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Non-invasive cardiac output monitoring (NICOM) in adult congenital heart disease patients with Fontan palliation☆

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ABSTRACT

Rationale: Fontan palliation for single ventricle malformations is an increasingly common reason for heart failure in the adult population. Cardiac output (CO) measurement in Fontan physiology is achieved by invasive cardiac catheterization (RHC). Noninvasive CO monitors using thoracic bioreactance (NICOM) have been validated in non-congenital patients but have not been studied in adult Fontan patients.
Objective: To compare RHC obtained values of CO using the Fick equation with those measured simultaneously by NICOM in a cohort of adults with Fontan palliation.
Methods and results: In nineteen patients undergoing routine outpatient RHC, we compared CO values as determined by Fick with those generated by the Starling SV NICOM device. Bland-Altman plots and intraclass correlation coefficients (ICCs) revealed internal consistency within NICOM measurements, however the agreement between RHC and NICOM for CO was poor (ICCs ~ 0.40). We performed sub-analyses using two-sample T-tests and ICCs to determine if clinical cyanosis, acute desaturation, or Fontan pressure affected the difference observed between RHC and NICOM. Neither chronic hypoxia, acute desaturation, nor Fontan pressure measures were found to be associated with the observed difference between the RHC and NICOM measured CO.
Discussion and conclusion: Our study did not find a correlation between RHC and NICOM derived measures of CO in a cohort of Fontan patients, even in sub-analyses of confounders of Fontan physiology. We observed internal consistency within the device, which may open a role for monitoring of trends rather than absolute values in Fontan patients. Our study was limited due to small sample size.

1. Introduction

Adult congenital heart disease (ACHD) is a significant, increasingly common, and poorly understood cause of heart failure [1]. Most children born with single ventricle physiology undergo Fontan palliative surgery, an effective method for improving pulmonary blood flow in the absence of a subpulmonary ventricle [2]. Fontan physiology is unique in that pulmonary blood flow and systemic blood flow are connected in series, rather than in parallel. The single ventricle provides systemic cardiac output (CO), and pulmonary blood flow is a passive process, impacted solely by pulmonary vascular resistance and ventricular diastolic function, without the aid of a pumping chamber. The long-term consequences following surgery include Fontan circulatory failure with heart failure symptoms, thrombosis, arrhythmias, and chronic venous insufficiency with end-organ damage, including renal disease and congestive hepatopathy [1]. Over time, these changes result in significant morbidity and mortality as these children grow into adults.

Accurate assessment of CO is essential to caring for complex ACHD patients in the ICU. The gold standard for measurement of CO is right heart catheterization (RHC). In single ventricle ACHD patients, the Fick equation rather than thermodilution method is used [3], given a preponderance of intracardiac shunts and significant atrioventricular valve regurgitation in this population, rendering thermodilution too inaccurate to be of use. There are several barriers to RHC for Fontan patients, particularly the relatively small number of physicians who are adequately trained in ACHD to perform the procedure and interpret the

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data. Other methods for measuring or at least estimating CO include echocardiography, cardiopulmonary exercise testing [4]; nuclear imaging, cardiac CT, and magnetic resonance imaging [5]. Each of these noninvasive methods have drawbacks, with only modest correlation with invasive CO determination [3], and an inability to provide real-time, minute-to-minute CO monitoring that would be useful for an unstable patient.

For adults with heart failure due to acquired heart disease, the use of non-invasive CO monitoring (NICOM) to assist in monitoring and management of fluid status and response to heart failure therapy is promising [6,7]. It is now used in many adult ICUs to assist in circulatory failure and fluid management. The Starling SV device by Cheetah Medical (Boston, Massachusetts) is FDA-approved in adults and measures thoracic bioreactance to calculate CO. It has been previously tested in a multicenter evaluation comparing NICOM to bedside thermodilution via pulmonary artery RHC as well as Fick-calculated CO by RHC [8]. The aim of this study is to determine if NICOM measurements would accurately assess CO in Fontan patients by comparing NICOM-derived measurements during hemodynamic RHC with Fick CO, to assess if there is a statistically significant correlation in CO with each method during identical loading conditions.

