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ORIGINAL ARTICLE

# Hemodynamic reference for neonates of different age and weight: a pilot study with electrical cardiometry

K-H Hsu[1], T-W Wu[1], Y-C Wang[1], W-H Lim[1,2], C-C Lee[1] and R Lien[1]

**OBJECTIVE:** Electrical cardiometry (EC) is an impedance-based monitor that provides noninvasive, real-time hemodynamic assessment. However, the reference values for neonates have not been established.

**STUDY DESIGN:** EC (Aesculon) was applied to hemodynamically stable preterm and term infants. Hemodynamic variables included cardiac output (CO), cardiac index (CI), stroke volume (SV) and heart rate (HR). Their gestational age (GA), weight and body surface area (BSA) were recorded.

**RESULTS:** A total of 280 neonates were studied. Their GA ranged from $26^{5/7}$ to $41^{4/7}$ weeks, weight 800 to 4420 g and BSA 0.07 to 0.26 $m^2$. CO was positively correlated to GA, weight and BSA ($r = 0.681$, 0.822, 0.830, respectively; all $P < 0.001$). Using regression analysis, CO was most significantly correlated to BSA. Mean CI was $2.55 \pm 0.37$ l $min^{-1}$ per $m^2$.

**CONCLUSION:** Hemodynamic reference by EC is notably distinct among neonates of diverse maturity. CO is most closely correlated to BSA.

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## INTRODUCTION

In the care of critically ill patients, hemodynamic assessment is crucial for both diagnosis and management; however, clinical assessment of cardiac output (CO) by the interpretation of indirect parameters such as blood pressure may be misleading. In addition, trend monitoring instead of spot measurements may be more informative.[1] The thermodilutional technique has long been recognized as a standard CO measurement in pediatric patients, but the invasiveness and technical impracticability restrict its usefulness in neonates. Noninvasively, functional MRI has shown promise as a tool to accurately access CO, but does not allow for monitoring for prolonged periods. More commonly, noninvasive assessment of CO is estimated by Doppler measurements on echocardiogram, but this is technically demanding and can only be obtained intermittently. Ideally, hemodynamic monitoring in neonates should be accurate, practical, noninvasive, continuous in absolute measurements and feasible to entire spectrum of age and weight.[2]

Electrical cardiometry (EC) has been proposed as a safe, accurate and reproducible technique for hemodynamic measurement in children and infants.[3] It is an impedance-based monitoring device that provides real-time cardiovascular assessment. A high-frequency, low-magnitude, alternative current is generated by two distant electrodes (from head to left lower extremity), whereas two in-between electrodes (positioned at the neck and axilla) measure electrical changes dependent on alterations in thoracic electrical bioimpedance during the cardiac cycle. The changes in electrical bioimpedance is related to aortic flow pattern, and more specifically, influenced by the alignment of red blood cells in the aorta. When aortic flow stops and aortic valve closes, red blood cells are randomly orientated and interfere with electrical conduction. As the left ventricle contracts and aortic valve opens, the ejection of blood forces red blood cells to align in parallel with the flow, and the electrical current in the aorta passes with less impedance, which results in decreased impedance and higher conductivity. The pulsatile impedance waveform corresponds to the cardiac cycle. Moreover, the rate of impedance change is used in the calculation of hemodynamic measures, such as blood velocity, contractility, SV and CO.[4,5]

