



Indexing haemodynamic variables in young children

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Background: Haemodynamic studies in children are rare and most studies have included few subjects in the youngest age group. Haemodynamic variables need to be indexed to establish a reference of normality that is valid in all populations. The traditional way to index haemodynamic variables with body surface area (BSA) is complicated in young children due to its non-linear relationship with body weight (BW). We examined several haemodynamic variables in children by indexing them with BSA and BW.

Methods: A single-centre, observational cohort study comparing non-indexed and indexed haemodynamic variables in children undergoing heart surgery (divided into three weight groups: 1-5 kg, >5-10 kg and >10-15 kg).

Results: A total of 68 children were included in this study, mean age 11.1 months \pm 11.1 month (range 0 to 43 months). All haemodynamic variables, cardiac output (CO), stroke volume (SV), total end-diastolic volume (TEDV), central blood volume (CBV) and active circulation volume (ACV), increased with weight without indexing ($P < .05$). Indexing variables with BW produced a more linear relationship for all haemodynamic variables between weight groups than BSA. The mean BSA-indexed haemodynamic values were $Cl_{BSA} 3.5 \pm 1.1$ L/min/m² and $SVI_{BSA} 27.3 \pm 8.9$ ml/min/m². The mean BW-indexed haemodynamic values were $Cl_{BW} 180 \pm 50$ ml/min/kg and $SVI_{BW} 1.34 \pm 0.38$ ml/kg. Blood volume variables indexed with BW were $TEDV_{BW} 12.0 \pm 2.8$ ml/kg, $CBV_{BW} 21.3 \pm 6.6$ ml/kg and $ACV_{BW} 70.3 \pm 15.2$ ml/kg.

Conclusions: Indexing haemodynamic variables with BW produces a more appropriate body size-independent scale in young children than BSA.

Summary statement: In this study, we studied indexing of haemodynamic variables and estimation of blood volumes in young children undergoing corrective heart surgery using an indicator dilution technology.

1 | INTRODUCTION

In order to identify and treat unnatural circulatory changes in critically ill patients, it is important to know the limits of normality. Indexing of haemodynamic variables has therefore been used to establish comparable body size-independent reference

values valid for the whole population.¹ In the growing child, haemodynamic reference values are constantly changing making their estimation challenging.²⁻⁴ Indexing is also complicated by the fact that children have a relatively larger body surface area (BSA) compared with body weight (BW) than adults, resulting in a non-linear-indexed haemodynamic variables.⁵ Empirical formulas

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used to determine BSA in children often disagree in their calculations, adding to possible errors regarding estimations of indexed haemodynamic variables.⁶

In 1963, Jegier and colleges published their landmark paper using dye dilution method, on the relationship between cardiac output (CO) and body size, comparing indexing with BSA and BW.⁷ They found that although both size variables had a similar correlation with CO, there was a significant difference between age groups when BSA was used for CO indexing. However, their conclusion was that this difference in indexing with BSA and BW was not significant enough to justify a change in the already established tradition of using BSA for indexing of haemodynamic variables. These findings, almost 60 years ago, strongly suggested that indexing CO with BSA might be suboptimal due to its non-linear relationship with BW in young children.

Our hypothesis in the present study was that BW would be a more appropriate indexing alternative than BSA, to establish body size-independent reference values for haemodynamic variables in young children. The primary aim was to examine several haemodynamic variables indexed with BSA and BW. A secondary aim was to define indexed reference blood volume values and investigate the effect of intracardiac shunts on their estimations.

2 | MATERIALS AND METHODS

We performed a single-centre, retrospective observational cohort study in young children with congenital heart defects undergoing corrective heart surgery of atrial septal and/or ventricle septal defects. The inclusion criteria for this study were written informed parental consent, elective open-heart surgery and weight less than 15 kilograms. All children included in this study were enrolled from two similar haemodynamic studies^{8,9} at Lund Children's Hospital from February 2010 to March 2017. These studies were approved and registered by the Ethics Committee of Lund University, Sweden (Dnr 2009/708 and Dnr 2013/636).

