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ORIGINAL ARTICLE

Noninvasive cardiac output monitoring using bioreactance-based technique in pediatric patients with or without ventricular septal defect during anesthesia: in comparison with echocardiography

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Summary

Background: We evaluated the use of bioreactance-based noninvasive cardiac output (CO) monitoring technique (NICOM™, CO_{NICOM}) in pediatric patients with or without ventricular septal defect (VSD) during anesthesia induction to determine its agreement with the measurements assessed by echocardiography (echo, CO_{ECHO}).
Methods: Twenty-eight pediatric patients with normal heart anatomy (group NHA) and 32 with isolated ventricular septal defects (group VSD) were included in this study. The cardiac output was measured simultaneously in minute-by-minute using NICOM and echo (Simpson's rule) during anesthesia induction and intubation. Linear regression and revised Bland–Altman analyses were performed to evaluate the agreement by comparing the paired CO results. The mean percent error $((CO_{ECHO}–CO_{NICOM})/CO_{ECHO} \times 100\%)$ was used to assess the impact of congenital heart disease on the agreement.
Results: The measurements of CO by NICOM and echo techniques were highly correlated in group NHA ($\gamma = 0.96$, $P < 0.005$) and VSD ($\gamma = 0.84$, $P < 0.005$). The mean bias ($CO_{ECHO} - CO_{NICOM}$) between the two methods was 0.03 and 0.31 $l{\cdot}min^{-1}$ with the limits of agreement (LOA) −0.29 to +0.35 $l{\cdot}min^{-1}$ and −0.44 to +1.05 $l{\cdot}min^{-1}$, which include 96.9% (31/32) and 89.3% (25/28) of all patients' different data in group NHA and VSD, respectively. The median percent errors were significantly lower at all time points in group NHA than those in group VSD (all $P < 0.05$).
Conclusion: In children without heart defects, the CO measured by NICOM shows a good agreement with the echo during anesthesia induction. The NICOM technique underestimates echo although a strong correlation exists between two methods in children with ventricular septal defect.

Introduction

Hemodynamic compromise during the anesthesia is one of the major concerns, especially in children with congenital heart disease undergoing high-risk surgery. Cardiac output (CO) is a major index that reflexes global hemodynamic performance, and CO monitoring often helps to detect the early sign of cardiac dysfunction perioperatively in those critical patients.

An ideal CO monitoring technique should feature the accuracy, reliability and safety, and real-time and continuous assessment. Routine blood pressure monitoring and ECG are unable to reflex CO. Pulmonary artery thermodilution and simplified direct Fick technique can

provide accurate and continuous assessment of cardiac function, but its invasiveness and prolonged arterial catheter dwelling have limited their routine clinical application, especially in small children (1–3), and therefore, their uses cannot be justified in patients with stable hemodynamics. In the past few decades, some noninvasive techniques have been developed for better and safer CO monitoring. The Simpson's rule-based echocardiographic assessment of CO has been widely used with the advantages of accuracy and noninvasiveness (4,5). Its probe maneuver is operator dependent and the reliability of CO monitoring is signal and patient dependent. It is inconvenient and impossible for continuous assessment of CO in many surgeries (6).

Recently, the transthoracic bioreactance-based NICOM system has been developed to provide accurate, noninvasive, and continuous CO measurement with advantages of small equipment and easy setup (7). It could be used during the whole course of anesthesia. Its cardiac monitoring data have been confirmed to be comparable with the results measured by some invasive techniques such as thermodilution and a pulse wave contour-based system (FloTrac-Vigileo) (8,9). The principle of CO calculation is based on the analysis of the variation in the frequency spectra of a delivered oscillating current which traverses through thoracic cavity and is detected through electrical leads placed on the skin. A few of trial studies with NICOM in ICU and during anesthesia have shown promising outcome in adults, some of them with heart failure (10–13). So far, limited data are available in children. Clinicians have been hoping to adapt NICOM technique in pediatric patients because children with congenital heart disease are the most appropriate population requiring continuous perioperative CO monitoring.

