Journal of Clinical Monitoring and Computing (2019) 33:767–776
https://doi.org/10.1007/s10877-018-0217-1

ORIGINAL RESEARCH

The accuracy and trending ability of cardiac index measured by the fourth-generation FloTrac/Vigileo system™ and the Fick method in cardiac surgery patients

Takuma Maeda[1,2] · Eisuke Hamaguchi[1] · Naoko Kubo[1] · Akira Shimokawa[1] · Hiroko Kanazawa[1] · Yoshihiko Ohnishi[1]

Received: 19 July 2018 / Accepted: 1 November 2018 / Published online: 7 November 2018

Abstract

To compare the accuracy and trending ability of the cardiac index (CI) measured by FloTrac/Vigileo™ (CI_{FT}) or derived by the Fick equation (CI_{Fick}) using E-CAiOVX (enables continuous monitoring of oxygen consumption) with that measured by thermodilution (CI_{TD}) in patients with off-pump coronary artery bypass surgery. Twenty-two patients undergoing elective off-pump coronary artery bypass surgery were included. CI_{FT} and CI_{Fick} were determined simultaneously at six time-points during off-pump coronary artery bypass surgery. At each time-point, phenylephrine (50 µg) was administered to increase systematic vascular resistance, with CI measured before and after administration (CI_{TD} used as reference method). Agreement of each method was evaluated by Bland–Altman analysis, while trending ability was evaluated by four-quadrant plot analysis and polar plot analysis. By Bland–Altman analysis, CI_{FT} and CI_{Fick} showed percentage errors of 49.5% and 78.6%, respectively, compared with CI_{TD}. Subgroup analysis showed a percentage error between CO_{FT} and CO_{TD} of 28.9% in patients with a CI ≥ 2.4 L/min/m^2, and 78.1% in patients with a CI ≥ 2.4 L/min/m^2. The concordance rate of four-quadrant plot analysis was 93.3% for CI_{FT} and 66.7% for CI_{Fick} in datasets where CI_{TD} ≥ 2.4 L/min/m^2 before and after phenylephrine administration were included. CI_{FT} and CI_{Fick} had wide limits of agreement with CI_{TD}, and were below acceptable limits for tracking phenylephrine-induced CI changes. However, subgroup analysis showed improved accuracy and trending ability of CI_{FT} when only points where CI_{TD} ≥ 2.4 L/min/m^2 were included, while there was no improvement in CI_{Fick} accuracy or trending ability.

Keywords Blood pressure monitor · Cardiac output · Fick principle · Thermodilution

1 Introduction

With recent technological advances, a number of minimally invasive monitors have been developed for measuring cardiac index (CI). For example, the FloTrac/Vigileo™ measures pulse pressure-derived CI without external calibration, and is widely used perioperatively in operating theaters and intensive care units, at least in part, because of concerns regarding complications related to pulmonary arterial catheterization. However, the accuracy of CI measured by FloTrac/Vigileo™ (CI_{FT}) can be unreliable in some patients, especially those with a high or low systemic vascular resistance (SVR) [1, 2]. The FloTrac/Vigileo™ was upgraded and the algorithm modified several times to overcome this limitation, although it was recently reported to be inaccurate in patients with a low CI, likely because of the high SVR in these patients [3–5]. For the fourth-generation FloTrac/Vigileo™, the algorithm was improved by adding a correction factor to follow changes in SVR, which markedly improved the trending ability after phenylephrine administration in patients undergoing cardiac surgery [6]. However, the effect of low CI on the accuracy and trending ability of the fourth-generation

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10877-018-0217-1) contains supplementary material, which is available to authorized users.

✉ Takuma Maeda
takuma@ncvc.go.jp

1 Department of Anesthesiology, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan

2 Division of Transfusion Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan

FloTrac/Vigileo™ in patients undergoing cardiac surgery remains unclear. Recently, techniques for real time measurement of oxygen consumption ($\dot{V}O_2$) were also developed, allowing calculation of CI using the Fick equation. However, the accuracy and trending ability of CI derived by the Fick equation (CI_{Fick}) during cardiovascular surgery is unknown.

A wealth of experimental and clinical studies have validated the accuracy, reliability, and clinical relevance and utility of thermodilution-based CI measurements [7], and bolus thermodilution is the most accepted reference method [8–10]. Thus, the aim of the present study was to compare the accuracy and trending ability of CI_{FT} and CI_{Fick} with the thermodilution technique (CI_{TD}; reference method) in patients undergoing off-pump coronary artery bypass surgery, as well as the effect of low CI on these parameters.

2 Methods

2.1 Patients

This study was prospective observational single center study. The study protocol was approved by the ethics committee of the National Cerebral and Cardiovascular Center, Osaka, Japan, (file number: M26-023-5), and met the guidelines of the Helsinki Declaration. All patients gave informed consent to participate in the study, which included a prospective analysis of 22 patients who underwent off-pump coronary artery bypass surgery from July 2014 to March 2016. All patients underwent off-pump coronary artery bypass surgery under general anesthesia. Exclusion criteria were severe valvular disease, arrhythmias, emergency surgery, or mechanical circulatory support.

After induction of anesthesia with fentanyl (1.5–2 µg/kg), midazolam (0.1 mg/kg), and continuous infusion of propofol (4–6 mg/kg/h), 1 mg/kg rocuronium was given to facilitate orotracheal intubation with a cuffed endotracheal tube. All patients were maintained under anesthesia with propofol (4–6 mg/kg/h) and remifentanil (0.3–0.5 µg/kg/min) using mechanical ventilation with a tidal volume of 8–10 ml/kg body weight at a frequency of 8–12 breaths per min, to maintain an end-tidal carbon dioxide at 35–40 mmHg. The fraction of inspiratory oxygen during surgery was maintained at 30–60%. Measurement of $\dot{V}O_2$ was performed using D-lite flow sensors (Datex-Ohmeda Division, Instrumentarium Co., Helsinki, Finland), which attach in-line to an artificial airway and include a side-stream sampling port for gas analysis and spirometry [11]. Continuous gas sampling through a gas sensor connected to a GE CARESCAPE B650 Monitor with an E-CAiOV Airway Module (GE Healthcare, Milwaukee, WI, USA) to provide breath-by-breath analysis of expired air, including measurement of $\dot{V}O_2$ [11, 12].

After anesthesia induction, the radial artery was cannulated, providing hemodynamic monitoring using the FloTrac/Vigileo™ system (version 4.00; Edwards Lifesciences, Irvine, CA, USA). The central venous catheter and the pulmonary arterial catheter (PAC) were inserted by the attending anesthesiologist. Correct positioning of the catheters was confirmed by pressure waves and transesophageal echocardiography. The Vigilance™ monitor (Edwards Lifesciences) was connected to the PAC to measure CI.

