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Performance of cardiac output measurement derived from arterial pressure waveform analysis in patients requiring high-dose vasopressor therapy

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Editor's key points

- Arterial pressure waveform analysis (APCO) provides a non-invasive method for monitoring cardiac output.
- The impact of vasopressor therapy on APCO validity was prospectively assessed by comparison with transpulmonary thermodilution measurements.
- Precision of APCO varied with systemic vascular resistance, and was not improved by introduction of the latest software version.

Background. Arterial pressure waveform analysis of cardiac output (APCO) without external calibration (FloTrac/Vigileo™) is critically dependent upon computation of vascular tone that has necessitated several refinements of the underlying software algorithms. We hypothesized that changes in vascular tone induced by high-dose vasopressor therapy affect the accuracy of APCO measurements independently of the FloTrac software version.

Methods. In this prospective observational study, we assessed the validity of uncalibrated APCO measurements compared with transpulmonary thermodilution cardiac output (TPCO) measurements in 24 patients undergoing vasopressor therapy for the treatment of cerebral vasospasm after subarachnoid haemorrhage.

Results. Patients received vasoactive support with [mean (SD)] 0.53 (0.46) μg kg^{-1} min^{-1} norepinephrine resulting in mean arterial pressure of 104 (14) mm Hg and mean systemic vascular resistance of 943 (248) dyn s^{-1} cm^{-5}. Cardiac output (CO) data pairs (158) were obtained simultaneously by APCO and TPCO measurements. TPCO ranged from 5.2 to 14.3 litre min^{-1}, and APCO from 4.1 to 13.7 litre min^{-1}. Bias and limits of agreement were 0.9 and 2.5 litre min^{-1}, resulting in an overall percentage error of 29.6% for 68 data pairs analysed with the second-generation FloTrac® software and 27.9% for 90 data pairs analysed with the third-generation software. Precision of the reference technique was 2.6%, while APCO measurements yielded a precision of 29.5% and 27.9% for the second- and the third-generation software, respectively. For both software versions, bias (TPCO–APCO) correlated inversely with systemic vascular resistance.

Conclusions. In neurosurgical patients requiring high-dose vasopressor support, precision of uncalibrated CO measurements depended on systemic vascular resistance. Introduction of the third software algorithm did not improve the insufficient precision (>20%) for APCO measurements observed with the second software version.

Keywords: cardiac output; hypertension; monitoring, physiological; subarachnoid haemorrhage; vasoconstrictor agents; vasospasm, intracranial

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Despite recent advances in surgical and medical treatment, subarachnoid haemorrhage (SAH) continues to exhibit a poor prognosis, carrying a 30 day mortality of up to 45% and leading to severe disability in a significant proportion of survivors.[1–4] One of the main complications of SAH is cerebral vasospasm that can cause delayed cerebral ischaemia and is considered one of the most important determinants of morbidity and mortality associated with SAH.[5] In an attempt to improve cerebral perfusion in the presence of cerebral vasospasm, a multimodal therapeutic strategy consisting of arterial hypertension, hypervolaemia, and haemodilution ('triple-H-therapy') has been recommended.[6 7] This therapy, however, can be associated with serious complications such as pulmonary oedema or cardiac failure, particularly in patients with poor cardiac reserve and intolerant to increased cardiac afterload and volume loading.[2] Therefore, monitoring of cardiac output (CO) is often indicated in patients undergoing 'triple-H-therapy' to guide and optimize haemodynamic therapy.[3 8]

While pulmonary arterial thermodilution has long been considered the clinical standard for measurement of CO, concerns about the risks of pulmonary artery catheterization have

driven the development of less invasive devices for monitoring CO. The FloTrac/Vigileo™ device (Edwards Lifesciences, Irvine, CA, USA) is based on a newly developed algorithm for arterial pulse contour analysis enabling continuous CO measurements (APCO) without external calibration.[9] This algorithm incorporates the proportionality between pulse pressure and stroke volume. It periodically analyses the arterial pressure waveform, thereby attempting to account for the effects of vascular tone on arterial pulse pressure. Validation studies using the first-generation software showed rather poor agreement with thermodilution measurements.[10 11] After refinement of the inherent mathematical algorithms and shortening the interval between consecutive computations of vascular tone (from 10 min in the first generation to 1 min in the second generation), the validity of uncalibrated pulse contour analysis using the second software generation has been demonstrated to be clinically acceptable as illustrated by a recent meta-analysis.[12] However, most studies were performed in cardiac surgical patients. Moreover, as the APCO algorithm critically depends on the mathematically complex computation of vascular tone, concerns have been repeatedly raised about the accuracy the FloTrac/Vigileo™ device in patients with altered vascular tone,[13–15] leading to the recent launch of third-generation software developed from a large human database containing a greater proportion of hyperdynamic and vasoplegic patients than for previous software versions.[16]

There are only limited data on the reliability of APCO monitoring in clinical settings outside of cardiac surgery and in patients with significantly altered vascular tone. The aim of the present study was therefore to assess the validity of APCO compared with intermittent transpulmonary thermodilution CO (TPCO) measurements in patients requiring extensive vasopressor support for hypertensive therapy of cerebral vasospasm. To the best of our knowledge, haemodynamic data from such patients have not been included in the human databases used for the development/refinement of the APCO algorithm.[16] We hypothesized that the changes in vascular tone induced by 'triple-H-therapy' affect the accuracy of APCO measurements independent of the software generation used.

