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CONTINUOUS, NON-INVASIVE TECHNIQUES TO DETERMINE CARDIAC OUTPUT IN CHILDREN AFTER CARDIAC SURGERY: EVALUATION OF TRANSESOPHAGEAL DOPPLER AND ELECTRIC VELOCIMETRY

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ABSTRACT. Background. Continuous and non-invasive measurement of cardiac output (CO) may contribute helpful information to the care and treatment of the critically ill pediatric patient. Different methods are available but their clinical verification is still a major problem. **Aim.** Comparison of reliability and safety of two continuous non-invasive methods with transthoracic echocardiography (TTE) for CO measurement: electric velocimetry technique (EV, Aesculon™) and transesophageal Doppler (TED, CardioQP™). **Methods/Material.** In 26 infants and children who had undergone corrective cardiac surgery at a median age of 3.5 (1–17) years CO and stroke volume (SV) were obtained by EV, TED and TTE. Each patient had five measurements on the first day after surgery, during mechanical ventilation and sedation. **Results.** Values for CO and SV from TED and EV correlated well with those of TTE ($r = 0.85$ and $r = 0.88$), but mean values were significantly lower than the values of TTE for TED ($P = 0.02$) and EV ($P = 0.001$). According to Bland-Altman analysis, bias was 0.36 l/min with a precision of 1.67 l/min for TED vs. TTE and 0.87 l/min (bias) with a precision of 3.26 l/min for EV vs. TTE. No severe adverse events were observed and the handling of both systems was easy in the sedated child. **Conclusions.** In pediatric patients non-invasive measurement of CO and SV with TED and EV is useful for continuous monitoring after heart surgery. Both new methods seem to underestimate cardiac output in terms of absolute values. However, TED shows tolerable bias and precision and may be helpful for continuous CO monitoring in a deeply sedated and ventilated pediatric patient, e.g. in the operating room or intensive care unit.

KEY WORDS. non-invasive, cardiac output, pediatric, Doppler echocardiography, electric velocimetry, transesophageal Doppler probe.

INTRODUCTION

Measurement of cardiac output (CO) by non-invasive techniques may contribute important information to the assessment of hemodynamics in the critically ill or post-operative patient [1]. Repeated invasive measurements can be performed using the thermodilution method with a pulmonary artery catheter or the Fick principle with

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determination of the arterial and mixed venous oxygen content [2, 3]. Invasive measurement of CO is not possible in newborns and small toddlers and may be biased in children due to the size of the pulmonary artery catheter (3–5 Fr) or the vessel size, if femoral arterial thermodilution is used [4, 5]. Infection, thromboembolic events and vessel occlusion are possible side effects of this approach in children [6–8]. Therefore the safety and efficacy of non-invasive methods to determine CO are of special interest. Pulsed Doppler-derived measurement of CO with transthoracic echocardiography (TTE) or transesophageal echocardiography is an established, validated non-invasive method and has been described in numerous studies as showing good correlation to invasive measurements (e.g. thermodilution or the Fick principle) [1, 9–12]. Esophageal Doppler probes are made for the continuous measurement of blood flow velocity in the descending aorta with measurement of CO and have been used in several clinical and animal studies [4, 5, 13, 14]. For continuous and minimally invasive CO monitoring several transesophageal Doppler probes (CardioQP™, Deltex Medical, UK; Dynema 3000, Sometec; COdopp monitoring, HemoSonic™ 100, Arrow Int.) have been developed and evaluated in a small number of clinical and animal studies, with conflicting results [5, 14–18]. Impedance cardiography or bioimpendance, an older technique that relates changes in electric conductivity to periodic changes in aortic blood volume and blood flow, determines stroke volume and cardiac output continuously and non-invasively [19, 20]. It has been studied in adult and pediatric patients with inconsistent results [21–23]. Electric velocimetry (EV) is a method similar to impedance cardiography, but electric conductivity is calculated from the direction and changes in the mechanical characteristics of erythrocytes. However, the usefulness and reliability of EV have so far not been evaluated in pediatric patients.

The purpose of this study was to assess whether acceptable continuous measurement of CO and SV may be achieved using the minimally invasive transesophageal Doppler probe Cardio QP™ or non-invasive electric velocimetry with the Aesculon™ device in mechanically ventilated children after open-heart surgery. The results of measurement by both methods are compared to the well-accepted non-invasive determination of CO using transthoracic Doppler echocardiography (TTE).