2.2 Study protocol

A series of CI data were measured using three different methods at six time-points, as follows: (T1) after anesthesia induction; (T2) after sternotomy; (T3) during anastomosis of the left anterior descending branch of the left coronary artery; (T4) during tilting of the heart; (T5) after protamine injection; and (T6) at the end of surgery. At each point, phenylephrine (50 µg) was administered to increase SVR, and CIs were obtained before and after administration. Twelve CIs were measured per patient.

The reference CI was measured using the conventional PAC thermodilution technique with ice-cold saline (10-mL bolus injection). The average of three consecutive CI measurements with PAC was used as the reference CI. We simultaneously recorded CI_{FT} from the FloTrac/Vigileo™, and standard hemodynamic data [heart rate, mean arterial pressure (MAP), and central venous pressure] and $\dot{V}O_2$ using E-CAiOVX (GE Healthcare). Immediately after the calculation of CI_{TD}, blood samples were collected simultaneously from the arterial catheter and the distal port of the PAC. Blood gas analyses were performed on a multi-wavelength optical blood analyzer (ABL800 FLEX; Radiometer Medical A/P/S, Copenhagen, Denmark).

2.3 Determining CI_{FT} using the FloTrac/Vigileo™ system

Stroke volume (SV) was calculated with the FloTrac/Vigileo™ system using arterial pulsatility (standard deviation [SD] of the pulse pressure over a 20-s interval), resistance, and compliance. Cardiac output (CO), CI, and SV were calculated as follows: $CO = HR \times SV$, $CI = CO/\text{body surface area}$, and $SV = K \times \text{pulsatility}$, respectively, where K is a constant quantifying arterial compliance and vascular resistance. K was derived from a multivariate regression model that included Langewouters' model of aortic compliance, mean arterial blood pressure, and variance, skewness, and kurtosis of the pressure curve [4, 5, 13]. The rate of adjustment of *K* was 1 min.

2.4 Determining CI_{Fick} using the FloTrac/Vigileo™ system

CI_{Fick} was calculated by applying the Fick principles using $\dot{V}O_2$ and the difference between arterial (CaO_2) and venous (CvO_2) blood oxygen contents. CaO_2 and CvO_2 were calculated as: hemoglobin [Hb] value × arterial Hb oxygenation × 1.36 and Hb × SvO_2 × 1.36, respectively. CO and CI were calculated as: $CO = \dot{V}O_2/CaO_2 - CvO_2$ and CI = CO/body surface area, respectively.

2.5 Statistical methodology

All data are expressed as mean ± SD or number. Patients' hemodynamic data were compared using a paired t-test. All statistical analyses were performed with statistical software (EZR statistical software, Saitama Medical Center, Jichi Medical University, Saitama, Japan; available at http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmedEN.html) [14], which is a modified version of the R commander (R Foundation for Statistical Computing, Vienna, Austria). A *P* value < 0.05 was considered statistically significant.

Agreement of each method was evaluated by the Bland–Altman method [15]. Bias was defined as the difference between the test method and the reference method, and represents the systematic error between methods. Precision was defined as the SD of the bias, and represents the random error or variability between the techniques. Limits of agreement was defined as the range in which 95% of the differences between the methods were expected to lie, and were calculated as bias ± 2SD. The percentage error was calculated as 2SD of the bias/mean CI of the reference method. The percentage error was considered clinically acceptable, and the tested method (CI_{FT} or CI_{Fick}) was regarded as interchangeable with the reference method (CI_{TD}), if it was < 30%, as proposed by Critchley et al. [16] To examine the effect of low CI on the association of CI_{FT} with CI_{TD}, or of CI_{Fick} with CI_{TD}, we subdivided the measured CI sets into two groups according to the measured CI_{TD}, as follows: (1) $CI_{TD} < 2.4$ L/min/m^2 and (2) $CI_{TD} \geq 2.4$ L/min/m^2. The cut off value of 2.4 L/min/m^2 was defined according to published literature, where a CI of < 2.2 L/min/m^2 represents shock, while a CI > 2.6 L/min/m^2 is considered normal [17, 18]. The Bland–Altman method was used for analysis in each group.

We used a four-quadrant plot analysis to examine the trending ability of CI_{FT} and CI_{Fick}, which can assess the concordance rate between percentage change in CI_{TD} (ΔCI_{TD}) and the percentage change in CI_{FT} (ΔCI_{FT}) or percentage change in CI_{Fick} (ΔCI_{Fick}). The concordance rate was calculated before and after phenylephrine administration at each time-point. As the direction of the change in CI at the center of the plot varied randomly, this can cause unreliability in the trending ability of the test methods. To avoid this limitation, we set an exclusion zone defined as the area of percentage change in CI < 10%, based on a previous study [2]. We then used polar plot analysis to assess the agreement between the two methods, using the angle of the vector with the line of identity (y = x) and the magnitude of change by the length of the vector [19, 20]. The plots used in four-quadrant plot analysis were rotated 45° clockwise. The following statistical variables were calculated from the polar plot analysis: (1) mean angular bias, which represents the average angle between all the polar data points and the polar axis; (2) radial limits of agreement, which represents the radial sector containing 95% of the data points; and (3) angular concordance rate, which represents the percentage of points in the 30° radial zone. A previous study suggested the following acceptance limits for polar plot analysis: (1) angular bias of < ± 5°, (2) radial limit of agreement < ± 30°, and (3) angular concordance rate > 95% [19].

3 Results

Twenty-two patients (three women, 19 men) were enrolled in this study. Patients' characteristics are shown in Table 1, and hemodynamic data are summarized in Table 2. MAP and systemic vascular resistance (SVRI) significantly increased after phenylephrine administration at each time-point (*P* < 0.05 for both MAP and SVRI). By

Table 1 Patient characteristics

	All patients (n = 22)
Age range (years)	31–81
Sex (M/F)	19/3
Height (cm)	162.7 ± 6.6
Body weight (kg)	62.3 ± 8.1
Fractional shortening (%)	36.3 ± 6.3
Valve	
TR (trivial/none)	2/20
PR (trivial/none)	4/18
MR (trivial/none)	15/7
AR (trivial/none)	1/21

Data are mean ± standard deviation or number

M male, *F* female, *TR* tricuspid valve regurgitation, *PR* pulmonary valve regurgitation, *MR* mitral regurgitation, *AR* aortic regurgitation

