



Systematic Review/Meta-analysis

Time to Calm the Fick Down? A Systematic Review and Meta-Analysis of Thermodilution Compared to Direct Fick in Tricuspid Regurgitation

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ABSTRACT

Background: Many clinicians consider thermodilution (TD) as a means to measure cardiac output (CO) to be unreliable in patients with tricuspid regurgitation (TR). No systematic appraisals of this clinical issue have been conducted. We hypothesized that the level of inac-

RÉSUMÉ

Contexte : De nombreux cliniciens considèrent que la thermodilution, lorsqu'elle est utilisée pour mesurer le débit cardiaque, n'est pas fiable chez les patients présentant une régurgitation tricuspide. Ce problème clinique n'a encore jamais été évalué de manière

Accurate measurement of cardiac output (CO) is essential in classifying disease states, such as pulmonary hypertension (PH) and heart failure (HF). Both the CO and cardiac index are particularly important for medication titration, informing decisions for mechanical circulatory support, and prioritizing listing status for cardiac transplantation.^{1,2} The gold standard for calculating CO is the direct Fick (DF) method, which is time-consuming and costly, and is not routinely available.¹

As a result, equations have been derived to estimate oxygen consumption (VO₂) to obtain a CO estimation using the indirect Fick (IF) method. Although the IF method is used commonly at bedside, IF calculations lack accuracy in subsets of patients who have a high body mass index, HF, or PH,³⁻⁶ as well as in acute illness states in which VO₂ may be dynamic. A commonly used IF equation excludes patients with a cardiac index of < 2.5 L/min/m².⁷ Thermodilution (TD) is a convenient alternative to both the DF and IF methods.

Although TD and IF method measurements have modest agreement, a low CO as measured by TD was a better predictor of mortality at 90 days and at 1 year in patients undergoing right heart catheterization at Veterans Affairs (VA) hospitals.⁵ However, studies comparing measurements made with the TD vs DF method have discordant results, with some showing a strong correlation between the 2⁸⁻¹⁰ and another reporting a > 25% difference in a third of patients.²

As tricuspid regurgitation (TR) theoretically impairs complete antegrade flow of the injectate, many clinicians consider TD to be unreliable in patients with this valvular condition. However, no systematic appraisals of the TD vs DF method have been made in patients with TR, despite decades of hemodynamic research and the wide implementation of TD. We hypothesized that the inaccuracy of TD measurements of CO in patients with TR is overstated, and accordingly, we conducted a systematic review and meta-analysis to address this issue.

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See page 1143 for disclosure information.

Methods

Data eligibility, sources, search, and study-selection approach

We searched MEDLINE, Embase, Web of Science, Scopus, the Cumulative Index to Nursing & Allied Health (CINAHL),

curacy of using TD in patients with TR, compared to the direct Fick (DF) method, to determine CO, is overstated.

Methods: We performed a systematic search of 6 major literature databases for the period from 1946 to July 2023. Studies were included if they included CO measurements determined with both TD and the DF method in patients with vs without TR. Meta-analysis of the correlation between the measurements determined by TD vs the DF method was performed, stratified by the presence of TR.

Results: A total of 1064 studies were identified, of which 8 met the inclusion criteria. Four of the studies were included in the pooled analysis. The presence of TR did not affect the correlation between CO measurements determined by TD vs the DF method (moderate-to-severe TR: $r = 0.90$, 95% confidence interval 0.76, 0.96; mild or no TR, $r = 0.86$, 95% confidence interval 0.71, 0.93). Many studies had high levels of heterogeneity and risk of bias.

