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Cardiac Output Assessment in Patients Supported with Left Ventricular Assist Device: Discordance between Thermodilution and Indirect Fick Cardiac Output Measurements

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Abstract

Cardiac output (CO) assessed by thermodilution (TD) and indirect Fick (iFK) methods is commonly employed in Left Ventricular Assist Devices (LVAD) patients, however no study has assessed agreement. This study assess correlation between these methods, and association with hemodynamic/echocardiographic data in LVAD patients. Discordance was defined as a 20% difference between TD and iFK CO measurements. Bias and agreement were determined via the Bland-Altman technique in both the overall sample and iFK stratified tertiles. Correlation with each assessment of CO and Right Heart Cath (RHC) hemodynamics was performed. Among 111 RHCs, the mean CO for TD and iFK were 4.65 ± 1.33 (Range: 1.44–9.30) and 5.37 ± 1.51 (Range 3.07–11.80) L/min respectively ($P < 0.001$) with a calculated discordance of 45.9%. correlation coefficient of 0.66 with a bias of -0.72 L/min was found. The lower and upper limit of precision were -3.12 and 1.68 L/min respectively. By tertile analysis, bias (lower and upper limit of precision) for the low, middle and high tertile groups were -0.24 (-1.88 and 1.40), -0.48 (-2.50 and 1.53) and -1.39 (-4.18 and 1.39) L/min respectively. No significant correlation was found between either method with right atrial pressure or pulmonary capillary wedge pressure or any valvular condition. Substantial discrepancies exist between TD and iFK CO in LVAD patients. Although fixed bias was small, the limits of agreement extend into the clinically relevant area, with larger bias being present at higher CO. Studies with flow probes are needed to define which method better represents CO in LVAD patients.

Keywords

LVAD; Cardiac Output; Indirect Fick; Thermodilution

Introduction

Heart failure (HF) is endemic in the United States with more than 5.7 million American older than the age of 20 affected with an estimated 915,000 new cases annually.¹ Continuous

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Conflicts of Interest

All other authors have no conflict of interests

Flow Left Ventricular Assist Devices (CF-LVADs) have become a common treatment option for patients with advanced HF both as a bridge to transplantation or as destination therapy. Evaluation of HF patient's includes invasive hemodynamics to assess both filling pressure and cardiac output (CO). number of studies have compared the thermodilution (TD) cardiac output (CO) to the indirect Fick (iFK) CO, with some reporting a percentage error between 56 and 83%.^{2,3} Nonetheless, these two methods of obtaining cardiac output have been validated independently but largely in non-critically ill patients where correlation and agreement have not been shown.⁴⁻⁶ Invasive hemodynamics assessment in general and CO in specific are particularly important in LVAD patients in which device speed optimization may be dependent on those measurements.^{7,8} To our knowledge no other study has compared TD and iFK CO in LVAD patients. The objective in this study was to assess the agreement, precision, and bias of these two methods of CO determination in a robust population of patients supported by LVAD at a large LVAD center.

Material and Methods

A retrospective chart review of all LVAD patients (both inpatient and outpatient) who underwent a right heart catheterization (RHC) during August 2009 to November 2015 was conducted. Patients who were on inotropic support at the time of RHC were excluded. Additionally, those without either a recorded TD or iFK were excluded. Data from the most recent RHC after LVAD implantation was included. Thermodilution cardiac output were obtained by the injection of 10 mL of chilled 0.9% sodium chloride in water in less than 8 second at end-expiration by operators. Fick Cardiac output were obtained by the following equation: $[125 \text{ ml O}_2/\text{BSA} * \text{Body surface area}]/[13.6 * \text{Hemoglobin (g/L)} * (\text{oxygen saturation} - \text{mixed venous saturation})]$.

Correlation was determined via linear regression analysis between measurements of TD and iFK CO. Further stratification were made based on iFK stratified by CO tertiles. Discordance was defined as a 20% difference between TD and iFK CO measurements. Agreement was determined via the Bland and Altman technique,⁹ with bias (defined as mean difference between the means) and precision calculated with appropriate 95% confidence intervals (CI). Additional linear regression models were used to correlate each method with right atrial (RA) pressure and pulmonary capillary wedge pressure (PCWP) for the sample, as well as iFK stratified by CO tertiles.

To assess the effect of echocardiographic valvular regurgitation on discordance between TD and iFK CO measurements, chi-squared analysis was used to evaluate the effects of significant tricuspid, mitral, and aortic regurgitation on CO discordance. Significant regurgitation was classified in two manners: either mild/moderate/severe or moderate/severe. Further, a discordance threshold of both 15% and 20% were used for the above analysis.