Table 2 Time course of changes in hemodynamic and laboratory data

	T1		T2		T3		T4		T5		T6	
	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
HR (bpm)	53 ± 8	50 ± 7	55 ± 8	52 ± 7	61 ± 8	58 ± 8	64 ± 10	61 ± 11	67 ± 10	65 ± 9	78 ± 10	75 ± 10
MAP (mmHg)	66 ± 10	88 ± 12*	68 ± 8	85 ± 12*	63 ± 5	85 ± 11*	64 ± 7	80 ± 8 *	65 ± 7	80 ± 10*	64 ± 6	79 ± 12*
CVP (mmHg)	7 ± 2	8 ± 2*	7 ± 2	8 ± 2*	7 ± 2	8 ± 2*	10 ± 3	11 ± 3	6 ± 2	7 ± 2	8 ± 2	9 ± 2
VO_2	161 ± 35	163 ± 37	153 ± 32	150 ± 27	152 ± 29	153 ± 29	150 ± 31	151 ± 32	160 ± 29	160 ± 32	151 ± 36	155 ± 41
$CaO_2 - CvO_2$	3.8 ± 0.6	3.6 ± 0.5	3.3 ± 0.7	3.6 ± 0.8	2.9 ± 0.7	3.0 ± 0.7	3.7 ± 1.0	3.7 ± 1.0	2.7 ± 0.7	2.7 ± 0.8	2.3 ± 0.8	2.5 ± 0.6
CI_{TD} (L/min/m^2)	1.8 ± 0.4	1.8 ± 0.3	1.9 ± 0.4	1.9 ± 0.4	2.2 ± 0.5	2.2 ± 0.5	1.8 ± 0.6	1.9 ± 0.6	2.6 ± 0.7	2.6 ± 0.7	2.9 ± 0.7	3.0 ± 0.6
CI_{FT} (L/min/m^2)	2.1 ± 0.3	2.2 ± 0.4	2.2 ± 0.5	2.2 ± 0.4	2.4 ± 0.5	2.5 ± 0.5	2.1 ± 0.5	2.2 ± 0.6	2.8 ± 0.6	2.9 ± 0.5	3.1 ± 0.6	3.0 ± 0.5
CI_{FICK} (L/min/m^2)	2.6 ± 0.5	2.7 ± 0.6	2.9 ± 0.9	2.6 ± 0.7	3.3 ± 1.1	3.2 ± 1.2	2.6 ± 1.0	2.7 ± 1.0	3.8 ± 1.0	3.7 ± 1.1	4.3 ± 1.7	4.0 ± 1.5
SVRI (dyne s/cm^5/m^2)	2794 ± 605	3616 ± 809*	2598 ± 542	3388 ± 751*	2235 ± 667	2996 ± 897*	2564 ± 794	3194 ± 865*	1953 ± 477	2386 ± 646*	1603 ± 385	1939 ± 534*

Data are mean ± standard deviation. ‘Before’ indicates immediately before phenylephrine administration. ‘After’ indicates immediately after phenylephrine administration

(T1) after anesthesia induction; (T2) after sternotomy; (T3) during anastomosis of the left anterior descending branch of the left coronary artery; (T4) during tilting of the heart; (T5) after protamine injection; (T6) at the end of surgery; HR, heart rate; bpm, beats per min; MAP, mean arterial pressure; CVP, central venous pressure; VO_2, oxygen consumption; $CaO_2 - CvO_2$, difference of arterial (CaO_2) and venous (CvO_2) blood oxygen contents; CI_{TD}, cardiac index measured by a conventional thermodilution technique; CI_{FT}, cardiac index measured with FloTrac/Vigileo™; CI_{FICK}, cardiac index calculated by Fick equation; SVRI, systemic vascular resistance index

*$P < 0.05$ compared with before phenylephrine administration

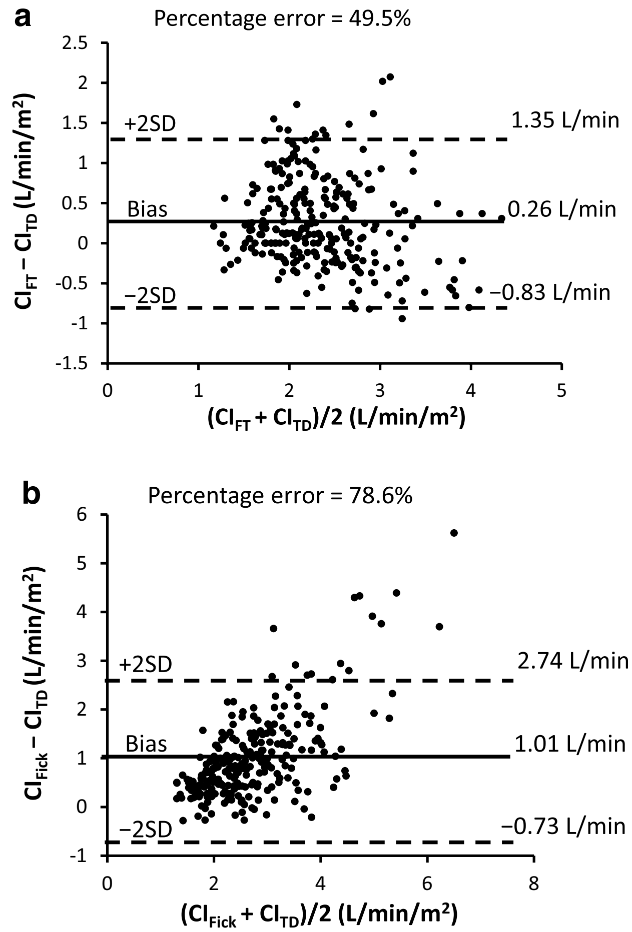


Fig. 1 Bland–Altman analysis of cardiac index (CI) measured by the different methods. **a** FloTrac/Vigileo™ (CI_{FT}) and the thermodilution method (CI_{TD}). **b** Fick equation (CI_{Fick}) and CI_{TD}. Mean bias (right line); 95% limits of agreement (dashed lines). *SD* standard deviation

contrast, there was no change in CI measured by three methods following phenylephrine administration at each time-point.

To clarify the accuracy and trending ability of CI_{FT} and CI_{Fick}, we first performed a Bland–Altman analysis to compare CI_{FT} and CI_{Fick} with CI_{TD}. Bland–Altman analysis results for comparisons between CI_{FT} and CI_{TD} for all measures (Fig. 1a) showed a percentage error of 49.5%, suggesting that CI_{FT} had a wide limit of agreement with CI_{TD}. Bland–Altman analysis results for comparisons between CI_{Fick} and CI_{TD} for all measures (Fig. 1b) showed a percentage error of 78.6%, suggesting that CI_{Fick} also had a wide limit of agreement with CI_{TD}.