2. Materials and methods

2.1. Study design and participant selection

This was a prospective observational study conducted at Riley Hospital for Children at Indiana University Health with Institutional Review Board approval. Participants were selected based on a convenience sample of patients ≥18 years who had undergone Fontan-palliation as a child, were followed in the IU Health ACHD Program, and were referred to the Cardiac Catheterization lab at Riley Hospital for Children for clinical reasons, as determined by each patient's primary ACHD physician. Catheterizations were performed only by pediatric or ACHD interventionalists to ensure accurate hemodynamic evaluation of all subjects. Exclusion criteria included age <18 years, incomplete Fontan (Hemi-Fontan or Bidirectional Cavopulmonary anastomosis), non-English speaking, developmental delay, inability to provide consent, prisoner or ward of the State, and pregnancy. Once enrolled, subjects were connected to a NICOM device (Starling SV, Cheetah Medical, Boston, MA, USA) per device recommendations, prior to initiating the cardiac catheterization procedure. Data collection was completed by a dedicated research nurse. Data from both NICOM device and measurements from RHC were collected simultaneously so that CO derived by both methods would be under identical anesthesia and loading conditions, in order to minimize confounding variables. Per standard protocol in cardiac catheterization, oxygen saturation and pressure measurements were obtained when the participant was believed to be in a steady state condition, to provide a homeostatic representative calculation of cardiac output.

As the NICOM device reports continuous data, we elected to select specific time points during the RHC to collect data from the Starling SV device. Data was obtained from the Starling SV device readout at the following four discrete time points during RHC: T0, prior to anesthetic induction; T1 following anesthesia but prior to invasive measurements; T2, following invasive measurements but prior to any interventions; and T3, at completion of procedure, including any interventions, but prior to waking from anesthesia.

2.2. NICOM device and thoracic bioreactance

The Starling SV NICOM device relies on thoracic bioreactance technology [9] for its measurements. Thoracic bioreactance is a technique of analyzing the frequency spectra variation from a delivered oscillating current through the thoracic cavity. The oscillating current emitted and received by the NICOM device causes a dynamic change in volume within the aorta, which can be calculated by measuring a phase shift caused by the current between the applied alternating electrical current emitter and the thoracic voltage measured by the receiving electrodes. The measured phase shift determines the aortic flow (dP/dT) as well as the ventricular ejection time (VET) to calculate stroke volume (SV) by the equation SV = dP/dT x VET. Once SV is calculated, the machine determines CO as SV x HR (bpm).

2.3. Variables collected

Data collection included demographics, cardiac diagnosis at birth, concomitant valvular diseases, Fontan-related complications, and indication for cardiac catheterization. Reasons for catheterization were identified as valvular regurgitation or stenosis, cyanosis, Fontan-associated lymphatic disease such as protein-losing enteropathy or plastic bronchitis, congestive hepatopathy, and/or chronic kidney disease, as obtained from chart reviews and most recent cardiology office notes. Hemodynamic data was collected according to routine clinical catheterization protocol with CO determined by Fick equation. Systemic arterial saturation for Fick equation was determined via arterial blood gas measurement. An estimated VO_2 for each patient was obtained from normative tables [10]. Sedation was used at the discretion of the anesthesia team, and all patients were on room air throughout the procedure. It is expected to have hemodynamic changes with anesthesia/sedation. Due to concerns that the Fontan venous pressure or chronic hypoxia might alter the NICOM analysis, arterial blood gas information was also reviewed.