2.1 | Experimental protocol

Anaesthesia was performed with a bolus of fentanyl (5 µg/kg) and thiopental (5 mg/kg). Pancuronium (0.2 mg/kg) was used for muscle relaxation and to facilitate endotracheal intubation. Isoflurane (0.5–1.0%) was used for maintaining anaesthesia for the duration of the operation. A Dräger Apollo anaesthesia machine (Drägerwerk AG & Co, Lübeck, Germany) maintained ventilation with tidal volumes of 7–8 ml/kg and FiO₂ <0.40. All children received a central venous catheter (Multicath triple lumen 6 cm, 4.5 F, Vygon Ltd, Swindon, UK) into the internal jugular vein and a peripheral arterial catheter in the radial artery (Neoflon 24 G < 5 kg patient and Venflon 22 G > 5 kg patient, BD Ltd, Wokingham, UK). The COstatus monitor and the arteriovenous loop were then connected to the arterial and central venous catheters in preparation for measurements. Up to five repeated consecutive haemodynamic measurements were performed before and

Editorial Comment

Using a small cohort of young children undergoing open-heart surgery, the authors compared indexed and non-indexed haemodynamic variables in three weight groups of children. The findings support the idea that weight-indexed haemodynamics may produce a more appropriate body size-independent scale compared to body surface area.

after the surgical correction.^{8,9} Transoesophageal echocardiography was performed after correction to exclude residual shunts.

2.2 | Determination of cardiac output

The determination of CO was obtained by the novel COstatus monitor device (Transonic Systems Inc, New York, USA). It uses an extracorporeal arteriovenous circuit (AV loop) connected to the arterial and central venous catheters where blood flow is regulated by a roller pump. External ultrasound sensors are attached to the venous and arterial sides of the AV loop. The ultrasound sensor on the venous side determines the amount of blood dilution after a venous injection of a normothermic saline bolus (0.5–1.0 ml/kg), and the ultrasound sensor on the arterial side determines the level of dilution after transcadiopulmonary passage of the blood. CO is determined by analysing the transcadiopulmonary blood dilution curve based on Stewart-Hamilton's indicator dilution principle.^{10–12} CO and derived variables, such as stroke volume (SV), are displayed on the monitor. The technology used by COstatus has been validated and shown to be accurate, precise and safe in several paediatric studies.^{9,13–16}

2.3 | Determination of blood volume

The use of an AV loop with constant blood flow enables measurements of other haemodynamic variables, such as total end-diastolic volume (TEDV), central blood volume (CBV) and active circulation volume (ACV), from the dilution curve.

Total end-diastolic volume (TEDV) is defined as blood volume in the four chambers of the heart at the end of diastole. Its calculation is based on the assumption that the increase in width of the arterial dilution curve, compared to the venous dilution curve, is due to a delay in the propagation of the indicator when it travels through a volume expanding capacitor, such as the heart chambers.¹⁵ The width of the dilution curves is determined at half their height and is denoted as chords (CH). CH_{art} and CH_{ven} are the length of the chords of the arterial and venous curves in time units.

$$TEDV = (CO * (1.62/HR + 0.77 * CH_c))$$

HR: Heart rate (beats per minute).

$$CH_c = \left(CH_{art}^2 - CH_{ven}^2 \right)^{1/2}$$

This approach has been evaluated in models and patients and has proved to be a robust descriptor of intracardiac blood volume.¹⁷ The assumption is not true if shunts are present, and when the chords' length increases, limiting the TEDV calculation to patients without intracardiac shunts.

Central blood volume (CBV) is defined as the blood volume between the injection of the indicator saline bolus (central venous line) and the recording site (arterial line). This blood volume includes the volume in the heart, lungs and larger central vessels. It is determined by calculating the volume of measured CO distributed into this part of circulation during the mean transit time (MTT) it takes for the indicator to travel through the lungs, heart and central arteries. The time is determined as the time of the indicator travelling from the site of injection (venous sensor) to the site of detection (arterial sensor) (MTT_a), minus the MTT from venous injection until detection by the venous sensor (MTT_v), minus the MTT of the indicator in the AV loop until it is detected by the arterial sensor (MTT_t). $MTT_t = V_a/Q_a$, where V_a is the priming volume of the AV loop system and Q_a is the constant blood flow in the AV loop. To determine V_a , a correction factor ($\Delta_{location}$) is applied automatically to the program to correct different locations of the venous catheter, which may affect the transit time of the indicator on the venous side.

$$CBV = (CO * (MTT_a - MTT_v - MTT_t)).$$

Active circulation volume (ACV) is defined as the blood volume that the saline indicator mixes in within 1 minute from the time of injection. It represents the blood volume in all the major organs (heart, lungs, brain, kidneys and liver) and large vessels.