Next, we divided the measured CI sets into two groups for subanalysis according to the measured CI_{TD}, as follows: (1) $CI_{TD} < 2.4$ L/min/m^2 (177 sets) and (2) $CI_{TD} \geq 2.4$ L/min/m^2 (87 sets). The percentage error of CI_{FT} improved to 28.9% in the $CI_{TD} \geq 2.4$ L/min/m^2 group, but was 56.2% in the $CI_{TD} < 2.4$ L/min/m^2 group (Fig. 2a). This suggests

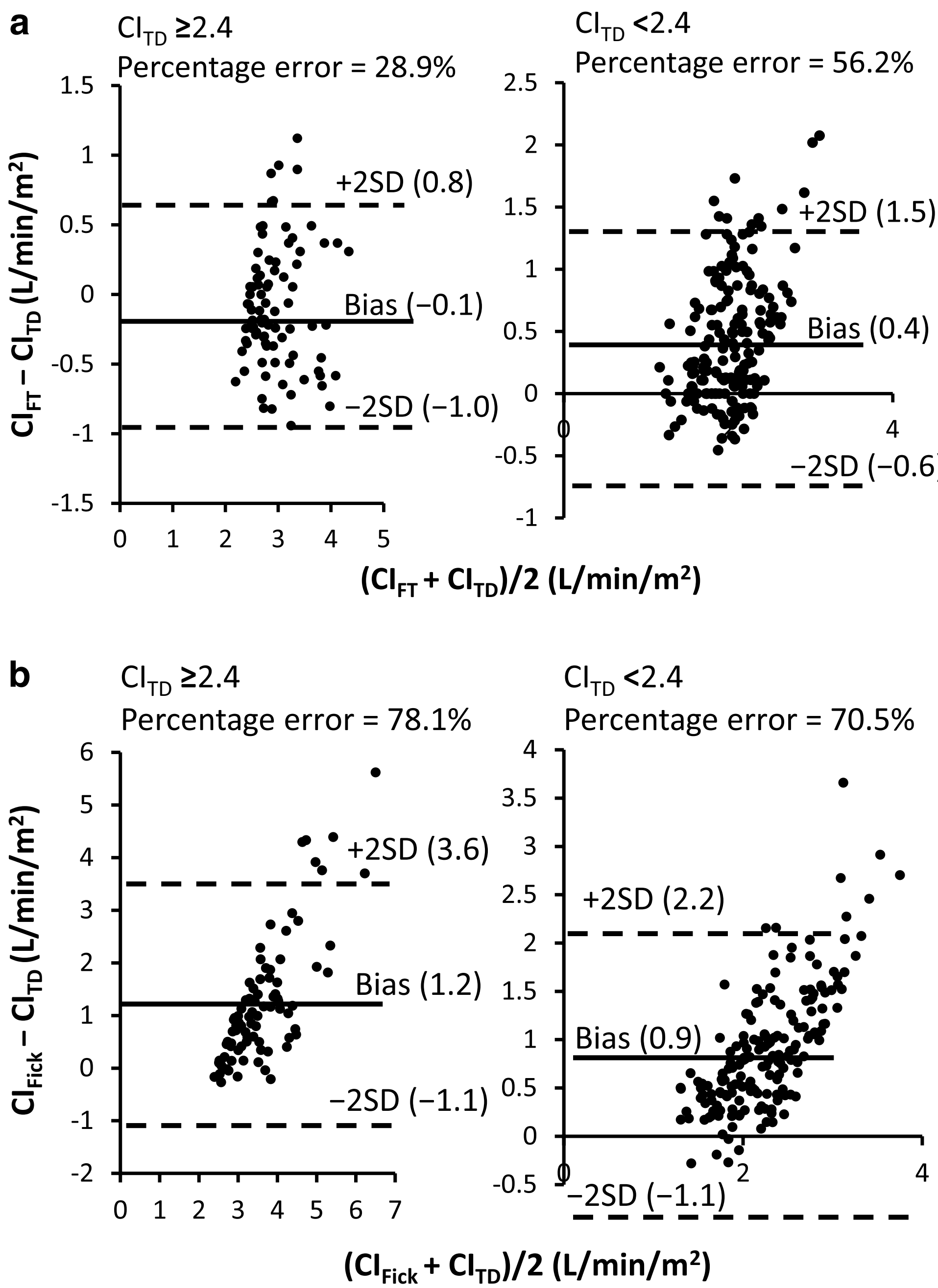


Fig. 2 Bland–Altman analysis of CI using the $CI_{TD} \geq 2.4$ L/min/m^2 and $CI_{TD} < 2.4$ L/min/m^2 subgroups. **a** CI_{FT} and CI_{TD}. **b** CI_{Fick} and CI_{TD}. Mean bias (right line); 95% limits of agreement (dashed lines)

that the FloTrac/Vigileo™ was not accurate in patients with a low CI, particularly those with a CI < 2.4 L/min/m^2. By contrast, the percentage error of CI_{Fick} was 78.1% in the $CI_{TD} \geq 2.4$ L/min/m^2 group, and 70.5% in the $CI_{TD} < 2.4$ L/min/m^2 group, showing acceptable limits in both groups (Fig. 2b). SVRI was significantly higher in patients with a $CI_{TD} < 2.4$ L/min/m^2 versus the $CI_{TD} \geq 2.4$ L/min/m^2 group (1798 ± 446 versus 3003 ± 786 dyne s/cm^5/m^2, respectively; $P < 0.001$), which may have affected the accuracy of the FloTrac/Vigileo™.

We then examined the trending ability of CI_{FT} and CI_{Fick} using four-quadrant plot analysis. The concordance rate was 85.9% for CI_{FT} (Fig. 3a) and 63.6% for CI_{Fick} (Fig. 3b). These concordance rates were below 92%, which is considered the acceptable cut-off [20]. Next, we examined the trending ability of CI_{FT} and CI_{Fick} using polar plots analysis, which showed a mean angular bias of −0.6° and 10.1°, respectively, radial limits of agreement of 39.7° and 64.1°, respectively, and concordance rates of 73.1% and 57.4%, respectively (Fig. 4a, b). Both

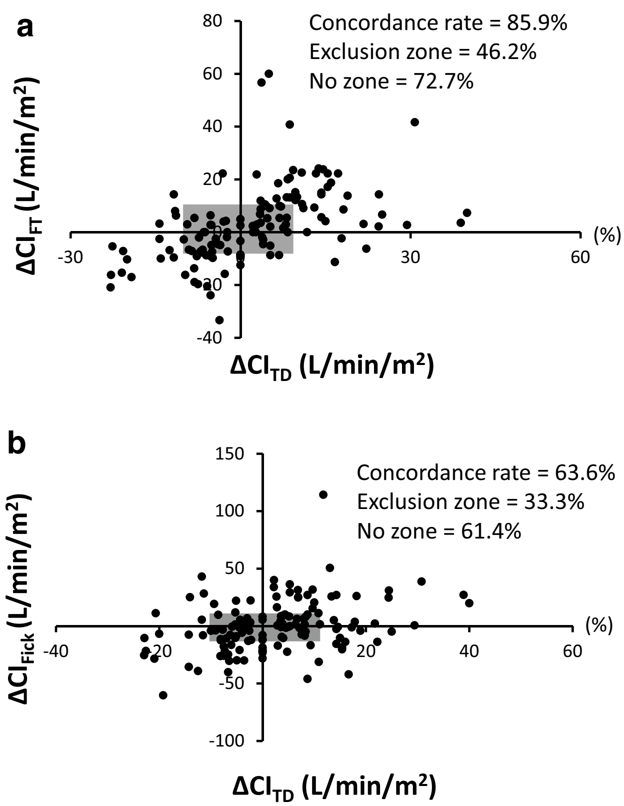


Fig. 3 Four-quadrant plot analysis of trending ability. **a** Change in CI_{FT} (ΔCI_{FT}) versus ΔCI_{TD}. **b** ΔCI_{Fick} versus ΔCI_{TD}. The plots at the center represent an exclusion zone (shaded black area) set as the percentage change in cardiac output < 10%

of the angular concordance rates were below the acceptable limit (> 95%).

