Critical Care and Resuscitation 26 (2024) 108–115

Contents lists available at ScienceDirect

Critical Care and Resuscitation

journal homepage: www.elsevier.com/locate/ccrj

Original Article

Bias, trending ability and diagnostic performance of a non-calibrated multi-beat analysis continuous cardiac output monitor to identify fluid responsiveness in critically ill patients

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ARTICLE INFORMATION

Article history:
Received 23 February 2024
Received in revised form
26 April 2024
Accepted 28 April 2024

Keywords:
Cardiac output
Hemodynamic monitoring
Preload dependence
Fluid responsiveness
Bias
Pulse contour

ABSTRACT

Objective: To evaluate the accuracy of non-calibrated multi-beat analysis continuous cardiac output (CCO_{MBA}), against calibrated pulse-contour analysis continuous cardiac output (CCO_{PCA}) during a passive leg raise (PLR) and/or a fluid challenge (FC).
Design: Observational, single-centre, prospective study.
Setting: Tertiary academic medical intensive care unit, Lyon, France.
Participants: Adult patients receiving norepinephrine, monitored by CCO_{PCA}, and in which a PLR and/or a FC was indicated.
Main outcome measures: CCO_{MBA} and CCO_{PCA} were recorded prior to and during the PLR/FC to evaluate bias and evaluate changes in CCO_{MBA} and CCO_{PCA} ($\Delta\%CCO_{MBA}$ and $\Delta\%CCO_{PCA}$). Fluid responsiveness was identified by an increase >15% in calibrated cardiac output after FC, to identify the optimal $\Delta\%CCO_{MBA}$ threshold during PLR to predict fluid responsiveness.
Results: 29 patients (median age 68 [IQR: 57–74]) performed 28 PLR and 16 FC. The bias between methods increased with higher CCO_{PCA} values, with a percentage error of 64% ($_{95\%}$confidence interval: 52%–77%). $\Delta\%CCO_{MBA}$ adequately tracked changes in $\Delta\%CCO_{PCA}$ with an angular bias of 2 ± 29°. $\Delta\%CCO_{MBA}$ during PLR had an AUROC of 0.92 ($P < 0.05$), with an optimal threshold >14% to predict fluid responsiveness (sensitivity: 0.99, specificity: 0.87).
Conclusions: CCO_{MBA} showed a non-constant bias and a percentage error >30% against calibrated CCO_{PCA}, but an adequate ability to track changes in CCO_{PCA} and to predict fluid responsiveness.

1. Introduction

Assessment of preload responsiveness using dynamic manoeuvres (such as passive leg raising, PLR) requires the use of continuous monitoring of cardiac output with a high temporal sampling rate.[1] Nowadays, multiple less-invasive devices (as compared to the reference Swan-Ganz method) using the arterial pressure waveform to estimate CCO continuously are available and allow the evaluation of fluid responsiveness in clinical routine. Yet, this advantage is hampered for some of the less-invasive devices due to the lack of calibration of CCO absolute values, as they use populational models to estimate some characteristics of the cardio-

Abbreviations: AUROC, area under the receiver-operating curve; CCO, continuous cardiac output; CI_{TPTD}, cardiac index measured by transpulmonary thermodilution; CO, cardiac output; CO_{TPTD}, cardiac output measured by transpulmonary thermodilution; CCO_{MBA}, continuous cardiac output measured by multi-beat analysis; CCO_{PCA}, continuous cardiac output measured by pulse contour analysis; CE, coefficient of error; CV, coefficient of variation; $\Delta\%CCO_{MBA}$, relative change in continuous cardiac output measured by multi-beat analysis; $\Delta\%CCO_{PCA}$, relative change in continuous cardiac output measured by pulse contour analysis; $\Delta\%CO_{TPTD}$, relative change in cardiac output measured by transpulmonary thermodilution; ICU, intensive care unit; LSC, least significant change; PLR, passive leg raising; Pr, precision; SAPS-2, simplified acute physiology score 2; SD, standard deviation; SOFA, sepsis-related organ failure assessment.

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https://doi.org/10.1016/j.ccrj.2024.04.003

circulatory system, whose relevance may be challenged in patients with vasoplegic shock under vasopressors.[2]

Among these non-calibrated systems, the Argos monitor (Retia Medical, White Plains, MA, USA) estimates CCO using the diastolic portion of the AP waveform to fit a decaying exponential function to determine vascular resistances, stroke volume and CCO.[3] The device had the advantage of connecting directly to the AP module of the ICU monitor, without requiring changing the arterial catheter. The device analyses the AP waveform over multiple heartbeats to account for confounding wave reflections and was identified as having a percentage error >30% in a post-cardiac surgery population,[4–8] but its diagnostic performance to predict fluid responsiveness remains to date unknown. On the other hand, devices calibrated using transpulmonary thermodilution assess CCO with potentially higher precision (below the 30% percentage error) using pulse-contour analysis of AP waveform, at the price of requiring the placement of specific catheters and frequent recalibration.[9,10]

We hypothesized that a non-calibrated multi-beat analysis CCO monitoring device would provide a biased estimate of cardiac output, but would have adequate ability to track changes in CCO and evaluate fluid responsiveness in critically ill patients under vasopressors, although with a different CCO threshold to predict fluid responsiveness as a consequence of the biased measure. Consequently, the objectives of the study were to assess the accuracy, trending ability and clinical relevance of non-calibrated CCO, as compared to a calibrated CCO monitoring method in this population.