Therefore, we designed the current study to analyze the correlation and agreement between the CO values assessed by bioreactance-based NICOM and echocardiography (echo) during anesthesia induction in pediatric patients with or without isolated VSD.

Methods

Patients

Following the approval by the Institutional Review Board of Shanghai Children's Medical Center, this prospective observational study was conducted over a 3-month period. The written informed consent was obtained from parents prior to start. A total of 60 patients, American Society of Anesthesiologists (ASA) physical status class I or II, aged 3–60 months and scheduled for elective surgery under general anesthesia, were enrolled in this study. Among them, 32 patients had isolated ventricular septal defect (group VSD) and 28 patients had normal heart anatomy (group NHA).

CO measurement

The bioreactance-based NICOMTM technique (Cheetah Medical, Wilmington, DE, USA) comprises of a current injecting device (high frequency, 75 kHZ alternating current) and four dual sensing electrodes placed on the skin surrounding the heart, in which two leads were on the upper chest and two were on the lower ribs, as instructed by the manufacturer. The disposable electrodes are the same one as used in adults. After the study period was completed, all the electrodes were removed for the surgical procedure.

The signal processing unit of the system determines the relative phase shift ($\Delta\Phi$), which reflects the instantaneous changes in blood flow in the aorta. The stroke volume (SV) is estimated by the formula of $C \times VET \times d\Phi/dtmax$; where C is a constant of proportionality, VET is ventricular ejection time, and $d\Phi/dtmax$ is phase shift. Then, CO was calculated as the product of SV and heart rate. All data were stored in an internal database automatically at the end of 60-s interval. The NICOM device was set up to a logging mode of every 1 min, and the CO data were displayed on the screen in numerical terms, which was blinded to the echocardiographer.

Echocardiography

Two-dimensional echo was performed with ultrasound scanner (SONOS 5500, Philips, Bothell, WA, USA) equipped with a transducer (S4, 2–4 Hz, Philips). The probe was placed and left on the apical window of the chest wall to obtain 2-and 4-chamber view loop during the whole study. The images of three cardiac cycles were captured at the beginning of every minute. The values from three cardiac cycles were averaged, and CO was calculated based on the biplane Simpson's rule by evaluating the area under a curve drawn from values of the ordinate and the abscissa (14) (EnConcert, Philips Medical Systems).

Both devices were synchronized with an internal timer, and in this way, the measurements of CO by NICOM and echo took place simultaneously at the same time. The values obtained from each minute by NICOM and CO were paired up for analytic comparison.

Anesthesia induction and intubation

Standard oximetry, ECG, and noninvasive blood pressure were applied after patients arrived to the operation room, and four NICOM leads were placed

over the chest. After a peripheral intravenous access was established, the patient was induced with 0.05 $mg \cdot kg^{-1}$ midazolam and 1.0 $mg \cdot kg^{-1}$ ketamine, and then, the CO was measured based on the minute-by-minute over 5 min with both NICOM and echo techniques. Over the next 4-min period, 2 $\mu g \cdot kg^{-1}$ of fentanyl and 0.6 $mg \cdot kg^{-1}$ of rocuronium or 2 $\mu g \cdot kg^{-1}$ of sufentanil and 0.6 $mg \cdot kg^{-1}$ of rocuronium were administered in NHA and VSD group, respectively, and patients were intubated after paralytic took effect. Sufentanil instead of fentanyl was chosen in VSD group because of its greater analgesic effect, longer duration, rapid induction, and quicker emergence for cardiac surgery and anesthesia (15). CO was measured four times over this 4-min duration and then was recorded five times over 5 min after intubation.

