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Differences in Direct Fick and Thermodilution Measurements of Cardiac Output: Impact on Pulmonary Hypertension Classification

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ABSTRACT

Direct Fick (DF) and bolus thermodilution (TD) are endorsed by pulmonary hypertension (PH) guidelines to measure cardiac output. In contemporary practice, agreement between methods is unknown, as are the diagnostic consequences of disagreement. We sought to evaluate the frequency and degree of disagreements between cardiac output measurement techniques and assess their impact on the hemodynamic assessment of PH. This was a single-center study that included 182 patients who had cardiac output concurrently measured by DF and TD. Oxygen consumption was measured by indirect calorimetry. Agreement between DF and bolus TD cardiac output was assessed using Bland–Altman analysis. The median DF and TD cardiac outputs were 5.42 L/min (interquartile range [IQR] 3.90–7.41) and 4.10 L/min (IQR 3.47–5.10), respectively. Significant disagreement was observed with DF yielding higher cardiac output results than TD. Mean error was proportional to cardiac output (−3.75% at 3 L/min to +44.5% at 7 L/min), and limits of agreement were wide. Disagreement was increased by 19.2% in the presence of least moderate tricuspid regurgitation and by 16.0% in patients with atrial fibrillation. Among 152 patients with PH, hemodynamic classification discordance occurred in 18 (11.8%) patients. Disagreement between DF and TD was observed, which resulted in a discrepant hemodynamic classification in approximately 12% of patients. These techniques should, therefore, not be used interchangeably for serial surveillance, and without a clinical gold standard, a rationale exists for utilizing both methods concurrently in certain clinical situations.

1 | Introduction

Measurement of cardiac output (CO) during right heart catheterization (RHC) is required to calculate pulmonary vascular resistance (PVR) [1, 2]. Accurate determination of PVR is essential for the diagnosis of pulmonary hypertension (PH), to guide pulmonary vasodilator therapy, for determining preoperative risk assessment, and for assessing the severity of valvular and congenital heart disease [2–4].

Abbreviations: AF, Atrial fibrillation; CO, Cardiac output; DF, Direct Fick; IQR, Interquartile range; LLOA, Lower limit of agreement; mPAP, Mean pulmonary artery pressure; OR, Odds ratio; PCWP, Pulmonary capillary wedge pressure; PE, Percentage error; PH, Pulmonary hypertension; PVR, Pulmonary vascular resistance; RHC, Right heart catheterization; RV, Right ventricle; SD, Standard deviation; SE, Standard error; TD, Thermodilution; TR, Tricuspid regurgitation; ULOA, Upper limit of agreement; VO2, Oxygen consumption; WU, Wood units.

Luke R. Fletcher and Garry W. Hamilton contributed equally to this manuscript.

The gold standard for measuring CO is the direct Fick (DF) method performed at a steady state in a controlled environment [2]. However, bolus thermodilution (TD) [5, 6] and indirect Fick (IF) [7–9] are alternatives used in cardiac catheterization laboratories. These modalities have several limitations and assumptions but have been favored over DF methodology because accurate measurement of oxygen consumption (VO_2) is challenging.

The 2022 ESC/ERS guidelines for diagnosis and treatment of PH endorse either DF or TD methods for CO measurement [1]. However, data supporting the use of the DF method are limited [10–18] and have mostly been derived using techniques and equipment not routinely used in clinical practice. Given this and the increased availability of compact indirect calorimeters to measure VO_2 [19], we aimed to assess the agreement between DF and bolus TD measurements of CO, to identify clinical factors associated with disagreement between techniques, and to investigate the impact of disagreement on individual patient hemodynamic classification.

2 | Methods

This was a single-center retrospective cohort study in a university teaching hospital that serves as a specialist referral center for the diagnosis and management of PH. This project was approved as a clinical audit; a waiver of patient consent was granted by the local human research ethics committee (ethics approval number removed).

2.1 | Patient Selection

Patients who underwent RHC in the cardiac catheterization laboratory between August, 2017, and July, 2022, in whom CO was simultaneously measured by both DF and TD methods were eligible for inclusion. Patients were excluded if an intracardiac shunt was present. [20].

