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ORIGINAL ARTICLE

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Effect of solute temperature in the measurement of cardiac output in children using the thermodilution technique

Shyam Sathanandam, MD[1] | Pooja Kashyap, MD[1] | David Zurakowski, PhD[2] | Lindsey Bird, MSN[1] | Vera McGhee, BSc[3] | Jeffrey Towbin, MD[1] | Benjamin Rush Waller III, MD[1]

[1]Department of Pediatrics, Division of Pediatric Cardiology, LeBonheur Children's Hospital, University of Tennessee, Memphis, Tennessee, USA

[2]Department of Biostatistics, Harvard Medical School, Boston, Massachusetts, USA

[3]UTHSC Health Science Center, College of Medicine, Memphis, Tennessee, USA

Correspondence
Shyam Sathanandam, University of Tennessee Health Science Center, 848 Adams Avenue, Memphis, Tennessee 38103, USA.
Email: shyam@uthsc.edu

Abstract

Objectives: The primary aim of this study was to compare thermodilution (TD) cardiac index (TDCi) measured by injecting cold saline (C-TDCi) to saline at room temperature (R-TDCi). The secondary aim was to assess the change in body temperature with cold saline injections in children.

Design: This is a prospective, case control study.

Setting: Cardiac catheterization lab at Le Bonheur Children's Hospital, Memphis, Tennessee.

Patients: Eighty-six children $\leq$18 years of age that underwent cardiac catheterization between April 2013 and April 2015, excluding patients with admixing lesions, on inotropic support and with ejection fraction $<$ 30%.

Interventions: A TD catheter in the main pulmonary artery was used to measure cardiac output (CO). Each patient received manual injections of saline at room temperature followed by cold saline to calculate the CO.

Outcome Measures: CO by C-TDCi, R-TDCi, and Fick-Ci were compared using four different statistical methods.

Results: R-TDCi and Fick-Ci had a strong linear correlation (rho = 0.91 and 0.77, respectively; $P < 0.0001$) to C-TDCi. R-TDCi and Fick-Ci also had high 1:1 intra-class correlation to C-TDCi (ICC-rho= 0.82 and 0.68, respectively; $P < 0.01$). 96% confidence limits by equivalence testing for R-TDCi and Fick-Ci were 0.98-1.02 and 0.96-1.05 respectively ($P < 0.0001$), when compared to C-TDCi. Mean difference ($\pm$SD) calculated by Bland-Altman analysis showed a higher score for R-TDCi (0.012 $\pm$ 0.32 L/min/m^2) compared to Fick-Ci (0.2 $\pm$ 0.72 L/min/m^2), but it was not statistically different ($P = 0.25$). In a subgroup analysis of children $\leq$2 years (n = 27), the results from all 3 techniques were equivalent. There was a 0.2 $\pm$ 0.16°C drop in BT compared to a 0.08 $\pm$ 0.19°C drop in those $>$2 years ($P > 0.05$).

Conclusions: Cardiac indexes determined by Fick, C-TDCi, and R-TDCi were equivalent in children. Saline at room temperature can be used as an alternative to cold saline to avoid potential drop in body temperature of these patients.

KEYWORDS
cardiac output, catheterization, pediatrics

TABLE 1 Summary of the protocol employed in thermodilution cardiac output measurements in children of different weights for cold saline and saline at room temperature

Weight (kg)	Catheter size (Fr)	Volume of saline at 22°C (mL)	Volume of saline at 4°C (mL)	Average number of measurements	Cal Factor for saline at 22°C	Cal Factor for saline at 4°C
<10	5	5	5	3	0.303	0.267
10–20	5	5	5	3	0.303	0.267
20–30	7	10	10	3	0.601	0.541
>30	7	10	10	3	0.601	0.541

Fr, French catheter scale in mm (diameter in mm = Fr/π, 7Fr = 2.3 mm, 5Fr = 1.67 mm).

1 | INTRODUCTION

Cardiac output (CO) is the single most important indicator of functional effectiveness of circulation in humans.[1] CO reflects the volume of blood ejected by the heart over time and is the product of heart rate and stroke volume. Hence, CO varies with body size. Typically, it is indexed to the patient's body surface area and is referred to as cardiac index (Ci). Fick principle is a less invasive, easier and cheaper method to calculate Ci.[2] Fick principle can be used to calculate Ci by dividing the oxygen consumption of the body by the arterial-venous oxygen difference.[3,4] However, the Fick method is subject to both random and systematic errors.[5] In addition, measurement of oxygen consumption is not always practical. In clinical practice, therefore, the TD technique, rather than the Fick method, is often considered the gold standard for Ci measurement.