Clinical applications of EC have been widely studied. In comparison with the thermodilution technique, the usefulness of EC in providing hemodynamic measurements has been verified in piglet models[6] and adult population.[7] Furthermore, a good correlation was found between CO measurements by EC and pulmonary artery catheter thermodilution in children receiving catheterization.[8] EC has been shown to be comparable to direct Fick-oxygen method[9] and transesophageal Doppler[10] in CO measurements in infants with congenital heart disease. By using transthoracic echocardiogram, the accuracy of EC in children,[11,12] neonates[13,14] and even preterm infants[15–17] has been demonstrated. A recent study indicates that SV measurements by EC significantly correlated with measurements by transthoracic echocardiogram in preterm infants with gestational age (GA) 25 to 34 weeks.[18] Previously, we used EC to continuously monitor preterm infants during surgical ligation of the patent ductus arteriosus and found a significant CO deterioration upon termination of ductal shunting.[19] Cote *et al.*[20] also demonstrated clinical usefulness of EC in monitoring hemodynamics for children undergoing surgery.[20] Although the utilization of EC in the care of critically ill patients have gained popularity, normal hemodynamic parameters based on EC for neonates of different age and weight have not been reported. The clinical utilization relies heavily on measurement trends and not absolute values. Thus, we conducted this observational study to determine the reference ranges for hemodynamically stable neonates of diverse maturity and weight.

[1]Division of Neonatology, Department of Pediatrics, Chang Gung Memorial Hospital Linkou Branch and School of Medicine, Chang Gung University, Taoyuan, Taiwan and [2]Division of Neonatology, Department of Pediatrics, Chang Gung Memorial Hospital Keelung Branch, Keelung, Taiwan. Correspondence: Dr R Lien, Division of Neonatology, Department of Pediatrics, Chang Gung Memorial Hospital Linkou Branch and School of Medicine, Chang Gung University, 5, Fu-Hsing Street, Kweishan, Taoyuan 333, Taiwan. E-mail: reyinl@cgmh.org.tw
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## METHODS

### Study population

This prospective study was conducted in the neonatal department of Chang Gung Children Hospital from January to July 2013. The neonatal unit is a referral center with 37 intensive care beds, 70 sick-baby nursery beds and an annual admission of ~1800 infants. Our candidates were newborn neonates, either inborn or outborn, who were admitted before 72nd hour of life, and were evaluated for cardiovascular status between postnatal age third to fourth day of life. Only neonates with normal blood pressure according to *Philadelphia Neonatal Blood Pressure Study Group*,[21] normal heart rate, normothermia and adequate urine output $>1$ ml kg$^{-1}$ per day were considered hemodynamically stable and enrolled into the study. We excluded those with major malformations, inotrope support or sedative, structural heart disease other than a patent foramen ovale or atrial septal defect, excessive weight loss defined as $>10\%$ of birthweight, Apgar score $<7$ at 5-min, clinical evidence of perinatal asphyxia, ultrasound-confirmed intraventricular hemorrhage, bacteremia, hydrops fetalis or pleural effusion. Neonates with intrauterine growth restriction (IUGR, i.e., neonates born with birthweight $<10$th percentile for GA) were also identified. Institutional Review Board approved this study and written informed consent was obtained.

To evaluate the impact of invasive or noninvasive ventilator support on hemodynamic status, we performed a preliminary comparison before the design of the study. Adjusting for distinct demographic characteristics, we recognized that neonates with invasive mechanical ventilation had lower mean arterial pressure (MAP) and CO. However, there was no statistically hemodynamic difference between neonates breathing room air, using nasal cannula or with noninvasive ventilation support (i.e., continuous positive airway pressure, CPAP). Consequently, we also excluded neonates with invasive respiratory support in our study.

### EC setting

EC (Aesculon; Osypka Medical, Berlin, Germany) was applied by means of four standard surface electrocardiogram electrodes over the infants' forehead, left lower neck, left mid-axillary line at the level of xiphoid process and lateral aspect of left thigh. EC was set to record measurements at 1-min intervals. Sixty cardiac cycles were used for averaging parameters and for stroke volume variation (SVV) calculation. Default central venous pressure (CVP) by Aesculon was 3 mm Hg. This value was used in the calculation of systemic vascular resistance (SVR), based on the following formula: SVR = 80 x (MAP − CVP)/CO, reported in units dyn·s cm$^{-5}$.

### Parameters

Demographic descriptions, including gender, GA, weight, body surface area (BSA) and Apgar scores, were recorded. Weight at the time of experiment or birthweight, whichever was heavier, was adopted for EC calculation. BSA was computed according to the Boyd formula by Aesculon. Their respiratory condition was labeled as breathing room air, nasal cannula or nasal CPAP.