Methods

Patients

After approval by the institutional review board and written informed consent by either the patient or legal representative, 24 consecutive patients (19 females and five males) were enrolled from 2008 to 2010. The trial was not registered since it was observational and not randomized. Underage patients (<18 yr), pregnant patients, patients where no written informed content could be obtained and patients with occlusive peripheral arterial disease were excluded from the study. All patients had SAH (Hunt and Hess grade I–V) due to the rupture of a cerebral aneurysm and the subsequent development of cerebral vasospasm. High-dose vasopressor therapy was initiated after the cerebral aneurysm had been surgically clipped (19 patients) or intravascularly coiled (five patients) and cerebral vasospasm had been detected by daily transcranial Doppler ultrasonography (TCD) with blood flow velocities exceeding 120 cm s^{-1} in the middle cerebral, the anterior cerebral, and/or the internal carotid artery with a Lindegaard index >3.[17]

Haemodynamic monitoring

Routine haemodynamic variables were recorded continuously (Agilent Technologies, Böblingen, Germany). As part of standard monitoring in these patients, a 5 F thermistor-tipped catheter (PV2015L20A, Pulsiocath, Pulsion Medical Systems, Munich, Germany) was inserted into the femoral artery. In order to monitor and optimize haemodynamic therapy, CO and intrathoracic blood volume (ITBV) were measured by means of intermittent TPCO (PiCCOplus V 5.2.2, Pulsion Medical Systems, Munich, Germany).[18] Indicator dilution measurements were performed by quadruple bolus injections of 20 ml of ice-cold saline 0.9% into the right atrium.

An arterial catheter (20 G; Vygon, Ecouen, France) was inserted into a radial artery and connected to the FloTrac/Vigileo™ system (MHD6, Edwards Lifesciences, Irvine, CA, USA) which continuously calculates CO from arterial pressure waveform characteristics (APCO) without the need for external calibration using the following equation:

$$\mathrm{APCO} = \mathrm{HR} \times \sigma_{\mathrm{AP}} \times \chi \quad (1)$$

where HR is the heart rate, σ_{AP} the standard deviation of arterial pressure, assessed by sampling arterial pressure at 100 Hz over 20 s, and χ the lumped constant quantifying arterial compliance and arterial resistance.

The constant χ is derived from each patient's characteristic data (height, weight, age, and sex) according to Langewouters and colleagues.[19] Changes in vascular tone and the site of arterial cannulation are automatically corrected for by analysing skewness, kurtosis, and other aspects of the arterial pressure waveform.[20] Since the introduction of the second-generation operating system (v.1.07 or later), these correction variables are updated every 60 s.

Of the 24 patients, 10 were investigated with the second generation (v.1.14) and the following 14 with the third-generation software (v.3.02) FloTrac™ system as the manufacturer (Edwards Lifesciences) performed a software update during the study.

Haemodynamic parameters including heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), ITBV, systemic vascular resistance (SVR), TPCO, and APCO were assessed at the following time points: inclusion (T_0), 2 h (T_2), 6 h (T_6), 12 h (T_{12}), 24 h (T_{24}), 48 h (T_{48}), and 72 h (T_{72}) after inclusion.

Patient management

All patients were maintained in a 30° head-up position. Twenty-one patients (H&H grades II–V) were mechanically ventilated using pressure control and applying tidal volumes of 6–8 ml kg^{-1} of predicted body weight. Respiration rate was set to maintain a Pa_{CO_2} of 4.7–5.3 kPa. Mechanically ventilated patients were sedated with continuous infusions of

midazolam and sufentanil. An adequate depth of sedation had to be supplemented by a continuous infusion of ketamine in 16 of these patients.

TCD was performed daily over the temporal bone windows. High-dose vasopressor therapy was initiated if mean blood flow velocity exceeded 120 cm s^{-1}, or in patients who were neurologically assessable and clinically presented a delayed ischaemic neurologic deficit. Hypertension was induced by infusion of norepinephrine to achieve systolic arterial pressure of ~140–220 mm Hg.[2 3] Infusion of crystalloid and colloid solutions was initiated targeting high normal values for ITBV. Haemodilution was passively achieved subsequent to the induction of hypervolaemia.

