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Comparison of electrical velocimetry and transpulmonary thermodilution for measuring cardiac output in piglets

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Summary

Background: Monitoring of cardiovascular function is essential during major pediatric and pediatric cardiac surgery. Invasive monitoring of cardiac output (CO) and oxygen delivery is expensive and sometimes associated with adverse events. Therefore, we investigated the accuracy of a new noninvasive CO monitoring device using electrical velocimetry (EV) in comparison with the more invasive transpulmonary thermodilution (TPTD) method.

Methods: In five fasted, anesthetized and mechanically ventilated piglets, CO was measured simultaneously using EV and TPTD under normal conditions, volume loading, inotropic support and exsanguination.

Results: In five piglets, 169 measurements could be performed. The correlations between EV–CO and TPTD–CO were significant for absolute values ($P < 0.0001$, $r = 0.82$) and relative changes from baseline ($P < 0.0001$, $r = 0.93$). The receiver operating characteristic (ROC) curve analysis of the relative changes of the EV–CO values in relation to the first EV–CO measurement showed a sensitivity of 91% and specificity of 94% (AUC 0.974, 95% CI 0.96–0.99). Changes in TPTD–CO greater than 15% lead to a change of EV–CO in the same direction in 93%. Bland–Altman analysis showed a mean difference between the two methods of -0.63 l·min^{-1} with an SD of 0.64 l·min^{-1}. The lower and upper limits of agreement were -1.88 and 0.62 l·min^{-1}, percentage limit of agreement was ±82.8%.

Conclusions: The results show that EV is a safe, simple, noninvasive and cost-effective method for continuous trend monitoring of CO in piglets. The agreement of the EV–CO with TPTD–CO is not good enough to replace the standard method in our animal model. A correction factor for body habitus in piglets may be beneficial.

Keywords: cardiac output; transpulmonary thermodilution; hemodynamic monitoring; thoracic electrical bioimpedance; transthoracic impedance cardiography; electrical velocimetry

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Introduction

Monitoring of cardiocirculatory function is essential during major pediatric surgery and pediatric intensive care especially in critically ill small patients because it is the rationale for goal-oriented therapy. For direct and continuous measurement of cardiac output (CO) only invasive methods such as pulmonary artery thermodilution, transpulmonary thermodilution (TPTD) with pulse contour analysis or transesophageal Doppler ultrasound are available (1). The use of the catheter techniques is expensive, time consuming and associated with inherent risks, i.e. inadvertent carotid artery puncture, catheter-related infections, arrhythmias or arterial thrombosis especially in small infants (2–4). The transesophageal Doppler ultrasound has a low morbidity but adequate probe fixation is difficult, which may interfere with the signal quality. Furthermore, the absolute estimation of CO varies between patients (1). Several noninvasive methods of assessing CO have been studied in the past including impedance cardiography (ICG), which was introduced in the clinical setting almost 40 years ago (5). Studies comparing ICG with thermodilution were largely inconclusive and reviews seem to disagree on the validity because of varying results (6–9). In contrast to the classical approach of ICG, electrical velocimetry (EV) was recently reported as a new method which interprets the maximum rate of change of thoracic electrical bioimpedance as the ohmic equivalent of mean aortic blood flow acceleration (10). Compared with former bioimpedance techniques, the EV device has a modified algorithm. The basic equation now focuses on the compartment with the greatest conductivity, the blood in the aorta. Minor changes in high-resistance low-conductivity compartments such as the lung, gas and surrounding tissues are neglected. The influence of the volume of the surrounding tissues, which is highly variable and might interfere with the results of the traditional bioimpedance, is now reduced (10).

In a study of Schmidt *et al.*, CO assessed by EV correlated compared well with transesophageal Doppler echocardiography in adults (11). Studies evaluating the validity of this new noninvasive and easily applicable method in children over a range of CO conditions are missing. Hence, this study compares EV and TPTD in a piglet model. We tested the new device on a wide range of COs that could not be tested in humans for ethical reasons.