Hemodynamic parameters comprised of CO, cardiac index (CI), heart rate (HR), SV, SVV, thoracic fluid content (TFC), index of contractility (ICON) and SVR were provided by EC. CI is the product that relates CO to BSA (CO/BSA) and is used for evaluating cardiac performance among infants of different size. TFC is derived from the thoracic electrical base impedance (1/base impedance), which is dependent on thoracic intravascular and extravascular fluid. Larger TFC indicates a higher total thoracic fluid volume. ICON is derived from the maximum rate of change of thoracic electrical impedance. As ventricular contractility increases, the impedance falls at a faster rate, which results in a higher ICON value. Both TFC and ICON are unitless. Each individual's concurrent MAP and axillary temperature were also gathered.

### Measurement protocols

We performed EC measurement for each study neonates between postnatal age 72 to 96 h. The timing of examination was chosen to reduce the hemodynamic impact of patent ductus arteriosus, as most physiologic ductus arteriosus were functionally closed before age 24 to 48 h.[22] For neonates weighting $<1500$ g or $<32$ weeks of gestation, echocardiogram were performed to confirm closure of the ductus. We executed the measurements in the supine position during sleep, if feasible, or consoled them to avoid agitation. Phototherapy, if applied, was discontinued temporarily during the measurement. Blood pressure was recorded noninvasively with appropriate neonatal cuff immediately before EC measurement.

We defined at least five continuous and qualified signals (i.e., signal quality index, provided by Aesculon, $\geqslant 70\%$) before starting measurement as steady condition. Once one's condition was steady, five continuous and qualified measurements over the duration of 5 min were collected and subsequently averaged.

### Data analysis and statistics

Study neonates were sorted by GA ($\leqslant$28, 29 to 30, 31 to 32, 33 to 34, 35 to 36, 37 to 38, 39 to 41 weeks), weight ($<1000$, 1000 to 1499, 1500 to 1999, 2000 to 2499, 2500 to 2999, 3000 to 3499, $\geqslant 3500$ g) and BSA ($\leqslant$0.1, 0.11 to 0.13, 0.14 to 0.16, 0.17 to 0.19, 0.20 to 0.22, $\geqslant$0.23 m$^2$).

Statistical analysis was performed using IBM SPSS Statistics version 20 (Armonk, NY, USA). Correlation between parameters was assessed by Pearson's coefficient. When determining the relation between CO and GA, weight and BSA, and between CO and HR and SV, multiple regression analysis using step-wise model was also applied to adjust correlation. Statistical significance was defined as $P<0.05$.

## RESULT

A total of 280 hemodynamically stable neonates (148 male and 132 female; 118 term and 162 preterm babies) were recruited into the study. Their median (range) GA, weight and BSA were 36 (26 to 41) weeks, 2370 (800 to 4420) g and 0.17 (0.07 to 0.26) m$^2$, respectively. Their Apgar scores (mean ± s.d.) were 8 ± 1 and 10 ± 1 at 1 and 5 min of life. There were 29 IUGR neonates in this study. The demographic distribution and respiratory status are summarized in Table 1.

Hemodynamic measurements grouped by GA, weight and BSA are listed in Tables 2, 3 and 4, respectively.

### CO, CI and their correlation to GA, weight and BSA

CO ranged from 0.14 l min$^{-1}$ (GA 27 weeks, 800 g, BSA 0.07 m$^2$ preterm baby) to 0.94 l min$^{-1}$ (GA 40$^{6/7}$ weeks, 4410 g, BSA 0.25 m$^2$ infant). The CO reference for hemodynamically stable neonates was diverse. CO was significantly correlated to GA, weight and BSA ($r=0.681$, 0.822, 0.830, respectively; all $P<0.001$), which verified that larger neonates generally have higher CO. After regression analysis, CO was best correlated to BSA (adjusted $r^2=0.688$, $P<0.001$; Figure 1).

