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Uncalibrated arterial pressure waveform analysis for cardiac output monitoring is biased by low peripheral resistance in patients with intracranial haemorrhage†

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Editor's key points

- Cardiovascular instability is common after intracranial haemorrhage; cardiac output (CO) monitoring may be needed.
- The FloTrac/Vigileo™ system is an alternative to the pulmonary artery catheter but reports of its accuracy vary.
- In this study of patients with intracranial haemorrhage, the FloTrac/Vigileo™ system underestimated CO.
- This may relate to low peripheral resistance with increasing bias at lower measured systemic vascular resistance values.

Background. Cardiac output (CO) monitoring by uncalibrated arterial pressure waveform analysis (APCO) using the FloTrac/Vigileo™ is feasible in patients with intracranial haemorrhage, but the results of validation studies are contradictory. The aim of the present study was to analyse the clinical agreement between the intermittent bolus thermodilution technique (TDCO) and APCO in patients with non-traumatic intracranial haemorrhage.

Methods. This was a prospective observational clinical study in a university level intensive care unit. We studied patients who underwent CO monitoring according to clinical indications using TDCO. Simultaneously, APCO was applied using the radial arterial pressure curve. The difference in CO values measured by APCO with a mid-chest calibration level was compared with a calibration level at the angle of the eye.

Results. A total of 407 data pairs from 16 patients were obtained. The mean CO_{TDCO} was 7.6 litre min^{-1} and CO_{APCO} was 6.0 litre min^{-1}, with a bias corrected for repeated measures of 1.5 litre min^{-1} and 95% limits of agreement of −2.4 to 5.4 litre min^{-1}. The percentage error was 58%. The increasing bias correlated with low peripheral resistance ($\rho = -0.53$, $P = 0.036$). The calibration level at the patient's eye angle did not affect CO values (median bias 0 litre min^{-1} with 25th–75th percentile −0.1 to 0.2 litre min^{-1}).

Conclusions. The second generation of FloTrac®/Vigileo® monitoring system underestimates the TDCO in patients with non-traumatic intracranial haemorrhage. The bias correlates with measured systemic vascular resistance. The upper calibration level does not affect the results.

Keywords: cardiac output; diagnostic equipment; intracranial haemorrhage; monitors, arterial pressure

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Haemodynamic instability is an important factor which impacts on mortality and functional outcome after subarachnoid haemorrhage (SAH). It has been recommended that cardiac function should be optimized using pulmonary artery catheters (PACs) in these patients.[1] Cardiac complications have been reported in patients with types of intracranial haemorrhages other than SAH, and the importance of haemodynamic optimization and the need for cardiac evaluation have also been realized in these patients.[2] The PAC is regarded as the 'gold standard' for the measurement of cardiac output (CO), but its use has been increasingly criticized because of its invasive nature, the risks of serious complications,[3] and concerns over its effectiveness in clinical practice.[4] Less invasive methods for measuring CO based on the properties of the arterial pressure waveform have been developed. Their ease of use and the additional haemodynamic variables which they provide has made them an attractive alternative to the PAC.[5]

In recent years, a device for monitoring CO continuously and with self-calibration has been introduced. The FloTrac/Vigileo™ (Edwards Lifesciences, Irvine, CA, USA) system is minimally invasive and easy to set up and use.[5] The results of studies testing the validity of the FloTrac/Vigileo™ are, however, contradictory. Some studies have reported that the FloTrac/Vigileo™ device with the updated algorithm (software versions 1.07 and higher) displays acceptable accuracy.[6 7] Studies reporting an association between a low systemic vascular resistance (SVR) and bias have been made in patients undergoing liver surgery.[8 9] The FloTrac/Vigileo™ has also been tested in septic patients, a condition associated with peripheral vasodilatation and a low SVR, and CO underestimation has been noted.[10] In the study of Slagt

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and colleagues,[11] however, the measurements for CO using the software version 1.10 were more accurate than those with version 1.07 in septic patients.

The FloTrac/Vigileo™ device can be used to monitor CO in patients with intracranial haemorrhage, but its validity is questionable. The aim of this study was to analyse the clinical agreement between the intermittent bolus thermodilution technique (TDCO) by PAC and arterial pressure waveform analysis (APCO) for CO monitoring using the 1.10 and 1.14 versions of software for the FloTrac/Vigileo™ system in patients with non-traumatic intracranial haemorrhage [SAH, intracerebral haemorrhage (ICH), and intraventricular haemorrhage (IVH)]. We also evaluated the effect of the calibration level on the values given by the FloTrac/Vigileo™.