The indicator-dilution method for measuring flow was first described by Stewart in 1921.[6] Indocyanine green was used as an indicator earlier, but it was unstable and required standardization, calibration and blood sampling. Recirculation required the extrapolation of the indicator concentration-time curve to the baseline making CO measurement at high and low flow states potentially inaccurate.[7–9] In 1954, Fegler[10] described a thermal indicator technique. It overcame most of the shortcomings of indocyanine green. The TD involves injecting cold saline through a catheter in the right heart. Ci is calculated based on the change in temperature of the blood-saline solution as it moves from the injection port to the catheter tip. Injecting cold saline can potentially lower a child's body temperature (BT) and may cause bradycardia.[11,12] The primary aim of this study was to compare thermodilution cardiac index (TDCi) measured by injecting cold saline (C-TDCi) to saline at room temperature (R-TDCi) and with Fick-Ci. The secondary aim was to assess the change in body temperature with cold saline injections in children.

2 | METHODS

This is a prospective, case control study of children ≤18 years of age that underwent cardiac catheterization between April 2013 and April 2015 at a single center. The study was conducted in compliance with the University of Tennessee institutional review board (IRB). Informed consent from parents and assent from children ≥ 8 years of age were obtained as per the IRB requirements. Patients with admixing lesions, on inotropic support and with ejection fraction < 30% on the pre-catheterization echocardiogram were not included in the study. In each patient, CO was determined using the three techniques, viz., C-TDCi, R-TDCi, and Fick-Ci as part of the routine diagnostic evaluation.

All patients were mechanically ventilated in a supine position, with no supplemental oxygen, with physiologic settings and with no positive end expiratory pressure. A TD catheter was used to measure CO. The catheter was connected to a GE Healthcare's Mac-Lab IT hemodynamic recording system for TDCi measurements. The recording system was calibrated based on catheter size, temperature and volume of the solute injected. The calibration was done by entering a Cal Factor provided by the manufacturer as shown in Table 1. The recording system uses the standard Stewart-Hamilton equation.[13] The catheter is placed in the main pulmonary artery under fluoroscopic guidance from either the femoral or the jugular venous approach through an introducer sheath. The position of the catheter is double checked by the presence of a clear and undamped pulmonary artery waveform to ensure that the thermistor sensors free floating in the injectate is adequately mixed with blood. The volume of the injectate was determined by the patient's weight as outlined in Table 1.

The injectate used was a solution of normal saline. Initially, each patient received 2–3 manual injections of saline at room temperature (20°C–24°C), timed equally over the same phase of the ventilatory cycle, to calculate the CO. The mean value was calculated and reported as R-TDCi for that patient. This was followed by 2–3 injections of cold saline of temperatures between 0°C and 8°C manually injected during the same phase of the ventilatory cycle. These injections yielded another set of COs which were averaged and reported as C-TDCi for the same patient. The volume of saline injected and the number of injections were based on the patient's size as detailed in Table 1. The injections were performed at a rate of 2–3 s each. It was ensured that the TD curve configuration was smooth, with a rapid upstroke to peak and a gradual downslope to baseline. The time-temperature curves that had gross inflections in the upslope or downslope due to uneven injection, marked baseline drift, oscillations due to respiratory cycle, inadequate amplitude due to poor signal to noise ratio were discarded. C-TDCi was performed after R-TDCi to prevent any drop in the core body temperature of the patient, so that the results of the saline injection at room temperature were not affected.

All patients had arterial blood gas measurements and continuous arterial blood pressure monitoring via an invasive catheter in a peripheral artery. Any significant change in the acid-base balance of the patient was corrected before the TDCi measurements were made. The core body temperature was measured continuously using either a rectal or an esophageal probe. The patient temperature was recorded prior to and after all the cold saline injections. Any change in the temperature was recorded. The patient's hemoglobin level was measured from a venipuncture performed 30 min prior to the procedure. Fick-Ci was calculated indirectly, using standard assumed oxygen consumption (VO_2) tables based on the patient's age, sex and heart rate. Arterial and mixed venous oxygen saturations were simultaneously obtained via the arterial line and the distal pulmonary arterial opening of the TD catheter, respectively.