2.2 | Outcomes

The primary outcome was the agreement between DF-derived (CO_{DF}) and TD-derived CO (CO_{TD}) determined by Bland–Altman analysis. Secondary outcomes included agreement between DF-derived PVR (PVR_{DF}) and TD-derived PVR (PVR_{TD}), the influence of clinical variables on the agreement between CO_{DF} and CO_{TD}, and the frequency of hemodynamic classification discordance between the two measurements. Sources of disagreement were determined based on clinical variables selected a priori and included PH severity, right ventricular (RV) dilatation or dysfunction, tricuspid regurgitation (TR), and atrial fibrillation (AF) during RHC.

2.3 | Study Definitions

PH was defined as a mean pulmonary artery pressure (mPAP) > 20 mmHg, and an elevated PVR was defined as > 2.0 Wood units (WU). PH hemodynamic classifications were as per the 2022 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension [1]. Ventricular function and valvular disease severity were assessed by echocardiography within 6 months of RHC, based on American Society of Echocardiography (ASE) guidelines [21–23].

2.4 | Procedural Details

All patients underwent RHC in the supine position using a standardized protocol (Appendix: Right Heart Catheter Protocol). CO_{TD} was measured with the bolus TD technique and taken as the average of at least three measurements within 10% of each other [5]. VO_2 was measured continuously throughout the procedure using a fitted face mask connected to an open-circuit indirect calorimeter (CCM Express, MGC Diagnostics, Saint Paul, Minnesota, the United States) and taken as the average measurement at steady state. Arterial and mixed venous blood gases were collected to measure arterial oxygen saturation (SaO_2), mixed venous oxygen saturation ($SmvO_2$), and hemoglobin (Hb), and CO_{DF} was measured as per the DF equation:

$$CO = \frac{VO_2}{1.34 \times Hb \times (SaO_2 - SmvO_2)}$$

2.5 | Data Collection

Patient demographics, comorbidities, pathology reports, and echocardiographic reports were collected from the electronic medical record (Cerner Millenium, North Kansas City, Missouri, the United States).

2.6 | Statistical Analysis

All data were audited for collection or coding errors before analysis. Discrete variables are expressed as proportions or percentages. The mean and standard deviation (SD) are reported for normally distributed variables. The median and interquartile range (IQR) are reported for non-normally distributed variables.

Bland–Altman analysis was employed to evaluate the agreement between measurements of CO and PVR obtained via DF and TD [24]. Key parameters including the mean percentage error (PE), SD, standard error (SE) of the PE and SD, and 95th centile upper and lower limits of agreement (95% ULOA and 95% LLOA, respectively) were calculated and reported. Concordance plots were generated using reduced major axis regression to visually assess the agreement between the two methods. Linear regression analysis was conducted to determine the attributable PE ± SE between CO measurements obtained via DF and TD for each clinical variable. Proportional bias and variance were accounted for using linear regression, with the mean of DF and TD measurements (μ) included where appropriate. Logistic regression analysis was employed to ascertain the odds ratio (OR) ± SE of hemodynamic classification discordance for each clinical variable.

A two-tailed p value < 0.05 was considered statistically significant. Statistical analyses were performed using Stata/SE version 15.1 (StataCorp, College Station, Texas, the United States).

3 | Results

3.1 | Patients

Of the 255 patients that presented during the study period, a total of 182 patients satisfied the inclusion and exclusion criteria, with a median age of 70 years. Comorbidities included chronic kidney disease (stage III–V; 40.7%), heart failure (27.5%) with preserved (20.9%) and reduced (6.6%) ejection fraction, history of AF (26.4%), diabetes mellitus (22.0%), obstructive sleep apnea (21.4%), chronic obstructive pulmonary disease (19.2%), and ischemic heart disease (17.6%, Table 1).

Most patients were undergoing RHC for the evaluation of PH (75.7%, Table 1). RV systolic dysfunction was present in 46.9% of patients, and 28.5% had at least moderate TR. Most patients had normal LV systolic function (86.7%). The mPAP was 35.6 ± 13.8 mmHg and mean PCWP was 15.4 ± 8.0 mmHg. The mean VO_2 was 241.9 ± 86.7 mL/min (Table 2).