Results

Among 111 unique subjects with either a continuous flow axial or centrifugal devices, 111 consecutive RHC were identified with TD and iFK CO measurements and baseline characteristics as described in Table 1. In brief, 81.1% of patients were male with a mean

age of 56.5 ± 11.5 years. Of the patients included in the study 62.2% received LVAD as Destination Therapy with 36.0% of patient having a diagnosis of ischemic cardiomyopathy as the indication for implantation. Axial flow LVADs were present in 73.0% of patients, while all others had a centrifugal flow pump. Mean CO for TD was 4.65 ± 1.33 (Range: 1.44–9.30) L/min. Mean CO for iFK was 5.37 ± 1.51 (Range 3.07–11.80) L/min. A clear, but moderate correlation (coefficient of 0.66) was noted (Figure 1), similar results were noted with tertile stratified results. A calculated discordance between TD and iFK of 45.9% was calculated using a 20% threshold of discordance. When limited to just those patients with Heart Mate 2 devices, a similar correlation coefficient of 0.64 was noted as compared to the total sample. Further, a similar calculated discordance between TD and iFK of 39.2% was calculated using a 20% threshold of discordance as compared to the total sample.

In the overall sample, when comparing TD vs iFK a fixed bias of -0.72 L/min (95% CI: -0.95 to -0.49) with upper and lower limits of 1.68 (95% CI: 1.28 to 2.07) and -3.12 (95% CI: -3.52 to -2.73) L/min respectively was found (Figure 2). In tertile stratified analysis, mean bias (95% CI) for those with iFK CO 4.40 , 4.42 – 5.60 , and 5.63 were -0.24 (-1.88 to 1.40), -0.48 (-2.49 to 1.53), and -1.39 (-4.18 to 1.39) L/min respectively. Mean percent difference between iFK and TD for the lowest, middle, and upper iFK tertiles were 5.7%, 8.4%, and 16.8% respectively.

No association was seen with either CO method and RA pressure or PCWP in the entire sample or tertile specific analysis (Figure 3). Furthermore, no significant association was noted between discordance between cardiac output methods and the levels of regurgitation at either the tricuspid, mitral or aortic valve (Table 2). These results persisted despite limiting analysis to just those with moderate/severe disease at each valve position, and when the threshold level of significance was set to 15%.

Discussion

In the current study we compared cardiac output assessments by both iFK and TD in CF-LVAD patients. Our main findings are as follow: (1) Clinically relevant discrepancy in CO measurements for the two methods commonly employed was found. (2) The level of discordance between the methods was higher in patients with higher CO. (3) No correlations between CO and filling pressure were observed in LVAD patients, regardless of the CO method that was used (iFK or TD). (4) No correlation between the level of discordance and the presence of valvular abnormalities was noted regardless of the CO method used (iFK or TD).

Evaluation of hemodynamics in HF patients, specifically in those supported by CF-LVAD, is crucial for patient management. The assessment of filling pressure (RA, PAP, PCWP) is identically measured at the end of expiration. However, the reliability of CO derived from iFK or TD becomes important as the level of agreement in patients may vary. In this study we report a clinically relevant discrepancy in CO measurements between iFK CO vs TD CO. While only a moderate bias (-0.72 L/min) was noted between these two methods in the overall sample, the 95% confidence interval did not encompass the zero point. Furthermore,

the precision of the upper and lower limits of agreement of the sample was large, clearly showing the two methods for CO determination do not agree. In LVAD patients, these two methodologies are not interchangeable. This is particularly important given that no clear relationship was present between either method and hemodynamic parameters. Although a clear correlation was present between the two methods, it is important to recognize that this correlation is likely weakened as true CO increases, given that the mean bias was highest in those with the highest CO.

It remains unclear the reasoning for the large discrepancy between iFK and TD CO, and which method is superior. In prior studies of non-LVAD patients, it has been noted that thermodilution yields consistently lower CO measurements than that of the iFK method for individuals with tricuspid regurgitation.¹⁰ However, our results show that the discrepancy in the results is unlikely to be due to valvular disease. Cardiac output is not measured directly in either method, and each method has distinct sources of error. Prior studies that have also noted similar discrepancies in non-LVAD patients for calculating CO by focusing largely on operator dependent variation for calculating TD and individual patient characteristics in the measurement of oxygen consumption by iFK.¹¹ However, it may be possible that in patients with LVADs one method is just intrinsically more accurate.

TD CO measurement is widely used despite the common concern the TD overestimates CO in the setting of heat loss with low flow conditions.^{5,12} However, given the ability of LVADs to augment CO, it could be assumed that this weakness would be less relevant in this population. Nonetheless, LVADs are also likely to complicate TD CO calculations by cyclic flow patterns, similar to what one may see in mechanical ventilation.¹³ Recently, our group reported iFK in patients supported with HeartAssist 5 (Reliant Heart, ReliantHeart Inc., Houston, Texas, USA strongly correlated flow reported by the optic flow probe on top of the outflow cannula, especially after closure of the aortic valve.¹⁴ These results support the reliability of the iFK method in patients supported with this specific type of axial flow pump.