2.1 | Statistical analysis

Normally distributed, continuous variables were expressed as a mean ± standard deviation (SD). Skewed, continuous variables were expressed as a median and interquartile range (IQR). Categorical variables were expressed as a number with a percentage of the total. The Kruskal-Wallis test was used to test the change in temperature between those ≤ 2 y of age to those >2 y of age. CO was analyzed in a continuous fashion without transformation. CO by C-TDCi, R-TDCi, and Fick-Ci were compared using 4 different methods:

1. Spearman's correlation coefficients were computed to determine the relationship across the three techniques.
2. Intra-class correlation (ICC) coefficient was used as an estimate of reliability.
3. Bland-Altman plots were used to determine errors in the estimates and patterns of variation of the three methods.
4. Paired equivalence tests were used to compare all three techniques to determine if the 96% confidence limits of the geometric mean were within bounds of the predefined equivalence limits of 80%–125%.

A subgroup analysis of patient's ≤2 y of age was performed. The CO by C-TDCi, R-TDCi, and Fick-Ci were compared for this subgroup. Another comparison of C-TDCi, R-TDCi, and Fick-Ci was performed comparing those with Ci ≤ 3 L/min/m^2 by any method to those with Ci > 3 L/min/m^2. A *P* value <0.05 was considered statistically significant. For statistical analysis, SPSS-22.0.1 for Mac (SPSS, Inc., Chicago, IL) was used.

3 | RESULTS

A total of 86 patients (45 males and 41 females) were identified who satisfied the entrance criteria. The patient demographics are detailed in Table 2 and overall results are detailed in Table 3. Repaired congenital heart disease with no residual admixing lesions was the most common diagnosis of children undergoing catheterizations (46.5%). Children with pulmonary hypertension (31.4%) or with heart failure ± orthotopic heart transplantation (22.1%) comprised the rest.

TABLE 2 Demographics and Diagnosis of children included in the study

Demographics	N = 87
Age (y)	8.1 ± 6.6
Weight (kg)	37.1 ± 33.3
BSA (m^2)	1.0 ± 0.6
Gender (male)	46 (52.9%)
Race	
African American	23 (26.4%)
Caucasian	49 (56.3%)
Other	15 (17.3%)
Systolic BP (mm Hg)	92.1 ± 18.1
Diastolic BP (mm Hg)	51.5 ± 14.7
Ejection fraction (%)	62.3 ± 13.8
HR (bpm)	97.1 ± 27.2
Hb (g/dL)	12.9 ± 1.5
pH	7.4 ± 0.1
$paCo_2$	37.0 ± 8.5
paO_2	119.2 ± 72.7
HCO_3	22.3 ± 3.9
Temp Δ (°C)	−0.1 ± 0.2
C-TDCi (L/min/m^2)	3.7 ± 0.9
R-TDCi (L/min/m^2)	3.7 ± 0.9
Fick-Ci (L/min/m^2)	3.6 ± 0.9
Diagnosis	
CHD	41 (47.12%)
CHF/OHT	19 (21.84%)
PHT	27 (31.04%)

Data expressed as mean ± SD or count (% of total).
BSA, body surface area; Hb, hemoglobin; CHD, repaired congenital heart disease with no admixing residual lesions; CHF/OHT, congestive heart failure/post orthotopic heart transplant; HR, heart rate in beats per minute (bpm); Temp Δ, change in core body temperature with cold saline injection; PHT, pulmonary hypertension.

3.1 | Comparison of cardiac index estimates by C-TDCi, R-TDCi, and Fick-ci

Both R-TDCi and Fick-Ci had a strong, linear correlation (rho = 0.94 and 0.80, respectively; $P < 0.001$) to C-TDCi (Figure 1). R-TDCi and Fick-Ci also correlated well with each other (rho = 0.78; $P < 0.001$). There was a high 1:1 ICC between the 3 techniques (Table 3). The 96% confidence limits by equivalence testing for R-TDCi and Fick-Ci were 0.98-1.02 and 0.96-1.05, respectively, ($P < 0.0001$ for both), when compared to C-TDCi (Figure 2). Mean difference (±SD), calculated by Bland-Altman analysis (Figure 2), showed a smaller difference for R-TDCi (0.012 ± 0.3 L/min/m^2) compared to Fick-Ci (0.11 ± 0.52 L/min/m^2) to predict C-TDCi but were not statistically different ($P = 0.25$). Table 3 summarizes the comparison of Ci measured using the three techniques for the entire cohort.