MATERIALS AND METHODS

In this prospective study 26 ventilated patients aged 1 month to 18 years were included. Inclusion criteria were congenital heart disease and hemodynamically stable conditions after corrective cardiac surgery in children (<18 years) who still needed respiratory support with a mechanical ventilator at the Deutsches Herzzentrum Berlin between 01/06 and 12/07. Informed consent was given by the parents of each patient. Exclusion criteria were hemodynamic instability, elevated atrial pressures, lack of consent, contraindication for esophageal probe placement (e.g. esophagus atresia) and pleural or pericardial effusion. All patients were on their 1st postoperative day, with a central venous, atrial and arterial line with continuous pressure measurements. Continuous sedation was achieved with either midazolam and fentanyl infusion or propofol (Disoprivan®) infusion with piritramide boluses. Mechanical ventilation was pressure controlled using Servo-i Universal (Maquet, Solna, Sweden), which was adjusted to normal blood gases (arterial carbon dioxide of 35–50 mmHg). None of the patients had FiO_2 of above 0.5. Central venous saturation was measured in all patients at the beginning and the end of the study. Measurements were made at five time-points for each patient within 2 h. Before starting serial measurements, the TED probe and the EV electrodes were brought into position and were not removed until all five measurement series were finished. Additionally, all children were deeply sedated (analgosedation) and did not awake due to the TTE. With the cooperation of two doctors all three measurements were taken and noted at exactly the same time-points and an increase in CO due to manipulation can be excluded because heart rate and blood pressure remained stable during the study process.

Transesophageal Doppler (TED)

Since 2004 a new continuous wave transesophageal Doppler probe (Cardio QP™, Deltex Medical, Chichester, UK), with a 4 MHz transducer mounted at the tip of a transesophageal probe (5.5 mm diameter), has been developed especially for use in children (>3 kg and up to 50 kg in weight or up to 16 years old). Following oral introduction, the CardioQP™ transesophageal probe was advanced gently until its tip was located in the mid-esophagus, approximately 15–30 cm from the incisors for the majority of children, and then rotated so that the transducer faced posterior direction and a characteristic aortic blood flow signal was obtained [14]. Probe position was optimized to record peak velocity in the descending aorta by slow rotation in the long axis and alteration of the depth of insertion into the mid-esophagus to generate a clear signal. The blood flow velocity profile after spectral analysis of the reflected Doppler-shift signal (Fast Fourier Transformation) is continuously displayed. The gain setting was adjusted to obtain the best outline of the aortic velocity waveform. Patient data (weight, height) were registered in the monitor and BSA was calculated automatically according to the Haycock formula [24]. Continuous point-to-point measurement of stroke distance (SD), which is the distance of systolic movement of the blood in the descending aorta, was performed. SV was calculated as a mean from five cycles as the product of SD and De, where De is the calibration constant from a pediatric normogram based on the patient's age, weight and height [14]. Estimating CO according to a pediatric normogram carries a small margin of error in comparison to measurements of the patient's vessel diameter [14, 25]. Heart rate (bpm) was also measured and CO (l/min) was calculated according to the formula: CO (l/min) = SV × HR and CI (l/min/m^2) = CO divided by BSA. The pediatric probe offers easy handling, single use and a 72 h period for measurements and storage of patient data.

Transthoracic echocardiography (TTE)

Transthoracic echocardiography with pulsed wave/continuous wave Doppler was performed using the VingMed System 5 Echocardiography System™ (General Electrics, Healthcare, USA). The aortic valve diameter and valve area (cm^2) and the velocity time integral (cm) were measured and the heart rate (HR) (bpm) was determined directly from the R-R interval of the simultaneously recorded electrocardiograph. Cross-sectional area (CSA) of the aortic valve was estimated from the two-dimensional parasternal long axis, with the aortic inner dimension measured distal to the aortic sinuses, as described and correlated by Gardin et al. [26]. Stroke volume (SV) was calculated with the systolic velocity time integral according to the formula: SV (ml) = CSA (cm^2) × VTI (cm). Cardiac output (CO) was calculated as follows: CO (l/min) = SV (ml) × HR (bpm) and CI was CO divided by BSA [2].