We considered the possibility that persistent hypoxemia or high Fontan venous pathway pressure, both of which are common in Fontan physiology, may affect our device measurements. Persistent hypoxemia indicates a concern for increased shunting across a Fontan fenestration, pulmonary vascular disease, diminished cardiac function, or the presence of significant veno-venous collateral vessels. It is unclear if these disease states, or even high Fontan venous pressure alone, may interfere with thoracic bioreactance. Therefore, we decided to conduct sub-analyses accounting for Fontan pressure and hypoxemia. Fontan pressure was directly measured during cardiac catheterization, and hypoxemia was defined as either a clinical diagnosis as reason for referral for RHC, or as directly measured SpO2 at the time of catheterization.

2.4. Statistical analyses

To establish internal reliability within the Starling SV device recordings, Bland-Altman plots and intraclass correlation coefficients (ICCs) were used to evaluate the agreement between the NICOM measurements for each pair of time points (T0, T1, T2, T3). To compare the device to RHC calculations, Bland-Altman plots and ICCs were used to evaluate the agreement between the Fick-derived cardiac output and the NICOM measurements at each time point (T0, T1, T2, T3). Two-sample t-tests were used to determine if desaturation as reason for catheterization was associated with the difference between the RHC results and NICOM measurements. Correlation coefficients were used to determine if oxygen saturation (SpO2) or Fontan pressure were associated with the difference between RHC results and NICOM.

3. Results

Nineteen (19) Fontan-palliated patients were identified based on the feasibility of study completion within one year from initial recruitment, as well as contemporary patient volume and visit data. Demographics data is presented in Table 1. RHC data is presented in Table 2 and hemodynamic data from NICOM is presented in Table 3. Table 2 shows our sample population had a mean saturation of 91.5% (range 81–97%), and a mean Fontan pressure of 14.3 mmHg (range 7–22 mmHg). In our experience, these numbers are generally representative of the adult Fontan population. As mentioned above, T0 represents data obtained from the NICOM device after patch placement but prior to anesthesia

Table 1
Demographic data.

		Range	Mean (SD)
Age		22.2–51.8 years	31.8 (7.2)
Weight		40.8–132.4 kg	76.9 (24.2)
BMI		15.4–48.6 kg/m2	28.1 (8.2)
		Number (n)	Percentage of participants
Gender	Male	7	37%
	Female	12	63%
Comorbid disease	Total	*12*	*63%*
	Valvular Disease	1	5%
	Protein-Losing Enteropathy	0	0%
	Congestive Hepatopathy	7	37%
	Chronic Kidney Disease	0	0%
	s/p ICD placement	2	11%
	s/p Pacemaker placement	5	26%
	Atrial arrhythmias	10	53%
	Ventricular Arrhythmias	1	5%
	Fontan Circulatory Failure	5	26%
	Other Comorbidities	0	0%
Initial CHD diagnosis	Tricuspid Atresia	9	47%
	Pulmonary Atresia-Intact Septum	1	5%
	Hypoplastic Left Heart Syndrome (HLHS)	2	11%
	Double Inlet Left Ventricle (DILV)	4	21%
	Double Outlet Right Ventricle (DORV)	3	16%
	Unbalanced AV canal	3	16%
	D-transposition with VSD	1	5%
Reason for Cath	Hepatic Congestion/ Cirrhosis	7	37%
	Congestive Heart Failure	2	11%
	Desaturation/Cyanosis	13	68%
	Possible coarctation	1	5%

Table 2
Hemodynamic measurements by cardiac catheterization.

Catheterization Data (n = 19)	Mean (SD)	Min	Max
Cardiac output	4.89 (1.93)	2.35	10.42
Sp02	91.5 (4.2)	81	97
Pa02	68.7 (5.5)	55	79
Fontan pressure	14.3 (3.9)	7	22

Table 3
Hemodynamic measurements by NICOM.