Conclusions: The accuracy of CO measurements made using TD, compared to the gold-standard DF method, may not be meaningfully affected by the presence of moderate-to-severe TR. Given the high levels of heterogeneity and risk of bias of the included studies, these findings should be replicated in a modern cohort.

and the Cochrane Library databases for the time period from 1946 to July 21, 2023. Studies were included in the primary analyses if they compared CO as measured by TD with CO as measured by the DF method in adult patients with TR. Studies with comparator values, such as quantitative echocardiography, also were considered for possible sensitivity analysis. Cohort studies and randomized trials were eligible for inclusion, whereas conference abstracts were excluded due to their limited reporting of data and high risk-of-bias level. The search strategy was devised by an information specialist (M.P.H.) and is included in [Supplemental Appendix S1](#). The search strategy was preregistered in the National Institute for Health and Care Research International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42023447899). Title and abstract screening, full-text review, and extraction were all independently completed by 2 authors, with conflicts being resolved by a third. The data were managed using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines¹¹ for reporting this work.

Data items

We collected all data related to CO measurements and to comparisons between them (correlation, bias, limits of agreement, etc). CO data other than that from the TD and DF methods were included, such as echocardiographic measures

systématique. Nous avons formulé l'hypothèse voulant que le degré d'inexactitude associé à l'utilisation de la thermodilution pour déterminer le débit cardiaque chez les patients présentant une régurgitation tricuspидienne était surestimé, comparativement à la technique directe de Fick.

Méthodologie : Nous avons réalisé une recherche systématique couvrant la période de 1946 à juillet 2023 dans 6 grandes bases de données publiées. Les études étaient incluses si elles comprenaient des mesures du débit cardiaque réalisées par thermodilution et à l'aide de la technique directe de Fick chez des patients présentant et ne présentant pas une régurgitation tricuspидienne. Nous avons réalisé une méta-analyse de la corrélation entre les mesures réalisées par thermodilution et celles réalisées à l'aide de la technique directe de Fick, stratifiée selon la présence d'une régurgitation tricuspидienne.

Résultats : Au total, 1 064 études ont été identifiées, dont 8 qui répondaient aux critères d'inclusion. Quatre études ont été utilisées dans l'analyse combinée. La présence d'une régurgitation tricuspидienne n'a pas influencé la corrélation entre les mesures du débit cardiaque par thermodilution et à l'aide de la technique directe de Fick (régurgitation tricuspидienne modérée à sévère : $r = 0,90$; intervalle de confiance [IC] à 95 % : 0,76 à 0,96; régurgitation tricuspидienne légère ou absence de régurgitation tricuspидienne : $r = 0,86$; IC à 95 % : 0,71 à 0,93). De nombreuses études présentaient un niveau élevé d'hétérogénéité et un risque de biais.

Conclusions : La précision des mesures du débit cardiaque par thermodilution comparativement à la méthode par excellence, la technique directe de Fick, pourrait ne pas être influencée de manière significative par la présence d'une régurgitation tricuspидienne modérée à sévère. Compte tenu du niveau élevé d'hétérogénéité et du risque de biais des études incluses, ces résultats doivent être reproduits dans une cohorte moderne.

of CO, and the IF estimate. We also collected relevant information about the disease states of the included cohorts.

Risk-of-bias assessment

Two reviewers independently, in duplicate, assessed risk of bias, and applicability, using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool for quality assessment of diagnostic-accuracy studies.¹² Conflicts were resolved by a third reviewer.

Outcomes, data synthesis, and evidence certainty

The primary analysis was of the correlation of CO as measured by TD vs the DF method, stratified by the presence of moderate-to-severe TR, as defined in the included studies. Because between-study variation in outcome was expected, we used a random-effects model (DerSimonian–Laird inverse variance method). In studies in which a standard deviation was not reported, it was imputed as the mean of the standard deviations of the other included studies. Heterogeneity was quantified with the I^2 statistic, reflecting the percentage of total variability in outcome estimates that was due to between-study heterogeneity rather than chance.¹³ Given the small number of pooled studies, analysis for publication bias and certainty assessment were not performed. All analyses were performed using R statistical software (version 4.1.2) and the R metafor package (both R Project for Statistical Computing, Vienna, Austria).¹⁴