Electric velocimetry

Electric velocimetry™ (EV) was performed using Aesculon™ (Osypka Medical, Berlin, Germany and La Jolla, California, USA). Electrodes were placed according to the manufacturer's specifications. Body weight and length were needed for the measurement. HR, SV, CO and CI were measured and calculated using mathematical algorithms according to the Bernstein-Osypka equation [27, 28].

Data analysis and statistics

For all quantitative data, means, standard deviation, medians and ranges have been calculated. For qualitative data frequencies are given. Differences between median values for different patient groups are evaluated using the Mann–Whitney *U*-test. Significance was assumed at two-sided $P < 0.05$. Pearson's correlation was calculated to compare values of the different techniques. Bland-Altman plot was used to compare two different methods, where the average of two values on each row is graphed on the x-axis, and the difference between the measurements (A–B) on the *y*-axis. According to the Bland-Altman analysis bias (mean of the difference) and precision (two standard deviations of the mean difference) between TTE, TED and EV were calculated. Mean absolute percentage error (MAPE) for CO was calculated according to the formula: Sum $(CO^{1,2} - CO \text{ by } TTE/CO^{1,2})/N \times 100$ [%], where ^{1} = CO by TED and ^{2} = CO by EV [29, 30]. Calculations were performed with Prism (4.0) and SPSS 12.0 (Chicago).

RESULTS

The indications for cardiac surgery were: single ventricle with completed Norwood II ($n = 12$), tetralogy of Fallot ($n = 4$), atrial or ventricular septal defect ($n = 7$) and others ($n = 3$). Clinical characteristics of the 26 patients are summarized in Table 1. In all 26 patients both Doppler derived methods (TTE and TED) were performed; EV was measured in 13 patients. Notably, one third of patients were under the age of 12 months, representing a subset of pediatric patients with particular challenges to technical devices for heart function measurement, due to their small anatomy. Table 2 gives the patients' laboratory values, central venous saturation, catecholamines, and sedative medication.

Table 1. Clinical characteristics of patients: median with (range)

	Patients ($n = 26$)	
Age years	3.5	(0.1–17.5)
Male:female	13:14	
Weight kg	13.6	(2.6–47)
Height cm	97	(50–121)
Body surface m^2	0.63	(0.27–1.68)
Diagnosis		
Fontan	12	(46%)
Tetralogy of Fallot	4	(15%)
Atrial or ventricular septal defect (ASD/VSD)	7	(27%)
Others	3	(11%)

Table 2. Laboratory values and pharmacological treatment

Hemoglobin (g/dl)	13.4	(10.2–15.2)
Aortic valve diameter mm	14	(7–20)
Central venous saturation %		
Beginning of study	65 ± 8.8	
End of study	62 ± 9.5	
Adrenalin conc. μg/kg × min^{-1}	0.063 ± 0.079	
Noradrenalin conc. μg/kg × min^{-1}	0.011 ± 0.032	
Milrinone conc. μg/kg × min^{-1}	0.37 ± 0.299	
Cont. sedation midazolam (*n*)	12/26	40%
Cont. Sedation disoprivan (*n*)	14/26	60%
Mechanical ventilation (*n*)	26	100%

Mean values and t-test

Mean values of CO and SV for all three methods are shown in Table 3. *t*-Test analysis showed significant differences for TED and EV when compared with TTE.

Comparison of the three methods to determine cardiac output and stroke volume

A single point regression for each measurement showed a good correlation of CO and SV values obtained with TED to those with TTE ($r = 0.85$, see Figure 1a). Values of CO and SV obtained with electric velocimetry (EV) also correlated with those of TTE ($r = 0.88$, see Figure 2a). According to the Bland-Altman analysis bias for TED versus TTE was 0.36 l/min and precision was 1.67 l/min; see Figure 1b. A greater bias of 0.87 l/min and a precision of 3.26 l/min was obtained in the comparison of EV with TTE; see Figure 2b. Absolute values of CO and SV obtained with TED and EV were significantly lower than those measured by TTE (Table 3). The intra-patient variability for measurement of CO was 0.01–0.2 l/min for TTE, 0.02–0.1 l/min for TED and 0.02–0.6 l/min for EV; see Figure 3. The mean percentage error was calculated for both methods; it was