NICOM Cardiac Output (n = 19)	Mean (SD)	Min	Max
T0	5.1 (1.6)	3	8.9
T1	4.3 (1.6)	2.3	9.1
T2	4.2 (1.7)	2.7	9.4
T3	4.2 (1.4)	2.6	8.8

induction or sedation. Three participants required sedation prior to patch placement. In these participants, T0 represents immediately after patch placement although under anesthesia or sedation (similar to T1). For eight participants, the catheterization procedure included an intervention: coiling of veno-venous collaterals in six participants, coarctation stenting for one participant and Fontan fenestration closure for one participant. Physiologically, closure of veno-venous collaterals is unlikely to have any significant effect on hemodynamics. Although stenting of coarctation and Fontan fenestration closure could theoretically have an impact cardiac output, no significant change was observed between timepoints T2 and T3 for NICOM measurements. Per routine clinical procedures, Fick measurements were not repeated following these interventions.

NICOM-determined CO at T1, T2, and T3 had moderate agreement with T0 (ICCs 0.6–0.7), and the measurements at T1, T2, and T3 showed high agreement (ICCs $\geq$ 0.9), as shown in Table 4. Of note, T0 is marked as prior to anesthesia, and T1, T2, T3 are following anesthesia/sedation. Bland-Altman plots of the six time-point comparisons are shown in Fig. 1. These findings support internal consistency within the NICOM device during cardiac catheterization. Despite internal consistency with the device, agreement between RHC and NICOM for CO was poor as indicated by the Bland-Altman plots for all four time points as shown in Fig. 2, and by ICCs, with ICC approximately 0.40 for all four time points, as shown in Fig. 3. Table 5 shows T1 and T2 in bold, as these two time points most temporally associated with the Fick measurements.

As seen in Table 6, correlation coefficients were used to determine if oxygen saturation (SpO2) or Fontan pressure were associated with the difference between RHC results and NICOM. Neither chronic hypoxia (as reported reason for catheterization) nor the direct measurement of oxygen saturation during the RHC were significantly associated with the difference between the RHC and NICOM CO. Fontan pressure, also, was not significantly associated with the difference between the RHC and NICOM CO measurements.

With the sample size observed in this study, the study had 80% power to detect intraclass correlations of 0.55, correlations of 0.61, and effect sizes of 1.5 for the two-sample t-tests examining the effect desaturation as the reason for the catheterization on the difference between the catheterization and NICOM measurements.

4. Discussion

NICOM, a non-invasive and novel method of measuring CO in adults with acquired heart disease has shown correlation with thermodilution and Fick-calculated indices in prior studies [7,8]. We performed a pilot study to look for correlation between RHC data and NICOM variables in adult single ventricle patients who had undergone palliation with the Fontan procedure, in order to determine validity of a new diagnostic tool for assessing CO in complex ACHD patients Since NICOM measures thoracic bioreactance by analyzing inducible volume changes within the aorta, which should be preserved in Fontan physiology, we hypothesized that the technological concept would hold true for these patients. However, although our study design showed consistency within the NICOM device, we were unable to demonstrate a statistically valid correlation with invasive hemodynamic data in our sample of patients.

Our protocol included a sub-analysis to control for risk factors unique to Fontan physiology that might impair NICOM measurement, such as significant cyanosis and elevated Fontan venous pressure. Unfortunately, controlling for these risk factors did not significantly alter the poor correlation that was observed. It is conceivable that variations in the degree of hypoxemia or Fontan venous pressures could account for the

Table 4
Agreement between time points for NICOM.

NICOM Cardiac Output (n = 19)	ICC
T0 vs T1	0.68
T0 vs T2	0.67
T0 vs T3	0.64
T1 vs T2	0.92
T1 vs T3	0.9
T2 vs T3	0.92