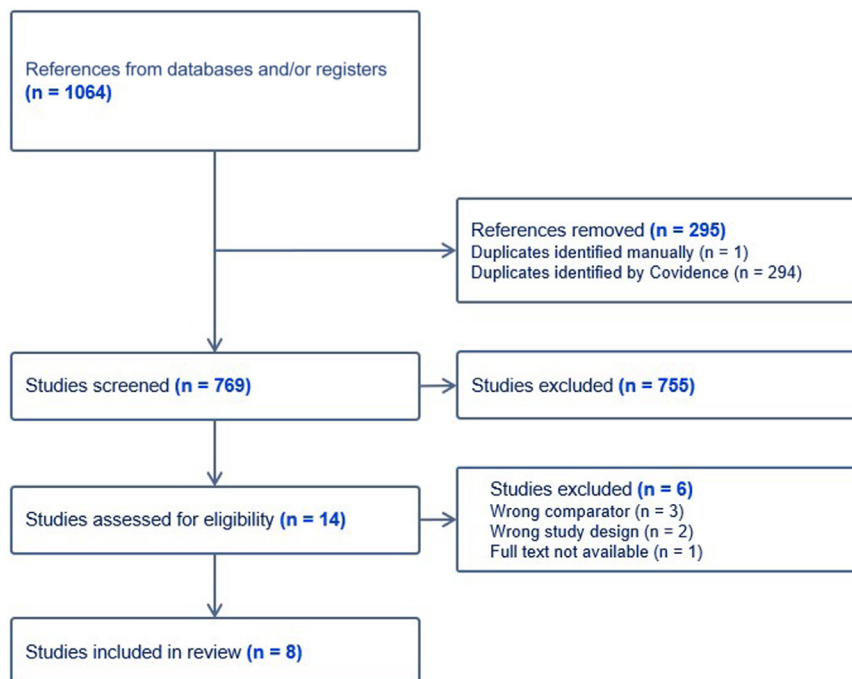


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram. Covidence is systematic review software (Veritas Health Innovation, Melbourne, Australia).

Results

Study selection and characteristics

Our search strategy identified 1064 references in the initial search, of which 14 were assessed using full-text review. Eight studies met the inclusion criteria, shown in [Figure 1](#) and [Table 1](#). Of the 8 studies included, all were conducted with observational cohorts (5 prospective and 3 retrospective). A total of 602 patients were included, 258 (42.9%) with TR. In 6 of the 8 studies, CO measurements made using TD were compared to measurements made using the DF method.¹⁵⁻²⁰ In 1 study, the TD CO measurement was compared to that from the acetylene rebreathing method as well as the DF method. Another study compared the TD CO measurement to the transesophageal echo CO measurement.²¹ Patient populations varied across studies, from those with PH to HF and shock states. Patient settings also varied from outpatients to critically ill, mechanically ventilated patients.

Risk of bias

The QUADAS-2 tool was used to assess the risk of bias in patient selection, index test, reference standard, and flow timing ([Supplemental Table S1](#)). Overall, the risk of bias across included studies was highest in the conduct and interpretation of the index test, TD CO. A summary of bias across studies in aggregate is reported in [Figure 2](#). Overall, the rate of bias was higher in the older studies (publication year earlier than 1999).

Outcomes

Two studies were excluded from direct comparison of the CO, as measured by TD vs the DF method, as they did not

report TR subgroup data to allow such analysis.^{9,17} As a result, a total of 4 studies were included in the pooled analysis. The presence of TR did not affect the correlation between the CO measurements made using TD vs the DF method (moderate-to-severe TR: $r = 0.90$, 95% confidence interval 0.76, 0.96; mild or no TR: $r = 0.86$, 95% confidence interval 0.71, 0.93; [Fig. 3](#)). Across studies, the level of heterogeneity was high ($I^2 = 71%$ and 68% for with vs without TR, respectively). Two studies found that the TD method significantly underestimated the CO in patients with severe TR, compared to that measured with the DF²⁰ and transesophageal echo²¹ methods.

Discussion

The findings of this systematic review and meta-analysis do not support the common contention that presence of TR invalidates the accuracy of CO measurement using TD, compared to that obtained with the gold-standard DF method. The 2 most recent studies, which also had the highest number of patients with TR, did not demonstrate a significant difference between the measurements from TD vs the DF method, and overall, these studies had a much lower risk of bias.^{15,16} Overall, the included studies spanned a wide range of publication dates, with heterogeneous patient populations and results.

