healthy participants ([$n = 11$][10] and [$n = 10$][11]).

The individual differences at rest in our study correspond to the differences in the studies mentioned above[7] or are somewhat greater.[6]

Some aspects are important in the assessment of individual differences between CO measurement methods: First, previously published studies had variable designs; they compared TD with the iFM or dFM, included different groups of patients or healthy participants, and reported the CO and cardiac index. Second, the CO fluctuates physiologically within 0.7 ± 0.3 L/min when measured at intervals of 15 min over a 2-h period.[12] Lastly, it is generally known that CO measurement using TD becomes unreliable in patients with relevant TR, intracardiac shunts, or low CO.[13,14] This is based on older studies that assumed that CO measurement using FMs was more accurate than that using TD.[15–17] By contrast, Hoeper et al.[6] and Fares et al.[7] reported that neither TR nor low CO (defined as <3 L/min) influenced the performance of TD compared with the FM in patients with and without PH. However, TD might underestimate higher CO values (>11 L/min) measured using the dFM in patients with unexplained dyspnea.[18] Our findings support the hypothesis that TR and impaired hemodynamics do not influence the performance of TD compared with the dFM during low-intensity and submaximal exercise. We found that ΔCO (TD vs. dFM) during exercise showed no significant difference between patients with normal and impaired hemodynamics at rest or between patients with and without TR.

As mentioned above, individual differences expressed as relative differences or percentages are of clinical importance. A previous study revealed a CO difference between TD and the dFM of ≥10% and ≥20% in 68% and 48% of patients, respectively, which was consistent in patients with and without pulmonary arterial hypertension (PAH).[7] A difference of >20% was also observed in 38.1% of patients in the largest published study, although the cardiac index was measured instead of the CO and TD was compared with the iFM rather than the dFM.[8] These results are consistent with our study findings which showed ΔCO > 1 L/min in approximately 50% and ΔCO > 2 L/min in approximately 20% of patients at rest and during exercise. Nevertheless, it is unclear whether these differences can result in clinical consequences. This aspect is illustrated in Figure 7, which shows (irrespective of vessel distensibility[19] and assuming a linear relationship between PAPm and CO)

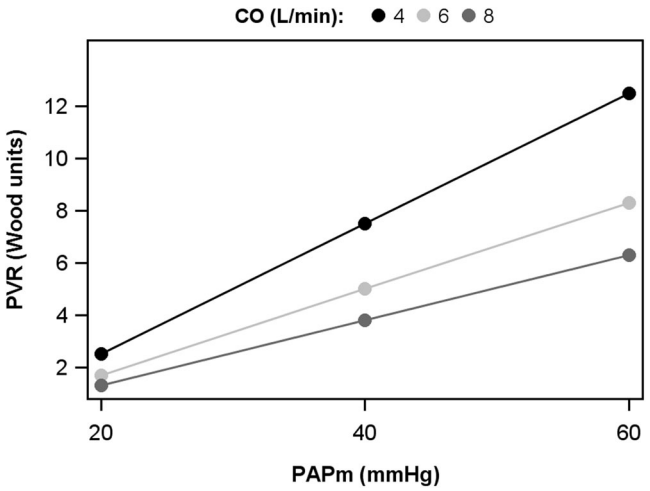

FIGURE 7 Relationship between PVR (pulmonary vascular resistance), PAPm (mean pulmonary artery pressure), and CO (cardiac output).

that in patients with relevant PH, a deviation in CO is a significant factor in PVR evaluation. However, PVR is included in the definition of PAH.[20] Therefore, a difference in the CO value between the measurement methods can lead to misclassification in PH subgroups. Fares et al.[7] used a PVR cut-off of >3 WU to define PAH and showed that switching between TD and the dFM for CO measurement caused diagnostic changes in 13% of patients. This was also illustrated in our study; assessment by TD compared with the dFM resulted in CO and PVR differences leading to discrepant diagnoses in 13.2% of patients at rest and 8.9% of patients at 25-W exercise.

CO measurement using the dFM is recommended in "steady state" assessments and in patients with shunts. The dFM measurement requires a steady oxygen uptake that is not assured before 3–5 min of unchanged conditions.[21,22] At rest, CO calculation using TD requires multiple measurements. We took the mean of all available measurements (after exclusion of outliers that were not within 20% of the other measurements); other approaches include taking five repeated measurements, excluding the highest and the lowest values, and calculating the mean of the remaining three values,[6] or excluding outliers if they do not fall within 10%–15% of the other three TD measurement values.[7] The TD method could be regarded as a "steady state" measurement method at rest, owing to the length of time required to collect all samples.[23] Taking five measurements may not be feasible under exercise conditions; therefore, two TD measurements are presently recommended during exercise.[1] Our study suggests that three TD measurements should be obtained to increase the accuracy of the values.

In conclusion, the measurement of CO is comparable between the TD method and the dFM during submaximal exercise (with averaging of at least three TD measurements) but not during unloaded cycling or at rest. Individual CO values can vary substantially between these methods and require critical interpretation to avoid CO misclassification.

AUTHOR CONTRIBUTIONS

Ralf Ewert, Susanna Desole, Christine Knaack, Alexander Heine were involved in the study conception. Ralf Ewert, Dirk Habedank, Susanna Desole, and Christian F. Opitz were involved in the study design. Susanna Desole, Alexander Heine, Christine Knaack, and Ralf Ewert included patients in this study. Anne Obst was the study statistician. Ralf Ewert, Anne Obst, Dirk Habedank, Christian F. Opitz, Susanna Desole, Franziska Hortien, and Beate Stubbe were involved in the analysis. Susanna Desole, Dirk Habedank, Christian F. Opitz, Ralf Ewert, and Beate Stubbe were involved in interpreting the data. Ralf Ewert, Susanna Desole, and Beate Stubbe wrote the first draft. All authors read and revised the draft of the work. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

We thank the staff of participating practices and institutions, especially Dagmar Fimmel, Kathrin Gutsche, and Jeannette Pieper.

We would like to thank Editage (www.editage.com) and Claire Mulligan, PhD (Beacon Medical Communications Ltd, Brighton, UK) for English language editing. Open Access funding enabled and organized by Projekt DEAL.

CONFLICTS OF INTEREST

RE: Honoraria for scientific lectures from Actelion, GSK, United Therapeutics, AstraZeneca, Novartis, Berlin Chemie, Boehringer Ingelheim, and OMT, and research funding from Boehringer Ingelheim and Actelion Germany. SD, AO, DH, CFO, CK, FH, AH, BS: No potential conflict of interest to report.

ETHICS STATEMENT

The study was approved by the Ethics Committee of Greifswald University (No. BB 215/20 of November 17, 2020, which was amended on January 28, 2021).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Desole S, Obst A, Habedank D, Opitz CF, Knaack C, Hortien F, et al. Comparison between thermodilution and Fick methods for resting and exercise-induced cardiac output measurement in patients with chronic dyspnea. Pulmonary Circulation. 2022;12:e12128. https://doi.org/10.1002/pul2.12128