3.2 | Cardiac Output

Compared with the TD technique, the DF method resulted in higher CO measurements, particularly with higher CO states. The median CO_{DF} was 5.42 L/min (IQR 3.90–7.41), while the median CO_{TD} was 4.10 L/min (IQR 3.47–5.10; Table 2). Bland–Altman analysis demonstrated that the error between CO_{DF} and CO_{TD} demonstrated significant proportional bias ($p < 0.001$). Specifically, the mean error between the two measurements was greater when CO increased: −4.75% for a mean CO of 3.0 L/min; +25.0% for a mean CO of 5.0 L/min; and +44.5% for a mean CO of 7.0 L/min. The SD between the two measurements was 38.5 ± 9.4%, and it did not demonstrate proportionality. The limits of agreement between CO_{DF} and CO_{TD} were: −69.9% to +60.4% for a mean CO of 3.0 L/min, −35.4% to +85.3% for a mean CO of 5.0 L/min, and −12.7% to +101% for a mean CO of 7.0 L/min (Figure 1).

3.3 | Pulmonary Vascular Resistance

Compared with the TD method, the DF technique resulted in lower PVR estimates. The median PVR_{DF} was 3.37 (IQR 1.75–5.39) WU, whereas the median PVR_{TD} was higher at 4.15 (IQR 2.57–6.85) WU. Bland–Altman analysis demonstrated that the error between PVR_{DF} and PVR_{TD} had significant proportional bias and was −36.3% at a mean PVR of 1 WU, −25.0% at a mean PVR of 3 WU, and −19.8% at a mean PVR of 5 WU. The SD between the two measurements was 33.4 ± 4.2% and did not demonstrate proportionality. The limits of agreement between PVR_{DF} and PVR_{TD} were: −101% to +29.1% for a mean PVR of 1 WU, −98.3% to +39.9% for a mean PVR of 2 WU, and −93.8% to +54.3% for a mean PVR of 5 WU (Figure 1).

TABLE 1 | Baseline characteristics.

	N	Value
Demographics		
Age	182	70 (60–76)
Sex (male)	182	76 (41.2%)
BMI (kg/m^2)	182	27.4 (24.3–33.4)
RHC indication	182	
PH evaluation		138 (75.8%)
Valvular evaluation		31 (17.0%)
OLTx evaluation		13 (7.1%)
Comorbidities		
Pulmonary hypertension	182	130 (71.4%)
Ischemic heart disease	182	32 (17.6%)
Heart failure with reduced ejection fraction	182	12 (6.6%)
Heart failure with preserved ejection fraction	182	38 (20.9%)
History of atrial fibrillation	182	48 (26.4%)
COPD/emphysema	182	35 (19.2%)
Interstitial lung disease	182	24 (13.2%)
Obstructive sleep apnea	182	39 (21.4%)
Chronic kidney disease (III–V)	182	74 (40.7%)
Liver cirrhosis	182	20 (11.0%)
Rheumatological	182	29 (15.9%)
Diabetes mellitus	182	40 (22.0%)
Echocardiography		
LV systolic dysfunction	180	24 (13.3%)
LV ejection fraction (%)	126	60.4 ± 11.2
E/A ratio	126	0.88 (0.71–1.35)
E/E' ratio	139	11.7 (9.00–16.0)
RV systolic dysfunction	177	83 (46.9%)
RV dilatation	175	98 (56.0%)
RV systolic pressure (mmHg)	165	53.2 ± 22.2
Aortic stenosis	179	16 (8.9%)
Aortic regurgitation	178	4 (2.3%)
Mitral stenosis	179	5 (2.8%)
Mitral regurgitation	179	23 (12.9%)
Pulmonary stenosis	176	1 (0.6%)
Pulmonary regurgitation	176	6 (3.4%)
Tricuspid regurgitation	179	51 (28.5%)

Note: N (%), Mean ± SD, Median [IQR].
Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; LV, left ventricle; PH, pulmonary hypertension; OLTx, orthotopic liver transplantation; RHC, right heart catheterization; RV, right ventricle.

3.4 | Sources of Disagreement

The mean error between CO_{DF} and CO_{TD} measurements was +19.2% higher (SE = 5.60%, 95% CI = 8.22%–30.2%, $p = 0.001$)

TABLE 2 | Right heart and direct Fick measurements.