All patients received continuous infusion of nimodipine (2 mg h^{-1}).

Statistical analysis

Statistical analysis was performed using Sigma Plot (Sigma Plot® for Windows Version 11.0; Systat Software Inc., Chicago, IL, USA). All data are expressed as mean (SD) unless indicated otherwise. Data were tested for normal distribution using the Shapiro–Wilk test. Baseline characteristics of both groups were compared using Student's *t*-test or Fisher's exact test, where appropriate. Combined haemodynamic data measured with either the second- or the third-generation software were compared with baseline by analysis of variance (ANOVA) for repeated measurements. To compare groups in which APCO was measured with the two different software generations, the group *vs* time interaction was analysed using repeated-measures ANOVA with the within-factor 'time' and the grouping factor 'software version' (second *vs* third software generation).[21 22]

Table 1 Patient characteristic and biometric data. BSA, body surface area. Data are presented as mean (SD) if not otherwise indicated. All, combined data derived from all patients measured with either the second- or the third-generation software; 2nd Gen., data derived from patients measured with the second-generation APCO software; 3rd Gen., data derived from patients measured with the third-generation APCO software. *$P<0.05$ third generation *vs* second generation

	All	2nd Gen.	3rd Gen.
Gender (F/M)	19/5	8/2	11/3
Age (yr) (median/range)	47 (24–57)	45 (24–54)	50 (35–57)
Height (cm)	171 (8)	170 (8)	172 (8)
Weight (kg)	74 (12)	71 (7)	76 (14)
BSA (m^2)	1.86 (0.16)	1.81 (0.12)	1.89 (0.18)
Time of onset of vasospams (days) (median/range)	5 (3–13)	6 (2–13)	5 (3–9)
Hunt and Hess grade (median/range)	4 (2–5)	4 (2–5)	5 (2–5)
Therapeutical procedure (coiling/clipping)	18/6	10/0	8/6*

If the ANOVA tests revealed a significant effect, *post hoc* analysis and correction for multiple comparisons was performed using the Tukey HSD test. Linear regression analysis was used to describe the relationship between TPCO and APCO measurements, both for absolute values and for percentage changes in CO. Separate regression analyses were performed to assess correlation between the two methods for different ranges of CO changes: decreases in TPCO $>-10\%$, minor changes in TPCO ($-10\%<\Delta TPCO<10\%$), and increases in TPCO$<10\%$.

The relationship between SVR and the bias between TPCO and APCO were tested using logarithmic regression.

Bias and limits of agreement were calculated according to Bland and Altman.[23] Bias was defined as the mean difference between TPCO and APCO values. The limits of agreement were calculated as the bias (1.96) SD, thereby defining the range in which 95% of the differences between the two methods were expected to lie.

The percentage error (PE) was calculated according to Critchley and Critchley[24] for comparison of CO values:

$$PE = \frac{1.96 \times SD}{meanTPCO} \times 100\ (\%) \quad (2)$$

As recently suggested by Cecconi and colleagues,[25] we additionally assessed the accuracy and precision of the reference method by calculating the coefficient of variation (CV=SD/meanTPCO) and the coefficient of error (CE=CV/$\sqrt{n}$) of the repeated thermodilution measurements for each timepoint (in our study, quadruple TPCO measurements, $n=4$).

This allowed us to determine the precision of the APCO measurements by using the following equations:[25]

$$CV_{TPCO-APCO} = \sqrt{[(CV_{TPCO})^2 + (CV_{APCO})^2]} \quad (3)$$

where $CV_{TPCO\text{-}APCO}$ is the CV of the differences between the two methods, CV_{TPCO} the CV of TPCO measurements, and CV_{APCO} the CV of APCO measurements.

$Precision_{TPCO}$ is the precision for the reference method=2 CE_{TPCO}, $Precision_{APCO}$ is the precision for APCO=2 CV_{APCO}, and $PE_{TPCO-APCO}$ is the PE known from the Bland–Altman plot (=2 $CV_{TPCO-APCO}$)

Then:

$$PE_{TPCO-APCO} = \sqrt{[(Precision_{TPCO})^2 + (Precision_{APCO})^2]} \quad (4)$$

And ultimately:

$$Precision_{APCO} = \sqrt{(PE_{TPCO-APCO}) - (Precision_{TPCO})^2} \quad (5)$$

For the statistical comparison of both software generations, bias, PE, and precision were compared using Student's *t*-test for independent samples and the Wilcoxon rank-sum test, as appropriate.