2. Materials and methods

2.1. Study design and ethics

The study was an investigator-initiated, single-centre, prospective, observational study performed in an academic ICU of a tertiary centre in Lyon, France. The study was approved by the institution ethics comity (Comité Scientifique et Ethique des Hospices Civils de Lyon, reference number 23-5040). All included patients or their next-of-kin received information regarding the study. Due to the non-interventional design of the study, the ethics comity waived the obligation for signed consent. The present report follows the STROBE and STARD checklists for the report of observational and diagnostic accuracy studies.[11,12]

2.2. Study population

Consecutive patients admitted to the ICU were eligible if they were 18 years old or older, were receiving a continuous intravenous infusion of norepinephrine, had a transpulmonary thermodilution-calibrated CCO monitoring device in place, and if the clinician in charge indicated the realization of a postural manoeuvre to evaluate fluid responsiveness and/or of a fluid challenge with at least 500 ml of crystalloids. Exclusion criteria are reported in Supplemental Methods.

2.3. Study outcomes

The study's primary endpoint was the determination of the bias existing between the multi-beat analysis CCO monitoring device (evaluation) and the transpulmonary thermodilution-calibrated CCO monitoring device (reference), using repeated paired replicates. Secondary endpoints included the identification of the determinants of higher bias between methods, the assessment of bias in prespecified subgroups of patients, the evaluation of the trending performance of the non-calibrated CCO device to detect changes in CCO measured by the reference method, the precision of the evaluated device, and its ability to classify patients as fluid responders and non-responders.

2.4. Reference CCO method

The calibrated CCO monitoring device (PiCCO®, Pulsion Medical System, Feldkirchen, Germany) was connected to a dedicated proprietary femoral artery catheter and to the central venous catheter located in the internal jugular vein, and to the Intellivue® MP40 monitor (Philips, Amsterdam, Netherlands) equipped with the PiCCO® module (Supplemental Fig. S1). The device was calibrated using transpulmonary thermodilution with the triplicate injection of 15-ml of cold saline at inclusion and at the end of the fluid challenge, if applicable. All collected CCO measurements with pulse contour analysis (CCO_{PCA}) were collected after the baseline calibration. Cardiac output measured by transpulmonary thermodilution (CO_{TPTD}) was also indexed to the patient's body surface using the Du Bois formula and was expressed in $L.min^{-1}.m^{-2}$.[13]

Hence, the reference method in this study was CCO_{PCA} for analyses evaluating CCO and fast changes during hemodynamic studies (allowing a temporal sampling resolution similar to the evaluated device), and CO_{TPTD} in analyses evaluating fluid responsiveness after a fluid challenge.

2.5. Evaluated CCO device

The non-calibrated multi-beat analysis CCO monitoring device (Argos®, Retia Medical, White Plains, NY, USA) was connected directly to the AP module of the Intellivue® MP40 monitor, without requiring any physical interaction with the arterial line or the patient (Supplemental Fig. S1). The device required the following demographic data to determine CCO from multi-beat analysis of the arterial waveform (CCO_{MBA}): age, admission weight, height, and gender. From these variables, the device then determines the Windkessel time constant τ (the product of systemic vascular resistance by arterial compliance) by fitting a decaying exponential to the tail of the AP waveform over multiple heartbeats. The system then computes CCO_{MBA} knowing the mean arterial pressure and estimates the arterial compliance using the demographics listed above and a proprietary model resulting in the determination of systemic vascular resistances.[3]

Details regarding the modality of data extraction from both monitoring devices are described in Supplemental Methods.

2.6. Hemodynamic studies

In patients in the supine position, postural manoeuvres consisted in a 45° PLR manoeuvre (starting from the semi-recumbent position) for 1 min.[14] In patients in the prone position, a Trendelenburg manoeuvre (+13° to −13°) was performed for 1 min.[15] Patients in whom the clinician indicated the administration of a fluid challenge received 500 ml of Ringer Lactate solution over a period of 15 min or less. Detailed description of fluid bolus administration is given is Supplemental Methods, along with collected indications. Details regarding hemodynamic monitoring, protocolization of co-interventions (ventilation, sedation, vasopressors) are described in Supplemental Methods.

2.7. Study time points

Four hemodynamic time points were a priori defined, corresponding to the timing of paired replicates measurements: at baseline before the postural manoeuvre, and during the postural manoeuvre; and at baseline prior to the fluid challenge, and during the fluid challenge (Fig. 1).