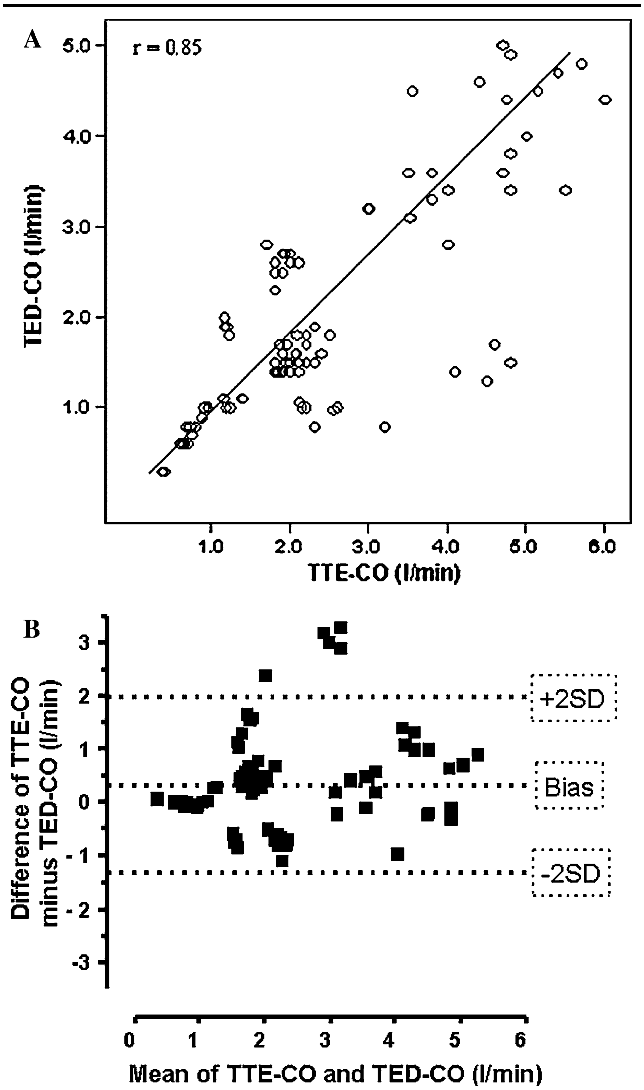

Fig. 1. (a) Comparative plot showing Pearson's correlation of cardiac output (CO) between echocardiography (TTE) and TED (Cardio QP™) in 26 patients with 106 measurements. (b) Bland and Altman plot shows a mean difference between the results of TTE and TED with bias of 0.36 l/min, precision of 1.67 l/min and limit of agreement from −1.28 to 2.0 l/min, respectively.

Table 3. Mean values ± SD of CO and SV obtained with TED and EV in comparison to TTE

	TED (*n* = 106)	Bias/precision	MAPE TTE vs. TED	TTE (*n* = 115)	(EV) (*n* = 72)	Bias/precision	MAPE TTE vs. EV
Cardiac output (CO) (l/min)	2.0 ± 1.3#	0.36/1.67 TTE vs. TED	8.2%	2.3 ± 1.4	1.8 ± 1.0⋆	0.87/3.26 TTE vs. EV	48.2%
Stroke volume (SV) [ml]	19 ± 15#	nd	nd	22 ± 17	16 ± 13⋆	nd	nd

n = Number of measurements in 26 (TTE and TED) and 13 (EV) patients; MAPE = Mean absolute percentage error: Sum ($CO^{1,2}$ – CO by TTE/$CO^{1,2}$)/N × 100 [%], where CO^1 = CO-TED and CO^2 = CO-EV; *t*-test # $P = 0.02$, ⋆ $P = 0.001$.