Methods

After approval by the animal authorities (Protocol No. 05/946) five German landrace piglets (mean weight 12.92 kg; range 11.2–13.8) were selected for this examination. After IM premedication with azaperon (a common neurolepticum in veterinary medicine) and atropine, the piglets were anesthetized with intravenous propofol and fentanyl, orotracheally intubated and mechanically ventilated with 1.5–2% isoflurane in oxygen. The tidal volume was adjusted to maintain an endtidal carbon dioxide tension of 4.6–5.8 kPa (35–45 mmHg). All animals received 10 $\mu g \cdot kg^{-1}$ fentanyl and 0.5 $mg \cdot kg^{-1}$ rocuronium before surgery and every following hour. Body temperature was maintained using an infrared lamp (Sollux 760, Heraeus, Hanau, Germany) and a circulating water mattress (HICO Variotherm 550, Hirtz, Cologne, Germany). Using standard cut down techniques 5F percutaneous sheath introducer sets (Arrow, Reading, MA, USA) were inserted in the jugular vein and carotid artery on the right side. Through the artery introducer set a 4F, 8-cm thermodilution catheter (Pulsiocath, Pulsion, Munich, Germany) was introduced so that the tip of the catheter was located in the proximal carotic artery or the aortic arch. Heart rates and endtidal carbon dioxide were measured using a patient monitoring system (S/5 light monitor, Datex-Ohmeda, Freiburg, Germany). Mean arterial pressure was recorded via the 4F thermodilution catheter with a calibrated pressure monitoring kit (PICCO, Pulsion, Munich, Germany) connected to a monitor (PICCO *plus*®, Pulsion, Munich, Germany). CO was determined by TPTD and EV, methods are described below.

After baseline measurements CO was increased firstly by stepwise infusion of 25 $ml \cdot kg^{-1}$ hydroxyethyl starch 6% (mean molecular weight 200 kDa, degree of substitution 0.5) and secondly by epinephrine infusion until heart rate reached more than 170 $b \cdot min^{-1}$. After that, CO was gradually decreased by discontinuation of the epinephrine infusion and exsanguination until the heart stopped beating. The hemodynamic and blood gas measurements were performed simultaneously at baseline and after each change of CO when EV–CO stability was achieved.

We could perform between 31 and 37 paired measurements in each piglet, which took 5 h including induction of anesthesia and implantation of the catheters.

Transpulmonary thermodilution

For the measurement of CO by TPTD the PICCO *plus* monitor was used, which consists of an in-line injectate sensor connected to a central venous line and a disposable single-use arterial thermistor-tipped 4F thermodilution catheter (Pulsiocath PV2014L08, Pulsion, Munich, Germany). 5-ml ice-cold isotonic saline bolus served as indicator. After the indicator had been injected into the central vein and had passed through the cardiopulmonary system, the thermistor on the tip of the arterial thermodilution catheter measured the downstream temperature changes. The CO was calculated by the PICCO *plus* monitor by means of the Stewart–Hamilton equation from the area below the TPTD curve. Every single CO measurement at every new reached hemodynamic situation was averaged over three TPTDs. We did not use any value calculated by pulse contour analysis.

Electrical velocimetry

Electrical velocimetry cardiac output (EV–CO) calculation is based on the bioimpedance technique, which measures changes in the transthoracic impedance during cardiac ejection caused by volumetric changes of the aorta and its major tributaries. The EV monitoring device (Aesculon Electrical Velocimetry, Osypka Medical GmbH, Berlin, Germany) emits a small sinusoidal current with high frequency (50 kHz) and low amperage (2 mA) through two outer electrodes at the left side/base of the neck and the inferior aspect of the thorax (Figure 1). Two additional electrodes inside the stimulating electrodes record the thoracic electrical bioimpedance Z.

$$Z = \frac{\text{sensed voltage}}{\text{applied current}}$$

These four electrodes are the only required disposables (in contrast with the thermistor-tipped catheters needed for TPTD). For our animal experimental setting, we used needles instead of ECG electrodes to overcome skin resistance of the pigs. The needles were located at the left side of the neck and the left side of the body.