To our knowledge, this systematic review is the first to evaluate this issue. Many of the included studies suffered from having moderate-to-high levels of bias and enrolling small numbers of patients. Due to limitations in reporting, making bias and agreement calculations was not possible. Two studies included a small sample with TR, making interpretation of the results difficult. One included only 4 of 18 patients with TR,¹⁷ and another included 5 of 30 patients with moderate-to-severe TR.²⁰ One of the studies with a high risk of bias did

Table 1. Study characteristics

Study	Design	Total participants (with TR), n	Population	Comparator	TR classification	CO, as measured by TD (with TR), L/min	Comparator CO (with TR), L/min	Author conclusions
Desole et al. ¹⁵ (2022)	RC	300 (112)	Arterial hypertension, A-fib, CAD, DM, COPD, and chronic thromboembolic disease; between 2005 and 2020	DF	Absent (0) Mild (+1) Moderate (+2) Severe (+3)	Mean: 5.18 Median: 5.03	Direct Fick method Mean: 5.48 Median: 5.29 Indirect Fick method Mean: 4.38 Median: 4.32	TR did not influence performance of TD, compared to the DF method in low-intensity and submaximal exercise. TD performed well for low CO (< 3 L/min) but may underestimate high CO (> 11 L/min).
Khirfan et al. ¹⁶ (2019)	PC	75 (48)	Patients with idiopathic or heritable PAH or moderate to severe right ventricular dysfunction; between 2012 and 2018	DF	Absent (0) Mild (+1) Moderate (+2) Moderate/severe (+3) Severe (+4)	Mean: 2.57	Direct Fick method Mean: 2.59 Indirect Fick method Dehmer: 2.56 Bergstra: 2.83 LaFarge and Miettinen: 2.17	Severity of TR had no influence on the accuracy or difference between TD and the DF method. The DF method remains more precise and should be used when TD cardiac index is < 2.5, or if clinical discordance is present.
Gonzalez et al. ¹⁷ (2003)	PC	18 (4)	Critically ill mechanically ventilated patients with PA catheter, septic, cardiogenic, hemorrhagic shock, and ARDS	DF	Unspecified	No subgroup of TR: 5.8	No subgroup of TR: 5.2	Although TR was rare in the patient series, it did not have a major impact on agreement between TD and DF method measurements.
Balik et al. ²¹ (2002)	PC	27 (19)	Mechanically ventilated patients with left, right, and diastolic HF	TEE	1st-degree (1.5 cm regurgitant into the right atrium) 2nd-degree (1.5-3.0 cm regurgitant into the right atrium) 3rd-degree (> 3.0 cm regurgitant into the right atrium)	1st-degree: 6.5 2nd-degree: 6.7 3rd-degree: 4.2	TEE 1st-degree: 6.61 2nd-degree: 6.7 3rd-degree TR: 6.1	In patients with 1st- and 2nd-degree TR, a significant correlation is present between TD and TEE CO. TD significantly underestimated CO, compared to TEE, in patients with 3rd-degree TR.
Hoepfer et al. ⁹ (1999)	PC	35 (11)	Patients with PH and recurrent thromboembolism	Acetylene rebreathing and DF	Absent (0) Mild (+1) Moderate (+2) Severe (+3)	Mean: 3.7	Mean: 3.7	TD and the DF methods did not differ significantly in patients with all TR severities for both low (< 3 L/min) and normal (> 3 L/min) CO.
Konishi et al. ¹⁸ (1992)	RC	92 (22)	DF	DF	Absent Mild Moderate Severe	Percent difference (SD): Mild: -7.5 ± 2 Moderate: -1.7 ± 1.2 Severe: 5.7 ± 0.6	Mild: 4.61 Moderate: 3.84 Severe: 3.03	The correlation between TD and the DF method in the moderate and severe group is stronger than that in the mild or no TR group.

Continued

Table 1. Continued.