When we included the 38 points where $CI_{TD} \geq 2.4$ L/min/m^2 before and after phenylephrine administration, the concordance rate of the four-quadrant plot analysis was 93.3% for CI_{FT} (Fig. 5a) and 66.7% for CI_{Fick} (Fig. 5b). The concordance rate for CI_{FT} was within the acceptable limit (> 92%), which is considered to represent a good trending ability. As for the polar plot analysis, the angular concordance rate of CI_{FT} was 90.9%, which was near the acceptable limit (> 95%) (Fig. 6a). The angular concordance rate of CI_{Fick} was 38.9%, below the acceptable limit (Fig. 6b).

4 Discussion

This study investigated the accuracy and trending ability of CI derived using the fourth-generation FloTrac/Vigileo™ (CI_{FT}) and the Fick method (CI_{Fick}) in patients undergoing off-pump coronary bypass surgery by comparing with CI_{TD}. Results showed that both CI_{FT} and CI_{Fick} had a wide limit of agreement compared with CI_{TD}, and that the trending ability of CI_{FT} and CI_{Fick} were below the acceptable limits for tracking phenylephrine-induced CI changes. However, subgroup analysis revealed that the accuracy of CI_{FT} and the trending ability of CI_{FT} both improved when only points where $CI_{TD} \geq 2.4$ L/min/m^2 were included. By contrast, there were no improvements in accuracy or trending ability in CI_{Fick} with subgroup analysis.

The accuracy of the fourth-generation FloTrac/Vigileo™ has been investigated in various clinical situations, including cardiac surgery, cardiac resynchronization therapy implantation surgery, and other elective surgeries requiring continuous arterial pressure monitoring [4–6, 21, 22]. The ability of FloTrac/Vigileo™ to follow changes in SVR was improved using the new algorithm. However, the calculation used for CI measurement is that same as previous versions. Thus, there is still a wide limit of agreement between CI measured by FloTrac/Vigileo™ and the reference method in previous studies [4–6, 21, 22], likely because the accuracy of FloTrac/Vigileo™ is strongly influenced by vascular tone. Our finding of an overall percentage error between CI_{FT} and CI_{TD} of 49.5% (suggesting that CI_{FT} had a wide limit of agreement with CI_{TD}) was comparable with those studies.

The trending ability of the fourth-generation FloTrac/Vigileo™ system after increased vasomotor tone induced by phenylephrine was reported to be markedly improved compared with previous versions [6, 21]. Our study revealed a concordance rate of 85.9%, which was less than the accepted cut-off of 92% [20]. However, if we included only points where $CI_{TD} \geq 2.4$ L/min/m^2 before and after phenylephrine administration, the concordance rate of the four-quadrant plot analysis improved to 93.3%. Further, the percentage error of CI_{FT} improved to 28.9% in the $CI_{TD} \geq 2.4$ L/min/m^2 group. These improvements may relate to the high SVRI in the $CI_{TD} < 2.4$ L/min/m^2 group. SVRI was significantly higher in patients with a $CI_{TD} < 2.4$ L/min/m^2 versus the $CI_{TD} \geq 2.4$ L/min/m^2 group (1798 ± 446 versus 3003 ± 786 dyne s/cm^5/m^2, respectively; $P < 0.001$). As a high SVRI can affect the accuracy of the FloTrac/Vigileo™, this may cause the inaccuracy of CI_{FT} in patients with a $CI_{TD} < 2.4$ L/min/m^2. Overall, these findings suggest that FloTrac/Vigileo™ may be more accurate and precise in patients with a higher CI.

In addition, we examined the unadjusted relationship between CI_{TD} and the ratio of the discrepancy of CI (i.e., either ($CI_{FT}-CI_{TD}$)/CI_{TD} or ($CI_{Fick}-CI_{TD}$)/CI_{TD}) using a