The least significant change in CO that has to be measured in order to recognize a real and true change was

Table 2 Haemodynamic data. Data are presented as mean (SD). T_0, baseline; T_x, timepoint × hours after inclusion; HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; TPCO, transpulmonary cardiac output; APCO, arterial pressure waveform-derived cardiac output; ITBV, intrathoracic blood volume; SVR, systemic vascular resistance; ICP, intracranial pressure; ICA, internal carotid artery; MCA, middle cerebral artery; All, combined data derived from all patients measured with either the second- or the third-generation software; 2nd Gen., data derived from patients measured with the second-generation APCO software; 3rd Gen., data derived from patients measured with the third-generation APCO software. ANOVA: First line: *P*-value for one-way ANOVA (combined haemodynamic data of all patients, in comparison with baseline). Second line: The *P*-values of the ANOVA are shown separately for the time-, group- and interaction- (INT, time × group) effects (comparison of patients measured either with the second- or the third-generation software). $^{**}P<0.05$ (0.01) *vs* T_0 (*vs* T_2 for cumulated fluid input). The statistically significant time-, group-, and interaction-effects are shown in italic type

	T_0	T_2	T_6	T_{12}	T_{24}	T_{48}	T_{72}	ANOVA, one-way		
								Time	Group	Int.
HR (beats min^{-1})										
All	88 (17)	88 (19)	89 (19)	86 (20)	89 (17)	85 (15)	88 (15)	0.99		
2nd Gen.	95 (13)	94 (18)	93 (20)	88 (22)	88 (15)	86 (13)	87 (13)	0.73	0.54	*0.039*
3rd Gen.	84 (17)	84 (18)	86 (19)	85 (18)	90 (19)	84 (16)	89 (17)			
MAP (mm Hg)										
All	101 (12)	100 (11)	101 (14)	101 (11)	106 (14)	109 (12)	111 (14)	*0.012*		
2nd Gen.	105 (13)	103 (14)	106 (18)	103 (15)	112 (16)	113 (9)	116 (15)	<0.001	0.07	0.84
3rd Gen.	98 (10)	98 (9)	98 (9)	99 (8)	101 (8)	105 (13)	107 (12)			
CVP (mm Hg)										
All	12 (3)	13 (4)	13 (4)	11 (4)	12 (6)	14 (4)	12 (4)	0.56		
2nd Gen.	13 (4)	13 (3)	14 (4)	12 (2)	13 (5)	14 (5)	13 (5)	0.31	0.48	0.87
3rd Gen.	12 (3)	12 (4)	13 (4)	10 (5)	12 (6)	14 (3)	12 (2)			
ITBV (ml)										
All	1619 (320)	1684 (396)	1682 (379)	1688 (304)	1669 (311)	1735 (342)	1742 (333)	0.90		
2nd Gen.	1537 (301)	1551 (287)	1581 (362)	1557 (308)	1524 (240)	1641 (245)	1701 (305)	0.08	0.17	0.37
3rd Gen.	1678 (320)	1779 (434)	1754 (375)	1781 (264)	1781 (313)	1821 (391)	1775 (350)			
SVR (dyn s^{-1} cm^{-5})										
All	928 (279)	919 (242)	907 (207)	918 (192)	978 (235)	1030 (287)	972 (230)	0.54		
2nd Gen.	864 (288)	862 (218)	896 (210)	894 (215)	1023 (257)	1094 (331)**	922 (136)	*0.003*	0.81	*0.026*
3rd Gen.	973 (262)	959 (250)	914 (204)	935 (173)	942 (209)	971 (224)	1012 (278)			
ICP (mm Hg)										
All	7 (4)	8 (4)	7 (3)	9 (4)	7 (5)	8 (4)	6 (4)	0.16		
2nd Gen.	7 (3)	8 (4)	8 (4)	10 (5)	8 (5)	10 (3)	8 (2)	0.18	0.51	0.14
3rd Gen.	7 (4)	9 (4)	7 (3)	8 (3)	7 (4)	6 (3)	4 (4)			
Blood flow velocity (cm s^{-1})										
ICA right	66 (25)				74 (34)	76 (40)	61 (26)			
ICA left	74 (28)				71 (28)	85 (41)	65 (33)			
MCA right	127 (37)				136 (45)	130 (52)	113 (33)			
MCA left	118 (51)				143 (54)	136 (43)	130 (51)			
Haemoglobin (g dl^{-1})										
All	11.2 (1.1)	11.1 (1.0)	11.1 (1.2)	11.0 (1.3)	11.5 (1.3)	11.2 (1.3)	10.8 (1.4)	0.64		
2nd Gen.	11.1 (1.0)	11.0 (0.9)	10.9 (1.0)	10.9 (1.5)	11.6 (1.1)	11.4 (1.0)	10.8 (1.4)	0.06	0.86	0.31
3rd Gen.	11.4 (1.1)	11.2 (1.0)	11.3 (1.4)	11.1 (1.1)	11.4 (1.4)	11.0 (1.4)	10.6 (1.4)			
Cumulated crystalloid input (ml)										
All		226 (146)	677 (306)	1230 (391)**	2445 (723)**	4664 (1317)**	6911 (1959)**	*<0.001*		
2nd Gen.		233 (172)	636 (316)	1213 493)	2214 (810)**	4299 (1209)**	6651 (2220)**	*<0.001*	0.42	0.71
3rd Gen.		221 (127)	703 (297)	1240 (308)	2618 (594)**	4962 (1326)**	7092 (1731)**			
Cumulated colloid input (ml)										
All		69 (149)	306 (336)	700 (795)	1216 (1218)**	2091 (1841)**	2695 (2544)**	*<0.001*		
2nd Gen.		132 (201)	392 (365)	1066 (995)	1716 (1449)	2647 (2262)	3823 (2875)	*<0.001*	0.13	0.12
3rd Gen.		29 (80)	250 (304)	464 (511)	842 (834)	1636 (1231)	1905 (1923)			
Norepinephrine (μg kg^{-1} min^{-1})										
All	0.57 (0.48)	0.56 (0.48)	0.61 (0.58)	0.65 (0.76)	0.63 (0.75)	0.47 (0.42)	0.42 (0.35)	0.78		
2nd Gen.	0.52 (0.23)	0.52 (0.21)	0.59 (0.29)	0.58 (0.32)	0.49 (0.23)	0.40 (0.23)	0.38 (0.16)	0.21	0.60	0.97
3rd Gen.	0.61 (0.60)	0.59 (0.61)	0.62 (0.72)	0.71 (0.96)	0.75 (0.97)	0.52 (0.52)	0.45 (0.43)			