Study	Design	Total participants (with TR), n	Population	Comparator	TR classification	CO, as measured by TD (with TR), L/min	Comparator CO (with TR), L/min	Author conclusions
Hamilton et al. ¹⁹ (1989)	PC	25 (25)	Patients with CHF before and after acute vasodilator and diuretic therapy	DF	Absent (0) Mild (+1) Moderate (+2) Severe (+3)	Moderate-to-severe TR Mean: 3.0		No significant difference between TD and the DF method in patients with severe HFrEF, regardless of the severity of TR.
Cigarroa et al. ²⁰ (1989)	RC	30 (17)	Patients with CAD, HF, cardiomyopathy, and valvular disease; between 1986 and 1988	DF	Mild (+2) Moderate (+3) Severe (+4)	Mean: 4.22	Mean: 4.99	TD and DF method measurements were similar in patients without TR. TD measurements were significantly lower than DF method measurements in patients with TR, although the small numbers of 3+ and 4+ did not allow for meaningful analysis.

ARDS, acute respiratory distress syndrome; A-fib, atrial fibrillation; CO, cardiac output; CHF, congestive heart failure; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DF, direct Fick; DM, diabetes mellitus; HF, heart failure; HFrEF, HF with reduced ejection fraction; PA, pulmonary artery; PC, prospective cohort; PPH, primary pulmonary hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; RC, retrospective cohort; SD, standard deviation; TD, thermodilution; TEE, transesophageal echocardiography; TR, tricuspid regurgitation.

not include the grading or severity of TR in the included patients.¹⁷

Because of its cost, limited portability, and difficulty in use, the DF method of CO measurement is not routinely available in all centres, and in many patient populations, it cannot be used, such as those who require a high level of supplemental oxygen, or have difficulty with mask fit, etc. Furthermore, many assumptions of the Fick principle have dubious

applicability to patients who are critically ill. The VO₂ in critically ill patients is driven by the metabolic rate, which is augmented by sympathetic tone.²² Many treatments often titrated by the care team, such as vasopressors and sedatives, manipulate the sympathetic tone and make VO₂ dynamic—violating the steady-state assumption of the Fick equation.²³ Consequently, the value obtained from the DF method is valid for only a set level of sympathetic tone. Repeating CO

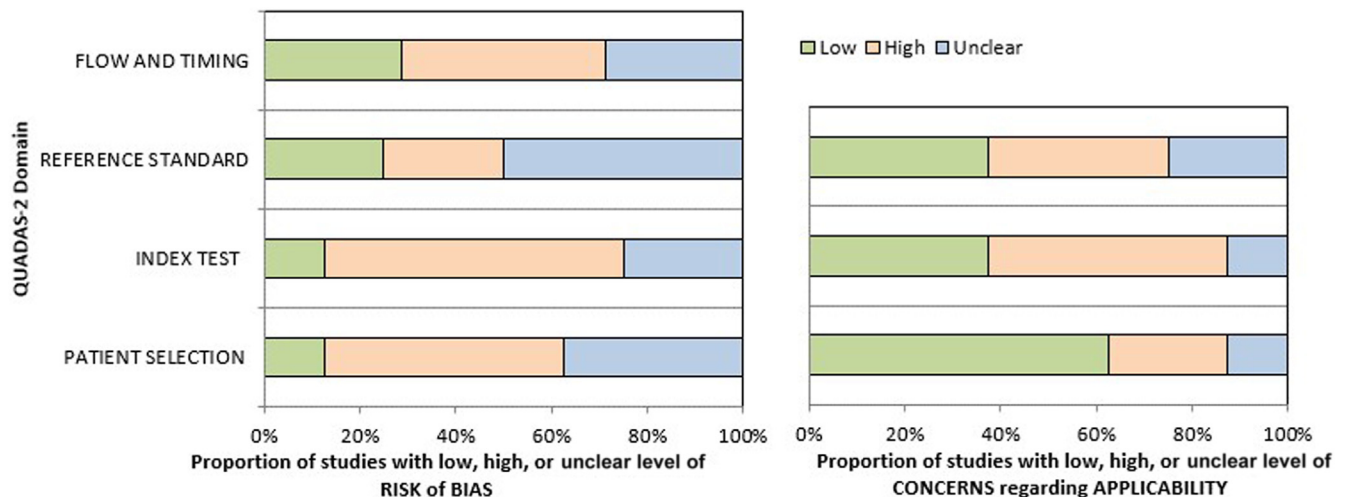


Figure 2. Risk of bias and applicability summary. QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies 2 tool.