	All patients ($N = 182$)
Cardiac output	
CO-TD (L/min)	4.10 (3.47–5.10)
CO-DF (L/min)	5.42 (3.90–7.41)
Pulmonary vascular resistance	
PVR-TD (mmHg/L/min)	4.15 (2.57–6.85)
PVR-DF (mmHg/L/min)	3.37 (1.75–5.39)
RHC	
PA systolic pressure (mmHg)	57.1 ± 23.0
Mean PA pressure (mmHg)	35.6 ± 13.8
PA diastolic pressure (mmHg)	22.1 ± 9.84
PCWP (mmHg)	15.4 ± 8.01
RV systolic pressure (mmHg)	58.2 ± 21.7
RVEDP (mmHg)	11.8 ± 6.0
RA pressure (mmHg)	10.9 ± 6.3
HR (/min)	74.3 ± 16.8
Direct Fick	
VO_2 measured (mL/min)	242.2 ± 87.7
Hb (g/L)	127.4 ± 19.8
SaO_2 (%)	94 (91–96)
$SmvO_2$ (%)	68 (61–73)

Note: N (%), Mean ± SD, Median [IQR].
Abbreviations: PCWP, pulmonary capillary wedge pressure; RHC, right heart catheterization; RV, right ventricle; RVEDP, right ventricular systolic pressure.

among patients with moderate or greater TR and +16.0% higher (SE = 6.17%, 95% CI = 2.9%–27.1%, $p = 0.010$) among those with AF during RHC. The disagreement between CO_{DF} and CO_{TD} measurements was not affected by the presence of RV systolic dysfunction ($p = 0.23$), RV dilation ($p = 0.33$), increasing mPAP ($p = 0.69$), or increasing PCWP ($p = 0.44$) (Table 3). The results of a post hoc analysis exploring other sources of disagreement are available in the supplementary appendix (Appendix: Table 3).

3.5 | Hemodynamic Classification Disagreement

The DF and TD methods agreed that PVR was elevated (> 2 WU) in 86.3% of patients. In the group of patients with disagreement, 21 (11.5%) were classified as having an elevated PVR by TD but not by DF, and 3 (2.2%) were classified as having an elevated PVR by DF but not by TD (Figure 2).

Among 152 patients found to have PH (mPAP > 20 mmHg), the DF and TD methodologies led to concordant hemodynamic classification in 88.2% of patients. There were 8 (5.3%) patients classified by DF as isolated post-capillary PH that were classified as combined pre- and post-capillary PH by TD, 7 (4.6%) were classified by DF as having unclassified PH that were classified as pre-capillary PH by TD, and 3 (1.9%) were classified by DF as having combined pre- and post-capillary PH that were classified as post-capillary PH by TD (Figure 2).

Disagreement between DF and TD methods on PVR elevation was less likely among patients with higher mPAP (OR = 0.53 ± 0.09, $p < 0.001$) and with RV systolic dysfunction (OR = 0.31 ± 0.15, $p < 0.018$). Neither the presence of TR ($p = 0.175$) nor AF during RHC ($p = 0.965$) was associated with disagreement in the derived PVR (Table 3). The results of a post hoc analysis exploring other sources of hemodynamic classification disagreement are available in the supplementary appendix (Table A3).

4 | Discussion

Accurate hemodynamic assessments during RHC are important, as erroneous measurements may lead to misdiagnosis and inappropriate treatment [2]. Although guidelines support the use of the DF technique for assessing CO [1], data supporting its accuracy and use in routine clinical practice are limited. Our study addressed this evidence gap and produced several key findings. Wide limits of agreement and significant proportional bias were observed between DF and TD measurements; the DF technique tends to produce higher CO measurements relative to the TD method. The presence of at least moderate TR and AF during RHC significantly increases the disagreement between DF and TD-derived CO. Finally, in 11.8% of patients with PH, the two CO methods led to discordant hemodynamic classification. Our findings suggest that without a clinical gold standard, the simultaneous use of both modalities may have utility in clinical practice.