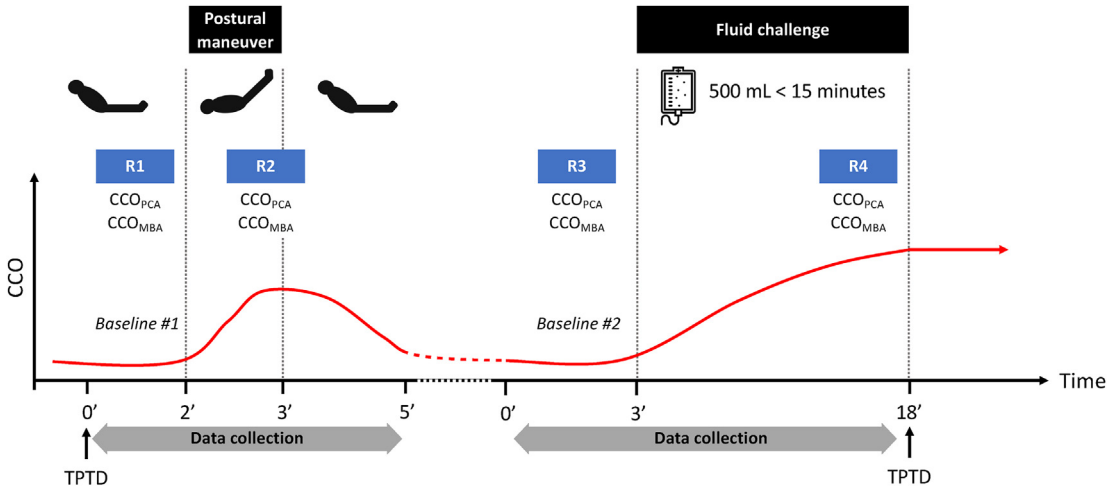

Fig. 1. Study procedures. The figure shows the study experimental design, in which patients who required an hemodynamic study were evaluated by a postural maneuver, possibly followed by a fluid challenge of 500 ml crystalloids administered in less than 15 min. Transpulmonary thermodilution to calibrate the continuous cardiac output monitoring device using pulse contour analysis was performed at study onset and immediately at the end of the fluid challenge administration. Postural maneuvers (either passive leg raising or Trendelenburg maneuver) were performed for 1 min, during which the highest CCO value was collected on both monitors (multi-beat analysis and pulse contour analysis). CCO data were continuously collected before and during postural maneuvers, and before and during fluid challenges, respectively. The figure also shows the time points at which CCO paired replicates (R1, R2, etc., up to a maximum of 4 replicates per patient) were collected (baseline and maximal values during interventions). The baseline periods corresponded to a 2-min timeframe for postural maneuvers and a 3-min timeframe for fluid challenges, respectively. The per-intervention period corresponded to a 3-min timeframe for postural maneuvers and a 15-min period timeframe for fluid challenges, respectively. CCO: continuous cardiac output; CCO_{MBA}: continuous cardiac output measured by multi-beat analysis; CCO_{PCA}: continuous cardiac output measured by pulse contour analysis; R1-4: replicate #1-4; TPTD: transpulmonary thermodilution.

2.8. Paired CCO replicates

Baseline CCO_{MBA} and CCO_{PCA} were defined as the mean value of CCO measured over the baseline period; maximal CCO_{MBA} and CCO_{PCA} corresponded to the highest value observed during the postural manoeuvre and/or the fluid challenge. From these paired measurements, we computed the relative change in CCO_{MBA} ($\Delta\%CCO_{MBA}$) and in CCO_{PCA} ($\Delta\%CCO_{PCA}$) for a given intervention (i.e. postural manoeuvre or fluid challenge). Hence, in a patient undergoing both a postural manoeuvre and a fluid challenge, a maximum of 4 paired CCO replicates could be obtained for analysis.

CO_{TPTD} measured at baseline before the postural manoeuvre and that measured after the fluid challenge were also collected to compute its relative change between these 2 time points ($\Delta\%CO_{TPTD}$).

2.9. Identification of fluid responsiveness using CCO_{MBA} during passive leg raising

In supine patients performing a PLR manoeuvre, diagnosis of fluid responsiveness was adjudicated using a $\Delta\%CCO_{PCA}$ during PLR >10%.[14] After adjudication, the ability of $\Delta\%CCO_{MBA}$ during PLR to correctly *identify* fluid responsiveness was evaluated. Fluid responsiveness was not evaluated in patients undergoing a Trendelenburg manoeuvre, due to the lower level of evidence regarding this postural manoeuvre and its diagnostic threshold (i.e. 8%).[15]

2.10. Prediction of fluid responsiveness using CCO_{MBA} after a fluid challenge

In patients who received a fluid challenge, a $\Delta\%CO_{TPTD}$ > 15% classified the patient as being fluid responsive.[14] After adjudication, the ability of $\Delta\%CCO_{MBA}$ during the postural manoeuvre preceding the fluid challenge to correctly *predict* fluid responsiveness was evaluated.

2.11. Statistics

Analyses were performed with the R Software, using packages *lme4*, *MuMIn*, *MethComp*, and *cutpointr*.[16–20] Sample size calculation is shown in Supplemental Methods. A P value < 0.05 was chosen for statistical significance. Data were reported by their median [interquartile range], or count (percentage), unless otherwise stated. 95% confidence intervals were computed using bootstrapping (1000 replicates). Continuous variables were compared between groups using Wilcoxon–Mann–Whitney test, and Fisher's exact test for categorical variables. In case of repeated measures, comparison between groups was performed using linear mixed-effects models, with the patient identification number as random effect.