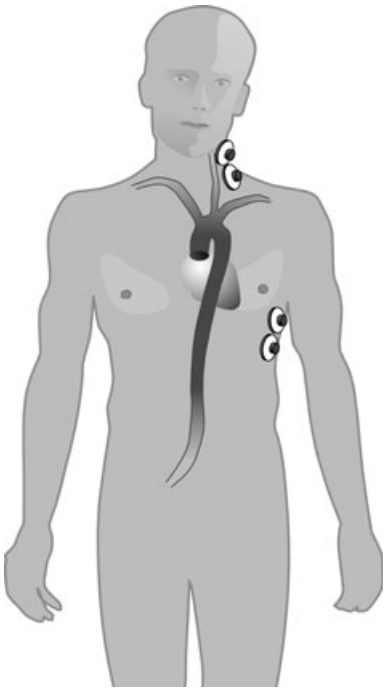

Figure 1
Position of the electrodes at the left side/base of the neck and the inferior aspect of the thorax.

Changes of the basic impedance (average value over 10 cardiac cycles) correlating with the cardiac cycle are ΔZ. These changes of impedance are not only caused by volumetric changes of the aorta and its major tributaries, they are also from an alignment of erythrocytes from random orientation prior to aortic valve opening to an orientation with their disk-shaped bodies parallel with the axial blood flow after opening of the aortic valve.

The EV monitoring device determines stroke volume (SV) using the following equation:

$$\text{SV} = V_{\text{EPT}} \times \bar{v}_{\text{LVET}} \times \text{LVET}$$

where V_{EPT} (ml) is the volume of electrically participating tissue derived from body mass and height, $\bar{v}_{\text{LVET}}$ (s^{-1}) is the ohmic equivalent of mean aortic blood velocity during left ventricular ejection and LVET (s) is the left ventricular ejection time (10) (Figure 2). The ohmic equivalent of mean aortic blood velocity during left ventricular ejection is transformed from the equivalent of mean aortic blood flow acceleration:

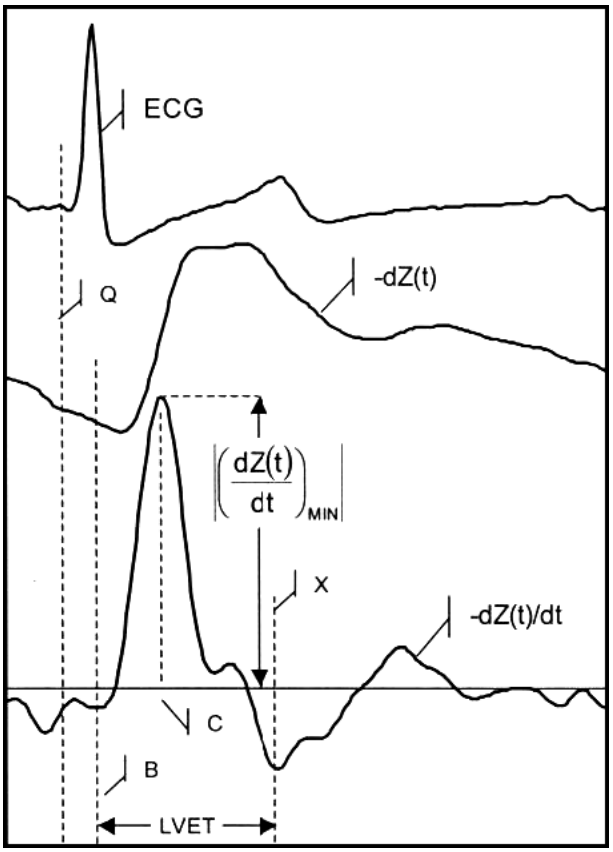

Figure 2
Representative figure of the different waveforms displayed by the monitor: ECG; ECG impedance waveform and first derivative of the impedance waveform (from top to bottom); d$Z(t)$ rapid change by reason of alignment of erythrocytes due to pulsatile blood flow; d$Z(t)$/dt_{min} peak acceleration of blood flow; d$Z(t)$/dt time derivative of velocity.