Given the discrepancy between iFK and TD CO, it is possible that measuring oxygen consumption by calorimetry as opposed to indirect calculation via derived estimations may be more accurate. This has been shown in patients with heart failure with reduced ejection fraction,¹⁵ and likely extends to those with LVADs in place. This may be particularly true when measuring LVAD patients set at high CO. Prior studies have validated calorimetry in high-output states like sepsis,^{16,17} where indirect Fick CO may be incorrect given discrepancies in oxygen content and pronounced decrease in myocardial oxygen consumption at high output speeds. Further, it is likely that CF-LVAD produces to some extent an arteriovenous shunt physiology, specifically that of intestinal shunting, which is not dissimilar to the physiology of sepsis.¹⁸ Given that prior studies have shown that estimates of oxygen consumption based on standard equations are poor substitutes for metabolic measurements of oxygen consumption in critically ill patients with sepsis it may be reasonable to extrapolate this to patients with CF-LVAD.¹⁹ Measurement of direct oxygen consumption often encounters resistance given the time-intensity involved, especially when calculating CO at each step in during a ramp test.

Interchangeability of iFK, TD and others non-invasive methods like direct FK for CO assessment in LVAD patients still require further validation in specific clinical scenarios. Although not addressed in this single center retrospective data analysis, it is possible that iFK and TD have better agreement in particular patient populations, such as those without critical illness. Furthermore, it is possible that differing LVAD types (axial vs. centrifugal devices, intra-abdominal vs. pericardial devices) may also influence the agreement between CO methodology. These factors are particularly difficult to assess as there is currently no gold standard for which CO should be measured. Nevertheless, the current study emphasizes the discordance between the tests, but does not confirm which method is superior.

In conclusion, it is clear that iFK and intermittent TD methods were not precise enough to agree over a wide range of cardiac outputs, particularly those with higher cardiac output values. While it is unclear what methodology is most accurate, other forms of CO evaluation such as direct FK, non-invasive methods with inert gas rebreathing, or use of optic flow probes when possible may also provide additional comparisons to evaluate the best balance for an accurate, precise, and timely method to assess CO. Given prior concerns for TD measurement inaccuracy in low flow states and our prior working showing good correlation between iFK CO measurements with the flow probe of the Heart Assist 5, we recommend the use of the iFK method over TD method for measurements of CO in patients with LVADs. Further studies, using one of the above direct techniques is needed to reconcile this question in not only all-comers with LVADs, but also those with specific clinical presentations such as moderate to severe right heart failure.

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Figure 1. Scatterplot of paired cardiac outputs using thermodilution and indirect Fick with the dotted line representing linear regression.

Figure 2.

Representation of agreement between thermodilution (TD) and indirect Fick (iFK) cardiac output methods. Bias represents the mean difference between TD and iFK and is further defined by the limits of agreement.

Figure 3A

Figure 3B

Figure 3C

Figure 3D

Figure 3.

Association of Cardiac Hemodynamics with both thermodilution and indirect Fick cardiac output methods.

Table 1

Characteristics of Study Subjects with Left Ventricular Assist Devices

Characteristic	Mean $\pm$ SD or N (%)
Male	90 (81.1)
Age (years)	56.5 (11.5)
Height (inches)	68.5 (3.8)
Weight (pounds)	200.1 (48.9)
Ischemic Cardiomyopathy	40 (36.0)
LVAD as Destination Therapy	69 (62.2)
Axial Flow LVAD	81 (73.0%)
Tricuspid Regurgitation (N=101)	
No significant	15 (14.9)
Trace	31 (30.7)
Mild	29 (28.7)
Moderate	19 (18.8)
Severe	7 (6.9)
Mitral Regurgitation (N=101)	
No significant	34 (33.7)
Trace	22 (21.8)
Mild	27 (26.7)
Moderate	16 (15.8)
Severe	2 (2.0)
Aortic Regurgitation (N=102)	
No significant	38 (27.5)
Trace	25 (24.4)
Mild	27 (26.4)
Moderate	10 (9.8)
Severe	2 (1.9)
Thermodilution CO (Liters/minute)	4.65 (1.33)
Indirect Fick CO (Liters/minute)	5.37 (1.51)

Notes. LVAD, Left Ventricular Assist Device; CO, Cardiac Output

Table 2

Valvular Regurgitation Relation to iFK vs TD CO Discordance

	Concordant N (%)	Discordant N (%)	P-Value
Total	48 (100)	53 (100)	
TR	29 (54.7)	26 (54.2)	
Without TR	24 (45.3)	22 (45.8)	
			1.00
MR	21 (43.7)	24 (45.3)	
Without MR	27 (56.3)	29 (55.7)	
			1.00
AR	18 (37.5)	24 (45.3)	
Without AR	30 (62.5)	29 (54.7)	
			0.54

Notes. Discordance is defined as a 20% difference between iFK and TD CO. Regurgitation was defined as having mild, moderate or severe regurgitation on a recent transthoracic echocardiogram at a unchanged speed from the time of cardiac output calculation from respective right heart cathetherizations.

iFK, indirect Fick; TD, Thermodilution; CO, Cardiac Output; TR, Tricuspid Valve Regurgitation; MR, Mitral Valve Regurgitation; AR, Aortic Valve Regurgitation.