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Prognostic value of cardiac cycle efficiency in children undergoing cardiac surgery: a prospective observational study

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Abstract

Background: Cardiac cycle efficiency (CCE) derived from a pressure-recording analytical method is a unique parameter to assess haemodynamic performance from an energetic view. This study investigated changes of CCE according to an anatomical diagnosis group, and its association with early postoperative outcomes in children undergoing cardiac surgery.

Methods: Ninety children were included with a ventricular septal defect (VSD; n=30), tetralogy of Fallot (TOF; n=40), or total anomalous pulmonary venous connection (TAPVC; n=20). CCE along with other haemodynamic parameters, was recorded from anaesthesia induction until 48 h post-surgery. Predictive CCE (CCE_p) was defined as the average of CCE at post-modified ultrafiltration and CCE at the end of surgery. The relationship between CCE and early outcomes was assessed by the comparison between the high-CCE_p group ($CCE_p \geq$75th centile) and the low-CCE_p group ($CCE_p \leq$25th centile).

Results: There was a significant time × diagnostic group interaction effect in the trend of CCE. Compared with the high-CCE_p group (n=23), the low-CCE_p group (n=22) required more inotropics post-surgery, had higher lactate concentrations at 8 and 24 h post-surgery, a longer intubation time and longer ICU stay, and higher frequency of peritoneal fluid.

Conclusions: Perioperative changes of CCE vary according to anatomical diagnosis in children undergoing cardiac surgery. Children with TOF have an unfavourable trend of CCE compared with children with VSD or TAPVC. A decline in CCE is associated with adverse early postoperative outcomes.

Clinical trial registration: ChiCTR1800014996.

Keywords: cardiac cycle efficiency; cardiac energetics; cardiac surgery; early outcome; paediatric; pressure-recording analytical method

Editor's key points

- This study evaluated the value of cardiac cycle efficiency (CCE) monitoring in the paediatric cardiac surgery patients.
- The preoperative values and course of CCE were different amongst distinct congenital heart defects.
- Lower CCE after surgery was associated with more inotropic need, higher lactate, and peritoneal fluid.
- Despite the small sample size, this study shows that CCE might be further developed as a dynamic indicator of cardiovascular performance in the paediatric setting.

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Perioperative haemodynamic compromise is a major cause of mortality and morbidity in children with congenital heart disease (CHD). The evaluation of the haemodynamic status in these children is still challenging. Goal-directed therapy has been advocated and proved to improve outcome, including mixed venous saturation of oxygen, regional tissue oxygen saturation, cardiac or vessel pressures, and biomarkers such as lactate, but mostly inefficient in a dynamic clinical setting.[1] Alternatively, energy-based variables may be used as early signs of haemodynamic compromise and prognostic indicators.[2–4]

Several methods have been developed to assess cardiac efficiency, including the argon technique,[5] updated MRI technique,[2] and echocardiography.[4] Echocardiography plays a fundamental role in evaluating cardiac efficiency through measuring ventricular–arterial coupling in clinical settings.[6,7] Despite its advantages, echocardiography has some drawbacks, including intermittent and operator dependence in the highly dynamic clinical setting. As an alternative, cardiac cycle efficiency (CCE) is a unique parameter derived from a minimally invasive pulse contour method using the pressure-recording analytical method (PRAM).[8] Although there is disagreement, it appears that the PRAM has been well established for the measurement of cardiovascular function parameters in various clinical settings.[9–13] The high rate of signal sampling (1000 Hz) enables the tracing of even the modest signal changes, but it might also be too sensitive to measure artefacts on the arterial waveform. CCE is an energetic view from pressure waveforms to compute the ratio of systolic energetic expenditure to the total energetic expenditure of the heartbeat. CCE has been investigated in critically ill adult cardiovascular patients, demonstrating that CCE is useful and prognostic in this population.[14,15] CCE was closely related to the ventricular–arterial coupling in a group of adult patients.[16] Thus far, there is scarce literature on assessing the role of CCE in critically ill children undergoing cardiac surgery.

The objective of this study was to determine changes in perioperative CCE in children undergoing biventricular repair of CHD. The second objective of this study was to investigate whether CCE is prognostic for early postoperative outcome.

Methods

Patient population

The Institutional Review Board of Beijing Anzhen Hospital approved this study. The study was registered at the Chinese Clinical Trial Registry (www.chictr.org.cn; ChiCTR1800014996). From March 2018 to February 2019, children scheduled for corrective cardiac surgery were enrolled in this prospective observational study. As a preliminary report, the common types of CHD were enrolled and standard clinical care was applied during the perioperative period. Eligibility criteria included surgery at less than 2 yr of age in three diagnostic groups: (i) ventricular septal defect (VSD); (ii) tetralogy of Fallot (TOF); and (iii) total anomalous pulmonary venous connection (TAPVC), elective surgery, and planned arterial and central venous lines. Exclusion criteria included aortic disease (e.g. aortic valve regurgitation and aortic coarctation), malignant arrhythmia, mechanical cardiopulmonary support system, ventricular assist device, unplanned reoperation, inappropriate identification of the dicrotic notch, and arterial waveform artefacts confirmed by the fast flush test.[16] Children with the number of extrasystoles exceeded 3 beats min^{-1} during the data collection period were also excluded.