Methods

Patients

This prospective single-centre study was approved by the Ethics Committee of Oulu University Hospital and the informed consent was obtained in all cases orally before initiating the study and in writing afterwards, from the patient or a legal surrogate. It is a part of an as yet unpublished study concerning cardiovascular dysfunction and monitoring in patients with non-traumatic intracranial haemorrhage requiring intensive care. The study was conducted in an adult tertiary level referral academic teaching intensive care unit (ICU). ICU patients admitted consecutively with non-traumatic intracranial haemorrhage between December 2007 and December 2009 were included. Patients were excluded if there was an intracranial haemorrhage resulting from tumour or recent head/neck operation, they were <18 yr of age, there was an ICU admission delay from hospital admission >48 h, or if study personnel were absent. For this substudy, patients requiring invasive CO monitoring by PAC were included. The need for PAC was assessed by the treating clinicians. According to our clinical practice, PAC is used if cardiovascular support requires a high dose of vasoactive drugs or if the patient has severe respiratory failure. The length of data recording was dependent on the need for PAC monitoring and the length of ICU stay, but was no longer than 6 days from ICU admission.

Clinical management

During the ICU stay, all patients were treated according to our normal practice based on the guidelines of the American Heart Association for the management of spontaneous ICH[12] and SAH.[13] Patients with aneurysmatic haemorrhage were treated by the endovascular or surgical method in the early phase. Vasospasm was prevented by i.v. nimodipine infusion (maximum 30 μg kg^{-1} h^{-1}), depending on haemodynamic data and by maintaining normovolaemia. A mean arterial pressure (MAP) was targeted individually from 60 to 80 mm Hg and cerebral perfusion pressure (CPP), when monitored, to be above 60 mm Hg. Vasoactive drugs and fluid administration were guided by the patients' haemodynamics (cardiac index >2.5 litre min^{-1} m^{-2}, pulmonary artery occlusion pressure >8 mm Hg, and central venous pressure >4 mm Hg). Normomagnesaemia was targeted (plasma Mg >0.70 mmol litre^{-1}). The blood haematocrit level was maintained above 0.30 and the blood glucose level between 6.0 and 8.0 mmol litre^{-1}. A normothermic body temperature was targeted. Surgical approaches, such as haematoma evacuation, the placement of intracranial pressure monitoring system, ventriculostomy, and decompressive craniotomy, were used according to the consideration of the treating neurosurgeons and intensivist.

Haemodynamic monitoring

Arterial pressure was measured invasively during ICU stay. A FloTrac™ device was connected to the existing radial artery catheter (20 G, 1.10 mm$\times$45 mm, Arterial Cannula, Becton Dickinson, Singapore) and connected to the Vigileo™ monitor, which was connected to the patient monitor (Datex-Ohmeda™, CS/3–S/5, GE Healthcare Finland) for receiving the arterial pressure curve. The calibration of the arterial pressure transducer was performed at the level of patient's eye angle, as in our clinical practice. The head of the patients' beds was kept elevated by $\sim$15–30°.

A PAC (7.5 Fr, CritiCath™ SP 5507H TD Catheter, Becton Dickinson) was inserted via the upper central vein through an introducer (SI-09875-E 8.5 Fr, Arrow®). The position of the catheter was confirmed by pressure curves and chest radiograph. Thermodilution CO measurements were performed with fast bolus injections of 10 ml of saline at room temperature. The morphology of the thermodilution curve was visualized and inspected for accuracy to exclude any artifact. An average of three to five measurements received from accepted thermodilution curves was recorded as TDCO. The measurements were performed by one of the authors (E.K.J.), the treating physician or a trained ICU nurse. TDCO measurements were taken $\sim$4 hourly and also when indicated clinically. The data from PAC and continuous arterial pressure monitoring were used for guiding the patient's therapy and cardiovascular optimization, but not those of APCO.