4.1 | Comparison With Prior Literature

A small number of prior studies evaluated the agreement between DF and TD techniques [10–18]. Only two of these were in the context of PH evaluation [12, 13]. The majority had relatively small sample sizes [10, 11, 15–18], were performed in critically ill patients in the intensive care setting [10, 11, 16, 18], utilized equipment that is impractical in a busy cardiac catheterization laboratory [14, 18], and some were performed prospectively where adherence to procedural protocols may be much higher than in routine clinical practice [10–12, 15–18].

In the current study, we found larger biases and limits of agreement between CO_{DF} and CO_{TD} than previously reported. A similar study in patients presenting for PH evaluation found a smaller bias (0.3 L/min) but limits of agreement were comparable (±2.69 L/min) [13], and using the historical definition for elevated PVR (> 3 WU) discordant hemodynamic classification was encountered in 13.2% of patients [13]. With more stringent procedural conditions, smaller biases (0.1 L/min) and tighter limits of agreement (±1.1 L/min) have been demonstrated [12]. However, these results required near-simultaneous performance of bolus TD and collection of arterial and mixed-venous blood gases, and VO_2 was measured using high-performance cardiopulmonary exercise testing equipment with a bulky face mask. No other studies, including ours, used such specialized

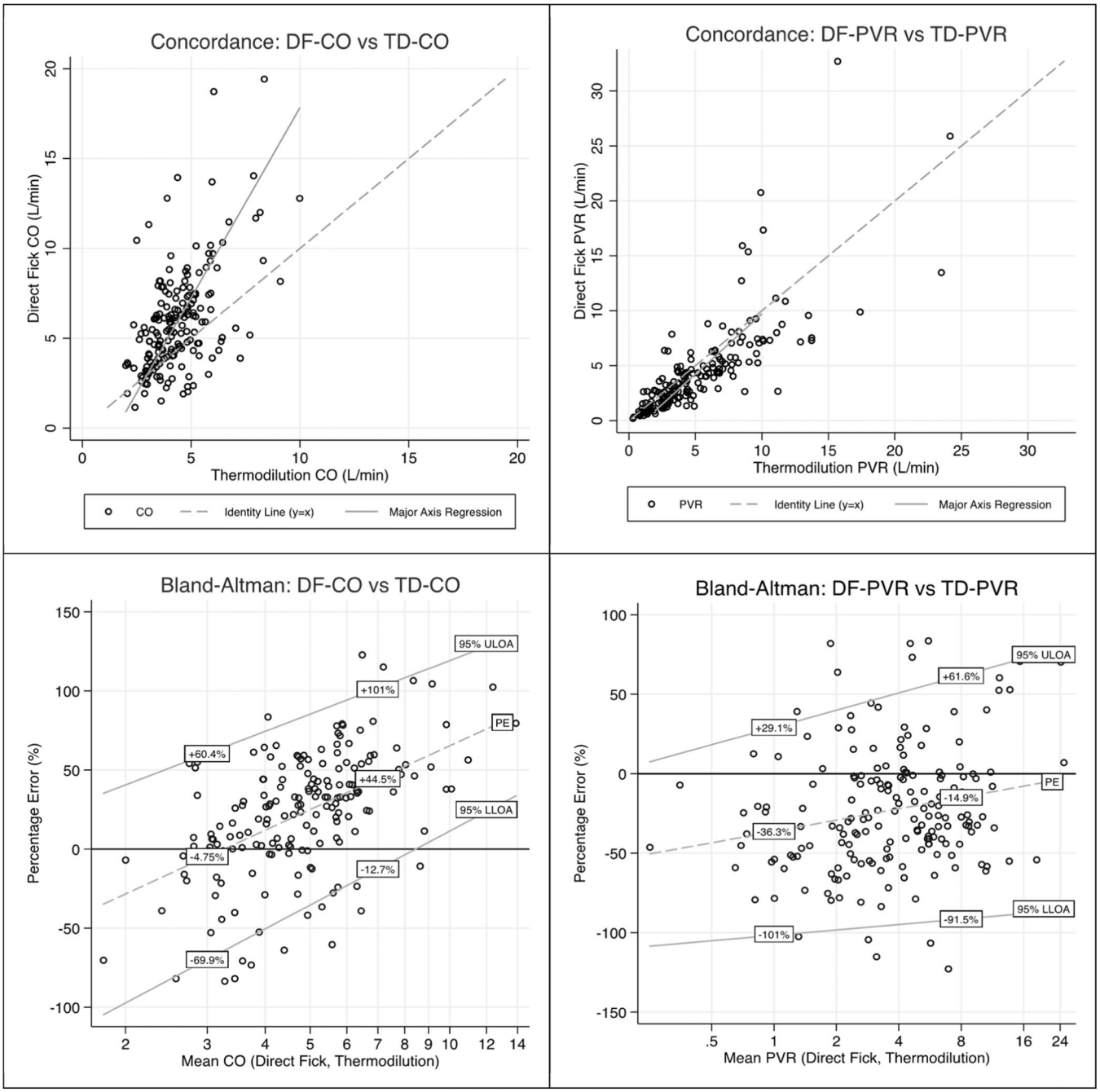

FIGURE 1 | Concordance and Bland–Altman analysis plots. Top Left: Concordance plot of CO_{DF} vs. CO_{TD}, with identity line (dashed line) and major axis regression (solid line). Top Right: Concordance plot of PVR_{DF} vs PVR_{TD}, with identity line (dashed line) and major axis regression (solid line). Bottom Left: Bland–Altman plot of relative CO_{DF} vs. CO_{TD}, with PE (dashed line), 95% ULOA (upper solid line), and 95% LLOA (lower solid line), plotted with logarithmic X-axis transformation. Bottom Right: Bland–Altman plot of relative PVR_{DF} vs. PVR_{TD}, with PE (dashed line), 95% ULOA (upper solid line), and 95% LLOA (lower solid line), plotted with logarithmic X-axis transformation. CO, cardiac output; DF, direct Fick; LLOA, lower limits of agreement; PE, percentage error; PVR, pulmonary vascular resistance; TD, thermodilution; ULOA, upper limits of agreement.