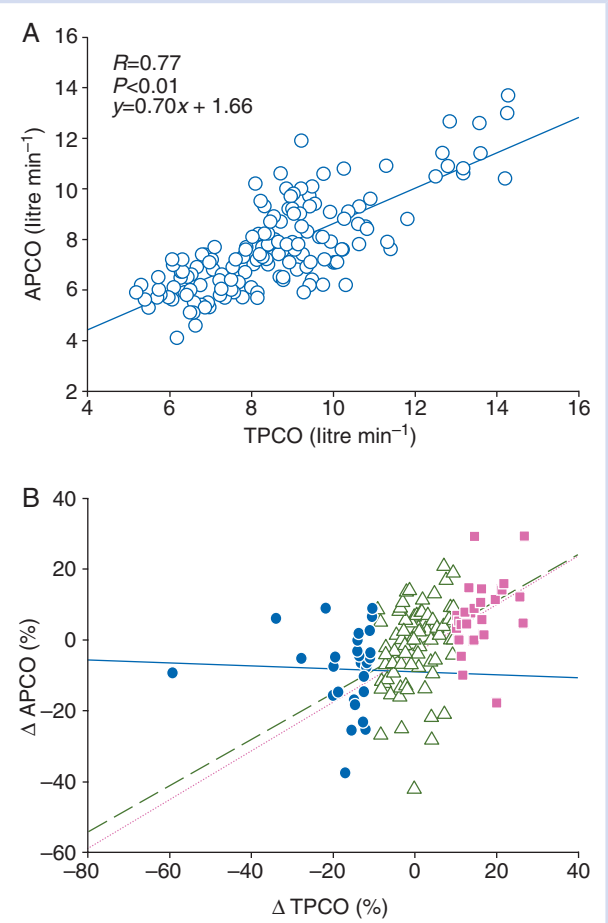

Fig 1 Linear correlation analysis between TPCO and APCO. (A) Analysis for original CO data. (B) Analysis for percentage change. Separate regression analyses were performed to assess the correlation between the two methods for different ranges of CO changes: (i) decreases in TPCO >10% (blue circles, solid line; R=0.0367, R^2=0.00134, P=0.85); minor changes in TPCO (−10%<ΔTPCO<10%) (open triangles, dashed line; R=0.315, R^2=0.0992, P<0.01); (ii) increases in TPCO >10% (pink squares, dotted line; R=0.346, $R2$=0.120, P=0.10).

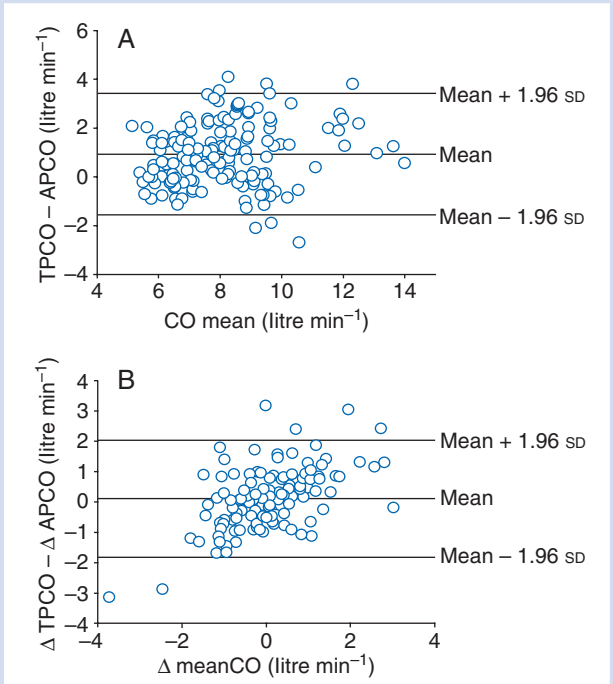

Fig 2 Bland–Altman analysis for CO measurements by TPCO and by APCO (arterial pressure waveform-derived cardiac output) for all data (A) and for changes in CO measurements (B).