Bias between CCO methods was evaluated using a linear mixed-effects model and Bland–Altman representation, considering the repetition of replicates in a given individual.[18,21,22] Bias was computed as:[23]

$$Bias = CCO_{MBA} - CCO_{PCA} \quad \text{Equation 1}$$

Since the bias between methods was identified as being non-constant and the existence of repeated replicates, the regression equation and limits of agreements were computed using alternating regression and represented graphically on Bland–Altman plots. The percentage error was computed as:

$$\%_{err} = 2 \cdot SD_{Bias} / \overline{CCO_{PCA}} \quad \text{Equation 2}$$

with SD_{Bias} the standard deviation of the bias, and $\overline{CCO_{PCA}}$ the mean of CCO_{PCA}. Bias was also evaluated using the same methodology in the following conditions: (1) using baseline CO_{TPTD} as the reference method; (2) after exclusion of patients in non-sinus rhythm. The percentage error was also evaluated and reported with its 95% confidence interval computed using bootstrapping (1000 replicates). To explore the impact of patient's characteristics and hemodynamics on the difference between CCO_{MBA} and CCO_{PCA} measurements, we performed a multivariate analysis of variables

associated with $CCO_{MBA} - CCO_{PCA}$, using linear mixed-effects models with the patient identification number as random effect (Supplemental Methods).

Ability of CCO_{MBA} to track changes in CCO_{PCA} was assessed using 4-quadrant and radial plots. The concordance rate was defined as the percentage of values that fell into the 2 concordant quadrants of the plot, after exclusion of relative changes in CCO <5%. Angular bias was computed as the mean angle between data points and the polar axis and compared to 0° using the Wilcoxon–Mann–Whitney test. Radial limits of agreement were computed similarly to the limits of agreement in Bland and Altman analysis.

Repeatability of CCO_{MBA} measurements was assessed using the data collected over the baseline period, and was described by the coefficient of variation, the coefficient of error, the precision and least significant change (LSC).

The diagnostic and predictive performance of $\Delta\%CCO_{MBA}$ (measured during PLR) to identify and predict fluid responsiveness was assessed using the area under the receiver operating curve (AUROC, Delong's method), using: (1) $\Delta\%CCO_{PCA}$ as the reference method to *identify* fluid responsiveness during PLR; and (2) $\Delta\%CO_{TPTD}$ as the reference method to *predict* fluid responsiveness after a fluid challenge. We then identified the CCO_{MBA} optimal threshold and determined the diagnostic metrics associated with it (Supplemental Methods).

3. Results

3.1. Population characteristics

Between April 4th, 2023 and June 16th, 2023, we enrolled 29 patients in the study (Supplemental Fig. S2), within a delay of 1 [1–2] day after ICU admission. Demographics of enrolled patients are shown in Table 1. At inclusion, most patients were in sinus rhythm (25/29), with a CO_{TPTD} of 5.2 [4.3–6.5] $L.min^{-1}$ and a norepinephrine dose of 0.3 [0.1–0.7] $\mu g.kg^{-1}.min^{-1}$ (Table 2).

Table 1
Baseline characteristics of the population.

Variables	N = 29
Age, years	68 [57–74]
Sex, male	22 (76%)
Weight, kg	78 [67–86]
BMI, $kg.m^{-2}$	27 [23–30]
Comorbidities	
Hypertension	11 (38%)
Diabetes	6 (21%)
Chronic heart failure	2 (7%)
Peripheral artery disease	4 (14%)
Severity of disease	
Admission category, medical, N (%)	26 (90%)
SAPS-2 score at ICU admission	66 [51–77]
SOFA score on inclusion day	12 [8–14]
Sepsis, N (%)	20 (69%)
Septic shock, N (%)	19 (66%)
Invasive mechanical ventilation, N (%)	23 (79%)
FiO_2 in ventilated patients on day of inclusion, %	35 [30–50]
Lowest PaO_2/FiO_2 ratio on day of inclusion, mmHg	189 [148–248]
PEEP, cmH_2O	5 [5–5]
ARDS, N (%)	9 (31%)
Highest creatinine on day of inclusion, $\mu mol.L^{-1}$	142 [106–192]
Renal replacement therapy, N (%)	6 (21%)
UF_{NET} flow rate at time of inclusion, $ml.h^{-1}$	75 [30–140]
Richmond Analgesia and Sedation Scale (RASS)	−5 [−5 to −2]

Data are presented as count (%) or median [interquartile range].
ARDS: acute respiratory distress syndrome; BMI: body mass index; FiO_2: inspired fraction in O_2; ICU: intensive care unit; PaO_2: arterial partial pressure in O_2; PEEP: positive end-expiratory pressure; SAPS-2: simplified acute physiology score 2; SOFA: sepsis-related organ failure assessment; UF_{NET}: net ultrafiltration.

Most patients underwent a postural manoeuvre (28/29, of which 26 were PLR), and 16/29 received a fluid challenge (Supplemental Table S1, fluid challenge indications reported in Supplemental Table S2), resulting in a total number of 88 CCO paired replicates (no missing data). Characteristics of patients who received and did not receive a fluid challenge are given in Supplemental Table S3.

3.2. Bias of CCO_{MBA}

Illustrative examples of individual AP curves, CCO curves, correlation and bias are shown in Supplemental Fig. S3. Fig. 2A shows the correlation between CCO_{PCA} and CCO_{MBA} paired measurements in all hemodynamic evaluations. The Bland–Altman representation in Fig. 2B showed a non-constant bias between methods, with a trend toward higher bias with higher CCO values. Limits of agreements reached ±3.41 $L.min^{-1}$, with a percentage error of 64% (95% confidence interval: 52%–77%). Biases between methods using baseline CO_{TPTD} as the reference method (instead of CCO_{PCA}), or after exclusion of patients in non-sinus rhythm are shown in Supplemental Figs. S4 and S5, respectively. In multivariate analysis, bias between CCO monitoring methods was significantly and independently associated with non-sinus rhythm, pulse pressure and age (Supplemental Table S4).