equipment or demonstrated such close agreement. Our indirect calorimeter is reflective of real-world practice—it is compact, transportable, easy to set up, and easy to service. It is unlikely that such stringent conditions could be reliably reproduced in cardiac catheterization laboratory practice, which questions their generalizability to routine clinical care.

We found that both TR and AF during RHC significantly increased the mean error between CO_{DF} and CO_{TD}. These are important data as TR is thought to underestimate CO_{TD} due to prolonged injectate transit time [25]; however, not all prior studies have found this to be the case [12, 26]. Furthermore, although AF has been shown to increase the variability of individual TD measurements [27], this is the first study to demonstrate its impact on disagreement between DF and TD methods. Additional data investigating the impact of specific clinical variables on the accuracy of the DF technique are required, and, presently, the preferred method for measurement

TABLE 3 | Sources of disagreement.

		CO (DF vs. TD) disagreement		PVR (> 2) disagreement	
	N	**PE ± SE**	***p* value**	**OR ± SE**	***p* value**
mPAP (10 mmHg)	182	0.74 ± 1.82	0.687	0.53 ± 0.09	< 0.001
PCWP (mmHg)	182	0.24 ± 0.31	0.440	1.00 ± 0.03	0.863
RV systolic dysfunction	177	6.28 ± 5.15	0.225	0.31 ± 0.15	0.018
RV dilatation	175	5.05 ± 5.20	0.333	0.47 ± 0.21	0.087
Tricuspid regurgitation	179	19.2 ± 5.60	0.001	1.84 ± 0.82	0.175
Atrial fibrillation	182	16.0 ± 6.17	0.010	0.98 ± 0.53	0.965

Note: For each clinical factor, linear regression was performed against the percentage error between DF and TD, and logistic regression was performed against disagreement between DF and TD methodologies as to whether PVR was elevated (> 2 WU) or not. Definitions: Tricuspid regurgitation, moderate or greater severity. Atrial fibrillation, present during right heart catheterization.
Abbreviations: CO, cardiac output; DF, direct Fick; mmHg, millimeters of mercury; mPAP, mean pulmonary artery; *N*, number of patients; PCWP, pulmonary capillary wedge pressure; PE, percentage error; PVR, pulmonary vascular resistance; RV, right ventricular; SE, standard error; TD, thermodilution.