calculated by multiplying the precision of the monitoring device with $\sqrt{2}$.[25]

Results

Patient characteristic and biometric data of enrolled patients are presented in Table 1. Patients measured with the second-generation software were comparable with those measured with the third-generation software in their baseline characteristics; however, aneurysms of patients measured with the second-generation software had been more frequently coiled.

Haemodynamic data obtained at each time point showed a significant increase in MAP and cumulated fluid input during the observation period, whereas all other parameters remained unchanged (Table 2). The analysis of group *vs* time interaction revealed no significant differences between patients measured either with the second- or the third-generation software, except for HR and SVR.

From the 24 patients enrolled, 158 sets of CO measurements were available for comparison of TPCO and APCO. One patient died after 12 h due to global cerebral hypoxia. Owing to technical problems, CO data pairs were available only for the first 24 h in two patients, and in three patients only for the first 48 h. TPCO ranged from 5.2 to 14.3 litre min^{-1} and APCO ranged from 4.1 to 13.7 litre min^{-1}.

Linear correlation analysis showed a positive correlation between absolute values of TPCO and APCO (Fig. 1A). APCO measurements showed a statistically significant correlation with TPCO only for minor changes <10% (Fig. 1B). In contrast, decreases in TPCO >10% and increases in TPCO >10% were not reliably tracked by APCO measurements.

For all data pairs, the Bland–Altman analysis revealed a bias of 0.9 litre min^{-1} and limits of agreement of 2.5 litre min^{-1} (Fig. 2A), resulting in an overall error of 29%. For the detected changes in CO between each time point, the Bland–Altman analysis yielded a bias of 0.11 litre min^{-1} and limits of agreement of 1.91 litre min^{-1} (Fig. 2B).

Detailed statistical analysis of the comparison of TPCO and APCO measurements is shown in Table 3, including a subgroup analysis of the performance of the second and the third APCO generation software for each time point. For all time points, CO values obtained by both software generations showed an average error of <30% for agreement with the reference technique. While the reference technique

Table 3 Statistical analysis of arterial pressure waveform-derived cardiac output measurements and of the reference technique. Data are presented as mean (SD). T_0, baseline; T_x, timepoint × hours after inclusion; T_{all}, mean values averaged over all timepoints; TPCO, transpulmonary cardiac output; APCO, arterial pressure waveform-derived cardiac output; CV, coefficient of variation; CE, coefficient of error; LOA, limits of agreement; PE, percentage error. 2nd Gen., data derived from patients measured with the second-generation APCO software; 3rd Gen., data derived from patients measured with the third-generation APCO software; All, combined data derived from all patients measured with either the second- or the third-generation software (for further details, see text)

	T_0	T_2	T_6	T_{12}	T_{24}	T_{48}	T_{72}	T_{all}
TPCO (litre min^{-1})	8.6 (2.3)	8.6 (2.1)	8.5 (1.9)	8.6 (1.8)	8.3 (1.7)	8.5 (1.7)	8.6 (1.9)	8.5 (1.9)
CV TPCO (%)	2.2	2.2	2.6	2.0	2.3	3.0	2.3	2.4
CE TPCO (%)	1.2	1.2	1.4	1.1	1.3	1.6	1.2	1.3
Precision TPCO (%)	2.4	2.4	2.8	2.2	2.6	3.2	2.4	2.6
APCO (litre min^{-1})								
All	7.5 (1.6)	7.5 (1.8)	7.5 (1.8)	7.6 (1.8)	7.5 (1.6)	7.6 (1.5)	8.1 (2.1)	7.6 (1.8)
2nd Gen.	7.9 (1.4)	8.3 (2.0)	7.9 (2.0)	7.9 (1.9)	7.4 (1.2)	7.7 (1.4)	8.4 (1.6)	7.9 (1.7)
3rd Gen.	7.2 (1.6)	7.0 (1.5)	7.3 (1.6)	7.4 (1.7)	7.6 (1.8)	7.5 (1.5)	7.9 (2.4)	7.4 (1.8)
Bias (litre min^{-1})								
All	1.2 (1.3)	1.1 (1.2)	1.0 (1.3)	1.0 (1.3)	0.8 (0.9)	0.9 (1.2)	0.5 (1.4)	0.9 (1.3)
2nd Gen.	1.6 (1.3)	0.9 (1.1)	0.9 (1.2)	0.7 (1.3)	0.7 (1.0)	1.0 (1.4)	0.3 (1.5)	0.9 (1.3)
3rd Gen.	0.9 (1.3)	1.2 (1.3)	1.0 (1.4)	1.1 (1.3)	1.0 (0.8)	0.9 (1.0)	0.5 (1.2)	1.0 (1.2)
LOA (litre min^{-1})								
All	2.6	2.4	2.6	2.5	1.8	2.4	2.7	2.5
2nd Gen.	2.6	2.2	2.4	2.5	2.0	2.8	3.0	2.6
3rd Gen.	2.5	2.5	2.7	2.5	1.6	2.0	2.4	2.3
PE APCO (%)								
All	30.6	28.0	30.3	29.1	22.0	28.8	31.2	29.2
2nd Gen.	26.9	24.0	27.7	29.1	24.8	32.9	34.4	29.6
3rd Gen.	31.7	30.7	32.3	29.6	19.3	24.1	28.0	27.9
Precision APCO (%)								
All	30.5	27.9	30.2	29.1	21.9	28.6	31.1	29.1
2nd Gen.	26.7	23.8	27.5	29.0	24.6	32.8	34.3	29.5
3rd Gen.	31.6	30.7	32.2	29.6	19.2	23.9	27.9	27.9