3.3. Trending performance of CCO_{MBA}

Fig. 3 shows the 4-quadrant plot of $\Delta\%CCO_{MBA}$ against $\Delta\%CCO_{PCA}$ in panel A, and the radial plot in panel B. $\Delta\%CCO_{MBA}$ adequately tracked changes in $\Delta\%CCO_{PCA}$, with a concordance rate of 90% (95% confidence interval: 0.75 to 0.97). The angular bias (mean ± standard deviation) was 2° ± 29° and was not significantly different from 0°, with radial limits of agreements of ±56°.

Table 2
Cardiovascular status and hemodynamics at inclusion.

Variables	N = 29
Time between ICU admission and inclusion, days	1 [1–2]
Cardiac rhythm	
Sinus rhythm	25 (87%)
Atrial fibrillation	1 (3%)
Paced	2 (7%)
Atrial extrasystoles	1 (3%)
Hemodynamics	
Heart rate, min^{-1}	96 [75–110]
Mean arterial pressure, mmHg	71 [67–76]
Diastolic arterial pressure, mmHg	53 [50–60]
Pulse pressure, mmHg	55 [43–63]
Central venous pressure, mmHg	6 [4–8]
CO_{TPTD}, $L.min^{-1}$	5.2 [4.3–6.5]
CI_{TPTD}, $L.min^{-1}.m^{-2}$	2.6 [2.2–3.4]
SVI, $mL.m^{-2}.beat^{-1}$	32 [23–38]
GEDVI, $mL.m^{-2}$	687 [614–835]
EVLWI, $mL.kg^{-1}$ PBW	9.3 [7.5–12.6]
Continuous cardiac index monitoring	
CCO_{PCA}, $L.min^{-1}$	5.2 [4.4–6.3]
CCO_{MBA}, $L.min^{-1}$	6.2 [3.9–8.1]
Arterial lactate, $mmol.L^{-1}$	2.4 [1.5–3.5]
Norepinephrine dose, $\mu g.kg^{-1}.min^{-1}$	0.3 [0.1–0.7]
Inotropic agent	1 (3%)

Data are presented as median [interquartile range] or count (percentage).
CI_{TPTD}: cardiac index measured by transpulmonary thermodilution; CCO_{MBA}: continuous cardiac output measured by multi-beat analysis; CCO_{PCA}: continuous cardiac output measured by pulse contour analysis; CO_{TPTD}: cardiac output measured by transpulmonary thermodilution; EVLWI: extravascular lung water index; GEDVI: global end-diastolic volume index; ICU: intensive care unit; PBW: predicted body weight; SVI: stroke volume index.

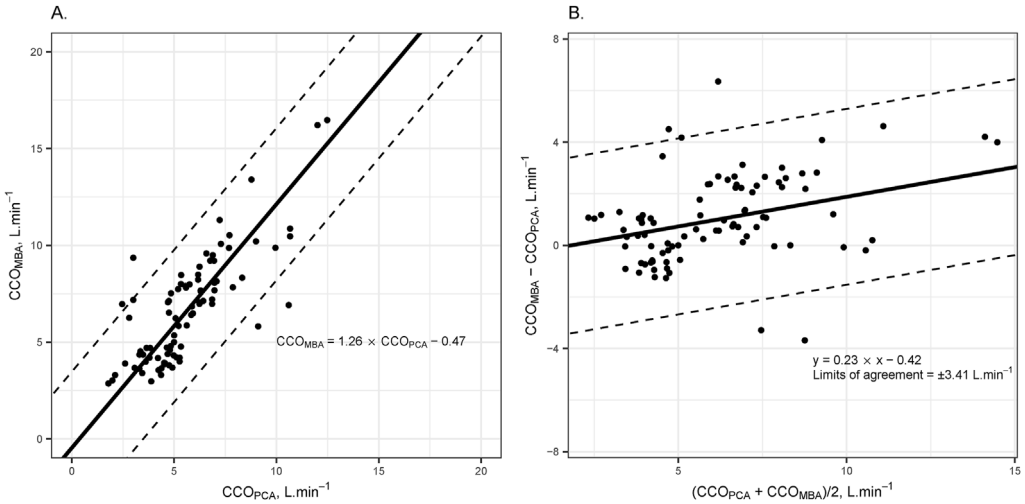

Fig. 2. Correlation plot and mean bias. The figure shows the correlation between CCO measured by pulse contour analysis and with multi-beat analysis in panel A, and the bias between methods in a Bland and Altman plot, using CCO_{PCA} as the reference method in panel B (N = 88 paired replicates). In panel A, the broad solid line shows the correlation line with its limits of agreement (dashed lines). The equation shows the mathematic relationship between CCO_{PCA} and CCO_{MBA} ($P < 0.01$). In panel B, the bias between CCO methods was identified as being non-constant across measured CCO values. The figure shows the equation of the non-constant bias and the range of limits of agreement. The broad solid line is the regression slope bias between methods, and the 2 dashed line represent the limits of agreement between methods. CCO: continuous cardiac output; CCO_{MBA}: continuous cardiac output measured by multi-beat analysis; CCO_{PCA}: continuous cardiac output measured by pulse contour analysis.