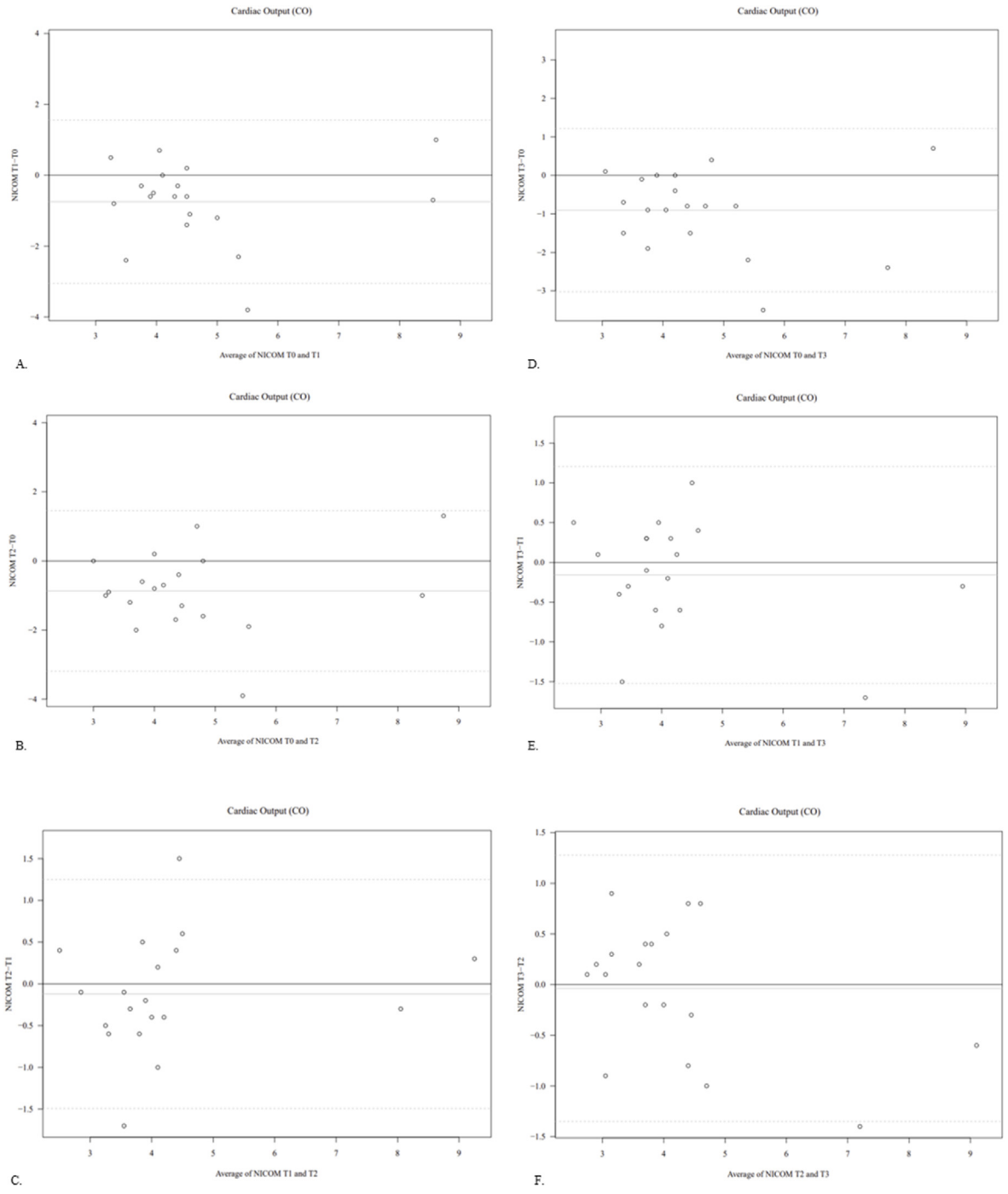

Fig. 1. Bland-Altman plots of agreement of NICOM across time points. (A. T0 vs. T1, B. T0 vs. T2, C. T1 vs. T2, D. T0 vs. T3, E. T1 vs. T3, F. T2 vs. T3).

differences observed between Fick and NICOM in our cohort, but due to small effect size, these analyses were underpowered.