CI was not associated with GA, weight or BSA, and mean CI was 2.55 ± 0.37 l min$^{-1}$ per m$^2$ of our neonates. Moreover, we applied CI to compare cardiac performance between IUGR and non-IUGR neonates, and found that there was no significant difference in CI between the two groups (Table 5).

### SV and HR

SV and HR ranged from 0.94 to 6.43 ml and 101 to 177 beats per minute, respectively. Testing for correlation, SV correlated with GA, weight and BSA ($r=0.488$, 0.558, 0.563, respectively; all $P<0.001$), which further confirms the relationship between SV and the individual's body size, whereas HR had a negative correlation with GA, weight and BSA ($r=-0.441$, $-0.453$, $-0.441$, respectively; all $P<0.001$). Importantly, although HR decreased with GA and weight in our study, CO increased due to an increase in SV.

However, SVV varied greatly in our neonates; it ranged from 5.3 to 27, with a mean of 15.8 ± 4.4. There was no significant correlation between SVV and GA, weight, BSA, CO, CI or SV.

### Thoracic fluid content

TFC ranged from 15.1 of our smallest neonate to 41.4 of a term infant. TFC had a poor correlation with GA, weight and BSA ($r=0.264$, 0.356 and 0.369, all $P<0.001$), and moderate correlation to CO and CI ($r=0.511$ and 0.415, $P<0.001$).

**Table 1.** The demographic distribution and respiratory condition of studied neonates

| *Subgroup* | N *(% total)* | *Male,* n *(%)* | *CPAP,* n *(%)* | *IUGR,* n *(%)* | *Median (range)* |
|---|---|---|---|---|---|
| *GA (week)* | | | | | |
| ⩽28 | 11 (4%) | 5 (45%) | 11 (100%) | 1 (9%) | 36 (26–41) |
| 29–30 | 12 (4%) | 4 (33%) | 10 (83%) | 1 (8%) | |
| 31–32 | 31 (11%) | 15 (58%) | 24 (77%) | 1 (3%) | |
| 33–34 | 51 (18%) | 27 (53%) | 9 (18%) | 12 (24%) | |
| 35–36 | 58 (21%) | 30 (52%) | 7 (12%) | 8 (14%) | |
| 37–38 | 51 (18%) | 29 (59%) | 1 (2%) | 5 (10%) | |
| 39–41 | 66 (24%) | 38 (58%) | 0 (0%) | 1 (2%) | |
| *Weight (g)* | | | | | |
| < 1000 | 5 (2%) | 3 (60%) | 5 (100%) | 2 (40%) | 2370 (800–4420) |
| 1000–1499 | 36 (13%) | 15 (42%) | 25 (69%) | 14 (39%) | |
| 1500–1999 | 63 (23%) | 31 (49%) | 27 (43%) | 8 (13%) | |
| 2000–2499 | 42 (15%) | 20 (48%) | 2 (5%) | 5 (12%) | |
| 2500–2999 | 60 (21%) | 31 (52%) | 2 (3%) | 0 (0%) | |
| 3000–3499 | 41 (15%) | 24 (59%) | 0 (0%) | 0 (0%) | |
| 3500–3999 | 23 (8%) | 19 (83%) | 1 (4%) | 0 (0%) | |
| ⩾4000 | 10 (4%) | 5 (50%) | 0 (0%) | 0 (0%) | |
| *BSA ($m^2$)* | | | | | |
| ⩽0.1 | 15 (5%) | 8 (53%) | 15 (100%) | 7 (47%) | 0.17 (0.07–0.26) |
| 0.11–0.12 | 29 (10%) | 10 (34%) | 19 (66%) | 7 (24%) | |
| 0.13–0.14 | 50 (18%) | 29 (58%) | 21 (42%) | 7 (14%) | |
| 0.15–0.16 | 45 (16%) | 18 (40%) | 2 (4%) | 7 (16%) | |
| 0.17–0.18 | 51 (18%) | 27 (53%) | 4 (8%) | 1 (2%) | |
| 0.19–0.20 | 42 (15%) | 22 (54%) | 0 (0%) | 0 (0%) | |
| 0.21–0.22 | 35 (13%) | 26 (74%) | 1 (3%) | 0 (0%) | |
| ⩾0.23 | 13 (5%) | 8 (62%) | 0 (0%) | 0 (0%) | |
| Total | 280 | 148 (53%) | 62 (22%) | 29 (10%) | |

Abbreviations: BSA, body surface area; CPAP, continuous positive airway pressure; GA, gestational age; IUGR, intrauterine growth restriction.