Statistical analysis

The differences in measurements between the two values are expressed as a percentage (percent error, $(CO_{ECHO}–CO_{NICOM})/CO_{ECHO} \times 100\%$). Results were expressed as mean and standard deviations (SD), median and interquartile (IQR) as appropriate. The data distribution was evaluated with the Shapiro–Wilk normality test. The difference in normally distributed continuous variables between two groups was analyzed by Student's *t*-test, while the comparison of abnormally distributed data between groups was assessed by the Wilcoxon rank sum test. Chi-square test was applied for categorical variables. The mixed model which can handle missing within-subject data was performed to determine differences within group and between groups for repeated measures data. Dunnett's method was used for multiple comparison adjustment when considering the changes in physical parameters compared with baselines. A paired *t*-test was used to compare the within-group difference between CO_{ECHO} and CO_{NICOM} at the same time point, and Holm's method was employed for multiple comparison adjustment. A *P* value of <0.05 was thought as significant. Software package SAS 9.3 (SAS Institute Inc., Cary, NC, USA) was used to perform all statistical analyses. We assessed agreement between the two methods using a modification of Bland–Altman methods (16), which takes into account repeated measurements on the same subjects, and the within-subject variance estimated by a random effects model including the mean measurements of the two methods for each measurement occasion. Pearson correlation was used for assessing the relation between CO_{ECHO} and CO_{NICOM} within-group. The root mean square (RMS) differences between NICOM and echo were calculated according to a formula in a previous article (17).

Results

For each individual patient, 14 paired CO measurements were generated by NICOM and echo techniques. So, a total of 392 pairs and 448 pairs created in NHA group and VSD group, respectively. Table 1 summarizes the demographic characteristics of two groups. There were no statistical differences in demographic distributions between groups (all $P > 0.05$). The elective surgeries and diagnosis in patients without heart anomalies included obstructive sleep apnea surgery (OSAS) ($n = 7$), hypospadias ($n = 5$), cryptorchidism ($n = 3$), hydronephrosis ($n = 3$), tethered cord release ($n = 2$), scalp mass ($n = 1$), retroperitoneal tumors ($n = 1$), biliary atresia ($n = 1$), orbital tumor ($n = 1$), renal tumor ($n = 1$), sacral rear bump ($n = 1$), hidden phimosis ($n = 1$), and developmental hip dysplasia ($n = 1$). In patients underwent VSD repair, 6 of 32 were defined as subarterial, fifteen as inlet, ten as perimembranous, and one as muscular ventricular septal defect.

As shown in Figure 1, heart rates (*left panel*) were fairly constant in both groups in the early induction of anesthesia and then increased and decreased significantly compared with baselines after intubation in group NHA and VSD, respectively ($P < 0.05$). Mean systemic pressure (*right panel*) remained relatively constant in group VSD, but it showed a decreasing temporarily followed by increasing in group NHA.

Figure 2 presents the minute-by-minute CO trend measured by NICOM and echo in patients. In group NHA (*left panel*), the CO measured by both techniques showed downward trends after IV induction agents were

Table 1 Patients' demographic data

Group	Age (Mo)	Height (cm)	Gender	Weight (Kg)	BSA (m^2)
NHA ($n = 28$)	24.0 (6.5, 36.0)	87.5 (67.5, 99.0)	17M/11F	13.7 (8.8, 16.8)	0.56 (0.38, 0.67)
VSD ($n = 32$)	18.0 (10.0, 36.0)	82.0 (71.5, 100.5)	22M/10F	11.2 (8.2, 16.0)	0.48 (0.39, 0.66)

Mo, months; BSA, body surface area; NHA, normal heart anatomy; VSD, ventricular septal defect.
Data are given as median (IQR) or numbers of patients.