TABLE 3 Correlation, Bland-Altman and equivalence analysis comparing Ci obtained by different techniques for the entire cohort

TDCi (n=87)	Spearman rho	Correlation P value	Intraclass rho	Correlation P value	Bland-Altman (MD ± SD)	Equivalence 96%CI	Equivalence P value
C-TDCi vs. R-TDCi	0.91	<0.0001	0.93	<0.0001	−0.012 ± 0.32	0.97	<0.0001
C-TDCi vs. Fick-Ci	0.77	<0.0001	0.82	<0.0001	−0.20 ± 0.47	0.96	<0.0001
R-TDCi vs. Fick-Ci	0.74	<0.0001	0.83	<0.0001	−0.19 ± 0.50	0.97	<0.0001

MD ± SD, mean difference ± standard deviation

3.2 | Comparison of cardiac index estimates by R-TDCi and Fick-ci for patients with low cardiac index by C-TDCi (≤ 3 L/min/m^2)

There were 18 patients in the cohort who had a Ci ≤ 3 L/min/m^2 by C-TDCi. Comparison of the Ci measured by the other 2 techniques was made to determine the accuracy to predict low CO states. R-TDCi had a stronger, linear correlation (rho = 0.84; $P < 0.001$) to C-TDCi than Fick-Ci (rho = 0.60; $P = 0.01$). However, both R-TDCi and Fick-Ci had high 1:1 ICC to C-TDCi (ICC-rho= 0.87 and 0.84, respectively; $P < 0.0001$ for both (Table 4). There was also a high 1:1 ICC between R-TDCi and Fick-Ci in those with low COs (rho = 0.84; $P < 0.0001$). Bland-Altman analysis showed that R-TDCi and Fick-Ci underestimated C-TDCi by 0.05 ± 0.24 and 0.08 ±0.36 L/min/m^2, respectively (Figure 2d-f).

3.3 | Comparison of cardiac index estimates by C-TDCi, R-TDCi and Fick-ci in patient's ≤ 2 years of age

There were 27 patients in the cohort who were ≤ 2 y of age. Comparison of the Ci measured by the three techniques was made to determine their accuracy in small children. Both R-TDCi and Fick-Ci had a strong, linear correlation (rho = 0.86 and 0.80, respectively; $P < 0.0001$) to C-TDCi (Table 5) and between R-TDCi and Fick-Ci (rho= 0.80; $P < 0.0001$). Both R-TDCi and Fick-Ci also had high 1:1 ICC to C-TDCi (ICC-rho= 0.92 and 0.86, respectively; $P < 0.0001$). Mean difference (±SD), calculated by Bland-Altman analysis (Figure 2g-i), showed that R-TDCi overestimated by 0.01 ± 0.32 L/min/m^2, whereas, Fick-Ci overestimated by 0.20 ± 0.47 L/min/m^2 when predicting Ci in children ≤ 2 y of age.

3.4 | Change in patient core body temperature with cold saline injections

For children ≤ 2 y (n = 27), there was a 0.2 ±0.16°C drop in the core body temperature compared to a 0.08 ± 0.19°C drop in those >2 y. Even though there appeared to be a greater decline in the core body temperature in children ≤ 2 y of age, there was no statistical difference between the 2 groups ($P = 0.15$) as shown in Figure 2. There was no change in the heart rate of any patient pre-and post-cold saline injection.

4 | DISCUSSION

Iced injectate was the solution of choice during the early research performed with TD as a technique to measure CO,[2,14] for several reasons. First, the pulmonary artery temperature varies by 0.01°C-0.02°C during the respiratory cycle, both during spontaneous respirations and while being mechanically ventilated. This variation in the pulmonary artery temperature creates a physiologic noise and decreases the signal-to-noise ratio. The noise creates an inaccurate temperature-time curve, thereby making the TDCi measurement inaccurate.[2,15,16] Since the signal-to-noise ratio has to be maximal in low flow states, iced injectate theoretically can provide the most accurate measurements. Second, minimal handling of the prefilled iced solution and use of the solution within 30 s provided the best time-temperature curves.[17–19] However, newer closed injectate delivery systems with an injectate temperature probe at the site of the injection have resolved some of the issues regarding injectate cool down and respiration induced signal-noise ratio.[20] Hence, theoretically, besides the rate and volume of the injected solution, factors such as the temperature of the solution, phases of the