It is calculated by dividing the volume of the injected isotonic saline indicator in millilitres (V_{inj}) by the level of isotonic saline concentration in blood (H_{blood}), as recorded by the arterial sensor 1 minute after injection.

$$ACV = (V_{inj} / H_{blood}).$$

2.4 | Statistical analysis

Data were registered in Windows Excel 365 (Microsoft Corporation, Washington, USA) and statistical analysis was performed with Statistica version 13 (Dell Inc, Oklahoma, USA).

A sensitivity power analysis was performed using G-Power 3.1 software (Kiel University, Kiel, Germany). In this retrospective cohort study (N = 68), it was showed that with a small effect size ($d = 0.4$) and a pooled standard deviation (SD) of 0.18 L/min (according to earlier studies), we should have detected a difference in mean CI_{BSA} values as low as 0.07 L/min between groups. This was considered to be adequate for statistical analysis, although the groups were not evenly divided.

Coefficient of error (CE) was used to calculate precision instead of the coefficient of variation (CV) to correct for repeated measurements (n), as suggested by Cecconi et al ($CE = CV/\sqrt{n}$).¹⁸ Precision is defined as $2 * CE$ and $<10\%$ was considered an acceptable precision.

Subjects were divided into three weight groups (1-5 kg, >5-10 kg and >10-15 kg) to analyse the effect of no indexing, indexing for BSA and indexing for BW. The Fisher's test and Kruskal-Wallis test were used to see if there was a significant difference between groups. Normal distribution was tested with the Shapiro-Wilk test. A statistical difference of $P < .05$ was considered significant.

3 | RESULTS

A total of 68 children (51% female) undergoing corrective heart surgery of atrial septal defect and/or ventricular septal defect (all classified as ASA IV) were included in this study. Their mean age was 11.1 months \pm 11.1 month (range 0-43 months), mean BSA 0.35 m² \pm 0.11 m² (range 0.18-0.59 m²) and a mean weight of 7.0 kg \pm 3.0 kg (range 2.7-14.1 kg). A total of 212 blood volume measurements were available before correction and 274 measurements after correction.

3.1 | Indexing of haemodynamic variables

Blood flow (CO) and blood volume (SV, TEDV, CBV and ACV) variables indexed for BSA and BW are presented in Table 1.

The mean BSA-indexed haemodynamic values were CI_{BSA} 3.5 \pm 1.1 L/min/m² and SVI_{BSA} 27.3 \pm 8.9 ml/min/m². The mean BW-indexed haemodynamic values were CI_{BW} 180 \pm 50 ml/min/kg and SVI_{BW} 1.34 \pm 0.38 ml/kg. CO without indexing increased with weight groups. CO indexed for BSA (CI_{BSA}) tended to increase with weight groups but was not statistically significant ($P = .091$). CO indexed to weight (CI_{BW}) did not change between the weight groups. A linear regression analysis of CO indexing for BSA (CI_{BSA}) and weight (CI_{BW}) showed a significant deviation of CI_{BSA} ($P = .003$), but CI_{BW} was stable in all the children's weights included in the cohort (Figure 1). BSA/BW ratio was exponentially increased in our study cohort compared expected BSA/BW ratio in older individuals confirming a non-linear relationship between BSA and BW in different age groups (Figure 2).

SV increased with weight groups and after indexing for BSA (SVI_{BSA}), but not when it was indexed for weight (SVI_{BW}).

TEDV increased with weight groups and after indexing for BSA ($TEDVI_{BSA}$), but it did not when indexed for weight ($TEDVI_{BW}$).

CBV increased with weight groups and after indexing for BSA ($CBVI_{BSA}$), but not when it was indexed for BW ($CBVI_{BW}$).

ACV increased significantly with weight. After indexing for BSA ($ACVI_{BSA}$), it tended to increase, but this was not statistically significant. ACV indexing with BW ($ACVI_{BW}$) did not change between weight groups.