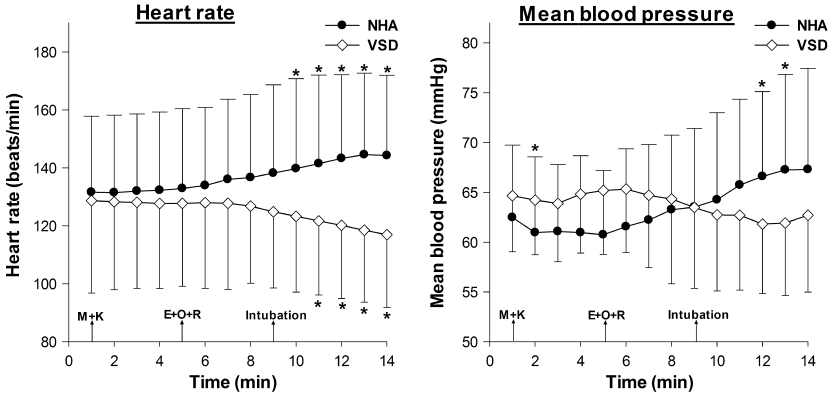

Figure 1 Heart rate (*left panel*) and mean blood pressure (*right panel*) at the different experimental stages. NHA, normal heart anatomy; VSD, ventricular septal defect; M, midazolam; K, ketamine; E, etomidate; O, opioids; (fentanyl was used in group NHA and sufentanil was used in group VSD); R, rocuronium. Significant differences are given for within-group comparison. $^{*}P < 0.05$ vs baselines.

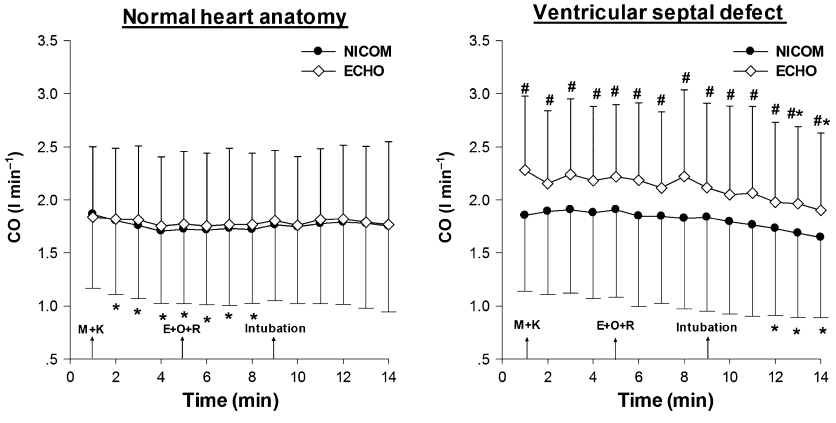

Figure 2 CO measured by NICOM and echo in group NHA (*left panel*) and group VSD (*right panel*) at the different experimental stages. NHA, normal heart anatomy; VSD, ventricular septal defect; M, midazolam; K, ketamine; E, etomidate; O, opioids; (fentanyl was used in group NHA and sufentanil was used in group VSD); R, rocuronium. $^{*}P < 0.05$ vs baseline; $^{\#}P < 0.05$ vs within-group CO measured by NICOM at the same time point.

given and then remained constant for the rest of anesthesia induction and intubation. Little difference in CO values between NICOM and echo at any given minute has been found ($P > 0.05$). In group VSD (*right panel*), the results collected from both techniques showed similar trends that the CO remained steady after injection of IV induction agents and tended to move lower gradually after narcotics and muscle relaxant were given and intubation was performed. However, the mean CO value from NICOM at all given time point was significantly lower than that from echo results (all $P < 0.05$). The median calculated percent error $((CO_{ECHO}–CO_{NICOM})/CO_{ECHO} \times 100\%)$ at all given time point in the group NHA was lower than that in the group VSD (all $P < 0.05$, Table 2).

As shown in Figure 3, there was a good correlation between the CO results collected from NICOM and echo techniques during the study course ($\gamma = 0.96$ and 0.84 in group NHA and group VSD, respectively, $P < 0.005$). The *upper panels* depicted the regression equations and scatter plots of both groups. The revised Bland–Altman plots were used to analyze the difference between mean CO values from two monitoring tools. In group NHA as seen in *lower left panel*, the difference in the means between NICOM and echo (termed bias) is 0.03 $l \cdot min^{-1}$, with the limits of agreement between −0.29 and +0.35 $l \cdot min^{-1}$. Looking at the dot distribution as a whole, only 3.1% (1/32) of all patients' different data was out of the confidence band extending. In group VSD as showed in *lower right panel*, the bias is 0.31 $l \cdot min^{-1}$, with the confidence band extending between −0.44 and +1.05 $l \cdot min^{-1}$. 10.7% (3/28) of all patients' different data was out of the limits of agreement.