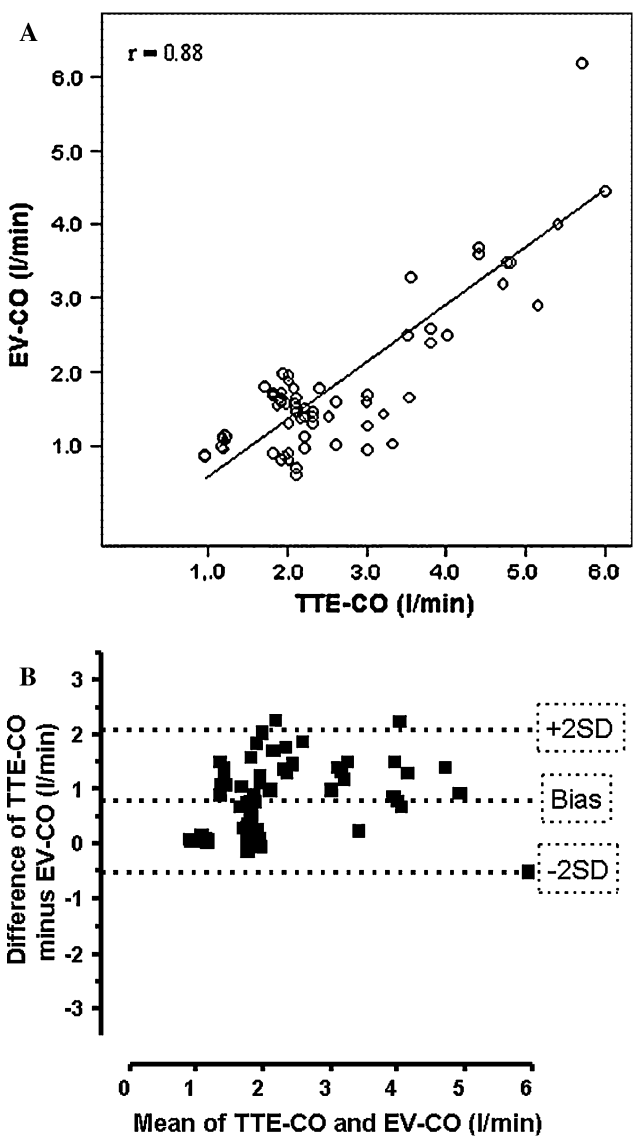

Fig. 2. (a) Comparative plot showing Pearson's correlation of cardiac output (CO) between TTE and electric velocimetry (Aesculon™) in 13 patients with 72 measurements. (b) Bland and Altman plot shows a bias of 0.87 l/min between the results of TTE and EV with precision of 3.26 l/min and limit of agreement of −2.32 to 4.1 l/min, respectively.

8.2% for CO from TED vs. TTE and 43% for CO from EV vs. TTE (see table 3).

Cardiac index

This significant difference also persists if the values for the cardiac index (CI) are compared for the three different methods; see Figure 4.

Age related analysis of stroke volume

We compared the absolute values for stroke volume (SV) with age-related values, sorted by body surface area according to the study by Poutanen et al.; see Figure 5. TTE is the most appropriate method for stroke volume measurement and yielded values between the 5 and 95th percentile (especially for patients with BSA of 0.5–1 m^2). SV values obtained by TED were mostly adequate, but values from EV were below the 5^{th} percentile in a majority of patients (Figure 5).

DISCUSSION

Non-invasive hemodynamic monitoring in pediatric patients should be safe, precise, easy reproducible and reliable [23, 33, 34]. Moreover, CO in the critically ill patient may respond quickly to changes in volume status, catecholamine infusion or the setting of mechanical ventilation. For these reasons it may be useful to have minimally invasive or non-invasive but continuous and online measurement of the CO to be able to react efficiently with therapeutic interventions. In this study both methods of CO monitoring, TED, EV were reliable techniques and were safe as compared with TTE [35–37]. Measurements with transesophageal Doppler probe (TED, Cardio QP™) and electric velocimetry (EV, Aesculon™) revealed a good correlation of values for CO and SV with values obtained by transthoracic Doppler echocardiography (TTE). Hence the two continuous techniques may be

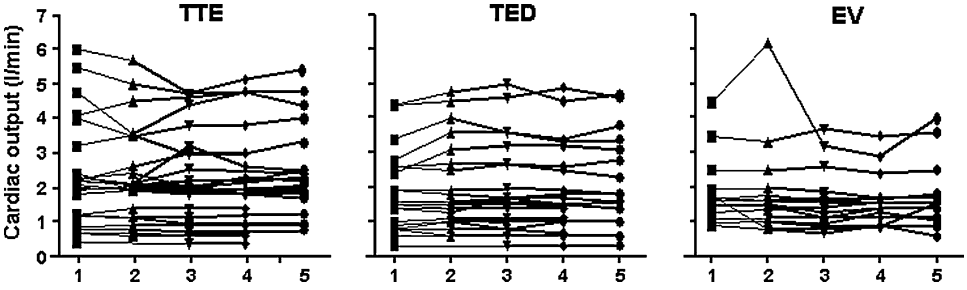

Fig. 3. Comparison of original values during the 5 repeated measurements for each method and each patient showing intra-patient variability.