yielded a very high precision of <3%, precision of the APCO measurements exceeded 20%.

Introduction of the third-generation software was not associated with a statistically significant improvement in performance of APCO measurements as expressed by differences in bias (P=0.77), limits of agreement (P=0.23), PE (P=0.96), or precision (P=0.96).

Logarithmic correlation analysis showed a significant inverse relationship for bias between TPCO and APCO and for SVR between the second- and the third-generation software (Fig. 3A and B).

Discussion

In patients requiring extensive vasoactive support, CO measurements by minimally invasive uncalibrated pulse contour analysis showed a PE of <30% for agreement with transpulmonary thermodilution. However, detailed statistical analysis demonstrated that the precision of arterial pressure waveform-derived CO-measurements using both software generations was inadequate.

Owing to its ease of use, reduction of inherent procedural risks and reduced cost, minimally invasive CO monitoring has become increasingly popular in the haemodynamic management of perioperative and critically ill patients.[26–29] Recently, uncalibrated arterial pressure waveform analysis has been introduced into clinical practice as a new method for the continuous monitoring of CO. This device applies an advanced mathematical algorithm to the arterial pressure tracing, calibrating itself intermittently and therefore obviating the need for calibrations with an external reference technique such as transpulmonary thermodilution.[30]

While the majority of validation studies tested uncalibrated arterial pressure waveform analysis in cardiac surgical patients receiving only moderate vasopressor doses, if any,[9 31 32] we analysed the validity of APCO measurements beyond the setting of cardiac surgery and—in more extreme circulatory conditions,[33] namely in neurosurgical patients requiring high-dose vasopressor support for treatment of cerebral vasospasm due to SAH. This contributes to the novelty of the study as the studied patient population presented with a unique haemodynamic profile, that is, high flow, high arterial pressure, and near to normal SVR.

No consensus has been reached on the most appropriate statistical methodologies for validation of continuous CO monitoring techniques.[34] For analysis of agreement between APCO measurements and the reference technique

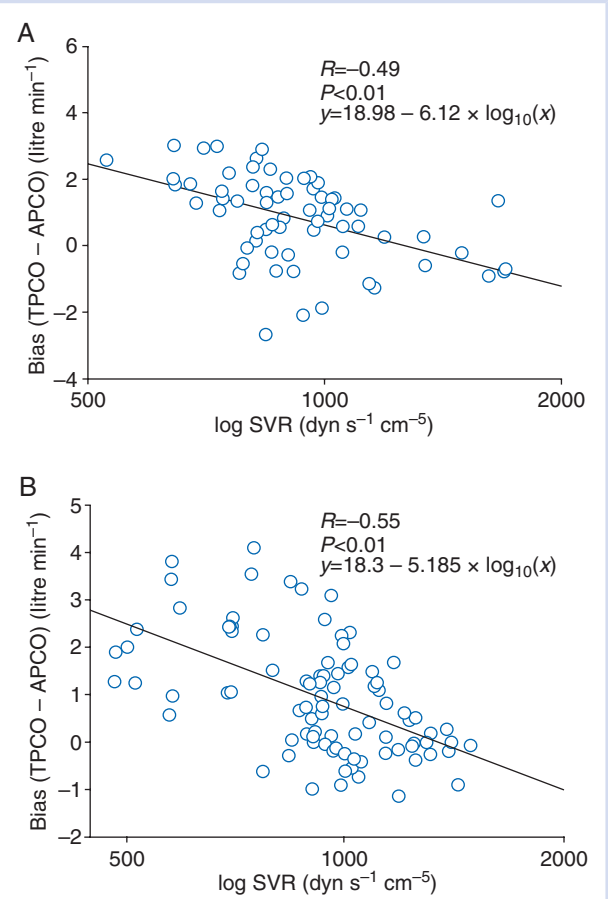

Fig 3 Logarithmic correlation analysis of the relationship between SVR (systemic vascular resistance) and TPCO–APCO for second-generation FloTrac software (A) and for third-generation FloTrac software (B).