TABLE 1 Haemodynamic variables and blood volume by separate weight groups (N = 68)

Haemodynamic variables	Weight groups (N = number of subjects)			Statistical significance
	1 - 5 kg (N = 22)	>5 - 10 kg (N = 32)	>10 - 15 kg (N = 14)	P value
Mean (CO) ±SD (l/min)	0.77 ± 0.28 ^{#^***}	1.24 ± 0.53 ^{#^***}	2.07 ± 0.46 ^{#^***}	<.001
Mean (CO/BSA) ±SD (l/min/m ²)	3.18 ± 1.04	3.48 ± 1.07	4.01 ± 1.03	.091
Mean (CO/BW) ±SD (ml/min/kg)	190 ± 50	180 ± 50	180 ± 50	.669
Mean (SV) ±SD (ml)	5.7 ± 2.0 ^{#^***}	9.8 ± 4.7 ^{#^***}	17.7 ± 4.1 ^{#^***}	<.001
Mean (SV/BSA) ±SD (ml/m ²)	23.0 ± 6.6 ^{^***}	27.4 ± 8.9	33.8 ± 8.5 ^{^***}	.002
Mean (SV/BW) ±SD (ml/kg)	1.4 ± 0.4	1.4 ± 0.4	1.5 ± 0.4	.577
Mean (TEDV) ±SD (ml)	52.4 ± 17.6 ^{#^***}	76.7 ± 24.9 ^{#^***}	143.6 ± 30.8 ^{#^***}	<.001
Mean (TEDV/BSA) ±SD (ml/m ²)	214.0 ± 61.5	221.2 ± 45.5 ^{^**}	278.6 ± 68.5 ^{^**}	.006
Mean (TEDV/BW) ±SD (ml/kg)	12.7 ± 3.6	11.4 ± 1.9	12.4 ± 3.3	.430
Mean (CBV) ±SD (ml)	82.8 ± 42.2 ^{#^***}	132.7 ± 67.0 ^{#^***}	269.3 ± 70.5 ^{#^***}	<.001
Mean (CBV/BSA) ±SD (ml/m ²)	355.8 ± 150.0 ^{^***}	372.1 ± 134.0 ^{^**}	521.7 ± 147.4 ^{^***}	.001
Mean (CBV/BW) ±SD (ml/kg)	19.8 ± 8.5	19.3 ± 5.5	23.2 ± 7.2	.104
Mean (ACV) ±SD (ml)	312.0 ± 93.6 ^{#^***}	475.2 ± 138.1 ^{#^***}	785.0 ± 167.2 ^{#^***}	<.001
Mean (ACV/BSA) ±SD (ml/m ²)	1269.9 ± 311.3	1366.1 ± 282.0	1517.4 ± 332.9	.113
Mean (ACV/BW) ±SD (ml/kg)	75.5 ± 19.5	69.8 ± 13.3	67.6 ± 16.1	.322

Abbreviations:: CO, cardiac output; SD, standard deviation; BSA, body surface area; BW, body weight; SV, stroke volume; TEDV, total end-diastolic volume; CBV, central blood volume; ACV, active circulation volume.

[#]Significance between 1-5 kg and > 5-10 kg; [^]Significance between >5-10 kg and >10-15 kg; [^]Significance between 1-5 kg and >10-15 kg (*P < .05, **P < .01, ***P < .001).

3.2 | Reference values for indexed haemodynamic variables

Values for the haemodynamic variables indexed for BW are presented in Table 2. The effects of a surgical closure of an intracardiac shunt on haemodynamic variables are shown in Figure 3(A-D). Statistically, the haemodynamic variables CI_{BW} , SVI_{BW} , $CBVI_{BW}$ and $ACVI_{BW}$ did not change significantly after surgical correction.

3.3 | Effect of intracardiac shunt on precision

The variability of the measurements decreased and precision improved for CI_{BW} , SVI_{BW} and $CBVI_{BW}$ after the correction of the intracardiac shunt (Table 3). Repeated haemodynamic measurements were available from 44 children before and after correction.

4 | DISCUSSION

In young children, BW was a more appropriate indexing alternative than BSA to eliminate the influence of body size on haemodynamic variables. This indexing enables the comparison of values between children of different sizes and makes it possible to define normal haemodynamic reference values.