Perioperative clinical management

After admission to the operating room, standard monitoring included five-lead electrocardiography, digital pulse oximetry, and noninvasive blood pressures. After induction of anaesthesia, radial artery catheterisation was achieved and connected to a standard arterial line (Edwards Lifesciences, Irvine, CA, USA) for routine vital signs and advanced haemodynamic monitoring using MostCare® (Vytech, Padova, Italy). A 4.0–5.5 Fr central venous catheter was inserted in the right internal jugular vein or alternatively in the femoral vein to measure central venous pressure; children with TOF or TAPVC had one more 4 Fr central venous catheters in the right internal jugular vein with the tip placed to the left atrium intraoperatively by surgeons for pressure monitoring. Anaesthesia was maintained with i.v. midazolam 0.2–0.4 mg kg^{-1} h^{-1}, sufentanil 2–4 μg kg^{-1} h^{-1}, and pipecuronium 0.08–0.16 mg kg^{-1} h^{-1}.

Cardiopulmonary bypass (CPB) was established with a membrane oxygenator (Sorin, Mirandola, Italy) with a blood flow of 100–150 ml kg^{-1} min^{-1}. Deep or moderate hypothermia was used according to surgical difficulty. A pH-stat strategy was used during core cooling. Inotropic agent (dopamine 1–5 μg kg^{-1} min^{-1} or epinephrine 0.01–0.05 μg kg^{-1} min^{-1}) was administered at the onset of rewarming, targeting an age-appropriate mean arterial pressure with an atrial filling pressure (either central venous or left atrial pressure) of 4–12 mm Hg at separation from CPB. Modified ultrafiltration was routinely performed for all patients.

Postoperative management in ICU followed standard procedures. Routine monitoring included three-lead electrocardiography, invasive arterial pressure, atrial pressure, blood gas analysis, and advanced monitoring with MostCare. Sedation was facilitated with continuous infusion of midazolam and sufentanil; intermittent injection of a neuromuscular blocking agent was given as necessary. Inotropic and vasoactive agents (dopamine, epinephrine, norepinephrine, isoprenaline, and nitroglycerin) and fluid infusions (albumin 5%, blood products, and crystalloids) were administered according to standard protocols.

Cardiac cycle efficiency measurements

The design and set-up of CCE measurements using MostCare have been described in a previous study.[17] To estimate stroke volume, the whole area under the systolic portion of the pressure curve is measured. Simultaneously, arterial impedance is directly determined from both the systolic phase and the diastolic phase of the pressure waveform in real time. Hence, no preloaded data or calibration is necessary for MostCare to derive cardiac function parameters. The Philip pressure module in the main monitoring system was dual output, with the spare one for the connection of MostCare. CCE, along with other haemodynamic variables, is automatically calculated and displayed on the screen in real time. For each variable, measurement parameters at 30 s intervals were stored and downloaded with dedicated software to spreadsheets for offline analysis.

Concept of cardiac cycle efficiency

In a cardiac cycle, the energy required to generate a given stroke volume depends on the ventricular–arterial coupling.[16] The factors implicated in the arterial system include arterial elastance and reflected waves. The latter is composed of many

wavelets generated by reflection of previous beats at branch point and distal resistive arterioles (backward waves), but also at the aortic valve (forward waves). Depending on their timing according to aortic valve closure and direction, the power generated by reflected waves can either increase heart work (counted as a negative component in CCE) or facilitate ejection (counted as a positive component in CCE).[8,16] Briefly, CCE is computed as $CCE=W_{sys}/W_{beat}\times K_{(t)}$, where W_{sys} is the power function from the systolic pressure wave, W_{beat} is the power function from the entire cardiac cycle pressure wave, and $K_{(t)}$ is the ratio of mean pressure expected over mean pressure measured. Unlike purely mechanical performance, CCE is dimensionless and could have a negative value when the energy expenditure for 'compensations' increases to maintain cardiovascular homeostasis.[8] Usually, the numerical value of CCE ranges from −1 to +1, with the former meaning worse work–consumption status, whilst the latter indicates better work–consumption.

Data collection

Conventional data collected in the study include patient characteristics, preoperative data (left ventricular end-diastolic diameter, left ventricular ejection fraction, and Spo_2 of the right upper limb), operative data (total bypass time and aortic cross-clamp time), and postoperative data (inotropic score,[18] duration of intubation, and length of ICU stay). Postoperative peritoneal fluid was confirmed by ultrasound and noted.

CCE, along with heart rate (HR), diastolic and systolic blood pressure, stroke volume index (SVI), cardiac index (CI), the maximal slope of systolic upstroke (dp/dt_{max}), and system vascular resistance index (SVRI), were continuously recorded and eventually downloaded for offline analysis. Haemodynamic readings were considered unstable and excluded if CCE fluctuated by 0.10 in the 3 min before data collection. Haemodynamic variables were noted at planned time points (i.e. after anaesthesia induction [T0]; opening the pericardium [T1]; post-modified ultrafiltration [T2]; end of surgery [T3]; and postoperatively at 1 h [T4], 8 h [T5], 24 h [T6], and 48 h [T7]).