$$\bar{v}_{LVET} = \left(\frac{\left|(dZ(t)/dt)_{min}\right|}{Z_0}\right)^n$$

where d$Z(t)$/dt_{min} is the maximum rate of change of impedance due to peak acceleration of blood flow and Z_0 is the base impedance.

The mean of 10 successive CO values was displayed as EV–CO on the monitor.

Statistical analysis

The correlation and the linear regression of the different CO values were calculated using a data analysis and graphing software (Origin™ Version 5.0, Microcal, Northampton, MA, USA). Values of $P < 0.05$ were considered as statistically significant. Sensitivity and specificity were calculated by an ROC analysis with a criterion of ≤2 vs >2 l·min^{-1}. For a further trend analysis, we determined whether a variation of CO observed by TPTD was recognized by EV in the same, i.e. positive or negative, direction. First we analyzed all data and then only changes in TPTD–CO greater than 15%. For the statistical investigation with the Bland–Altman (12) method for evaluation of studies, GraphPad Prism 4 software (GraphPad Software, San Diego, CA, USA) was used. Bias was calculated as the mean difference between EV–CO and TPTD–CO. The upper and the lower limit of agreement were calculated as bias ±2 SD and defined the range in which 95% of the differences between the methods were expected to lie. Percentage limits of agreement also called percentage error were calculated as the ratio of twice the standard deviation and the mean CO. A percentage error up to ±30% was defined as acceptable (13).

Results

We were able to gather 31–37 measurements in each piglet, so a total of 169 paired data were evaluated. Pooled CO determined by TPTD ranged from 0.29–4.5 l·min^{-1} and EV–CO ranged from 0.39 to 2.79 l·min^{-1}. The initial CO values were 1.57 ± 0.22 l·min^{-1} and 1.10 ± 0.20 l·min^{-1} ($n = 5$) respectively. Figure 3a shows a scatter plot of the data with the linear regression line. Correlation between the two methods was significant ($P < 0.0001$) with a coefficient of $r = 0.82$. EV–CO was linearly related to TPTD with a y-intercept of 0.39 and slope of the line of 0.44, the EV–CO values underestimate high and overestimate low CO values. Comparing the relative changes of the EV–CO values (actually measured EV–CO value divided by individual initial EV–CO value) with TPTD (Figure 3b), we found a correlation coefficient of $r = 0.93$ ($P < 0.0001$). The ROC analysis of the relative changes of the EV–CO showed a sensitivity of 91% and specificity of 94% (AUC 0.974, 95% CI 0.96–0.99). For a further trend analysis, we evaluated whether a variation of CO observed by TPTD was recognized by EV in the same, i.e. positive or negative, direction: 81% of all measurements did so. When focusing on changes in TPTD–CO greater than 15%, one can state that the EV showed alterations in the same direction in 93% of the cases. The results of the Bland–Altman analysis are shown in Figure 4. The mean difference