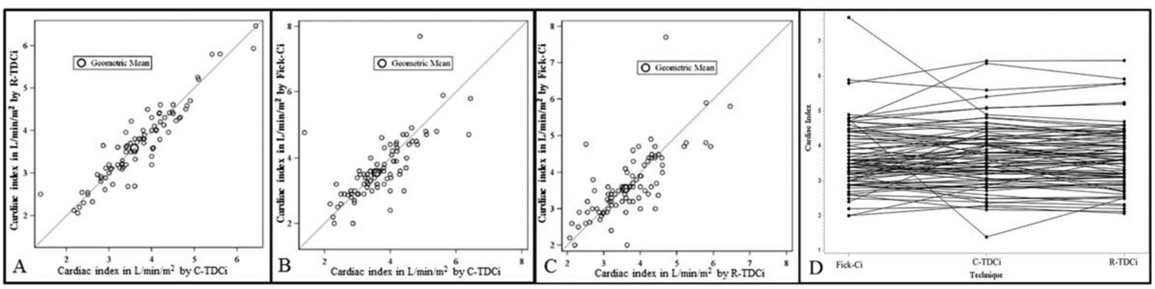

FIGURE 1 Spearmen correlation comparing Ci obtained by different techniques for the entire cohort. (A) C-TDCi and R-TDCi. (B) C-TDCiandFick-Ci. (C) R-TDCiandFick-Ci. (D) Paired profiles of cardiac index measured by R-TDCi and calculated by Fick- Ci compared to C-TDCi. The tests were equivalent ($P < 0.0001$)