To evaluate the relationship between CCE and early outcome data, a predictive CCE (CCE_p) was defined as the average of CCE at post-modified ultrafiltration ($CCE_{p\text{-}mu}$) and CCE at the end of surgery (CCE_{es}): $CCE_p=(CCE_{p\text{-}mu}+CCE_{es})/2$. According to CCE_p, children were allocated into two groups (i.e. the low-CCE_p group [defined as the $CCE_p \leq$25th centile] and the high-CCE_p group [defined as the $CCE_p \geq$75th centile]).

Serial detection of arterial blood lactate concentrations was examined. Arterial blood samples were sampled routinely as needed during the surgery, every 2 h during the first 24 h post-surgery, and every 4 h during 24–48 h post-surgery. Generally, laboratory data were recorded at the same time as haemodynamic data collection.

Statistical analysis

The sample size was determined to detect a significant difference in length of ICU stay between the high-CCE_p group and the low-CCE_p group. In a pretest study, the mean (standard deviation [SD]) lengths of ICU stay were 131 (72) and 230 (132) in the two groups, with α-error of 0.05 and β-error of 0.2; we estimated that at least 20 subjects in each group (i.e. 80 in total) were required. To allow for attrition, 96 children were enrolled. The statistical software was SPSS (version 20.0; SPSS Inc., Chicago, IL, USA). Normally distributed data were expressed as mean (SD), non-normally distributed data were expressed as median (25th–75th percentile), and categorical data were presented as the number (percentage). Comparisons of non-haemodynamic variables across the three diagnostic groups were made using one-way analysis of variance for normal distribution variables, Kruskal–Wallis test for non-normal distribution variables, and χ^2 test for categorical variables. Changes of haemodynamic variables were assessed with the general linear model (GLM) for repeated measures to analyse the main effect of time after adjusted to polynomial test (i.e. linear, quadratic, cubic, etc.) (indicated by P_{time}), the main effect of group (indicated by P_{group}), and their interactions (indicated by $P_{time\times group}$). To allow for GLM repeated measures analysis, incomplete data were replaced by bringing in the last previous observation. *Post hoc* test for multiple comparisons was made using the least significant difference *t*-test with Bonferroni correction. General linear model for repeated measures was also used to analyse the main effect of time after adjusted to polynomial test for assessing haemodynamic change in each diagnostic group. Greenhouse–Geisser correction was used whenever the assumption of sphericity was violated, according to Mauchly's sphericity test. Comparison between the high-CCE_p group and the low-CCE_p group was made using the independent sample *t*-test for normal distribution variables, Mann–Whitney *U*-test for non-normal distribution variables, and χ^2 test for categorical variables. Correlation between two variables of the entire cohort was assessed using the Pearson correlation coefficient. All tests were two sided. A *P*-value <0.05 was considered statistically significant.

Results

General characteristics

Of 96 children enrolled in this study, six children, including one with VSD, three with TOF, and two with TAPVC, were excluded because of inappropriate identification of the dicrotic notch or arterial waveform artefacts. Ninety-five children survived until hospital discharge. Three group pairings of data (708) from anaesthesia induction (n=90); opening the pericardium (n=90); post-modified ultrafiltration (n=90); end of surgery (n=90); and 1 h (n=90), 8 h (n=90), 24 h (n=90), and 48 h (n=78) post-surgery were included in the analysis. Patient characteristics are shown in Table 1. Comparisons of

Table 1 Patient characteristic data according to the diagnosis group. Values are median (25th–75th percentile) or number (n). TAPVC, total anomalous pulmonary venous connection; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Variable	VSD group	TOF group	TAPVC group
n	30	40	20
Age (months)	0.6 (0.5–1.0)	0.9 (0.7–1.0)	0.2 (0.1–0.3)
Body weight (kg)	6.8 (6.4–9.0)	8.7 (7.3–9.9)	4.6 (3.8–5.3)
Height (cm)	68 (64–74)	73 (68–76)	59 (54–60)
Body surface area (m^2)	0.35 (0.33–0.42)	0.40 (0.36–0.43)	0.26 (0.23–0.28)
Sex (F/M)	15/15	18/22	10/10

perioperative characteristics and early outcome data according to the diagnostic group are shown in Table 2.

Haemodynamic variables

Changes in CCE, CI, dp/dt_{max}, HR, SVI, and SVRI according to diagnostic group are shown in Table 3 and in Supplementary Figures S1–S6. In the VSD group, CCE showed a decrease followed by an increase. In the TOF group, there were no significant fluctuations in CCE over time. In the TAPVC group, CCE showed an increase over time. There was a significant time × diagnostic group interaction effect in the trend of CCE between any two groups of the three groups. CCE was different amongst groups, with a lower CCE in the TOF group than in the VSD group.

CI showed a decrease from T0 to T3, followed by an increase. In the VSD group, CI showed an increase over time, whilst the TOF and TAPVC groups showed a decrease followed by an increase in CI. There was a time × diagnostic group interaction effect in the CI trend between the TOF group and the VSD and TAPVC groups, but not between the VSD and TAPVC groups. The CI was not different amongst the three groups.