**Table 2.** Neonatal hemodynamic reference of different age groups

| *GA (weeks)* | *CO (l $min^{-1}$)* | *CI (l $min^{-1}$ per $m^2$)* | *HR (beats $min^{-1}$)* | *SV (ml)* | *Thoracic fluid content* | *Index of contractility* | *SVR (dyn·s $cm^{-5}$)* |
|---|---|---|---|---|---|---|---|
| ⩽28 | 0.23 ± 0.03 | 2.31 ± 0.26 | 149 ± 11.4 | 1.56 ± 0.28 | 23.0 ± 3.4 | 77.7 ± 10.9 | 13 756 ± 3485 |
| 29–30 | 0.29 ± 0.06 | 2.45 ± 0.24 | 145 ± 8.7 | 1.99 ± 0.44 | 22.6 ± 5.4 | 86.1 ± 15.3 | 10 959 ± 3393 |
| 31–32 | 0.35 ± 0.07 | 2.69 ± 0.36 | 142 ± 8.9 | 2.53 ± 0.47 | 25.2 ± 4.8 | 88.7 ± 16.2 | 8931 ± 2827 |
| 33–34 | 0.35 ± 0.07 | 2.54 ± 0.32 | 142 ± 15.7 | 2.49 ± 0.60 | 24.6 ± 4.6 | 82.1 ± 16.4 | 9911 ± 2722 |
| 35–36 | 0.43 ± 0.08 | 2.64 ± 0.33 | 136 ± 13.5 | 3.22 ± 0.70 | 27.7 ± 6.1 | 78.4 ± 14.6 | 8539 ± 1849 |
| 37–38 | 0.47 ± 0.10 | 2.49 ± 0.39 | 131 ± 11.9 | 3.67 ± 0.72 | 27.8 ± 5.1 | 70.0 ± 16.0 | 8534 ± 2405 |
| 39–41 | 0.53 ± 0.14 | 2.60 ± 0.54 | 126 ± 12.1 | 4.24 ± 0.89 | 27.0 ± 5.5 | 69.7 ± 15.3 | 8391 ± 2500 |

Abbreviations: CI, cardiac index; CO, cardiac output; GA, gestational age; HR, heart rate; SV, stroke volume; SVR, systemic vascular resistance. Values are mean ± s.d.

### Index of contractility

The value of ICON varied between individuals, and it had mild negative correlation to GA, weight or BSA ($r = -0.332$, $-0.345$ and $-0.345$, all $P < 0.001$). It had no association to CO; however, it was moderately correlated to CI ($r = 0.678$, $P < 0.001$).

### Systemic vascular resistance

SVR had a negative correlation with GA, weight and BSA ($r = -0.398$, $-0.527$ and $-0.545$; all $P < 0.001$), and also a negative correlation with CO and CI ($r = -0.749$ and $-0.618$; $P < 0.001$).

## DISCUSSION

CO drives global oxygen delivery and a lower than reference value could serve as a negative prognostic indicator, which is highly valuable in the intensive care setting.[23] We recognize that the absolute value of CO measured by bioimpedance, echocardiogram, thermodilution or Fick's method are not interchangeable[24] and parameters may vary between different measuring methods.[12] Establishing reference parameters for EC is extremely important for clinicians, as measurements that fall out of the said reference range may be alarming.

We also believe that the reference value should be maturity-specific or body weight-specific. Unlike adults or older children, body size or maturity differs greatly from an extremely preterm baby to a post-term infant. This influences cardiac function accordingly. Neonates are therefore a special population that deserves a precise and comprehensive hemodynamic reference. Our study is the first to exhibit hemodynamic measurements for neonates of different size and age by the bioimpedance method.