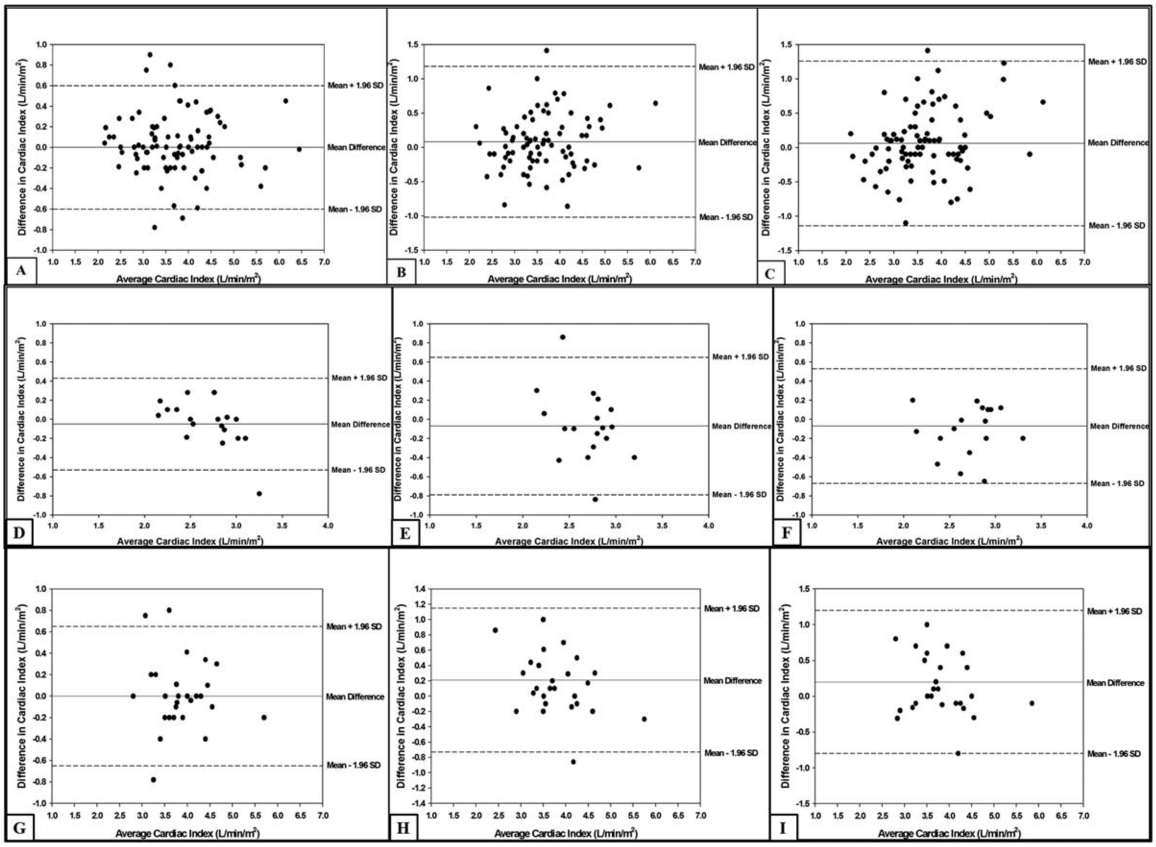

FIGURE 2 Bland-Altman plots comparing Ci obtained by different techniques for the entire cohort. (A) C-TDCi and R-TDCi. (B) C-TDCiandFick-Ci. (C) R-TDCiandFick-CiBland-Altman comparing Ci ≤ 3 L/min/m^2 obtained by different techniques. (C) R-TDCi and C-TDCi. (D) C-TDCiandFick-Ci. (F) R-TDCiandFick-CiBland-Altman comparing Ci in children ≤ 2 years of age by different techniques. (G) R-TDCi and C-TDCi. (H) C-TDCi and Fick-Ci.I. R-TDCi and Fick-Ci

TABLE 4 Correlations and Bland-Altman analysis comparing Ci obtained by different techniques for a subgroup of children with C-TDCi ≤ 3 L/min/m^2

C-TDCi ≤ 3 L/min/m^2 (n=19)	Spearman rho	Correlation *P* value	Intraclass rho	Correlation *P* value	Bland-Altman (MD ± SD)
C-TDCi vs. R-TDCi	0.74	<0.0001	0.78	<0.0001	0.01± 0.21
C-TDCi vs. Fick-Ci	0.86	<0.0001	0.94	<0.0001	−0.01 ± 0.42
R-TDCi vs. Fick-Ci	0.82	<0.0001	0.84	<0.0001	−0.1 ± 0.4

MD ± SD, mean difference ± standard deviation.

respiratory cycle, the position of the patient, concomitant infusions, and other biological variability should no longer influence thermodilution CO measurements.

Room temperature injectate and iced injectate for TDCi measurements were found to be comparable in many clinical settings[21,22] in adults with a normal CO. However, iced injectate is still used as the

TABLE 5 Correlations and Bland-Altman analysis comparing Ci obtained by different techniques for a subgroup of children ≤ 2yrs of age

Subgroup (age ≤ 2yrs) (n = 27)	Spearman rho	Correlation *P* value	Intraclass rho	Correlation *P* value	Bland-Altman (MD ± SD)
C-TDCi vs. R-TDCi	0.86	<0.0001	0.92	<0.0001	0.01 ± 0.32
C-TDCi vs. Fick-Ci	0.73	<0.0001	0.86	<0.0001	0.20 ± 0.47
R-TDCi vs. Fick-Ci	0.74	<0.0001	0.84	<0.0001	0.19 ± 0.50

MD ± SD, mean difference ± standard deviation.

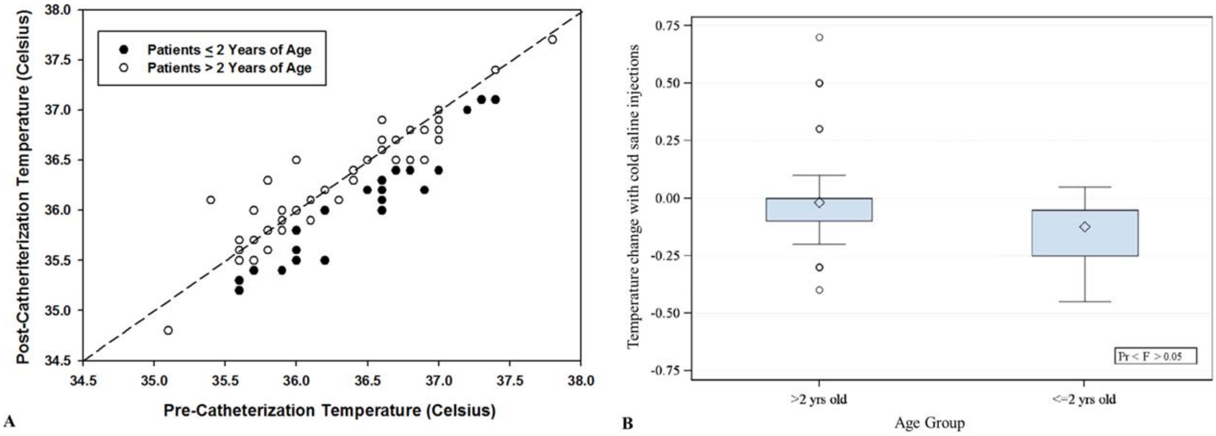

FIGURE 2 (A) Graph demonstrating a small drop in the core body temperature of all patients ≤ 2 y of age following cold saline injections. Only a few patients above the age of 2 y had a small drop in body temperature and the drop was not as pronounced as in children ≤ 2 y of age. (B) Mean change in core body temperature with cold saline injections performed during thermodilution in children ≤ 2 y of age and > 2 y of age.