Dp/dt_{max} showed an increase over time in the VSD and TAPVC groups. There was a time × diagnostic group interaction effect in the trend of dp/dt_{max} between the VSD and TOF groups. Overall, the dp/dt_{max} was different amongst groups, with lower values in the TAPVC group than that in the VSD group.

HR showed an increase over time in the TOF and TAPVC groups, whilst this increase was transient in the VSD group. There was a time × diagnostic group interaction effect in the trend of HR between the VSD and TOF groups, between the VSD and TAPVC groups, but not between the TOF and TAPVC groups. Overall, HR was different amongst groups, with lower values in the VSD group compared with the TOF or TAPVC group.

In the VSD group, SVI showed a decrease from T0 to T2, followed by an increase. In the TOF and TAPVC groups, SVI showed a decrease over time that was transient in the TAPVC group. There was a time ×diagnostic group interaction effect in the trend of SVI between the TOF and VSD groups, and between the TOF and TAPVC groups. SVI was not statistically different amongst groups.

SVRI showed an increase over time for all groups, but this was transient in the TAPVC group. There was no time × diagnostic group interaction effect in the trend of SVRI. The SVRI was different amongst groups, with lower values in the TAPVC group.

Association of cardiac cycle efficiency with early postoperative outcomes

Compared with the high-CCE_p group (≥−0.05; n=23), the low-CCE_p group (≤−0.40; n=22) required more inotropics at 1, 8, 24, and 48 h post-surgery; had higher lactate concentrations at 8 and 24 h post-surgery; had longer intubation time; had longer ICU stay; and had higher frequency of peritoneal fluid (Table 4).

Correlation of cardiac cycle efficiency with patient characteristics and haemodynamics

With an exception at T0, CCE did not correlate with age. CCE positively correlated with left ventricular end-diastolic diameter at T0, T1, and T2, and positively correlated with dp/dt_{max} at all individual study time points. It was negatively correlated

Table 2 Perioperative characteristics and early outcomes according to the diagnosis group. Values are median (25th–75th percentile), mean (standard deviation) or number (n). TAPVC, total anomalous pulmonary venous connection; TOF, tetralogy of Fallot; VSD, ventricular septal defect. *One-way analysis of variance test. †Kruskal–Wallis test. ‡χ^2 test.

Variable	Group VSD	Group TOF	Group TAPVC	P-value
n	30	40	20	
Preoperative characteristics				
Left ventricular end-diastolic diameter (mm)	32 (6)	22 (3)	14 (4)	<0.001*
Left ventricular ejection fraction (%)	66 (10)	69 (5)	78 (7)	<0.001*
Spo_2 (%)	98.1 (1.2)	85.6 (7.2)	85 (4.6)	<0.001*
Operative characteristics				
Cross-clamp time (min)	37.2 (9.2)	61.3 (12.6)	55 (21.3)	<0.001*
Total bypass time (min)	65.6 (14)	94.7 (19.8)	109.2 (38)	<0.001*
Postoperative characteristics				
Arterial lactate (mM)				
1 h post-surgery	1.2 (0.8–1.5)	1.9 (1.3–2.9)	3.5 (3.1–4.2)	<0.001†
8 h post-surgery	1.2 (1.1–1.9)	2.3 (1.7–2.7)	2.5 (1.9–3.4)	<0.001†
24 h post-surgery	0.9 (0.7–1.1)	1.1 (0.9–1.3)	1.4 (1.2–1.7)	<0.001†
48 h post-surgery	0.6 (0.5–0.9)	0.9 (0.6–1.0)	1.3 (1.0–1.7)	<0.001†
Inotropic score				
1 h post-surgery	5.1 (3.0)	10.9 (5.2)	11.7 (3.2)	<0.001*
8 h post-surgery	6.1 (3.6)	11.4 (5.2)	12.6 (3.3)	<0.001*
24 h post-surgery	8.1 (3.7)	13.1 (5.8)	15.0 (3.1)	<0.001*
48 h post-surgery	7.4 (3.6)	12.4 (5.4)	13.0 (2.5)	0.079*
Ascites (n, %)	8 (27)	22 (55)	4 (20)	0.010‡
Hours intubated	32 (20–51)	62 (26–101)	54 (42–90)	0.002†
Hours in ICU	70 (47–123)	148 (117–178)	191 (140–240)	<0.001†

Table 3 Changes in haemodynamics according to the diagnostic group with statistical significance by general linear model repeated measures. TAPVC, total anomalous pulmonary venous connection; TOF, tetralogy of Fallot; VSD, ventricular septal defect. T0, after anaesthesia induction; T1, opening the pericardium; T2, post-modified ultrafiltration; T3, end of surgery; T4–T7, post-operation at 1, 8, 24, and 48 h, respectively. Values are expressed as mean (standard deviation). NS, non-significant. *P-value for overall group. †Bonferroni-corrected *P*-value with TAPVC group after least significant difference (LSD) *t*-test; ‡Bonferroni-corrected *P*-value with VSD group after LSD *t*-test; ¶Bonferroni-corrected *P*-value with TOF group after LSD *t*-test.