The radial artery waveform obtained by the FloTrac™ device was used by the Vigileo™ monitor with the 1.10 and 1.14 versions of software (Edwards Lifesciences). According to the manufacturer, there are no differences in algorithms between these versions and CO results are comparable. The method is described in detail elsewhere.[5] In short, this system calculates continuous CO from arterial pressure waveform characteristics but does not require external calibration. It calculates CO by using APCO and an estimation of arterial compliance based on the patient characteristic data (age, gender, height, and weight). The direct proportionality between arterial pulsatility and the stroke volume in conjunction with heart rate is used to calculate CO. In the 1.10 version, the algorithm was improved to better account for hypertension, tachycardia, and volume loading.

The data from TDCO and APCO measurements were collected into our electronic patient database (CISMS, Clinisoft™, GE Healthcare Finland). Every TDCO measurements and the simultaneous APCO values were recorded and included in the analysis.

The FloTrac/Vigileo™ transducer was calibrated at the level of the patient's eye angle. For evaluating the effect of the calibration on the CO values, CO measurements performed by one of the authors (E.K.J.) were recorded at the level used and at the mid-chest level. MAP and CO measurements were recorded in sets of 4, resulting in two pairs of data: (i) MAP and CO values were first recorded as calibrated to the eye angle level, then the transducer was recalibrated to the mid-chest and weighted, whereas the correction variables were reset and those values recorded. (ii) After ~40 s, mid-chest calibration values were recorded again, then the calibration level was shifted back to the eye angle level and weighted, whereas the correction variables were reset and values recorded. To ensure stable haemodynamics, the infusion of large volumes of fluids or the bolus administration of vasopressors was not permitted during measurements. The results of these two calibration levels were compared in our subsequent analysis.

Statistical analysis

SPSS (version 15.0, SPSS Inc., Chicago, IL, USA) statistical software package was used for statistical analysis. Summary measurements were expressed as a mean with standard deviation (SD) or as a median [inter-quartile range (IQR)] unless otherwise stated. Minimum and maximum values were expressed when reasonable. Two-tailed *P*-values were reported and a *P*-value of <0.05 was deemed to be statistically significant.

TDCO and APCO were compared using the Bland and Altman method for repeated measurements.[14] The mean bias between TDCO and APCO and 95% limits of agreement (95% confidence interval for mean) were calculated. The percentage error was calculated as described by Critchley and Critchley[15] ($2\ SD_{bias}/CO_{mean}$). The relation between continuous parameters was tested using a logarithmic regression. Correlation was expressed by Spearman's ρ. The association between bias and the use of a vasoactive drug (norepinephrine or dobutamine) was tested with the Mann–Whitney *U*-test and correlation expressed by Spearman's ρ.

In evaluating the effect of the calibration level on CO values, the bias between CO values at different calibration levels was calculated and expressed as a median with 25th–75th percentiles. The difference in MAP between the different calibration levels was calculated.

Table 1 Patient characteristics ($n=16$), presented as mean (SD) or median (IQR) unless indicated. BSA, body surface area; BMI, body mass index; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; $SOFA_{max}$, the maximum SOFA sum score during the study period

Age (yr)	54 (13)
Gender male [*n* (%)]	6 (34)
BSA (m^2)	1.8 (0.2)
BMI ($kg\ m^{-2}$)	24.6 (3.2)
Aneurysmatic bleeding [*n* (%)]	13 (81)
APACHE II score	24.5 (20–28.8)
$SOFA_{max}$	10.5 (10–12)
Number of measurement pairs [mean (SD) (min, max)]	25 (9) (6, 43)
Study period (days)	3.2 (1.2)

Results

During the 2 yr study period, 191 patients with non-traumatic intracranial haemorrhage were treated and 110 were eligible for this study. Of these, 16 patients required PAC and were entered in this study. Patients were on average 54 yr old of normal weight (mean body mass index 25 $kg\ m^{-2}$) and more frequently female (66%) (Table 1). In 13 cases, the aetiology of the haemorrhage was aneurysmatic and i.v. nimodipine was used. Apart from cardiovascular instability requiring the use of norepinephrine, few patients needed inotropic drugs (Table 2). The need for norepinephrine support varied during the study period. The number of the measurement pairs varied according to the duration of the PAC use (Table 1).