In general, regarding all species, physiological metabolic variables, such as oxygen consumption and alveolar ventilation, seem to follow allometric principles in an exponential manner. Same exponential relationship has been believed to apply to CO as a physiological flow variable. At the same time, it has been noticed that volume variables tend to follow a more linear relationship with BW. Several efforts have been made to achieve haemodynamic reference values in young children in the past, but the cohorts are often small and based on the accepted routine to index the values according to BSA.¹⁹⁻²¹ These studies have shown that the use of BSA as an index, or normalization, is still unsupported by data in infants and that the exponential relationship between BSA and some haemodynamic variables in smaller children needs to be explained.^{22,23} This is supported by the exponential increase in the BSA/weight ratios that occurs in smaller children (Figure 2).

We found an extraordinarily good agreement in the indexing of CO to kilogram BW (CI_{BW}) in our weight groups of young children (Table 1). However, it is obvious that there is an upper cut-off weight where the indexing to BW overestimates CO (it is unrealistic to believe a normal individual weighing 100 kg to have a CO of 18 l/min). It has been shown that the Du Bois equation, which was used in this study, deviates significantly from the BSA versus BW curve in weights below 15 kg.⁵ This may indicate that there is an optimal weight level and that CO is better indexed by weight below this level. This must be defined, but according to our results, it is probably near our study maximal weight of around 15 kg.