Variables	T0	T1	T2	T3	T4	T5	T6	T7	P_{time}	P_{group}	$P_{time \times group}$
Cardiac cycle efficiency (unit)									<0.001*	0.015*	<0.001*
VSD	0.12 (0.23)	0.04 (0.25)	−0.27 (0.31)	−0.15 (0.27)	−0.06 (0.21)	−0.16 (0.27)	−0.08 (0.28)	−0.04 (0.11)	<0.001	NS†	<0.001†
TOF	−0.14 (0.40)	−0.12 (0.40)	−0.30 (0.34)	−0.25 (0.28)	−0.26 (0.31)	−0.18 (0.26)	−0.21 (0.31)	−0.22 (0.28)	NS	0.012‡	0.030‡
TAPVC	−0.27 (0.31)	−0.24 (0.27)	−0.27 (0.29)	−0.14 (0.09)	−0.06 (0.20)	−0.18 (0.25)	0.05 (0.07)	0.01 (0.08)	<0.001	NS¶	<0.001¶
Cardiac index (L min^{-1} m^{-2})									<0.001*	NS*	0.001*
VSD	2.8 (0.6)	2.9 (0.7)	2.8 (0.6)	3.1 (0.6)	3.2 (0.7)	3.2 (0.6)	3.0 (0.7)	3.4 (1.0)	0.028	NS†	NS†
TOF	3.0 (0.6)	3.1 (0.6)	2.7 (0.5)	2.6 (0.6)	2.5 (0.5)	3.0 (0.6)	2.6 (0.6)	2.7 (0.6)	0.007	NS‡	<0.001‡
TAPVC	2.9 (0.7)	2.9 (0.6)	3.1 (0.5)	2.8 (0.8)	2.9 (0.4)	2.9 (0.5)	2.7 (0.5)	3.5 (0.4)	0.008	NS¶	0.027¶
Diastolic blood pressure (mm Hg)									<0.001*	<0.001*	0.003*
VSD	40 (6)	44 (8)	49 (9)	51 (8)	56 (12)	56 (8)	53 (7)	61 (10)	<0.001	0.012†	0.003†
TOF	46 (8)	47 (9)	53 (12)	51 (8)	52 (9)	60 (7)	57 (8)	60 (8)	<0.001	NS‡	0.024‡
TAPVC	42 (14)	43 (15)	48 (6)	43 (12)	47 (6)	49 (8)	44 (7)	53 (7)	0.040	<0.001¶	NS¶
dp/dt_{max} (mm Hg ms^{-1})									<0.001*	0.018*	0.022*
VSD	0.96 (0.24)	1.09 (0.16)	1.11 (0.28)	1.23 (0.20)	1.30 (0.27)	1.21 (0.26)	1.20 (0.25)	1.29 (0.32)	<0.001	0.027†	NS†
TOF	0.97 (0.22)	1.10 (0.20)	1.09 (0.26)	1.04 (0.23)	1.03 (0.23)	1.13 (0.17)	1.07 (0.18)	1.07 (0.23)	NS	NS‡	0.036‡
TAPVC	0.82 (0.20)	0.90 (0.21)	1.08 (0.34)	1.04 (0.25)	1.08 (0.31)	1.06 (0.30)	1.11 (0.22)	1.11 (0.12)	<0.001	NS¶	NS¶
Heart rate (beats min^{-1})									<0.001*	0.001*	<0.001*
VSD	108 (12)	125 (18)	151 (14)	147 (14)	145 (15)	136 (12)	136 (14)	138 (21)	0.001	0.003†	0.009†
TOF	103 (16)	114 (17)	156 (12)	152 (17)	154 (17)	146 (17)	151 (17)	156 (14)	0.001	0.042‡	<0.001‡
TAPVC	125 (15)	135 (16)	155 (10)	149 (20)	155 (18)	151 (16)	156 (14)	149 (15)	0.001	NS¶	NS¶
Stroke volume index (ml m^{-2})									<0.001*	NS*	<0.001*
VSD	25.8 (6.1)	23.5 (7.4)	18.5 (4.8)	21.0 (6.0)	22.1 (6.0)	23.2 (5.9)	22.1 (6.5)	25.8 (7.4)	0.014	NS†	NS†
TOF	30.1 (8.1)	27.6 (7.5)	17.7 (4.4)	17.3 (5.6)	16.4 (5.3)	20.5 (6.3)	17.5 (5.6)	16.9 (4.5)	0.001	NS‡	<0.001‡
TAPVC	24.0 (7.3)	23.1 (7.8)	20.9 (2.6)	18.8 (5.4)	18.6 (3.0)	19.0 (3.7)	17.0 (4.0)	22.9 (3.1)	<0.001	NS¶	<0.001¶
Systemic vascular resistance index (dyne s cm^{-5} m^2)									<0.001*	<0.001*	NS*
VSD	1410 (332)	1499 (309)	1784 (351)	1722 (527)	1686 (296)	1672 (326)	1691 (255)	1763 (386)	<0.001	<0.001†	NS†
TOF	1501 (351)	1563 (362)	1823 (383)	1890 (529)	1924 (496)	1856 (396)	1933 (364)	1970 (353)	<0.001	NS‡	NS‡
TAPVC	1179 (239)	1238 (289)	1421 (353)	1347 (166)	1411 (100)	1475 (132)	1452 (234)	1342 (218)	0.002	<0.001¶	NS¶
Systolic blood pressure (mm Hg)									<0.001*	<0.001*	<0.001*
VSD	83 (14)	90 (13)	97 (15)	102 (14)	108 (18)	104 (12)	101 (11)	115 (17)	<0.001	<0.001†	NS†
TOF	90 (12)	96 (13)	93 (16)	91 (12)	91 (10)	101 (10)	94 (11)	98 (10)	NS	NS‡	<0.001‡
TAPVC	73 (21)	75 (24)	86 (16)	79 (22)	84 (12)	83 (12)	81 (10)	92 (10)	0.008	<0.001¶	0.039¶