Overall, the mean CO was 7.6 (SD 1.5) litre min^{-1} as measured with TDCO and 6.0 (SD 1.7) litre min^{-1} as measured with APCO. The bias corrected for repeated measures was 1.5 (SD 2.0) litre min^{-1} and 95% limits of agreement of -2.4 to 5.4 litre min^{-1} (Fig. 1). The percentage error was 45% for all data pairs and 58% for corrected variables. The bias of all 407 data pairs was greater if the patient received norepinephrine (0.8 *vs* 1.7 litre min^{-1}, $P=0.04$) and nimodipine (0.8 *vs* 1.7 litre min^{-1}, $P<0.001$) but not if the patient received dobutamine (1.5 *vs* 1.9 litre min^{-1}, $P=0.28$). There was only a small correlation between the bias and the rate of norepinephrine infusion and nimodipine infusion ($\rho=0.16$, $P=0.003$ and $\rho=0.25$, $P<0.001$), respectively. However, there was a

Table 2 Continuous vasoactive drug infusion doses at the time of measurements ($n=407$)

	Nimodipine	Norepinephrine	Dobutamine
Number of measurements [*n* (%)]	331 (81)	361 (89)	36 (9)
Median dose (25th–75th) ($\mu g\ kg^{-1}\ min^{-1}$)	0.3 (0.3–0.4)	0.4 (0.2–0.8)	4.2 (2.8–4.8)
Maximum dose ($\mu g\ kg^{-1}\ min^{-1}$)	0.4	2.1	6.9

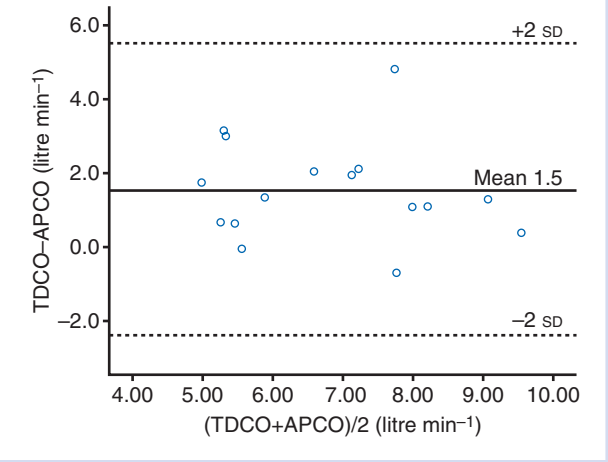

Fig 1 The Bland–Altman plot between TDCO–APCO for 16 study patients. APCO, cardiac output from arterial pressure waveform analysis, FloTrac™/Vigileo™; TDCO, cardiac output from intermittent bolus thermodilution technique via PAC.

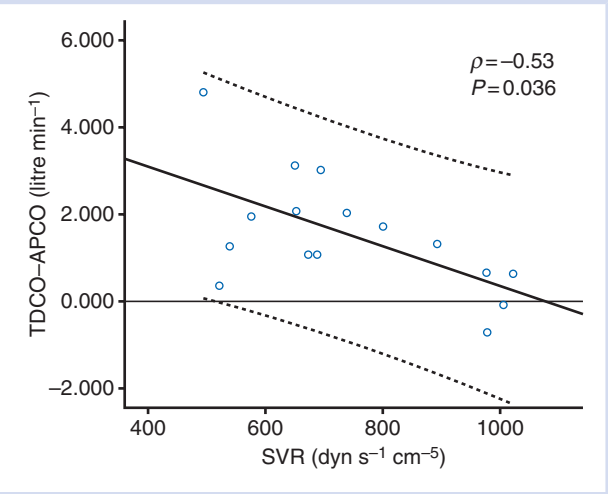

Fig 2 Regression plot between SVR and bias (TDCO–APCO) for 16 study patients. SVR, systemic vascular resistance; TDCO, cardiac output from intermittent bolus thermodilution technique via PAC; APCO, cardiac output from arterial pressure waveform analysis.

significant negative correlation between SVR and bias of all data pairs ($\rho = -0.44$, $P < 0.001$) and the bias corrected for repeated measures ($\rho = -0.53$, $P = 0.036$) (Fig. 2). There was no detectable change in bias during the study period, when the trend of bias was assessed graphically (graphics not shown).