In consideration of the hemodynamic influence from different modalities of noninvasive respiratory support, we found that there was no significant CO dissimilarity among neonates with ambient

**Table 3.** Neonatal hemodynamic reference of different weight groups

| *Weight (g)* | *CO (l min$^{-1}$)* | *CI (l min$^{-1}$ per m$^2$)* | *HR (beats min$^{-1}$)* | *SV (ml)* | *Thoracic fluid content* | *Index of contractility* | *SVR (dyn·s cm$^{-5}$)* |
|---|---|---|---|---|---|---|---|
| < 1000 | 0.19 ± 0.03 | 2.32 ± 0.17 | 155 ± 6.8 | 1.26 ± 0.20 | 20.4 ± 4.9 | 79.2 ± 6.2 | 15 790 ± 4117 |
| 1000–1499 | 0.27 ± 0.04 | 2.41 ± 0.28 | 145 ± 12.9 | 1.90 ± 0.35 | 22.2 ± 3.9 | 84.1 ± 16.1 | 12 280 ± 2865 |
| 1500–1999 | 0.35 ± 0.05 | 2.58 ± 0.35 | 141 ± 12.1 | 2.54 ± 0.40 | 25.5 ± 4.3 | 83.7 ± 17.3 | 9198 ± 2159 |
| 2000–2499 | 0.41 ± 0.06 | 2.58 ± 0.31 | 137 ± 13.6 | 3.01 ± 0.46 | 26.3 ± 4.7 | 78.0 ± 13.8 | 8710 ± 1962 |
| 2500–2999 | 0.46 ± 0.08 | 2.56 ± 0.44 | 131 ± 14.0 | 3.58 ± 0.61 | 28.2 ± 5.7 | 73.1 ± 16.2 | 8530 ± 1978 |
| 3000–3499 | 0.51 ± 0.09 | 2.58 ± 0.40 | 131 ± 12.3 | 3.96 ± 0.67 | 28.1 ± 5.6 | 68.9 ± 15.6 | 8022 ± 2323 |
| 3500–3999 | 0.54 ± 0.08 | 2.51 ± 0.36 | 126 ± 11.4 | 4.34 ± 0.61 | 27.8 ± 4.9 | 67.3 ± 13.4 | 7280 ± 1917 |
| ⩾4000 | 0.65 ± 0.11 | 2.76 ± 0.41 | 129 ± 9.8 | 5.10 ± 0.72 | 28.7 ± 5.4 | 70.5 ± 10.1 | 6575 ± 1385 |

Abbreviations: CI, cardiac index; CO, cardiac output; HR, heart rate; SV, stroke volume; SVR, systemic vascular resistance. Values are mean ± s.d.

**Table 4.** Neonatal hemodynamic reference of different BSA groups

| *BSA (m$^2$)* | *CO (l min$^{-1}$)* | *CI (l min$^{-1}$ per m$^2$)* | *HR (beats min$^{-1}$)* | *SV (ml)* | *Thoracic fluid content* | *Index of contractility* | *SVR (dyn·s cm$^{-5}$)* |
|---|---|---|---|---|---|---|---|
| ⩽0.1 | 0.22 ± 0.03 | 2.37 ± 0.18 | 151 ± 7.5 | 1.53 ± 0.23 | 21.3 ± 4.0 | 84.2 ± 9.9 | 13 951 ± 3089 |
| 0.11–0.12 | 0.29 ± 0.06 | 2.47 ± 0.35 | 144 ± 14.4 | 2.04 ± 0.35 | 22.6 ± 3.9 | 82.1 ± 17.2 | 11 208 ± 2613 |
| 0.13–0.14 | 0.35 ± 0.05 | 2.58 ± 0.34 | 142 ± 11.5 | 2.50 ± 0.40 | 25.6 ± 4.3 | 85.5 ± 16.8 | 9473 ± 2433 |
| 0.15–0.16 | 0.39 ± 0.05 | 2.54 ± 0.30 | 136 ± 14.5 | 2.91 ± 0.42 | 25.9 ± 4.6 | 77.9 ± 15.5 | 8799 ± 2007 |
| 0.17–0.18 | 0.45 ± 0.07 | 2.59 ± 0.42 | 133 ± 12.8 | 3.47 ± 0.57 | 28.1 ± 5.6 | 74.7 ± 15.8 | 8410 ± 1859 |
| 0.19–0.20 | 0.48 ± 0.08 | 2.47 ± 0.42 | 129 ± 14.2 | 3.78 ± 0.62 | 27.2 ± 5.2 | 67.5 ± 15.1 | 8715 ± 2299 |
| 0.21–0.22 | 0.55 ± 0.09 | 2.63 ± 0.38 | 128 ± 11.0 | 4.38 ± 0.62 | 29.2 ± 5.6 | 70.4 ± 14.6 | 7066 ± 1972 |
| ⩾0.23 | 0.62 ± 0.11 | 2.70 ± 0.41 | 132 ± 9.0 | 4.78 ± 0.78 | 28.2 ± 5.3 | 68.1 ± 12.2 | 6916 ± 1414 |