Table 4 Patient characteristics, perioperative characteristics, and early outcomes according to the high CCE_p (≥75th centile) and low CCE_p (≤25th centile) groups. TAPVC, total anomalous pulmonary venous connection; TOF, tetralogy of Fallot; VSD, ventricular septal defect. Values are median (25th–75th percentile), mean (standard deviation) or number (*n*). *One-way analysis of variance test. †Mann–Whitney *U*-test. ‡χ^2 test. CCE, cardiac cycle efficiency.

Variables	Low-CCE_p group (*n*=22)	High-CCE_p group (*n*=23)	P-value
Diagnosis			
VSD/TOF/TAPVC (*n*)	8/12/2	10/9/4	0.523‡
Patient characteristics			
Age (months)	7.6 (5.7–10.4)	10.8 (6.0–12.0)	0.286†
Weight (kg)	7.3 (6.0–8.9)	7.6 (6.4–9.6)	0.275†
Sex (F/M)	11/11	10/13	0.661
Preoperative characteristics			
Left ventricular end-diastolic diameter (mm)	22 (9)	27 (12)	0.149*
Left ventricular ejection fraction (%)	69 (10)	70 (7)	0.783*
Spo_2 (%)	83.7 (8.8)	91.5 (7.6)	0.018*
Operative characteristics			
Cross-clamp time (min)	61 (18)	47 (14)	0.014*
Total bypass time (min)	92 (26)	80 (24)	0.144*
Postoperative characteristics			
Arterial lactate (mM)			
1 h post-surgery	1.7 (1.4–3.0)	1.5 (0.9–2.8)	0.333†
8 h post-surgery	2.7 (2.1–3.0)	1.4 (0.9–1.9)	<0.001†
24 h post-surgery	1.2 (1.0–1.7)	0.9 (0.7–1.2)	0.025†
48 h post-surgery	0.8 (0.6–1.5)	0.9 (0.6–1.0)	0.813†
Inotropic score			
1 h post-surgery	12.5 (6.6)	7.2 (4.0)	0.006*
8 h post-surgery	12.3 (6.0)	7.8 (4.9)	0.021*
24 h post-surgery	14.2 (7.2)	10.2 (4.4)	0.045*
48 h post-surgery	15.2 (6.8)	10.1 (3.3)	0.010*
Ascites (*n*, %)	18 (82)	6 (26)	<0.001‡
Hours intubated	77 (48–140)	50 (22.5–69)	0.003†
Hours in ICU	164 (80–240)	111 (48–168)	0.021†

with SVRI at all individual time points and negatively correlated with the inotropic score at T4, T6, and T7 (Table 5).

Discussion

This study showed that perioperative CCE varied according to the type of cardiac malformation in children undergoing surgical cardiac repair. Children with TOF have an unfavourable trend of CCE compared with children with VSD or TAPVC. Lower CCE values were associated with higher inotropic doses, higher lactic concentrations, longer intubation time, longer ICU stay, and a higher frequency of peritoneal fluid.

Cardiac energetics are rarely evaluated in critically ill children. Nagata and colleagues[19] observed left ventricular efficiency deterioration within 24 h after ligation of patent *ductus arteriosus* for premature children. Lee and colleagues[20] examined right ventricle–pulmonary artery inefficiency as a diagnostic endpoint to optimise the timing of intervention in late years post-TOF repair.

Recently, Marinari and colleagues[7] concluded that ventricular–arterial coupling is impaired and fairly associated with CCE after paediatric congenital heart surgery, suggesting that CCE measurements may be useful in the evaluation of paediatric cardiac surgery. Data in adult cardiovascular patients suggest that CCE may have an important role as a predictor of outcome.[12,14,15,21,22] Our recent study[23] also demonstrated that CCE was useful in the monitoring of cardiac efficiency during the anaesthesia induction period in children with CHD.

VSD is the most common CHD diagnosis in children. In most cases, perioperative haemodynamic management is more challenging for children with TOF than those with VSD. In the current study, CCE in children with TOF was systemically lower compared with children with VSD, consistent with clinical experience that children with TOF are at higher risk of circulatory disorders.