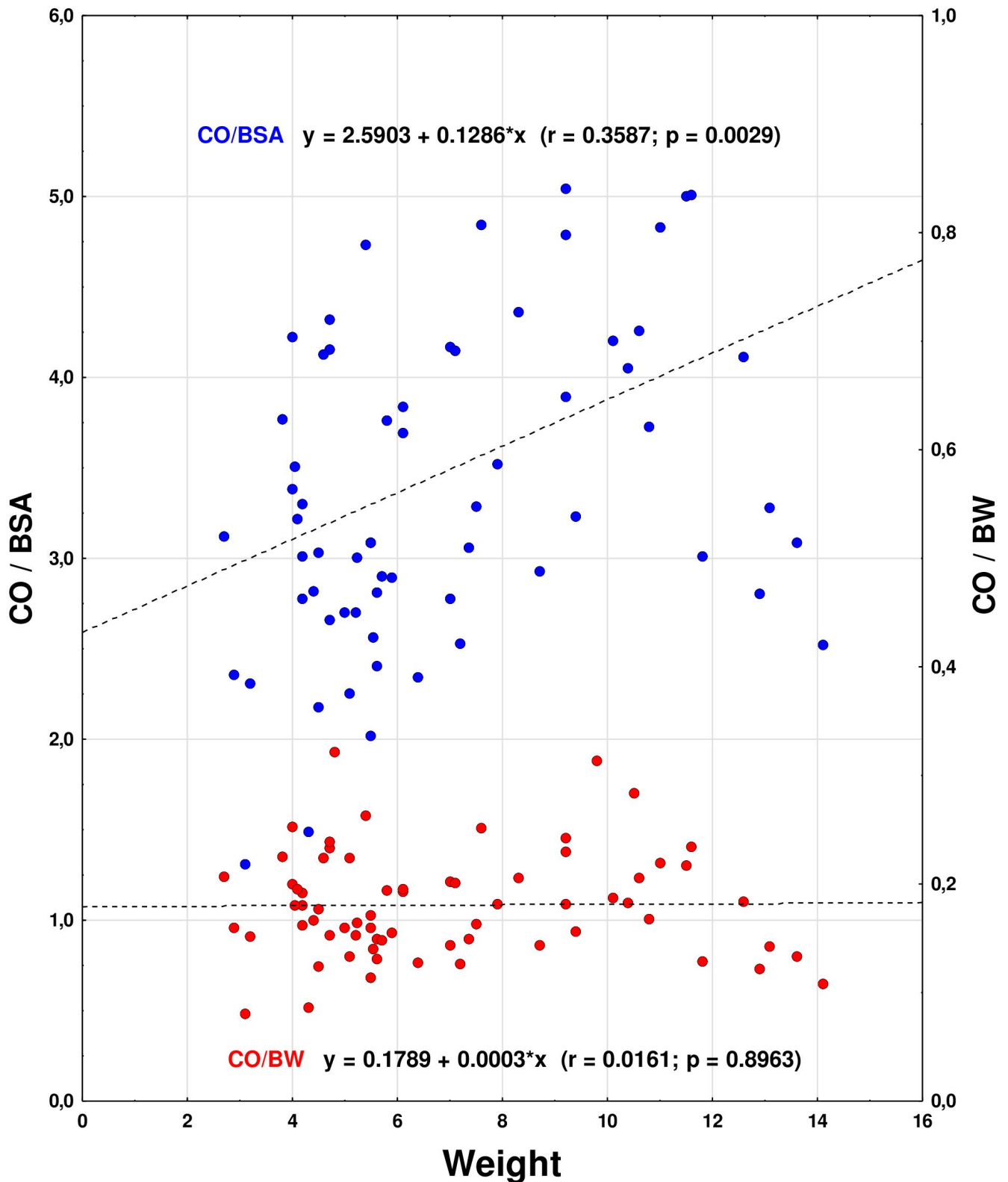


FIGURE 1 Cardiac output indexed for body surface area (BSA) and body weight (BW). Graph demonstrating the non-linear relationship between BSA and BW with increased weight. This implies that indexing with BSA will not produce indexed reference values that are valid in all weight groups

Intracardiac blood volumes, such as SV and TEDV, are routinely indexed for BSA, analogous to CO. In our analysis, both SV and TEDV increased after indexing for BSA, but, when indexing with

BW (SV_{BW} and $TEDV_{BW}$), they were remarkably stable across all weight groups. The same non-linear relationship between intracardiac blood volume and BSA was confirmed in a magnetic resonance

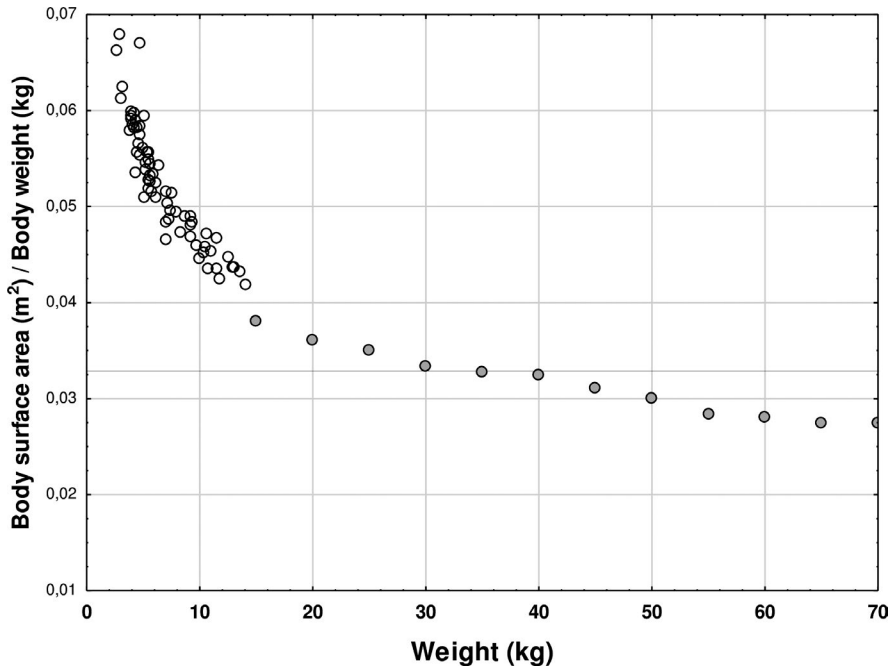


FIGURE 2 The relationship between body surface area (BSA) and body weight (BW) at different weights. BSA/BW ratio from the study cohort (white dots; children < 15 kg) compared with BSA/BW ratio in older individuals (grey dots; standard values 15-70 kg, established with Costeff weight-based empirical BSA formula: $[4W \text{ (kg)} + 7]/[90 + W \text{ (kg)}]$). This graph demonstrates how the BSA/BW ratio exponentially deviates from the baseline (horizontal line) in younger children

TABLE 2 Overview of haemodynamic values in children <15 kg (N = 68). Cardiac output, stroke volume and blood volume indexed for body weight in children after heart surgery

Variable	Mean \pm SD
CI_{BW}	180 ± 50 ml/min/kg
SVI_{BW}	1.34 ± 0.38 ml/kg
$CVBI_{BW}$	21.3 ± 6.6 ml/kg
$ACVI_{BW}$	70.3 ± 15.2 ml/kg
$TEDVI_{BW}$	12.0 ± 2.8 ml/kg

Note: All parameters indexed to kilogram body weight.