Discussion

A critically ill pediatric patient with congenital heart disease often requires a close and continuous CO monitoring perioperatively. Among the clinically available techniques, few meet all features of safer and less traumatic, accurate and reliable, continuing monitoring, and simple and convenient. A newly developed bioreactance-based NICOM system has shown all potential advantages of CO monitoring. In our study, we compared the continuous CO monitoring results obtained from NICOM and echo assessments during anesthesia induction and intubation, and we found that there was a good correlation and agreement between these two

Table 2 The median percentage differences of 14 consecutive recordings in anesthesia inducing period in both groups

Time (min)	Group NHA Percentage difference (%)	Group VSD Percentage difference (%)
1	−3.4 (−9.3, 3.6)	20.0 (8.0, 31.9)*
2	0.0 (−5.3, 7.1)	15.0 (6.2, 25.6)*
3	0.0 (−3.9, 8.3)	15.8 (8.0, 33.3)*
4	0.0 (0.0, 6.3)	16.5 (6.5, 27.6)*
5	0.0 (−4.5, 6.8)	14.0 (6.4, 26.4)*
6	0.0 (−4.7, 6.0)	14.6 (5.9, 29.8)*
7	0.0 (−3.8, 6.7)	15.4 (5.8, 26.3)*
8	0.0 (−1.0, 9.6)	16.7 (9.8, 27.3)*
9	0.0 (−3.4, 7.9)	13.8 (5.9, 29.1)*
10	2.9 (−5.3, 7.9)	13.4 (5.6, 25.0)*
11	3.6 (−1.8, 9.1)	11.8 (8.4, 26.4)*
12	0.0 (−4.0, 7.3)	16.0 (6.2, 25.0)*
13	0.0 (−3.9, 7.1)	15.6 (8.6, 25.0)*
14	0.0 (−4.1, 6.1)	14.4 (7.6, 25.0)*

NHA, normal heart anatomy; VSD, ventricular septal defect.
The mean percent error was calculated according to the formula: $(CO_{ECHO}–CO_{NICOM})/CO_{ECHO} \times 100\%$. Data are given as median (IQR).
*$P < 0.05$ vs the mean percent errors of group NHA at the same time.

techniques in patients with normal heart anatomy while a good correlation but no agreement in patients with isolated ventricular septal defects.

Because of higher risk-benefit ratio, whether or not using invasive CO monitors in children or infants has been debated for years (1,18). Many efforts have been made to develop new noninvasive, continuous CO monitoring techniques, specifically applicable and reliable for pediatric population. Bioreactance-based CO monitoring is a latest and potentially useful tool with more advantages (8,19,20). Several studies in adults covering a wide range of circulatory situations have shown a good correlation and agreement between bioreactance and other methods (12,21,22). With the features of noninvasiveness, continuation of real-time monitoring, easy use and setup, and less distraction to anesthesiologist, bioreactance-based CO measurement has become a very attractive method for CO evaluation in pediatric patients.