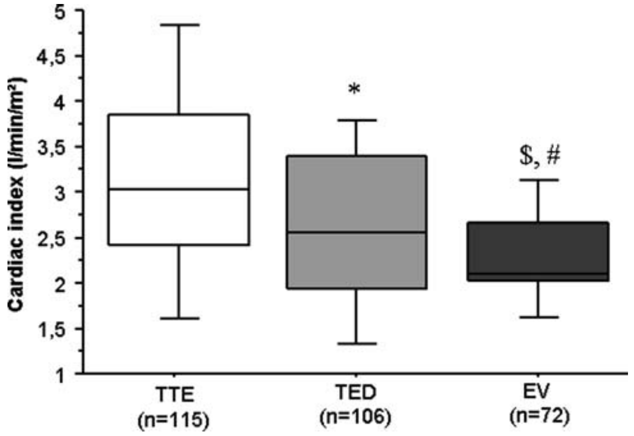

Fig. 4. Comparison of absolute values for cardiac index (CI) between TTE, TED and EV. Significant differences were seen: * *TTE vs. TED, P = 0.03,* $^{\#}$ *TTE vs. EV, P = 0.001,* $^{\$}$ *TED vs. EV, P = 0.005, n = number of measurements in 26/13 patients.*

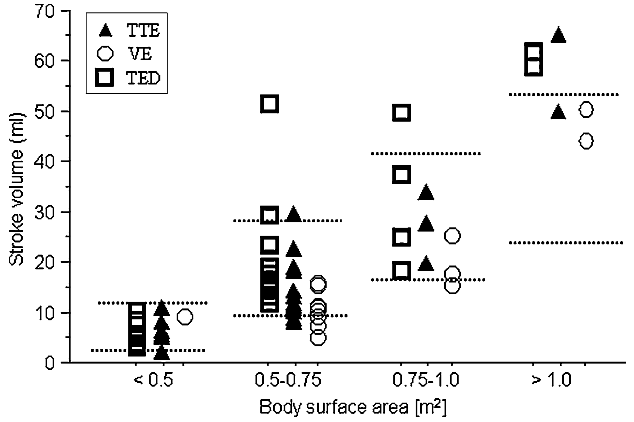

Fig. 5. Comparison of absolute values of CI between the three methods (TTE, TED, EV). Significant differences were seen in comparison to TTE and also between TED and EV. Dotted lines represent upper and lower limits of reference values of healthy individuals in relation to body surfaces area [31, 32].

better utilized to monitor trends in the changes in heart function rather than to determine absolute values [38].

Transthoracic echocardiography (TTE)

The precision of pediatric Doppler CO measurements compared to thermodilution, dye dilution, or the Fick method is around 30%. Bias is generally less than 10% but varies considerably [3]. Several studies have investigated the inter-observer and intra-observer variance of Doppler flow measurements at the aortic, pulmonary and mitral valves [39]. Comparable results have been described for Doppler-derived measurements of CO and stroke volume (SV) using the aortic, pulmonary or mitral valve [3, 40–42]. Additionally, M-mode measurements of the aortic valve have also been described [43]. Gardin et al. investigated also the day-to-day variability of aortic velocity integral measurements. The mean percentage difference reported was identical to the month-to-month variability found in the same study [26], but these measurements are still discontinuous. A newer ultrasound device has recently been developed: The cardiac output monitor (USCOM™) is an FDA approved non-invasive device that can quickly determine cardiac output in adult and pediatric patients based on outflow tract velocity measured by continuous Doppler and outflow valvular surface area as deduced by patients' height and weight; clinical evaluation is still ongoing [31, 32]. For these reasons we chose TTE as the standard measurement for CO and SV in this study to evaluate the newer continuous measurement devices for TED and EV. To test the accuracy of our measurements with TTE we compared SV to normal age and BSA related values from other studies and found that TTE values for SV in our patients were within the normal range; see Figure 5 [44–47]. Transesophageal echocardiography is hardly an alternative in small pediatric patients because of the probe size and has not been evaluated in children. A transesophageal approach may anyway not be needed in pediatric patients, as transthoracic echocardiography can be employed even in the artificially ventilated children. However, frequent measurement of TTE may need an echocardiographer or pediatric cardiologist and an echocardiography machine with these technical features. Thus frequent measurement of CO with TTE on a pediatric intensive care unit without these requirements may be difficult.