Abbreviations: $ACVI_{BW}$, active circulation volume index; $CVBI_{BW}$, central blood volume index; $TEDVI_{BW}$, total end-diastolic volume index; SD, standard deviation, CI_{BW} , cardiac index; SVI_{BW} , stroke volume index; 95% CI, 95% confidence interval.

study by Valsangiacomo Buechel et al, where normal ventricular volumes in children were quantified.²² Their results indicated that intracardiac blood volumes were better correlated with BW than with BSA. TEDV was analysed by COstatus and has been found to predict values within the expected physiological range.²⁴ Our data indicate a slightly higher $TEDVI_{BW}$ in our cohort of children, which can be expected due to a volume overloaded heart caused by the intracardiac shunting of blood. Our findings of appropriate TEDV indexing by BW in children strengthen the possibility of establishing reference values and potential clinical use, which also applies to SVI_{BW} . The circulatory blood volumes (TEDV, CBV and ACV) are potentially important and may be used to detect hypo- or hypervolaemia when normal reference values have been established.

The precision of the measurements improved in several of the haemodynamic variables (CI_{BW} , SVI_{BW} and $CVBI_{BW}$) after the correction of the intracardiac shunt (Table 3). This may have been caused

by a more pronounced ventilator-dependent circulatory variability with an existing shunt. Alternatively, this may also have been due to the difficulty of the program algorithm in exactly defining the right limits of the dilution curve, which was delayed in the presence of a shunt.²⁵

Our results raise a concern regarding the traditional way haemodynamic variables are indexed. All CO monitors on the market index CO with BSA for estimation of CI which may produce artificially lower reference values in children compared with adults. This means that derived variables, such as pulmonary vascular resistance index ($PVRI_{BSA}$) and systemic vascular resistance index ($SVRI_{BSA}$), might be overestimated in children. Inaccurate haemodynamic estimations may lead to decisions to treat children with unnecessary vasoactive medication and/or fluids. Anaesthesiologists should be aware of this problem when performing haemodynamic studies and measurements in young children.

Limitations of the study were that all our patients had congenital heart disease and all measurements were taken during anaesthesia, before and immediately after corrective cardiac surgery. Their haemodynamic values do not represent normal reference values in healthy children when they are awake. However, most haemodynamic research, to date, is based on children who have some underlying illnesses, as it would not be ethical to inflict invasive measurements on healthy children. There are similar ethical limitations and clinical challenges regarding the estimation of blood volume in children. It is highly doubtful that a comparative blood volume study using dyes, carbon monoxide or radioactive markers (eg iodinated albumin) as was used in the past, would be allowed in healthy children today. Several animal studies aimed to validate the ability of the technique to accurately detect different blood volumes are available.²⁶⁻²⁹ In this study, the focus was on the youngest and smallest children, who are often