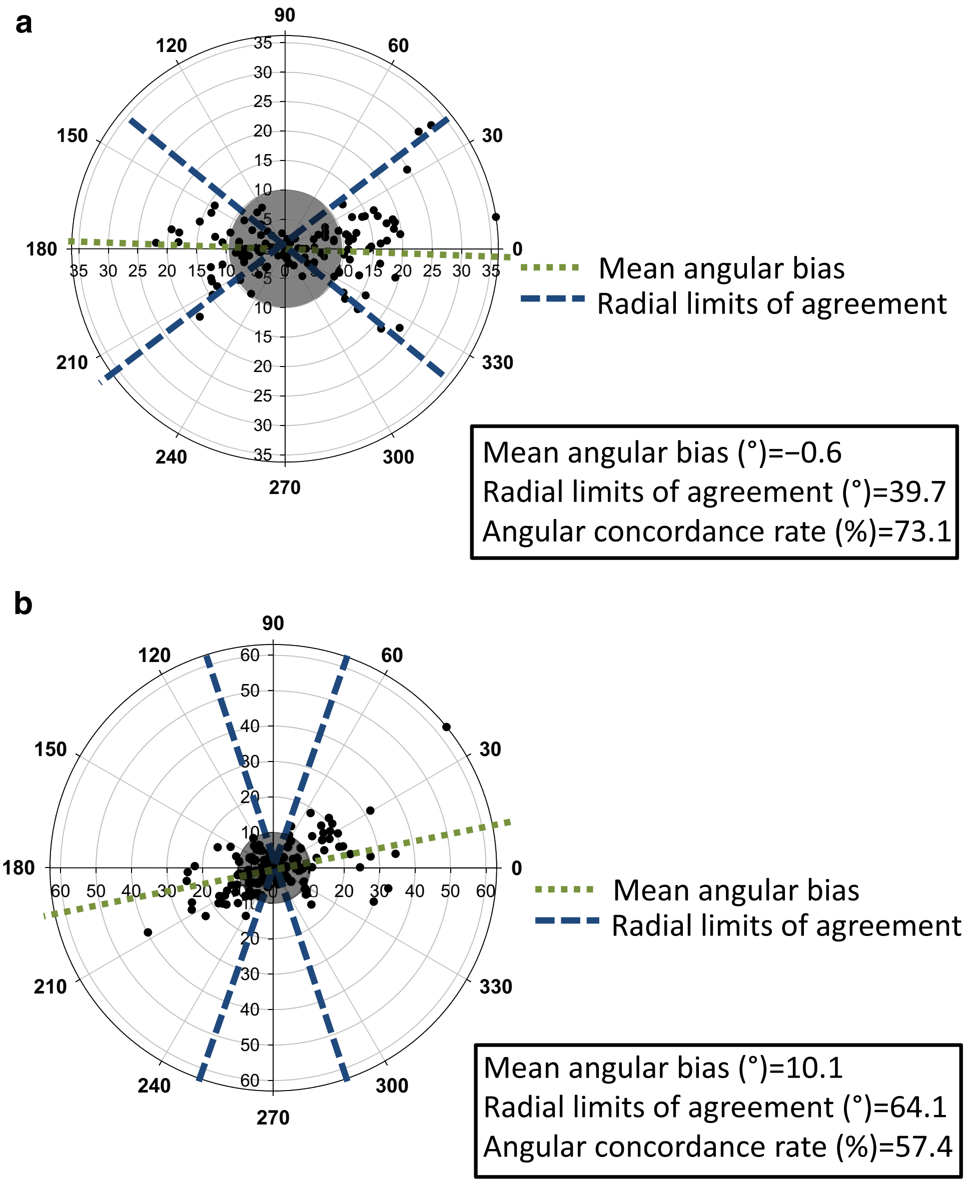


Fig. 4 Polar plots analysis of trending ability. **a** ΔCI_{FT} versus ΔCI_{TD}. **b** ΔCI_{Fick} versus ΔCI_{TD}. The angle from the axis (0°) shows agreement between the two methods. The shaded black area represents an exclusion zone of 10%

cubic spline function to identify any inflection point (Supplementary Fig. 1, Supplementary Fig. 2). Both the cubic splines related to the CI_{TD} and CI discrepancy were negatively sloped, showing that CI had a significant effect in the discrepancy of CI ($P < 0.05$). There was an inflection point at approximately 2.3–2.6 L/min/m^2 (Supplementary Fig. 1), after which the discrepancy of CI (($CI_{FT} - CI_{TD}$)/CI_{TD}) almost plateaued around zero. By contrast, this inflection point was not seen in Supplementary Fig. 2. In addition to CI_{TD}, we investigated the impact of heart rate, MAP, and SVRI on the discrepancy of CI by applying the cubic spline function for these data. Apart from the impact of SVRI on ($CI_{FT} - CI_{TD}$)/CI_{TD} (Supplementary Fig. 3), there was no association between the parameters and CI discrepancy (data not shown). These findings suggest that only SVRI affected the accuracy of the FloTrac/Vigileo™, resulting in the inaccuracy in patients with high SVRI.

We also investigated the accuracy and trending ability of CI measured by the Fick equation using $\dot{V}O_2$ derived from E-CAiOVX in patients undergoing off-pump coronary artery bypass. However, both the accuracy and trending ability were less than the acceptable limits, suggesting that these two methods are not interchangeable. This inaccuracy may relate to metabolic consumption of oxygen by the lung itself [23, 24], or diffusive loss of oxygen

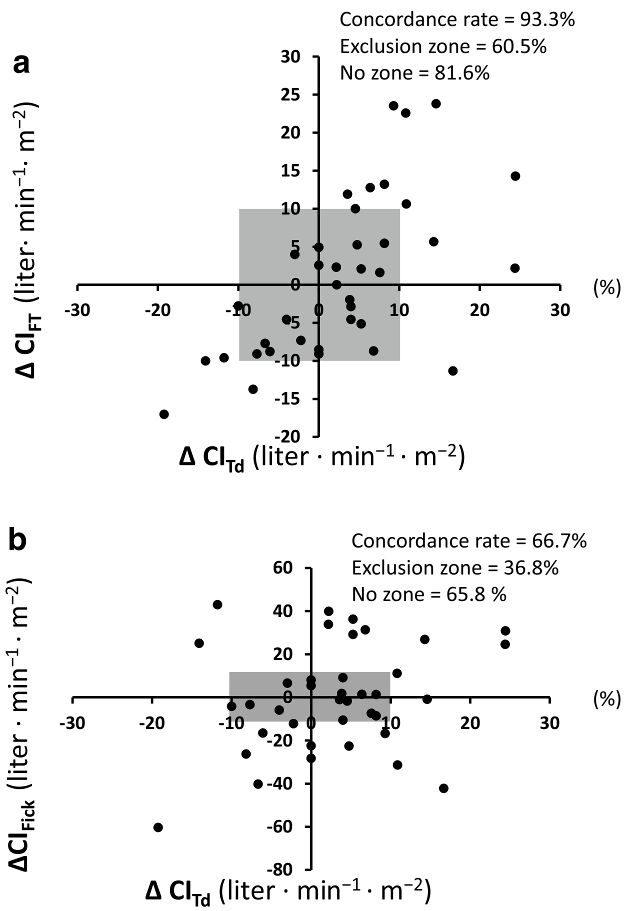


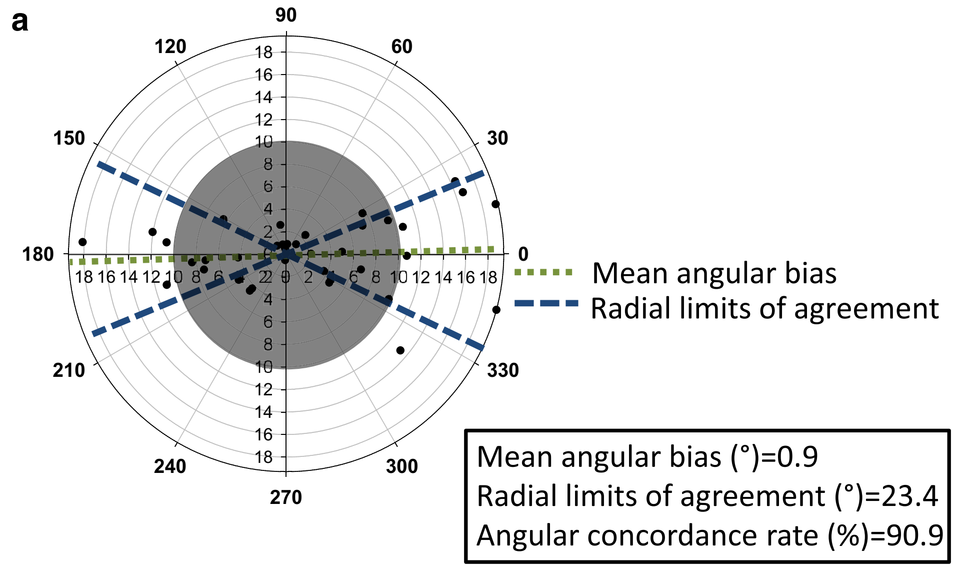
Fig. 5 Four-quadrant plot analysis of trending ability using 38 datasets where $CI_{TD} \geq 2.4$ L/min/m^2 before and after phenylephrine administration. **a** ΔCI_{FT} versus ΔCI_{TD}. **b** ΔCI_{Fick} versus ΔCI_{TD}. The plots at the center represent an exclusion zone (shaded black area) set as the percentage change in cardiac output < 10%