CCE can be considered as an atypical parameter of whole haemodynamic performance, as it is determined by the interplay of the cardiovascular system from different organs, including the heart, arterial vasculature, and pulmonary vasculatures.[8] The reduction in preoperative CCE in children with TOF could be mainly attributed to the reduced right ventricle–pulmonary artery compliance, which is caused by cardiovascular malformation, including right ventricular outflow tract obstruction and right ventricular hypertrophy. The unfavourable postoperative trend of CCE in children with TOF could be directed to a suboptimal restoration of right ventricle–pulmonary artery compliance, despite the use of inotropics. Firstly, myocardial function in children with TOF was more deteriorated because of pre-existing right ventricular dysfunction, longer CPB duration, and a larger wound surface. Besides, residual right ventricle outflow tract obstruction, a trans-annular patch, and pulmonary regurgitation are frequent underlying factors that minimise right ventricle–pulmonary artery compliance. Secondly, because of the negative effect from the right heart and lack of proper exercise, children with TOF are likely to have deteriorated left ventricular function as reflected in a lower dp/dt_{max} compared with children with VSD. We use left atrial pressure monitoring as a routine procedure to assess left ventricular function. Thirdly, although not different from children with VSD, the higher SVRI indicated a higher arterial afterload in children with TOF. This could be triggered by deteriorated myocardial contraction, more sympathetic reflex activity, and larger doses of inotropics to maintain blood pressure. In line with our findings, Senzaki and colleagues,[24] using catheter probe and echography, found that arterial elastance was higher in children with TOF as compared with control children with VSD, even 5 yr after the anatomical repair. This implies that the increase in arterial afterload may be long-term.

Children with TAPVC show cardiac dysfunction before surgery, and most of them require surgery during the first 2

Table 5 Correlation of cardiac cycle efficiency (CCE) with patient characteristic and haemodynamic variables. CI, cardiac index; HR, heart rate; LVED, left ventricular end-diastolic diameter; SVI, stroke volume index; SVRI, systemic vascular resistance index; T0, after anaesthesia induction; T1, opening the pericardium; T2, post-modified ultrafiltration; T3, end of surgery; T4–T7, post-surgery at 1, 8, 24, and 48 h, respectively.

	CCE (T0)	CCE (T1)	CCE (T2)	CCE (T3)	CCE (T4)	CCE (T5)	CCE (T6)	CCE (T7)
Age (months)	r=0.300 P=0.004	r=0.171 P=0.122	r=0.06 P=0.614	r=−0.05 P=0.640	r=−0.04 P=0.693	r=0.05 P=0.664	r=−0.05 P=0.678	r=−0.22 P=0.051
LVED (mm)	r=0.552 P<0.001	r=0.422 P<0.001	r=0.368 P=0.018	r=0.157 P=0.201	r=0.152 P=0.224	r=0.158 P=0.210	r=0.074 P=0.547	r=0.038 P=0.769
dp/dt_{max} (mm Hg ms^{-1})	r=0.52 P<0.001	r=0.478 P<0.001	r=0.626 P<0.001	r=0.475 P<0.001	r=0.513 P<0.001	r=0.320 P=0.005	r=0.285 P=0.010	r=0.294 P=0.016
SVRI (dynes cm^{-5} m^{-2})	r=−0.325 P<0.001	r=−0.432 P<0.001	r=−0.312 P<0.001	r=−0.455 P<0.001	r=−0.531 P<0.001	r=−0.226 P=0.025	r=−0.342 P=0.010	r=−0.504 P<0.001
CI (L min^{-1} m^{-2})	r=0.408 P=0.656	r=0.114 P=0.288	r=0.036 P=0.743	r=0.180 P=0.093	r=0.241 P=0.024	r=0.017 P=0.874	r=0.005 P=0.963	r=0.167 P=0.146
SVI (ml m^{-2})	r=0.087 P=0.418	r=0.076 P=0.480	r=0.042 P=0.695	r=0.235 P=0.027	r=0.250 P=0.020	r=0.046 P=0.673	r=0.021 P=0.843	r=0.172 P=0.156
HR (beats min^{-1})	r=−0.325 P=0.002	r=−0.176 P=0.102	r=0.074 P=0.493	r=−0.135 P=0.211	r=−0.240 P=0.025	r=−0.113 P=0.294	r=−0.048 P=0.653	r=−0.199 P=0.082
Lactate (mM)	—	—	—	—	r=−0.068 P=0.598	r=−0.168 P=0.193	r=−0.324 P=0.009	r=−0.173 P=0.194
Inotropic score	—	—	—	—	r=−0.252 P=0.038	r=−0.187 P=0.129	r=−0.279 P=0.030	r=−0.367 P=0.002

months of life. CCE was lower in TAPVC than in the other surgical categories. In children with TAPVC, right ventricle–pulmonary artery compliance was reduced because of extreme congestion, which was primarily responsible for the deterioration of CCE at baseline. Moreover, left ventricular function was impaired as a result of the insufficiency of preload and exercise, the adverse effect from right heart dilation. This was reflected in lower pre-surgical dp/dt_{max}, which was improved after surgery. The small disused left ventricle could be vulnerable to high pressure because of poor compliance; simultaneous pressure measurements in the left and right atria (using central venous pressure as surrogate) are necessary, and we strive to maintain the pressure difference below 5 mm Hg in our practice. Interestingly, the observed increasing trend of CCE over time was peculiar to the TAPVC group. The relief of congestive pulmonary circulation and right ventricle dysfunction may have positive effects on left ventricular function and cardiovascular performance, leading to improved CCE values.