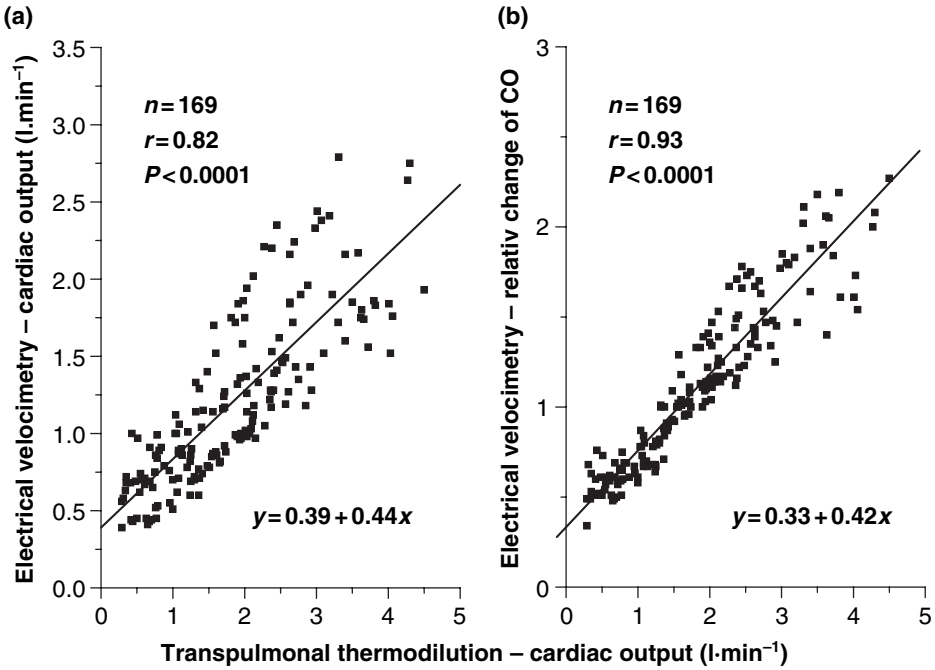

Figure 3
Scatter plot comparing cardiac outputs: (a) electrical velocimetry (EV) and transpulmonary thermodilution (TPTD); (b) relative change of EV (related to the first measurement of each animal) and TPTD.

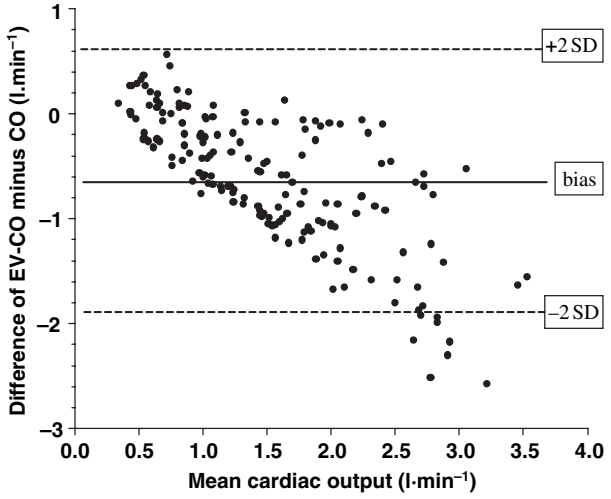

Figure 4
Bias plot of the difference in measurements by electrical velocimetry (EV) and transpulmonary thermodilution (TPTD) compared with the mean of the two results. Mean difference of EV minus TPTD was −0.63 l·min^{-1}, SD 0.64 l·min^{-1}, the lower and upper limits of agreement were −1.88 and 0.62 l·min^{-1} respectively.

between the two methods (bias) was −0.63 l·min^{-1} with an SD of 0.64 l·min^{-1}. The lower and upper limits of agreement were −1.88 and 0.62 l·min^{-1} respectively. The percentage error was ±82.8%. The Bland–Altman plot shows that the difference between the two measurements is dependent on its average. Moreover, this also holds for the variance of the differences. Therefore, the limits of agreement were calculated according to the approach for nonuniform differences (14). The results from the Bland–Altman analysis for individual piglets are presented in Table 1.