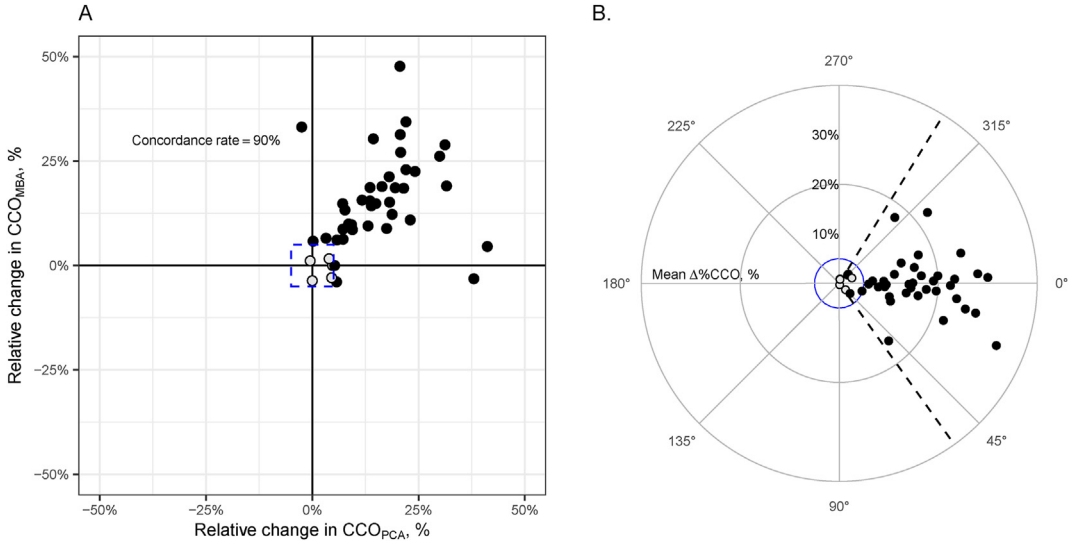

Fig. 3. Four-quadrant plot and polar plot. The figure shows a four-quadrant plot of $\Delta\%CCO_{PCA}$ against $\Delta\%CCO_{MBA}$ in panel A, and a polar plot assessing the trending ability of $\Delta\%CCO_{MBA}$ to detect a change in $\Delta\%CCO_{PCA}$ (N = 88 paired replicates). In panel A, each symbol is the relative change in CCO measured by pulse contour analysis on the x axis, plotted against the relative change in CCO measured by multi-beat analysis on the y axis, between baseline and the highest value measured during the postural maneuver and/or the fluid challenge. The vertical and horizontal solid lines delimit quadrant limits. The blue square identifies Δ%CCO values with a relative change <5% which were excluded from the computation of the concordance rate as they were deemed below the conservative threshold for least significant change.[30] The concordance rate was 90% [95% confidence interval: 75%–97%] ($P < 0.001$). In panel B, the better the agreement between Δ%CCO measurements, the closer data pairs will lie along the horizontal radial axis. The distance from the centre of each plot represents the mean relative change in CCO between methods (mean Δ%CCO) at each consecutive time points. Data points located between 315° and 45° refer to observations in which both $\Delta\%CCO_{PCA}$ and $\Delta\%CCO_{MBA}$ increased (north-eastern quadrant of the four-quadrant plot). The broad solid line represents angular bias, while dashed lines represent radial limits of agreement. The angular bias was (mean ± standard deviation) 2° ± 29° ($P = 0.67$ compared to 0°), and the upper and lower limits of agreements were 54° and 302°, respectively. Δ%CCO: relative change in continuous cardiac output; $\Delta\%CCO_{MBA}$: relative change in continuous cardiac output measured by multi-beat analysis; $\Delta\%CCO_{PCA}$: relative change in continuous cardiac output measured by pulse contour analysis.

3.4. CCO_{MBA} precision and least significant difference

Precision of repeated CCO_{MBA} measurements over a stable hemodynamic period was 1% (95% confidence interval: 1%–2%), and the least significant change in CCO_{MBA} was 2% (95% confidence interval: 1%–3%). These values were of similar magnitude compared to CCO_{PCA} measured in the same conditions (Supplemental Table S5).

3.5. Diagnostic performance of Δ%CCO_{MBA} to identify fluid responsiveness during PLR

Fluid responsiveness (adjudicated using $\Delta\%CCO_{PCA}$) was diagnosed in 14/26 of PLR manoeuvres, with 10/14 of preload-dependent patients receiving subsequently a fluid bolus. During PLR, $\Delta\%CCO_{MBA}$ was significantly higher in patients with a $\Delta\%CCO_{PCA} > 10\%$ (Supplemental Table S6), and had an AUROC of 0.88 (95%

confidence interval: 0.75–0.98) to identify a $\Delta\%CCO_{PCA} > 10\%$ during PLR (Supplemental Table S7). Cohen's kappa coefficient reached 0.64 (95% confidence interval: 0.35–0.92) when using a $\Delta\%CCO_{MBA}$ threshold of 10%.