The distribution of the bias between the CO values measured at the different calibration levels ($n = 36$) had high kurtosis. The median bias was 0 litre min^{-1} (IQR: −0.1 to 0.2 litre min^{-1}). The mean (SD) difference in MAP was 13 (5) mm Hg.

Discussion

The main results of this study are as follows: (i) in patients with non-traumatic intracranial haemorrhage, the FloTrac/Vigileo™ system with the 1.10 and 1.14 versions of software underestimates CO values. (ii) The cause of this bias appears to be a low peripheral resistance with increasing bias correlating with measured SVR values. (iii) A calibration level with the transducer at the patient's eye angle does not affect the CO values measured. This is the first study which compares the FloTrac/Vigileo™ system to the standard reference method, PAC, in patients with intracranial haemorrhage.

According to our study, in patients with non-traumatic intracranial haemorrhage, the FloTrac/Vigileo™ system underestimated CO values compared with the PAC. The individual variability of the bias and the small sample size are reflected by the wide 95% limits of agreement. The 58% percentage error of corrected variables and 45% percentage error of all data pairs do not meet the 30% limit of acceptability.[15] Our results are not in concordance with the studies by Breukers and colleagues[6] and by Hofer and colleagues.[7] Notably, the studies reporting the acceptable accuracy of FloTrac/Vigileo™ system have been performed mainly in cardiac surgical patients. The results of the studies in patients undergoing liver surgery,[8 9 16] septic patients,[10] and haemodynamically unstable patients[17] are in line with ours. Recently, the 'third generation' of FloTrac/Vigileo™ software has been introduced, and some preliminary results have been obtained, indicating that this may result in more accurate haemodynamic readings in septic patients than previous software versions.[18]

According to the literature, non-neurological organ dysfunctions are common in patients with neurogenic injury.[19] The effects of intracranial bleeding on vascular tone are unclear, but haemodynamic instability without evidence of myocardial dysfunction is a familiar phenomenon on ICUs with these patients. In addition, nimodipine, a vasodilating drug, is a part of cerebral vasospasm prevention in patients with aneurysmatic SAH.[20] It must be noted that it is normal for vascular tone to constantly vary with individual variations in the therapeutic need for vasoactive drugs. Abnormal vascular tone appears to be one of the most important factors causing errors associated with the FloTrac™ system and it must be taken into account during use. Calculating the SVR and including it in the algorithm could improve the accuracy of this method but this would increase its invasiveness.

Haemodynamic treatment in patients with intracranial haemorrhage and elevated intracranial pressure is based on the optimization of CPP. There are no international standards as to the recommended level of arterial pressure calibration with these patients, however, and clinical practices vary.[21] According to the FloTrac™ transducer manufacturer, it is recommended that the transducer be calibrated at the level recommended for arterial pressure calibration, which is usually the mid-chest position in the mid-axillary line. In this study, however, calibration was performed at the eye

angle level, that is, at the same level as intracranial pressure calibration. Nevertheless, our study results showed no effect on measured CO values as caused by the difference in MAP resulting from calibrating at two different levels.

Some inherent limitations must be recognized in this study. First, only patients with indications for a PAC were included. This caused a relatively small sample size and only haemodynamically unstable patients were selected. Secondly, using a calibration level at the eye angle resulted in an underestimation of SVR measurements. In this study, the correlation was the important finding, however, not the exact SVR values. Third, TDCO measurements were performed by regular ICU staff and study personnel, as the results were used for guiding the patient's therapy and haemodynamic optimization. Nevertheless, after analysing the measurements performed by one of the authors, E.K.J. (n=36), they were found to be similar compared with those performed by other caregivers [mean bias 1.6 (SD 1.2) litre min^{-1}]. Finally, the repeatability of TDCO method was not tested in this study.

In conclusion, according to our study results, the 'second-generation' software (versions 1.10 and 1.14) of the FloTrac™ monitoring system underestimates TDCO in some patients with non-traumatic intracranial haemorrhage. The reason for the bias seems to be a low peripheral resistance in these patients, as the increasing bias correlates with the SVR values measured. A 'third generation' of this monitoring system and its algorithm has been introduced, but validation studies are still insufficient. As long as abnormal SVR is not taken into account in the algorithm, however, the accuracy of this method in patients with low vascular resistance will be questionable.

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Conflict of interest

The Vigileo™ monitors were provided by Edwards Lifesciences during the data collection.

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