			Bolus Thermodilution							
			PVR ≤ 2			PVR > 2				
			No PH	UC-PH	Ipc-PH	No PH	Pc-PH	Cpc-PH		
Direct Fick	PVR ≤ 2	No PH	16	–	–	6	–	–	22	51
		UC-PH	–	3	–	–	7	–	29	
		Ipc-PH	–	–	11	–	–	8		
	PVR > 2	No PH	1	–	–	7	–	–	8	131
		Pc-PH	–	–	–	–	60	–	123	
		Cpc-PH	–	–	3	–	–	60		
			17	17		13	135			
			34			148				

FIGURE 2 | Hemodynamic classification discordance. Abbreviations: combined post- and pre-capillary pulmonary hypertension (Cpc-PH); isolated post-capillary pulmonary hypertension (Ipc-PH); pre-capillary pulmonary hypertension (Pc-PH); pulmonary hypertension (PH); pulmonary vascular resistance (PVR); unclassified pulmonary hypertension (UC-PH).

of CO in patients with TR and AF during RHC remains unknown.

4.2 | Clinical Implications

Many sources of error affecting CO measurement in clinical practice may be unrecognized at the time of RHC. The DF method using indirect calorimetry requires a well-fitted face mask with a tight seal and paired arterial and mixed venous blood gas measurements collected at a steady state [19, 28]. The TD method is dependent on injectate temperature, administration speed, and site of administration [5, 6]. Both methods depend on accurate equipment calibration and meticulous procedural protocols to minimize all modifiable sources of error. Simultaneous use of both DF and TD methods may assist in the recognition of erroneous measurements and prompt clinicians to consider whether patient and equipment factors may underlie any discrepancies. Although this may be impractical to perform in all cases, it is particularly relevant in patients with borderline measurements where inaccuracy may impact treatment eligibility [29].

When monitoring for disease progression or response to therapy, our data suggest that DF and TD methodologies should not be used

interchangeably for serial surveillance. For example, in patients with PH undergoing repeat RHC following initiation of pulmonary vasodilator therapy, switching from CO_{TD} to CO_{DF} may falsely reassure clinicians of an improvement in PVR, which may have important therapeutic implications. In this context, having both methods recorded at baseline would be useful, although the resource implications of using both techniques merit consideration.

As VO_2 estimation in the catheterization laboratory becomes increasingly accessible, the DF technique is likely to become more commonly utilized. All clinicians should, therefore, be aware of the potential pitfalls and comparative accuracy of invasive hemodynamic assessments, and all results need to be critically appraised in the appropriate clinical context. These data provide impetus to perform further prospective investigations to evaluate whether clinical outcomes are affected and to assess the impact of disagreement on invasive hemodynamic assessments of other conditions. Multicenter randomized trials should be considered comparing the two methods of CO assessment to assess which method better predicts response to specific therapies and, ultimately, whether hard clinical outcomes are affected.

4.3 | Limitations

Although the strengths of our study include its generalizability to routine clinical practice and its evaluation of potential clinical consequences of disagreement, several limitations are acknowledged. An observational, retrospective, single-center study is more prone to error than a prospective investigation, but our findings may be more generalizable to routine clinical practice. Our study only examined the agreement between DF and TD-derived CO measurements at rest in the supine position; therefore, the findings may not be applicable during exercise or in the semi-supine position [13]. Although other parameters measured during RHC can influence the calculated PVR, this study focused specifically on CO measurement. We did not evaluate the reproducibility of measured pulmonary artery pressure or pulmonary capillary wedge pressure beyond the standard of care outlined in the procedural protocol. Statistical power to identify all factors that were associated with disagreement between DF and TD methodologies may have been insufficient, and without a clinical gold standard, it is not possible to conclude whether one measurement technique is superior to the other.

4.4 | Conclusions

Disagreement was observed between DF and TD-derived CO, particularly in patients with TR and AF, leading to discrepant hemodynamic classification in approximately 12% of our cohort. The two techniques, therefore, should not be used interchangeably for serial surveillance, and without a clinical gold standard, there is a rationale for utilizing both methods simultaneously in certain clinical situations.

Author Contributions

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and the discussed interpretation.

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Ethics Statement

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.