Abbreviations: BSA, body surface area; CO, cardiac output; CI, cardiac index; HR, heart rate; SV, stroke volume; SVR, systemic vascular resistance. Values are mean ± s.d.

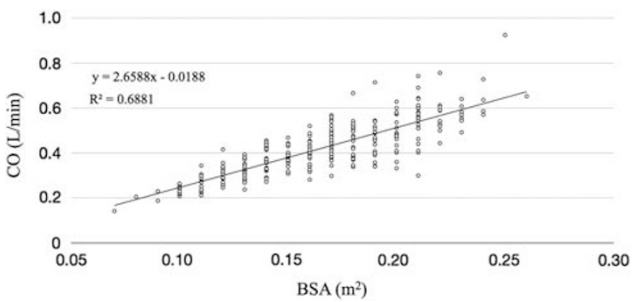


**Figure 1.** A good positive correlation is seen between cardiac output (CO) and body surface area (BSA), which indicates that CO values vary with individual's size.

**Table 5.** Comparison of CI between IUGR and non-IUGR neonates of corresponding BSA subgroups

| *BSA (m$^2$)* | *IUGR* | | *non-IUGR* | | P-*value* |
|---|---|---|---|---|---|
| | n | *CI (l min$^{-1}$ per m$^2$)*[a] | n | *CI (l min$^{-1}$ per m$^2$)*[a] | |
| ⩽0.1 | 7 | 2.35 ± 0.15 | 8 | 2.38 ± 0.22 | 0.794 |
| 0.11–0.12 | 7 | 2.40 ± 0.30 | 22 | 2.49 ± 0.37 | 0.567 |
| 0.13–0.14 | 7 | 2.46 ± 0.27 | 43 | 2.60 ± 0.35 | 0.364 |
| 0.15–0.16 | 7 | 2.42 ± 0.17 | 38 | 2.56 ± 0.31 | 0.252 |
| 0.17–0.18 | 1 | 2.65 | 49 | 2.59 ± 0.43 | N/A |

Abbreviations: BSA, body surface area; CI, cardiac index; IUGR, intrauterine growth restriction; N/A, not applicable. [a]Values are mean ± s.d.

breathing or CPAP. This is in line with previous echocardiographic studies where circulation compromise was not demonstrated in preterm infants using CPAP.[25] In contrast, invasive mechanical ventilation, positive end expiratory pressure can affect cardiac function and cause a fall in CO and SV,[26] but the degree of ventilation-associated hemodynamic compromise warrants further and more comprehensive hemodynamic investigation.