Optimising haemodynamic management in children post-cardiac surgery depends on early recognition and prompt correction of haemodynamic disorders. In addition to standard clinical parameters, many advanced instruments and biochemical markers are used, such as the inotropic score.[18] CCE was negatively related to the inotropic score and positively related to dp/dt_{max}, as children with deteriorated cardiac function typically had lower CCE values and required more inotropics. The use of inotropic agents may improve haemodynamic status and oxygen delivery, but at the expense of increased oxygen consumption, leading to unfavourable cardiac energetics, hence lower CCE. Serial measurement of lactate is a useful indicator of postoperative complications. Basaran and collegues[25] documented that a cut-off of 4.8 mM for mean serum lactate in children post-cardiac surgery could predict the adverse outcome. However, we could not find an association between lactate concentrations and an improvement in CCE and cardiac output at 48 h after surgery. A possible explanation was that smaller children had immature organ systems and impaired renal and hepatic metabolic function; thus, lactate clearance was delayed, recommending CCE might be a superior prognostic alternative than lactate in this population.

Another finding of this study was that lower CCE was associated with a higher frequency of peritoneal fluid as indicator of systemic oedema. Children undergoing CPB are vulnerable to extravascular fluid overload second to CPB-related haemodilution, inflammation, and intraoperative fluid infusion. The situation was further exacerbated by postoperative low cardiac output status and right ventricular dysfunction, especially in children with TOF. Extravascular fluid overload led to decreased cardiopulmonary compliance and haemodynamic efficiency; hence, theoretically lower CCE might provide information on systemic oedema. It has been reported that removal of extravascular fluid by ultrafiltration could modify CCE as a result of improved cardiac contraction (indicated by dp/dt_{max}) and reduced arterial resistance.[26,27] From a clinical standpoint, the observation of undesirable CCE combined with other clinical features may warrant echography confirmation; methods, including intraoperative modified ultrafiltration, fluid restriction, and aggressive diuretic treatment, should be used.

Even though many parameters have been introduced to evaluate haemodynamic performance in critically ill children, clinicians may benefit from an energetic parameter as it

precedes changes in a non-energetic parameter. With further validation, CCE monitoring may enhance early real-time identification of potential haemodynamic dysfunction and allow for pre-emptive action to prevent haemodynamic catastrophe. CCE might be a promising alternative for optimising haemodynamic management in critically ill children; a negative value or negative trend of CCE may stimulate the clinician to check the major determinants of CCE responsible for such deterioration: the initial diagnosis, the evolution related to anaesthesia induction, the impact of treatment (surgical or medical) of the CHD, the occurrence of complications during CPB, the misbalance between left and right ventricle pump function, the mismatch between pump function and arterial afterload, etc. From a pragmatic point of view, the data obtained during the stable anaesthesia induction phase could be seen as a reference value to be compared with pre- and post-surgical procedure data. The value of CCE_p can be used to stratify levels of postoperative care and seen as the baseline for the following recovering steps in the ICU.

There are limitations in this study. Firstly, as a preliminary report, the sample size is relatively small. Further studies involving varied types of CHD population are warranted. Secondly, the accuracy of PRAM in children with CHD is controversial.[28] There have been concerns of some factors that might limit the reliability of PRAM in paediatric patients, such as the location of arterial catheter, an over- or under-damping signal from arterial transducer.[29] We used fast flush test to discriminate whether signal artefact exists before data collection. A recent study[13] validated PRAM against the gold-standard Fick method in children with CHD undergoing cardiac catheterisation, and found a good level of agreement in the measurements of cardiac output between the two methods. Taking a step back, the trend of haemodynamic variables tracked by PRAM and comparison amongst groups are meaningful, regardless of absolute accuracy. In addition, although precautions were applied to avoid interference from tubing and transducers, there is a possibility that the ability of PRAM to trace even modest signal changes might contribute to the source of errors by analysing the signals falsely. Thirdly, the derivation of CCE is based on the forward and backward wave theory; it has been mainly studied experimentally or in adult patients. It has been known that, in older adults with reduced arterial compliance, reflective waves return to the left ventricle during systole, thus increase blood pressures and ventricular afterload. In young adults with normal arterial compliance, reflective waves return to the left ventricle during diastole and recoil at the aortic root.[30] The role of the reflective waves on left ventricle function needs to be extensively studied in children and infants, it is more a hypothesis based on adults study than an admitted concept. Finally, after the identification of CCE changes, it would be necessary to validate the CCE against echocardiography or other gold standards in a prospective cohort study before it is widely accepted in paediatric cardiac surgery.

Perioperative changes in CCE vary according to anatomical diagnosis in children undergoing cardiac surgery. Children with TOF have an unfavourable trend of CCE compared with children with VSD or TAPVC. A decline in CCE is associated with adverse early postoperative outcomes. After further validation, CCE might be a promising alternative target for optimising perioperative haemodynamic management in children undergoing cardiac surgery.

Authors' contributions

Study concept: CO-Y
Data collection: DH, SDP
Data analysis/interpretation: HL, LHM
Drafting of manuscript: DH
Critical review: LHM, YL

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Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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