Because of the accessibility and practicality, the CO measured by echo has been used as standard reference in comparison with NICOM results. Using aortic flow velocity time integral (VTI) and the cross-sectional area of the aorta to calculate echocardiographic CO, Weisz *et al.* (23) reported a strong correlation between the CO measured by NICOM and echo in 10 neonates without congenital heart disease. Ballestero *et al.* (24) conducted a study in ten pediatric patients with wider age

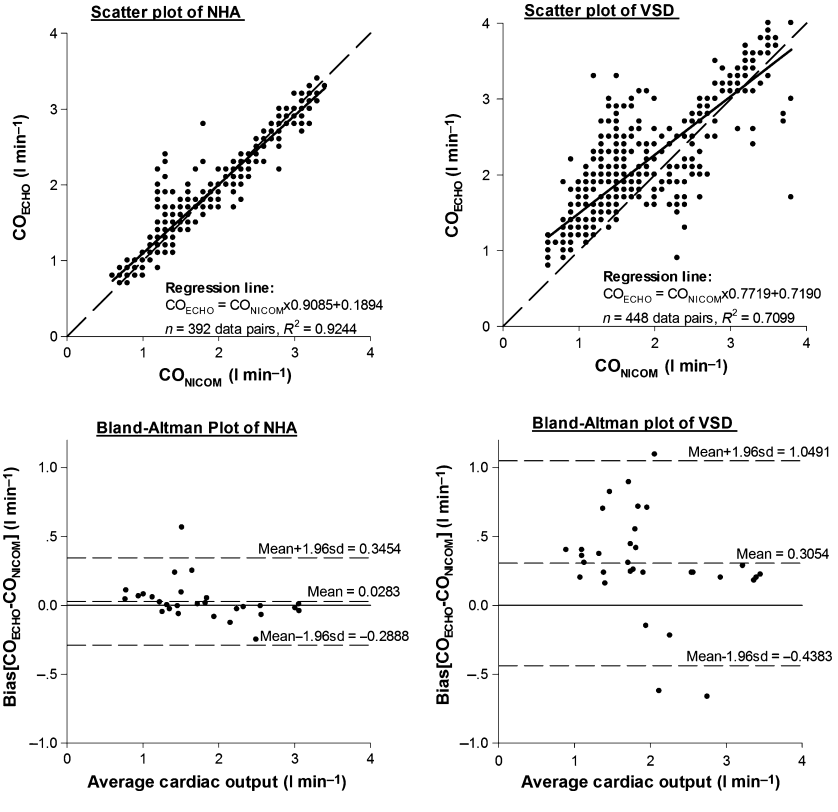

Figure 3 Regression between CO by echo and NICOM in group NHA (*upper right*) and group VSD (*upper left*) (dashed line is line of identity) with corresponding revised Bland–Altman plot (*lower left and lower right*). The correlations between the measurements are $r = 0.96$ and 0.84 in group NHA and VSD, respectively. The mean values of the difference between these two measurements (termed bias) are 0.03 l·min^{-1} (*lower left*) and 0.31 l·min^{-1} (*lower right*) with confidence bands −0.29 to 0.35 and −0.44 to 1.05 l·min^{-1}. As seen, there is a lower degree of correlation ($r = 0.84$), the bias is greater (0.31 l·min^{-1}), and the confidence band is broader (−0.44 to 1.05 l·min^{-1}) in group VSD. NHA, normal heart anatomy; VSD, ventricular septal defect.

distribution (1–144 months) and a variety of types of congenital heart disease, and they found that cardiac index (CI) accessed by NICOM was within normal range in children weighing >20 kg, while it was lower than the normal range in children weighing <20 kg and concluded that NICOM was not suitable for CI monitoring in children with stable hemodynamics and weight <20 kg. Their results showed significant CI differences between children weighing <10 kg (1.9 ± 0.73 l·min^{-1}/1.73 m^2), 10–20 kg (2.07 ± 0.7 l·min^{-1}/1.73 m^2), and >20 kg (3.7 ± 0.8 l·min^{-1}/1.73 m^2), all of which means that NICOM-derived estimates were consistently lower in children <20 kg. When body weight was normalized by surface area of 1.73 m^2, the mean CIs in VSD patients with weight <10 kg ($n = 15$) were 5.58 ± 1.14 l·min^{-1}/1.73 m^2 and 7.89 ± 1.84 l·min^{-1}/1.73 m^2 measured by NICOM and echo, respectively. In group of 10–20 kg ($n = 13$), the CIs were 6.38 ± 1.51 l·min^{-1}/1.73 m^2 and 6.98 ± 1.37 l·min^{-1}/1.73 m^2, and in >20 kg group ($n = 4$), the CIs were 6.60 ± 0.96 l·min^{-1}/1.73 m^2 and 6.01 ± 1.87 l·min^{-1}/1.73 m^2, respectively, all of which are higher than the lower limit of normal (2.5 l·min^{-1}·m^{-2}) (Table S1).