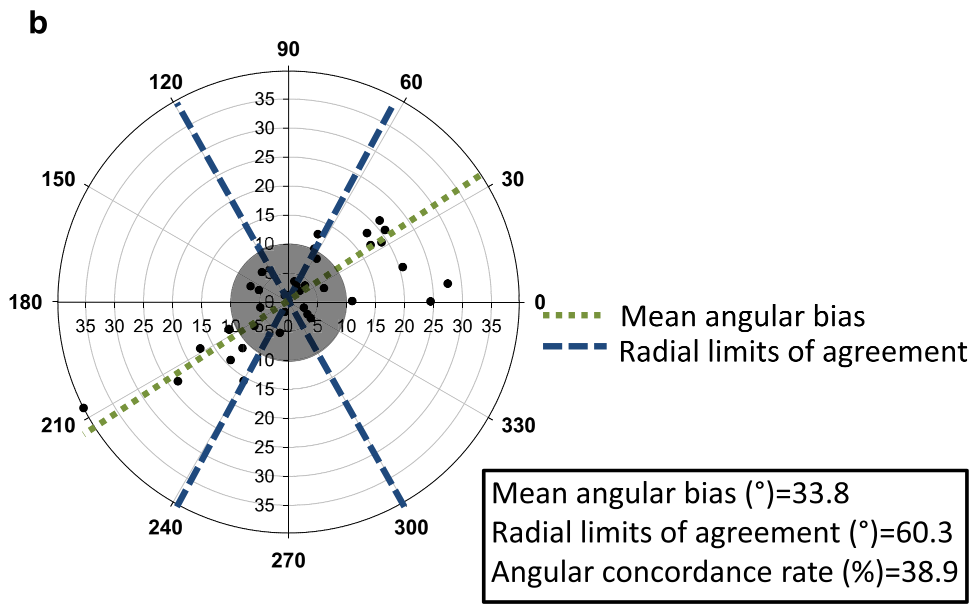
through the visceral pleura during the surgery [25, 26]. We maintained the fraction of inspiratory oxygen during surgery at 30–60%, which will increase the partial pressure of alveolar oxygen, and may lead to increased oxygen loss through the visceral pleura. These factors contribute to $\dot{V}O_2$ measured at the level of the mouth, but are not part of the net uptake of oxygen by the blood as it traverses the lung [24]. Thus, these confounders would not be affected by CI, which may explain the lack of improvement in accuracy and trending ability of CI_{Fick} in patients with a $CI_{TD} \geq 2.4$ L/min/m^2.

We acknowledge several limitations in our study. First, our sample size was relatively small, and there were only 38 data sets with a $CI_{TD} \geq 2.4$ L/min/m^2 for the subanalysis of trending ability. Second, catecholamine use was left at the discretion of the attending anesthesiologist. Norepinephrine (0.02–0.08 μg/kg/min) was used in all patients at T4, and low-dose dopamine (2.2–4.2 μg/kg/min) was used in all patients at T5 and T6, with or without norepinephrine (0.01–0.02 μg/kg/min). This may have affected the SVRI of patients, and contributed to the inaccuracy of the FloTrac/Vigileo™. To overcome this limitation, we excluded the T4, T5, and T6 datasets to conduct a Bland–Altman sensitivity analysis (four-quadrant plot), which showed a percentage error of 36.8% for CI_{FT} and 69.6% for CI_{Fick}, and a concordance rate of 86.4% for CI_{FT} and 73.3% for CI_{Fick}. Polar plots analysis for CI_{FT} and CI_{Fick} showed a mean angular bias of 3.0° and 14.7°, respectively, radial limits of agreement of 39.8° and 43.9°, respectively, and a concordance rate of 73.1% and 76.3%, respectively. Further, if we included 23 datasets with $CI_{TD} \geq 2.4$ L/min/m^2 for subanalysis, Bland–Altman analysis showed percentage errors of 25.0% for CI_{FT} and 83.6% for CI_{Fick}. If we included the nine points where $CI_{TD} \geq 2.4$ L/min/m^2 before and after phenylephrine administration, the concordance rate of the four-quadrant plot analysis was 100% for CI_{FT} and 60.0% for CI_{Fick}. As for the polar plot analysis, the angular concordance rate was 100% for CI_{FT} and 66.7% for CI_{Fick}. These subgroup-sensitivity analyses are comparable with those of the total data sets, suggesting that our data are robust. Finally, when sampling blood for measurements, we took care to avoid bubbles, and performed measurements immediately to avoid metabolic consumption of oxygen. However, it remains possible that these factors may have affected the accuracy of CaO_2 or CvO_2.

In conclusion, we found that both CI_{FT} and CI_{Fick} had a wide limit of agreement with CI_{TD}, and that the trending ability of CI_{FT} and CI_{Fick} were below the acceptable limits for tracking phenylephrine-induced CI changes. However, subgroup analysis revealed an improvement in the accuracy and trending ability of CI_{FT} when only points where $CI_{TD} \geq 2.4$ L/min/m^2 were included, while there were no improvements for CI_{Fick}.

Fig. 6 Polar plots analysis of trending abilities using 38 datasets where $CI_{TD} \geq 2.4$ L/min/m^2 before and after phenylephrine administration. **a** ΔCI_{FT} versus ΔCI_{TD}. **b** ΔCI_{Fick} versus ΔCI_{TD}. The angle from the axis (0°) shows agreement between the two methods. The shaded black area represents an exclusion zone of 10%





Acknowledgements We thank GE Healthcare for rental of the E-CAiOVX (GE Healthcare, WI, US), and Jane Charbonneau, DVM, from Edanz Group (http://www.edanzediting.com/ac), for editing a draft of this manuscript. We also thank the resident doctors who cared for the patients in this study.

Funding This study was supported in part by JSPS KAKENHI (Grant Number JP17K11100).