(TPCO), we used the method originally proposed by Critchley and Critchley[24] who suggested that any new CO monitor should have an equivalent precision to the chosen reference method. Critchley and Critchley used pulmonary arterial thermodilution as the reference which they described to yield a precision of ~20%. Hence, PE as assessed from the Bland–Altman analysis should be <28.3% (or, as simplified by many authors, <30%). In fact, APCO measurements in our study using both software generations exhibited a PE of <30% for agreement with transpulmonary thermodilution. Therefore—at first look—arterial pressure waveform analysis might be regarded as clinically interchangeable with thermodilution. However, the concept of focusing validation studies primarily on the analysis of the PE as the most important statistical criterion has recently been challenged.[25] The rigid application of the ±30% cutoff for PE can mask important information as two separate levels of precision contribute to it, which only in combination add up to the value of ±30%. Hence, a true interpretation of the total PE (i.e. the combined error of both the tested and the reference method) described in validation studies is only possible if the precision of each method is reported separately. In our study, the reference technique was performed with a high degree of rigour resulting in a precision of <3%, significantly lower than the 20% originally described by Critchley and Critchley. This high level of precision for the reference technique allowed compensation for a significantly lower precision of APCO measurements (>20%), and consequently to a PE of <30%. Therefore, the calculated PE in our study might have indicated the APCO technique as of clinically acceptable validity, despite its inappropriate level of precision.[24]

The precision of APCO measurements as found in our study has a profound clinical implication. In our patients, only changes in APCO exceeding ~40% would have reflected true and real changes in CO (least significant change). We were, however, unable to prove this assumption, as (with one exception) the observed CO changes did not exceed this cutoff value. Therefore, arterial pressure waveform analysis showed an acceptable agreement with the reference technique only for minor changes (i.e. <10%). TPCO changes >10% that are commonly considered as clinically relevant[35] were not reliably paralleled by changes in APCO measurements. Our results are confirmed by a recently published trial that demonstrated for uncalibrated waveform analysis a poor performance in detecting CO trends induced by therapeutic interventions such as volume loading or initiating/increasing vasopressor support.[36]

The accuracy of APCO measurements is limited during vasoplegia and hyperdynamic circulation as in patients with septic shock[13] or undergoing liver transplantation.[14 15] This has led to the recent launch of third-generation software. We were unable to find an improvement in the precision of APCO measurements by the newest software generation. For both software generations, there was an inverse correlation of bias between TPCO and APCO and systemic vascular resistance, with a higher bias for lower resistances. This characteristic dependency of the accuracy of APCO measurements on peripheral vascular tone has been previously described in patients with liver cirrhosis.[14 15]

Several limitations of the present study should be acknowledged. First, our study was performed in a highly selected group of critically ill patients not necessarily allowing extrapolation to other patient populations. Secondly, we refrained from aggressively trying to achieve hypervolaemia in our patients. Appropriate fluid management resulted in highly normal values for the volumetric preload indicator ITBV. The use of hypervolaemia in the treatment of vasospasm has recently been questioned as several trials found no or only modest impact of hypervolaemia on cerebral blood flow, vasospasm, or outcome.[37–39] Thirdly, all of our patients exhibited normal to supranormal CO. The accuracy of APCO measurements in patients with low CO could therefore not be analysed and remains to be elucidated. Fourthly, measurements were performed at a relatively steady state with only minor variations in CO. This should allow a true estimation of inherent APCO accuracy since in steady-state conditions, bias and precision are not affected by differences in

response times or other confounding factors during periods of dynamic CO changes.[40] Fifthly, our study design did not specifically test the well-known ability of APCO measurements to predict fluid-responsiveness in this selected group of patients.[41–43]

In conclusion, in neurosurgical patients requiring extensive vasopressor support, CO values obtained by arterial waveform analysis showed a PE of <30% for agreement with TPCO measurements as the reference technique. This error is commonly regarded as a criterion for method interchangeability, but resulted mainly from the high precision of TPCO measurement. The precision of uncalibrated CO measurements was clinically inappropriate, depended on systemic vascular resistance, and was not improved by introduction of the latest software generation.

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Conflict of interest

S.R. and G.M. have received speaking and advisory fees from Edwards Lifesciences, Irvine, CA, USA.

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