Transesophageal Doppler probe (TED, Cardio QP™)

For the newer Cardio QP probe information on its reliability in clinical use in children up to now is scarce [14, 18, 48]. We can confirm that TED (CardioQP™), which has been evaluated so far in only a small number of pediatric patients [14, 18, 48], is easy and safe. However, the absolute values of CO, SV and CI measured with TED were significantly lower than those of TTE, bias and precision for TED vs. TTE being acceptable. From adult studies we know the good reproducibility of CO, SV and CI in correlation to data from thermodilution [4, 5] but conflicting results have been published for the different TED probes and methods. Tibby et al. were the first to use a TED probe (Cardio QP) in critically ill children (3–60 kg), to provide useful data on changes in stroke volume and stroke distance after a fluid bolus, but without comparing these results with other methods for CO measurement [4]. In another study, CO from a different TED probe (Dynemo 3000) was compared to values obtained from transthoracic echocardiography; because aortic blood flow velocity with the measurement of aortic diameter showed a high bias of absolute values for CO, the authors concluded that TED with the Dynemo 3000 is not suitable for accurate CO measurement in children [11]. Although the Cardio QP does not provide aortic diameter and an error or limitation due to the calculation of SV according to a normogram is known [14], the device showed an acceptable variation in stroke volume compared with TTE and age related values [11]. Some other devices (e.g. HemoSonic™ 100, Arrow Int.) measure descending aortic diameter, but this does not improve the error for absolute CO determination compared to measurement with the normogram only [11].

The measurement of CO with Cardio QP™ was quite sensitive to any changes in probe position caused by the patient swallowing or moving; therefore full sedation of the patient was needed. This may be a limitation of the method in the critically ill patient or in patients without sedation. Additionally, left atrial (LA) pressures increased in an infant with body weight of 4 kg on insertion of the probe. LA pressure (measured continuously with an LA line in place) increased from 6 to 11 mmHg after positioning of the probe in the esophagus and decreased after removal of the probe, which was reproducible in this child several times.

Electric velocimetry (EV, Aesculon™)

EV is commercially available as Aesculon™ (Osypka Medical, Berlin, Germany) and reliable data on cardiac output in adults and animals, compared to the results of artery thermodilution, transesophageal Doppler echocardiography or the Fick (CO_2) method, have been reported [27, 28, 49, 50]. In this study it provided reliable coherent measurements for each patient, but values were significantly lower when compared to those obtained by TTE and TED. Over- or underestimation of CO and SV has been previously described in adults, with conflicting results in comparison to thermodilution [1, 2]. Additionally, mean percentage error and bias were too high and precision was not acceptable. It has to be discussed whether higher values of both SV and CO determined by TTE might also be caused by overestimation due to the measurement of aortic diameter. Contrary to this we saw a normal range of stroke volume values achieved with TTE and all patients were without signs of low cardiac output or lactate acidosis and had normal central venous saturation, which also makes TTE values more realistic [44–46]. In other studies cardiac bioimpedance also did not show a good correlation with invasive or non-invasive (e.g. Doppler-derived) measurements of CO and SV in adult patients and animals [51–55]. The calculation of CO with EV may need more thorough evaluation in pediatric patients, where the placement of the electrodes may influence signal quality and reliability of this method, especially in newborns and small children. Due to its ease of application it seems to us that this tool is worthy of additional critical and detailed evaluation, especially in younger children, before it can be used routinely in the clinical pediatric ICU setting.

Limitations of the study

Because most of the studies in adults have used thermodilution as a standard, one might use thermodilution for comparison. We do not believe that evaluation with pulmonary artery thermodilution is applicable in infants, although transpulmonary thermodilution using a 1.3 French thermistor via a 22G cannula as described by Tibby et al. may give additional information in children >3 kg, but with a risk of complications as described before. Data from EV was collected in all 26 patients, but lost in 13 patients due to a software failure. Therefore results from EV should be interpreted with caution and need further evaluation.

CONCLUSION

The bias and precision of this study indicate that non-invasive and continuous measurement of CO is possible with TED, producing values comparable to those of transthoracic echocardiography. Transesophageal Doppler with the CardioQP™ device is easy to perform but needs a sedated patient. Electrovelocimetry with Aesculon™ needs further evaluation in the pediatric patient.

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