Table 1
Bland–Altman results of individual pigs

Pig	*n*	*Bias*	SD	*CO range (l·min^{-1})*	*Mean CO (l·min^{-1})*	*% limits of agreement*	*Correlation coefficient (r)*
1	33	−0.29	0.45	0.49–2.72	1.39	±64.7	0.90
2	35	−0.89	0.51	0.48–2.78	1.35	±75.6	0.97
3	37	−0.99	0.63	0.43–3.22	1.60	±78.7	0.97
4	33	−0.52	0.72	0.34–2.93	1.32	±108.9	0.96
5	31	−0.37	0.55	0.72–3.53	1.97	±55.9	0.91

Further results observed using the PICCO *plus* monitor with TPTD are the intrathoracic blood volume with a mean of 169.8 ml (80.0–254.0; SD 47.77), the extravascular lung water with a mean of 160.7 ml (109.0–248.0; SD 28.88) and, determined with continuous pulse contour analysis, the systemic vascular resistance with a mean of 1879 dyn·sec·cm^{-5} (430.0–4890; SD 788.3).

Discussion

We compared the results of EV to results of TPTD. Transpulmonary thermodilution is not the gold

standard for CO measuring and has its limitations, especially when CO is low or high (15–18), but there are several studies which show the equivalence of CO measurement by TPTD and the Fick principle (19,20) or pulmonary artery thermodilution (21,22). Therefore and because of the easier operability, we decided to compare the new method with TPTD. We chose 6-week-old piglets because the results could be better transmitted to small children than from other animal models.

Our study shows a significant correlation of CO measurements using EV and TPTD in an animal experimental setting. The correlation coefficient increases when the relative changes of EV–CO are investigated. In addition, the correlation of the individual piglets was higher than the overall data. ROC analysis showed a good sensitivity and specificity and changes in TPTD–CO greater than 15% were discerned by EV–CO in the same direction in 93% of the cases. Bland–Altman analysis showed an overall bias of $-0.63\ l{\cdot}min^{-1}$ with a standard deviation of the differences of $0.64\ l{\cdot}min^{-1}$ (precision). The percentage error between the two methods was ±82.8%. It was markedly higher than the predefined level of ±30% for the interchangeability of two different methods for measuring CO.

The only recent investigation validating the new device (Figure 5) with transesophageal Doppler echocardiography found a high correlation ($r^2 = 0.86$) and a percentage error of ±29% in 37 patients with coronary vessel disease (11). They predicted the interchangeability of the two methods. The lower correlation of our investigation compared with the EV evaluation in humans or to preceding bioimpedance monitoring systems in a porcine model (23) might be explained by the extremely stimulated CO values and the lower correlation in this range. Another reason might be the animal itself: the location of the aortic arch in the thorax of the pig or the resistance of the skin might be different from humans. In addition, the large amount of fat and muscle around the neck region of the piglets might interfere with the technique. The new method is adjusted to humans so that a correction factor might be required for the use in piglets.

Figure 5
Electrical velocimetry monitoring device, Aesculon, Osypka Medical GmbH, Berlin, Germany

The thermodilution technique using a pulmonary arterial catheter is highly invasive and has been criticized repeatedly because of its uncertain risk–benefit ratio and cost (24–26). Additionally, this method has its limitations in small children and infants. The alternative method for obtaining CO is the TPTD. The smallest available femoral artery catheter has a size of 3F and a length of 7 cm. We usually do not use arterial 3F catheters in children weighing less than 10 kg because of the high rates of catheter-related arterial vascular occlusions in neonates and infants (27,28). The transesophageal Doppler ultrasound is another but also invasive method for continuous monitoring of cardiac function. It can be utilized in children only if they are intubated and mechanically ventilated. Pressure lesions might occur if the probe is left in the esophagus for several days, especially in combination with a gastric tube. Furthermore, the absolute estimation of CO varies between patients. EV is a completely noninvasive method for monitoring cardiac function continuously over an arbitrarily long period. In piglets it could be utilized for trend monitoring or scientific research.

Electrical velocimetry is a new safe, simple, noninvasive and cost-effective method to estimate cardiac function continuously in piglets. In our animal experimental setting the correlation with TPTD is sufficient for trend monitoring or research/scientific questions. We found only a poor agreement between the two methods, which we attribute to morphology differences between humans and piglets. In further investigations it should be validated, for example, by means of the Fick method or TPTD in infants.

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