The consistency of data within the device may prove beneficial in some clinical settings for patients with Fontan physiology for monitoring serial changes in CO in the same patient. NICOM may be useful for Fontan patients for minute-to-minute monitoring during critical illness, though more research is needed to determine accuracy in this setting. Given the cross-sectional design, we cannot evaluate this in the present study, but this could be addressed in a future, longitudinal study. Nonetheless, the numbers directly reported by the NICOM device did not correlate with RHC data and therefore should be interpreted with that understanding if this device is used clinically in this population.

This was a small and likely under-powered study, and further studies with a larger sample size may show a correlation. The total number of surviving adult Fontan patients is quite low, and such a study would need to be multicenter in design to be able to recruit an adequate number of patients. Further research into non-invasive methods of accurately determining CO measurements in Fontan patients should be pursued.

4.1. Limitations

Our study was limited by a small sample size. We recruited participants that met our inclusion criteria after they were referred for clinically indicated cardiac catheterization during a discrete time period. Additionally, we attempted to control for unique comorbidities of the Fontan circulation. However, these sub-analyses of an already small sample size

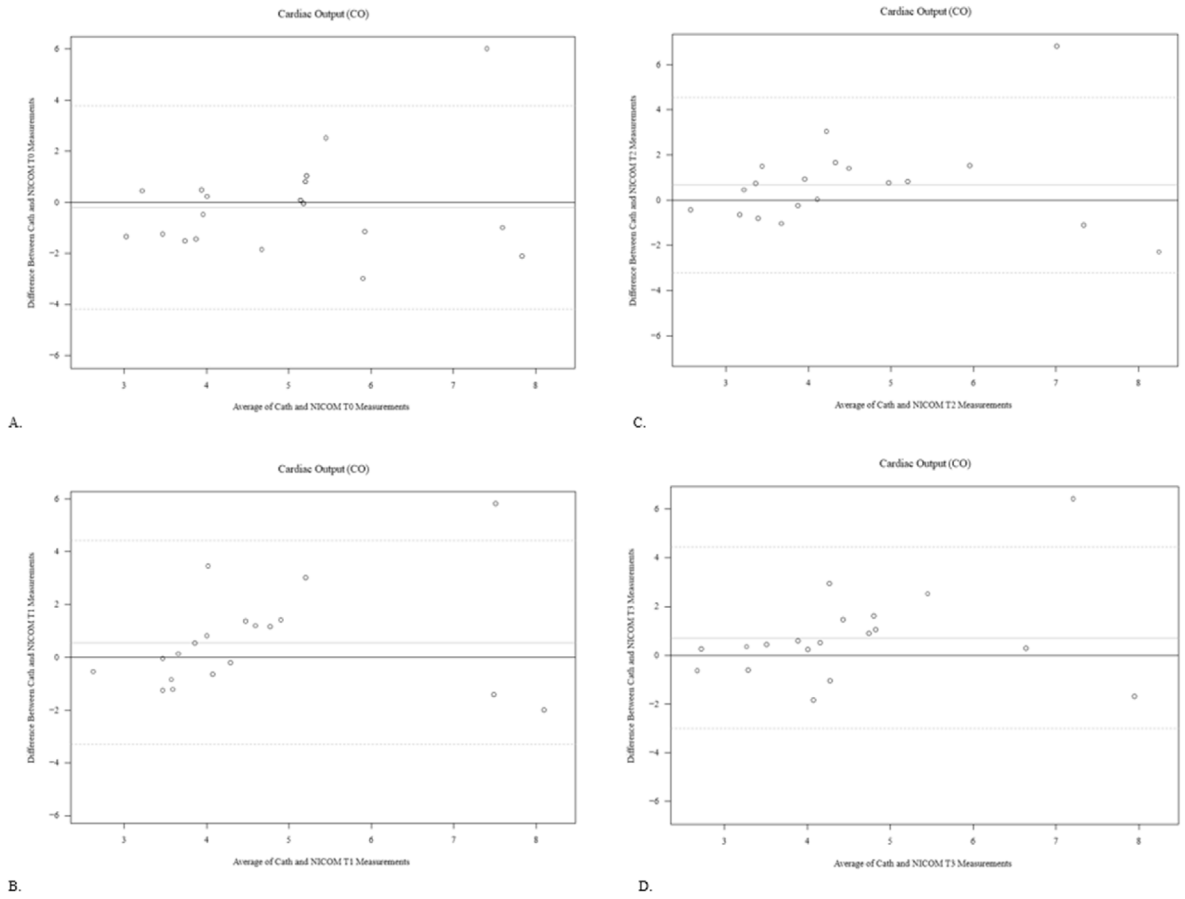

Fig. 2. Bland-Altman plots of agreement between NICOM and average Fick measurements at each time point, (A. T0, B. T1, C. T2, D. T3).

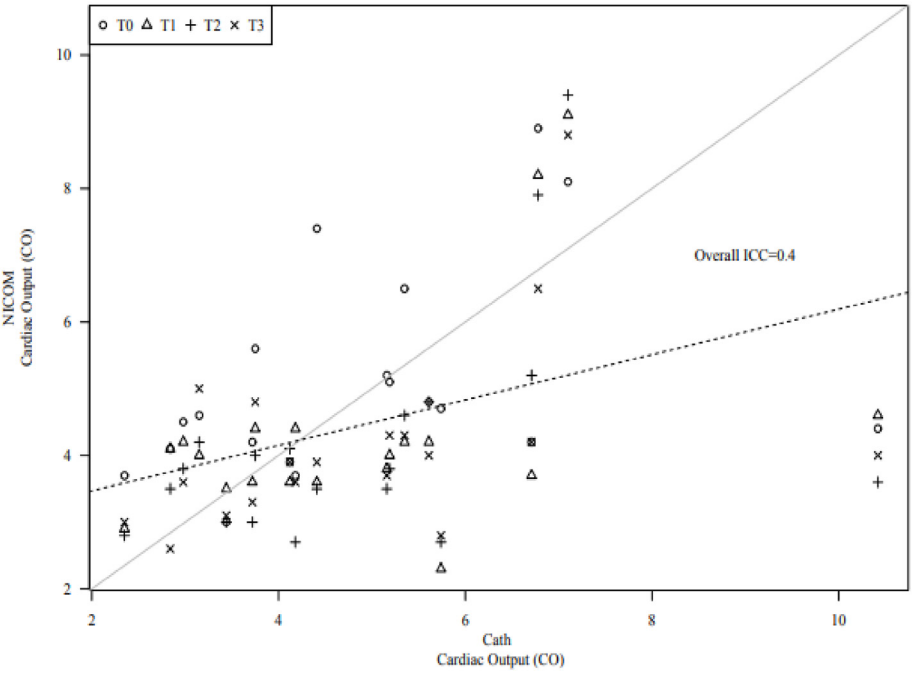

Fig. 3. Scatter plot of correlation between NICOM and RHC at all four times points. ICC ~0.40, as shown in Table 5. The dotted line represents the line of regression with our data, the solid line represents the ideal line of regression if NICOM = RHC.

Table 5
Agreement between catheterization and NICOM.

NICOM vs. Catheterization	
Cardiac Output (n = 19)	ICC
T0	0.38
T1	**0.41**
T2	**0.42**
T3	0.38

Table 6
Association of chronic hypoxia, measured oxygen saturation, and Fontan pressure with observed difference between catheterization and NICOM.

	Chronic hypoxia	Measured O2		Fontan Pressure	
	T-test p-value	Correlation	p-value	Correlation	p-value
T0	0.44	−0.09	0.71	0.06	0.81
T1	0.9	0.21	0.38	−0.06	0.82
T2	0.92	0.23	0.34	−0.16	0.53
T3	0.73	0.11	0.66	0	0.99

made them subject to further under-powering. A larger, adequately powered multicenter study may be able to demonstrate a correlation.

5. Conclusion

The present study did not show a significant correlation between RHC and NICOM measurements of CO and therefore does not support the use of NICOM for determining CO in adult Fontan patients.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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