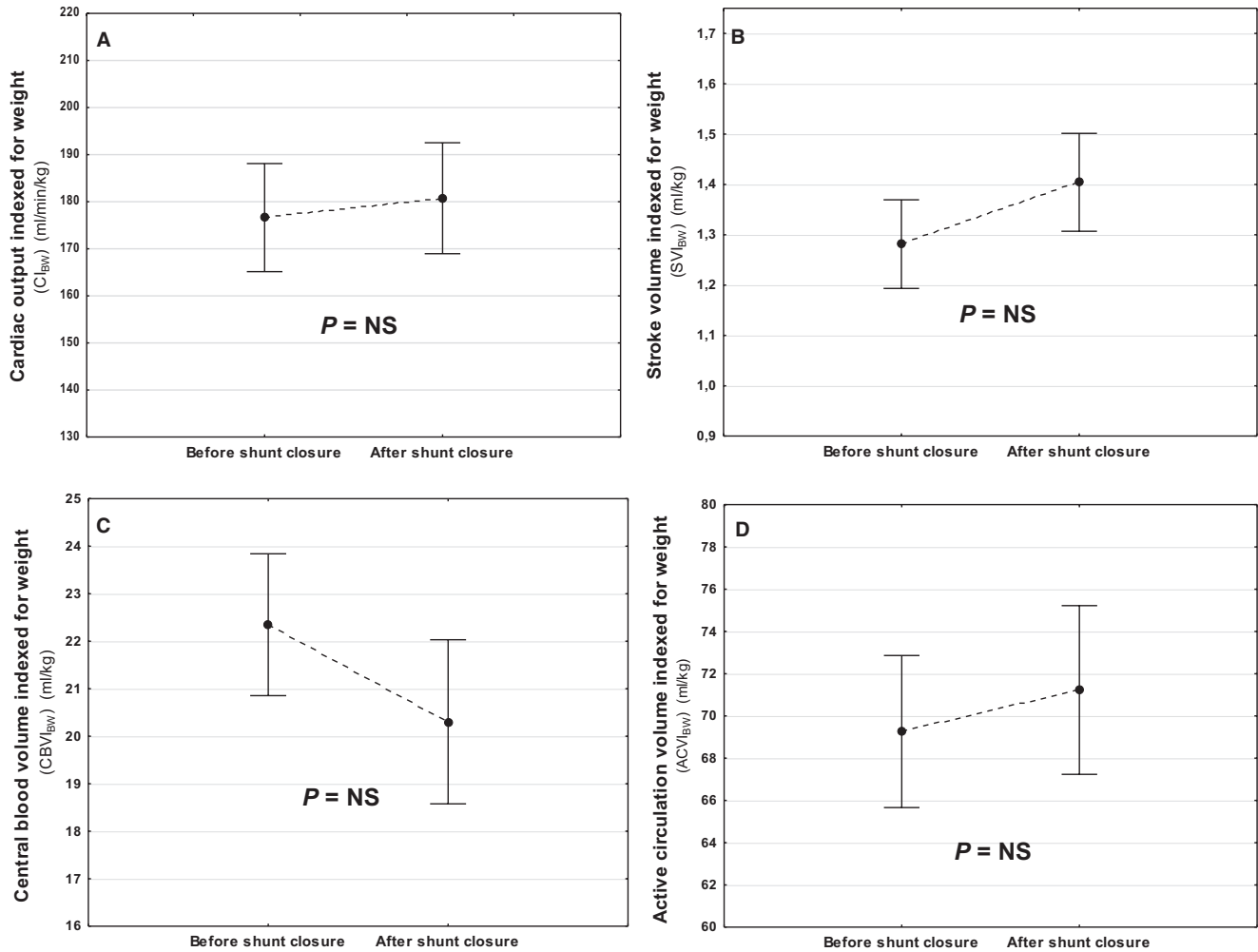


FIGURE 3 Effects of intracardiac shunt on haemodynamic variables (N = 68). There were no significant changes in Cl_{BW} (a), SVI_{BW} (b), $CBVI_{BW}$ (c) and $ACVI_{BW}$ (d) before and after surgical closure of an intracardiac shunt (values are means \pm 95% confidence interval)

TABLE 3 Variability of variables before and after correction of the intracardiac shunt (N = 44)

Variable	Before surgical correction	After surgical correction	P value
	Precision (%) (2*CE)*100	Precision (%) (2*CE)*100	
Cl_{BW}	8.1	3.5	<.001
SVI_{BW}	8.2	3.8	<.001
$ACVI_{BW}$	8.2	6.6	.14
$CBVI_{BW}$	5.6	3.4	.004
$TEDVI_{BW}^*$		3.4	

Abbreviation: CE, coefficient of error ($CE = CV/\sqrt{n}$) (CV, coefficient of variation, n, number repeated measurements).

Cl_{BW} , cardiac index; SVI_{BW} , stroke volume index; $ACVI_{BW}$, active circulation volume index; $CBVI_{BW}$, central blood volume index; $TEDVI_{BW}$, total end-diastolic volume index.

$TEDVI$ is not estimated in the presence of an intracardiac shunt*

Note: All variables indexed to kilogram body weight.

under-represented in larger haemodynamic studies that therefore give an inaccurate overall picture.^{1,30} In our opinion, the number of patients presented in this study was sufficient to give an overall view of haemodynamic values in these weight groups after heart surgery. All measurements were performed by the same researchers in a very homogenous group of patients. In general, minimal inotropic and vasopressor support was needed and there was no difference between weight groups. As all measurements were part of earlier comparison studies, good agreement and precision were confirmed, with a percentage error below 30%.

5 | CONCLUSION

Indexing haemodynamic variables with BW produces a more appropriate body size-independent scale in young children than BSA. Surgical correction of an intracardiac shunt did not affect the haemodynamic variables significantly but improved the precision of the measurement values.

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CONFLICT OF INTEREST

TSS declares no competing interest. LL declares no competing interest.

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