In our study, we demonstrated that the reference for neonatal hemodynamic measurements should be assessed according to individual age and body size. CO, SV and TFC were positively correlated to GA, weight and BSA, whereas HR, ICON and SVR were negatively correlated. In larger neonates, HR was generally lower and a relatively higher SV contributed to a higher CO. Because vascular resistance depends on vessels' diameter, it is inevitable that smaller neonates will have greater SVR and larger neonates have lesser SVR. Notably, we conclude that grouping CO measures based on BSA is more suitable than GA or body weight. Therefore, to compare cardiac performance between neonates, we recommend the use of CI, an indicator related to BSA, to minimize maturity difference. Furthermore, we found that the use of CI as a reference applies to IUGR infants as well, as no significant difference in CI was found between IUGR and non-IUGR infants. However, the utility of EC to evaluate specific contributing factors of CO, that is, preload, contractility and afterload, should be discussed.

Preload or intravascular volume is not assessed by EC. Preload is the end volumetric pressure that stretches the ventricles, which is usually measured as end diastolic volume in echocardiogram. There is no similar measurement to be achieved by EC. Although EC provides TFC as an indicator of total thoracic fluid, its usefulness is to evaluate either pulmonary fluid overload (pulmonary edema) or soft tissue edema. Larger neonates have a higher TFC; however, it does not adequately represent intravascular volume and the relationship between total thoracic fluid and intravascular volume is not clear. Another indicator, SVV, has been proposed as a predictor of fluid responsiveness for ventilated patients under surgery:[27] the greater the variation, the better the response to fluid expansion, suggesting a low preload status. In our experience, SVV fluctuates quickly when the neonate is active or crying, making it difficult to interpret.

EC only gives theoretical information about cardiac contractility, represented by the parameter ICON, based on the rate of change of thoracic impedance. Myocardial contractility denotes the ability of ventricle to contract and pump, which is commonly represented as ejection fraction in echocardiogram. Although ICON and CI are positively correlated in our study, its correlation to ejection fraction in echocardiogram is still unknown. EC also provides indirect measures of LV performance by pre-ejection period, left ventricular ejection time and systolic time ratio (by means of pre-ejection period/left ventricular ejection time),[28] but HR will notably affected by these parameters. When HR increases, pre-ejection period and left ventricular ejection time shorten, and systolic time ratio changes accordingly. As reference range of HR varied among cases, pre-ejection period, left ventricular ejection time and systolic time ratio were unavoidable affected as well, which limit their usefulness in comparison. Therefore, we remain speculative in the usefulness of these three parameters by EC in the neonatal population.

Vascular resistance is one of the factors that determine afterload, and SVR by EC is calculated by the formula: 80 x (MAP – CVP)/CO, under the assumption that CVP is 3 mm Hg. We recognize that such assumption may lead to imprecise SVR calculations. However, SVR can still be useful in trending changes within individual patients. Several limitations should be addressed. First, we did not compare EC with other conventional methods of measurements such as echocardiogram. As plenty of studies have tested the same device in pediatric population,[8–18] we did not intend to verify its effectiveness in our study. Furthermore, our results were compatible with previous comparison studies. Noori *et al*.[13] had performed paired measurements in 20 healthy neonates and concluded that EC is as accurate in measuring CO as echocardiogram. In that study, the mean CO was 0.534 l min$^{-1}$ for term infants weighing ~3 kg. Our results were comparable: for neonates aged GA $\geqslant$ 39 weeks, mean CO is $0.49 \pm 0.1$ l min$^{-1}$ and for those weighed 3000–3499 g, mean CO is $0.53 \pm 0.14$ l min$^{-1}$. However, we acknowledged that more data are needed to demonstrate accuracy, precision and utility of EC before it can be applied in clinical settings. Second, we excluded neonates who were invasively ventilated. As mentioned previously, insufficient understanding of ventilator-associated influence on EC may limit it usefulness in some critically ill neonates. Third, the reference could not be fully applied in neonates with structural heart disease other than a PFO or ASD. Because hemodynamics may be significantly altered among those with structural heart disease, measurements by EC should be interpreted with caution.

In conclusion, hemodynamic reference is notably distinct among neonates of differing maturity. We established the hemodynamic reference for EC, and found CO to be closely correlated to BSA. The reference table can aid in the bedside evaluation of neonatal cardiac performance and in clinical decision-making.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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