3.6. Predictive performance of $\Delta\%CCO_{MBA}$ to identify fluid responsiveness after a fluid challenge

In the subgroup of patients who performed a PLR manoeuvre followed by a fluid challenge (N = 14), $\Delta\%CCO_{MBA}$ during PLR was significantly higher in patients with a $\Delta\%CCO_{TPTD} > 15\%$ (N = 7, Supplemental Table S6). The optimal threshold of $\Delta\%CCO_{MBA}$ during PLR to predict fluid responsiveness after a fluid challenge was >14%, with a grey zone ranging from 12% to 23% and an AUROC of 0.92 (95% confidence interval: 0.75–1.00) (Fig. 4 and Supplemental Table S7).

4. Discussion

In this prospective, single-centre, observational study evaluating the bias and trending ability of a non-calibrated CCO monitoring device, we observed that (1) CCO_{MBA} demonstrated a non-constant bias, compared to CCO_{PCA}, with increasing bias with increasing CCO values, and a percentage error of 64%; (2) CCO_{MBA} displayed adequate capacity to track changes in CCO_{PCA} during hemodynamic studies evaluating fluid responsiveness; and (3) the predictive performance of CCO_{MBA} to identify fluid responsiveness was excellent, with a 14% optimal threshold during passive leg raising to identify fluid responsiveness after a fluid challenge.

Multi-beat analysis of the arterial waveform is a recent method to continuously assess cardiac output, using a minimally invasive device connected to the AP module of an arterial line. CCO_{MBA} displayed varying bias ranging between −0.15 $L.min^{-1}$ to 0.90 $L.min^{-1}$ with percentage errors between 38.2% and 70% in mixed ICU post-operative populations, using transesophageal doppler or pulmonary artery thermodilution as the reference method.[4–7] On the other hand, concordance rates depicting the accuracy of the device to detect changes in CCO were frequently adequate, above 88%. Most studies excluded patients with arrhythmia and with inadequate arterial line damping characteristics, and focused on post-cardiac surgery patients, in which median CCO values were below those measured in the present study. These previously published data demonstrated that CCO_{MBA} may not be interchangeable with pulmonary artery thermodilution, justifying cautious clinical interpretation of absolute CCO values displayed by the monitor.

Similar to these results, we observed that CCO_{MBA} was associated with a significant non-constant bias compared to transpulmonary thermodilution-calibrated CCO_{PCA}, with a percentage error well above the 30% threshold identified by Critchley and Critchley to estimate interchangeability between cardiac output methods, and within the range observed in previous studies.[8,23] However, we confirmed the ability of the monitor to efficiently detect changes in CCO when performing a postural manoeuvre or a fluid challenge. Interestingly, exclusion of patients in non-sinus rhythm did not substantially modify the bias between methods.

Furthermore, we evaluated the ability of the Argos® monitor to predict fluid responsiveness when performing a PLR test. Our results demonstrated the excellent performance of CCO_{MBA} to effectively predict fluid responsiveness after a fluid challenge (with a median normalized volume > the recommended 4 $ml.kg^{-1}$ [24]), at an optimal threshold of 14% during the preceding PLR test. However, this new threshold should be interpreted with caution, due to a wide grey zone, ranging from 12% to 23% and the low statistical power of this sensitivity analysis.[25] Of note, the lower boundary of the grey zone is higher than the classical threshold used to define fluid responsiveness with CCO_{PCA} during PLR. This is not unexpected, and is the result of the non-constant, increasing bias as CCO increases. Choosing between these boundary thresholds should be guided by clinical assessment of the risk-benefit compromise between fluid toxicity and fluid under-resuscitation. Also, we observed that diagnostic and predictive performance metrics were probably improved by optimal threshold determination, as compared to using the $\Delta\%CCI_{PCA}$ known thresholds for PLR (i.e. >10%).[14,15] Finally, it should be acknowledged that the study was