Compliance with ethical standards

Conflict of interest None.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Biancofiore G, Critchley LA, Lee A, Yang XX, Bindi LM, Esposito M, Bisa M, Meacci L, Mozzo R, Filipponi F. Evaluation of a new software version of the FloTrac/Vigileo (version 3.02) and a comparison with previous data in cirrhotic patients undergoing liver transplant surgery. Anesth Analg. 2011;113(3):515–22. https://doi.org/10.1213/ANE.0b013e31822401b2.
2. Suehiro K, Tanaka K, Funao T, Matsuura T, Mori T, Nishikawa K. Systemic vascular resistance has an impact on the reliability of the Vigileo-FloTrac system in measuring cardiac output and tracking cardiac output changes. Br J Anaesth. 2013;111(2):170–7. https://doi.org/10.1093/bja/aet022.

3. Maeda T, Yoshitani K, Inatomi Y, Ohnishi Y. Inaccuracy of the FloTrac/Vigileo system in patients with low cardiac index. J Cardiothorac Vasc Anesth. 2014;28(6):1521–6. https://doi.org/10.1053/j.jvca.2014.04.013.
4. Hattori K, Maeda T, Masubuchi T, Yoshikawa A, Ebuchi K, Morishima K, Kamei M, Yoshitani K, Ohnishi Y. Accuracy and Trending ability of the fourth-generation FloTrac/Vigileo system in patients with low cardiac index. J Cardiothorac Vasc Anesth. 2017;31(1):99–104. https://doi.org/10.1053/j.jvca.2016.06.016.
5. Maeda T, Hattori K, Sumiyoshi M, Kanazawa H, Ohnishi Y. Accuracy and trending ability of the fourth-generation FloTrac/Vigileo system in patients undergoing abdominal aortic aneurysm surgery. J Anesth. 2018;32(3):387–93. https://doi.org/10.1007/s00540-018-2491-y.
6. Suehiro K, Tanaka K, Mikawa M, Uchihara Y, Matsuyama T, Matsuura T, Funao T, Yamada T, Mori T, Nishikawa K. Improved performance of the fourth-generation flotrac/vigileo system for tracking cardiac output changes. J Cardiothorac Vasc Anesth. 2015;29(3):656–62. https://doi.org/10.1053/j.jvca.2014.07.022.
7. Pugsley J, Lerner AB. (2010) Cardiac output monitoring: is there a gold standard and how do the newer technologies compare? Semin Cardiothorac Vasc Anesth 14 (4):274–282. https://doi.org/10.1177/1089253210386386.
8. Thiele RH, Bartels K, Gan TJ. Cardiac output monitoring: a contemporary assessment and review. Crit Care Med. 2015;43(1):177–85. https://doi.org/10.1097/CCM.0000000000000608.
9. Squara P, Cecconi M, Rhodes A, Singer M, Chiche JD. Tracking changes in cardiac output: methodological considerations for the validation of monitoring devices. Intensive Care Med. 2009;35(10):1801–8. https://doi.org/10.1007/s00134-009-1570-9.
10. Joosten A, Desebbe O, Suehiro K, Murphy LS, Essiet M, Alexander B, Fischer MO, Barvais L, Van Obbergh L, Maucort-Boulch D, Cannesson M. Accuracy and precision of non-invasive cardiac output monitoring devices in perioperative medicine: a systematic review and meta-analysis dagger. Br J Anaesth. 2017;118(3):298–310. https://doi.org/10.1093/bja/aew461.
11. Seckeler MD, Hirsch R, Beekman RH 3rd, Goldstein BH. A new predictive equation for oxygen consumption in children and adults with congenital and acquired heart disease. Heart. 2015;101(7):517–24. https://doi.org/10.1136/heartjnl-2014-306378.
12. Masuda T, Kuramoto M, Tanimoto H, Yamamoto K, Ikeshima S, Kitano Y, Kuroda D, Shimada S, Baba H. Intraoperative baseline oxygen consumption as a prognostic factor in emergency open abdominal surgery. J Crit Care. 2016;32:42–7. https://doi.org/10.1016/j.jcrc.2015.11.014.
13. Langewouters GJ, Wesseling KH, Goedhard WJ. The pressure dependent dynamic elasticity of 35 thoracic and 16 abdominal human aortas in vitro described by a five component model. J Biomech. 1985;18(8):613–20.
14. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48(3):452–8. https://doi.org/10.1038/bmt.2012.244.
15. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;1(8476):307–10.
16. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. J Clin Monit Comput. 1999;15(2):85–91.
17. Gillies M, Bellomo R, Doolan L, Buxton B. Bench-to-bedside review: Inotropic drug therapy after adult cardiac surgery -- a systematic literature review. Critical Care. 2005;9(3):266–79. https://doi.org/10.1186/cc3024.
18. Abualsaud AO, Lowe BS, Guo K, Marelli AJ, Kaouache M, Guo L, Jutras L, Martucci G, Therrien J. Cardiac output as a predictor in congenital heart disease: are we stating the obvious? Int J Cardiol. 2016;210:143–8. https://doi.org/10.1016/j.ijcard.2016.02.071.
19. Critchley LA, Yang XX, Lee A. Assessment of trending ability of cardiac output monitors by polar plot methodology. J Cardiothorac Vasc Anesth. 2011;25(3):536–46. https://doi.org/10.1053/j.jvca.2011.01.003.
20. Critchley LA, Lee A, Ho AM. A critical review of the ability of continuous cardiac output monitors to measure trends in cardiac output. Anesth Analg. 2010;111(5):1180–92. https://doi.org/10.1213/ANE.0b013e3181f08a5b.
21. Ji F, Li J, Fleming N, Rose D, Liu H. Reliability of a new 4th generation FloTrac algorithm to track cardiac output changes in patients receiving phenylephrine. J Clin Monit Comput. 2015;29(4):467–73. https://doi.org/10.1007/s10877-014-9624-0.
22. Lin SY, Chou AH, Tsai YF, Chang SW, Yang MW, Ting PC, Chen CY. Evaluation of the use of the fourth version FloTrac system in cardiac output measurement before and after cardiopulmonary bypass. J Clin Monit Comput. 2017. https://doi.org/10.1007/s10877-017-0071-6.
23. Smithies MN, Royston B, Makita K, Konieczko K, Nunn JF. Comparison of oxygen consumption measurements: indirect calorimetry versus the reversed Fick method. Crit Care Med. 1991;19(11):1401–6.
24. Peyton PJ, Robinson GJ. Measured pulmonary oxygen consumption: difference between systemic oxygen uptake measured by the reverse Fick method and indirect calorimetry in cardiac surgery. Anaesthesia. 2005;60(2):146–50. https://doi.org/10.1111/j.1365-2044.2004.04044.x.
25. Shepard JW Jr, Minh VD, Dolan GF. Gas exchange in nonperfused dog lungs. J Appl Physiol. 1981;51(5):1261–7. https://doi.org/10.1152/jappl.1981.51.5.1261.
26. Light RB. Intrapulmonary oxygen consumption in experimental pneumococcal pneumonia. J Appl Physiol. 1988;(1985) 64(6):2490–5. https://doi.org/10.1152/jappl.1988.64.6.2490.