The presumable reason could be that we recruited the patients only with isolated ventricular septal defects, but not other heart defects in our study. These results remind us that the calibration of CO measurement in smaller children needs circumspect consideration of a variety of involving factors, such as age, weight, and disease status.

It should be noted that significant differences in CO measured by NICOM and echo do exist in VSD pediatric patients (Figures 2 and 3). A few contributing factors may help explain this finding in our study. The left-to-right shunt in children with VSD might be the more important factor. On the one hand, Simpson's rule is a geometric method for evaluating right and left ventricular end-diastolic volume and end-systolic volume by calculating all slices of end-diastolic and end-systolic volumes (5). In fact, this change in volume (CO) is composed of blood from both aorta and left-to-right shunt. Thus, CO determined by echo will be greater than by NICOM in VSD children. On the other hand, the principle of NICOM is based on that the pulsatile blood flow in the thorax causes an oscillating current phase shift, which can be captured and calculated as CO. It is not the true aortic diameter, but the blood flow ejected from the left ventricle that NICOM reflects (influence the $d\Phi/dt_{max}$). As above mentioned, aortic blood flow is only a part of volume measured by echo (CO). By another meaning, NICOM might be more accurate in estimating effective CO in infants with ventricular shunts than echo does, and its prospective application in children with congenital heart diseases could come into reality if further validation can be performed. This inference is also supported by the near perfect agreement between NICOM and echo in the absence of a ventricular shunt. In addition, whether the left-to-right shunt has negligible effect on the phase shift of injected electrical current or not is still unclear; however, this impact should not be ignored. All of above may account for the huge consistent discrepancy between NICOM and echo in VSD patients.

In our study, the variation and tendency of heart rate and mean blood pressure during induction was quiet different in two groups, which might be related to different anesthetic techniques and/or intracardiac shunting. Fentanyl used in group NHA had a limited hemodynamic effect up to 5–10 min, and sufentanil used in group VSD has a more prolonged and potent effect (25). Interestingly, the trend of CO was not consistent with that of heart rate and average blood pressure, especially in children with normal heart anatomy. Our findings showed that CO curves recorded from both NICOM and echo techniques had similar patterns. There was a good correlation between two trends, as was demonstrated in this study. However, the calculated CO from NICOM was consistently lower compared with that measured by echo at any given point, and the NICOM underestimated the CO in patients with isolated VSD.

Our study had several limitations. The first one is that we used fentanyl in noncardiac surgery and sufentanyl for cardiac patients. As sufentanyl is more potent and has longer duration, which may have different effects on CO, the potential for bias and error would still exist; therefore, it is difficult to determine whether the observations were attributable to differences in anesthetic techniques or in disease status. The second limitation is that our echocardiographic measurements were obtained by a single operator. Although this minimizes interobserver variability, it may lead to consistent operator-dependent bias.

In conclusion, we demonstrated that there is a good correlation and agreement between bioreactance-based CO monitoring and echo in children without cardiac anatomical defects during anesthesia induction. In pediatric patients with VSD, the CO measured by NICOM had similar trend but yielded lower numeric readings in comparison with echo results. Reactance-based noninvasive CO monitoring could be a promising technique in sick pediatric patients during the management of anesthesia, but further studies are warranted, especially in patients with more complex congenital heart defects and in children with the wider age and weight difference before it can be applied routinely in pediatric patients.

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Conflict of interest

No conflicts of interest declared.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1 Cardiac index measurements divided by body weight.

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