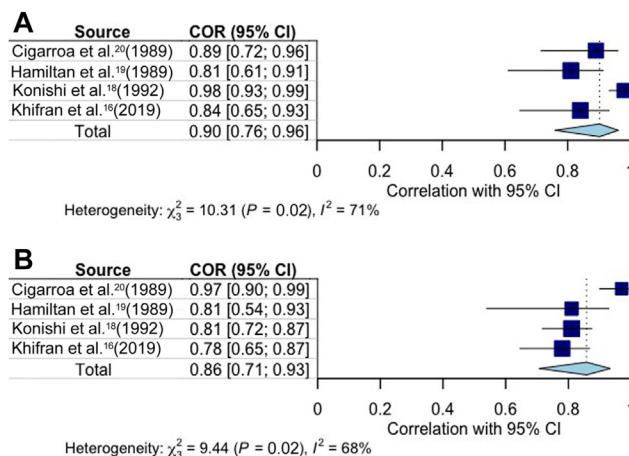


Figure 3. Pooled analysis with vs without tricuspid regurgitation (TR). (A) Patients with moderate-to-severe TR (B) Patients with mild or no TR. CI, confidence interval; COR, correlation.

measurements using the DF method is often impractical. In comparison, the TD method of CO measurement can be easily repeated, affording both precision and accuracy.

An additional assumption of the Fick equation is the absence of intracardiac shunt, as the presence of shunt would require venous sampling from the superior and inferior vena cava, rather than the pulmonary artery. Unsurprisingly, presence of shunt is a common finding in the critically ill. For example, moderate-to-large shunts may be present in 19.2% of patients with acute respiratory distress syndrome.²⁴ Depending on the directionality and severity of the shunt, the denominator of the IF equation (oxygen content of arterial blood – oxygen content of mixed venous blood [oxygen content of arterial blood – oxygen content of venous blood]) is impacted, potentially leading to erroneous estimates of CO. Further research is needed to determine when the DF method of CO measurement should be pursued rather than the TD method.

This study has limitations. We performed an exhaustive literature search, although possibly, not all eligible studies were captured. Furthermore, the older studies suffered from a higher rate of incomplete or inconsistent reporting of methods and results, which makes interpretation of those findings more difficult. Grading of TR severity also was not uniform across the included studies, and the criteria used for TR grading have changed over time.²⁵ Future investigations evaluating the accuracy of CO measurement methods, by the presence vs absence of TR, should be performed using rigorous reporting of methods to decrease the bias observed in this study.

Historical concerns regarding TD inaccuracy in TR may be overstated, as the *effective* forward flow may be estimated properly by the TD technique, vs the DF method. In acutely ill patients, greater scrutiny should be employed in the use of IF methods, given that many of the necessary assumptions are not met. As in all diagnostic decision-making, no single value should be regarded as representing “the truth,” and an integrated hemodynamic and clinical assessment is necessary.

Conclusion

The accuracy of CO measurement using TD, compared to that made with the gold-standard DF method, may not be meaningfully affected by the presence of moderate-to-severe

TR. Given the high level of heterogeneity and risk of bias of the included studies, these findings should be replicated in a modern cohort.

Ethics Statement

The authors confirm that Ethics board approval is not applicable to this article.

Patient Consent

The authors confirm that patient consent is not applicable to this article, as it is a systematic review of prior published studies.

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Disclosures

A.R.T. reports participating in advisory boards for Janssen and Merck. All the other authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjcopen.ca/> and at <https://doi.org/10.1016/j.cjco.2024.05.008>.