gold standard in most adult and pediatric catheterization labs to determine CO[14] Cold saline injections have been shown to cause a drop in the heart rates of critically ill adults.[11,12,23] It can potentially have the same effect in children. Moreover, it can drop the core body temperature in infants.[24] Furthermore, maintaining iced solutions can be costly and time consuming.

For these reasons, many investigators have considered using saline at room temperature as a thermal indicator to measure Ci in animal as well as in adult human subjects. In adult patients with a normal CO, at least 5 studies[16,21,22,25,26] have compared TDCi by cold and room temperature saline injections and found correlations ≥ 0.9. Similar studies were performed with varying temperatures (34°C–38°C) and a wide range of COs (2–11 L/min) and found correlation coefficients of 0.92–1 for measurements using room and iced solutions. In children there have been studies comparing C-TDCi and Fick-Ci.[27,28] However, no similar study comparing cold versus room temperature saline injectate for TD has been conducted in children.

Woog and McWilliams[29] found that in adults, although the TDCi measured using room and cold saline injectate correlated (rho = 0.93), R-TDCi underestimated it by 25% or more. Similar finding was noted also by Runciman et al.[30] in a previous large animal study. Bourdillon and Fienberg[31] found that there was variation in the measurements obtained by R-TDCi and C-TDCi. An average of seven measurements of R-TDCi when compared to an average of four measurements of C-TDCi were used to decrease variability. Conversely, Daily and Mersch[32] found that R-TDCi correlated better with Fick-Ci (rho = 0.84), than C-TDCi with Fick-Ci (rho = 0.72). In this pediatric study, we found good linear and 1:1 correlations between C-TDCi and R-TDCi. Both C-TDCi and R-TDCi had good 1:1 ICC with Fick-Ci as. However, Fick-Ci overestimated both C-TDCi and R-TDCi. We also performed equivalence testing which determined that Ci by C-TDCi, R-TDCi, and Fick-Ci were equivalent for all three tests. Even in subgroups of children ≤ 2 y and in children with TDCi ≤ 3 L/min/m^2, there were good linear and 1:1 correlations between C-TDCi R-TDCi, and Fick-Ci. This is the first pediatric study to show that cardiac index determination by Fick principle, TD technique using cold saline, and TD technique using saline at room temperature were all equivalent. This information is useful for clinicians while treating children.

Other advantages to using room temperature injectate over cold saline solution may include prevention of bradycardia in critically ill children, easier maintenance of equipment, and cost reduction. We did not address these issues in this study. However, the study is strong because it was performed prospectively and the tests were compared using varying statistical analyses. As each patient acted as their own control, randomization was not required. Additionally, we compared subgroups of children with lower COs and those ≤ 2 y of age. In the subgroup of children ≤ 2 y of age, there seemed to be a greater drop in the core body temperature compared to those over 2 y. This change, however, was not statistically significant.

5 | CONCLUSIONS

Cold saline injections could potentially lower the core body temperature of neonates and infants. Cardiac index determined in children by the Fick principle and by the TD technique using either cold saline or saline at room temperature, are equivalent. This holds true even for children ≤ 2 years of age and those with cardiac index ≤ 3 L/min/m^2. Saline at room temperature can be used as an alternative to cold saline for determination of CO by the TD technique in children.

AUTHOR CONTRIBUTIONS

Shyam Sathanandam, M.D.- Concept/design; data collection and analysis/interpretation, Pooja Kashyap, M.D.- Concept/design; data collection and analysis/interpretation; drafting article, David Zurakowski, PhD- Data analysis/interpretation; statistics, Lindsey Bird, MSN- Data collection; drafting article; critical revision, Vera McGhee, B.Sc.- Critical revision of article, Jeffrey Towbin, M.D.- Concept/design; approval of article, Benjamin Rush Waller III, M.D. – Concept/design; approval of article.

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