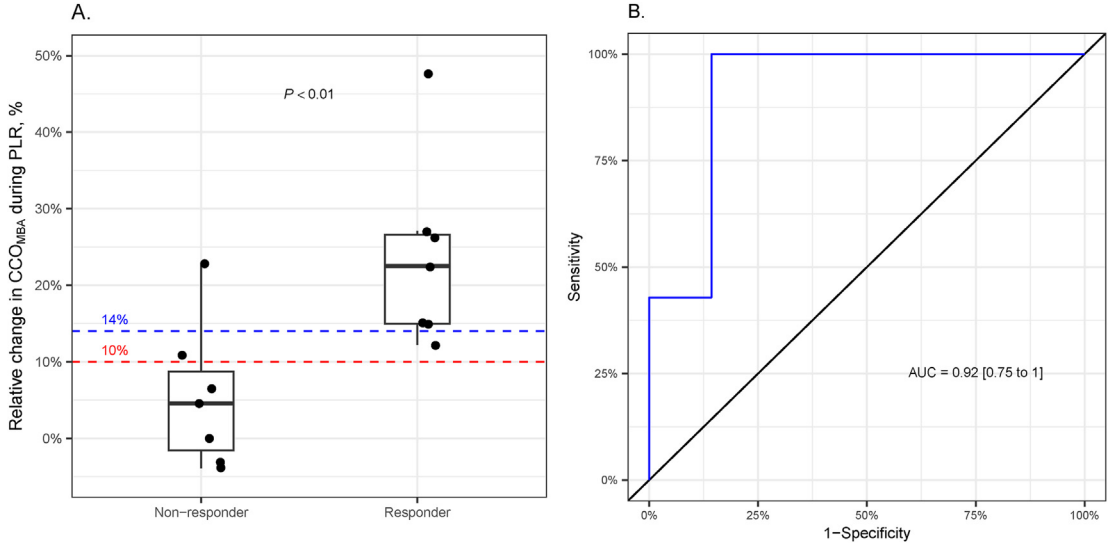

Fig. 4. $\Delta\%CCO_{MBA}$ performance during PLR to predict fluid responsiveness. The figure shows $\Delta\%CCO_{MBA}$ values during a passive leg raising maneuver preceding a fluid challenge after adjudication of the fluid response based on CO_{TPTD} (panel A) and the associated AUROC in panel B, in patients who performed both a passive leg raising maneuver and a fluid challenge (N = 14). In panel A, the red line identifies the validated threshold of 10% to identify fluid responsiveness using $\Delta\%CCO_{PCA}$ during PLR, and the blue line the optimal threshold of 14% using $\Delta\%CCO_{MBA}$ during PLR. The *P* value evaluates the statistical difference in $\Delta\%CCO_{MBA}$ values between fluid responders and non-responders, using the Wilcoxon–Mann–Whitney test. In panel B, the area under the receiver operating curve is displayed with its 95% confidence interval between brackets. The AUROC of $\Delta\%CCO_{MBA}$ to predict fluid responsiveness was significantly different from 0.50. AUROC: area under the receiver operating curve; $\Delta\%CCO_{MBA}$: relative change in continuous cardiac output measured by multi-beat analysis; $\Delta\%CCO_{PCA}$: relative change in continuous cardiac output measured by pulse contour analysis; $\Delta\%CO_{TPTD}$: relative change in cardiac output measured by transpulmonary thermodilution.

performed in a specific ICU subpopulation, a majority of which were under mechanical ventilation (and consequently PEEP) and with low RASS scores, physiological conditions that may have impacted bias estimation to an unknown degree.

Rapid changes in vascular tone have been shown to significantly impact CCO measurements and bias (with conflicting results), which subsequently mandated frequent recalibration of devices to appropriately assess cardiac output.[2,26,27] On the other hand, non-calibrated devices, which use demographics and population-based models to estimate the characteristics of the arterial tree (such as the arterial compliance), are less capable of identifying alterations in the vasculature and may incorrectly interpret changes of their root signal (i.e. the arterial waveform) as being related to systemic vascular resistances and not to arterial compliance. In the specific case of the Argos® monitor, changes in the tail section of the arterial waveform will systematically be interpreted by the device as being related to changes in vascular resistances (and subsequently CCO), as the system only adjusts arterial compliance based on the mean arterial pressure (and fixed demographics). Indeed, we observed that CCO_{MBA} bias was significantly impacted by the interaction of age and pulse pressure, while norepinephrine dosage or diastolic pressure were not retained in the multivariate model. Our interpretation is that high pulse pressure is both an indicator of decreased systemic vascular resistance (as it encompasses the decrease in diastolic pressure due to low vascular tone, and the increase in cardiac output secondary to low resistances), and/or decreased arterial compliance related either to age or vasopressors. As a result, and because the population-based model on which the device relies is proprietary, we can only hypothesize that it will perform better in older patients with limited vasoplegia and/or with high arterial compliance.

Our study shows that CCO_{MBA} has the potential to detect changes in CCO during hemodynamic studies evaluating preload dependence, and is capable to predict fluid responsiveness during PLR, at an optimal threshold of 14%. These results suggest that this minimally invasive device is of clinical use in hemodynamically unstable patients requiring advanced monitoring and in which fluid management should be guided using dynamic challenges. Furthermore, the ease of use of the monitor allows its implementation in clinical practice early during patient management, without requiring the implantation of a new catheter. Also, compared to other devices, the Argos monitor has the advantage of not requiring any consumable (i.e. single-use) material to assess CCO. These advantages are however mitigated by the fact that the absolute value of CCO_{MBA}, being positively and non-constantly biased compared to the reference method, may lead clinicians to make drastically different therapeutical decisions based on it. In those patients in which the absolute value of CCO is critical (e.g. cardiogenic shock, absence of clinical improvements after 6 h of management using non-calibrated CCO monitoring), clinicians should hence consider converting the CCO monitoring method from a non-calibrated one to a calibrated one.[28]

Our study has several strengths. First, we evaluated CCO_{MBA} in a medical ICU environment in patients with sepsis and septic shock. Second, linked repeated replicates were collected during hemodynamic studies evaluating fluid responsiveness. Third, we used advanced metrology methodology to evaluate bias (including the evaluation of non-constant bias and the adjustment for paired replicates), trending ability and precision of CCO_{MBA}, to extensively report the performance of this new device.[18,21,22] Fourth, we used CCO_{PCA} as the reference method, which as the dual advantage of being calibrated by transpulmonary-thermodilution and of continuously measuring CCO using pulse contour analysis with limited drift over the first hour after calibration.[27] Furthermore, CCO_{PCA} has demonstrated limited bias and lower percentage errors when compared to the pulmonary artery thermodilution-measured cardiac output.[9,10,29] Finally, statistical analyses took into account the specificities of the experimental design, including the repetition of replicates in a given participant.

Several limitations should also be acknowledged. First, this is a single-centre, observational study, which limits the generalizability of our results. Second, not all postural manoeuvres were followed by a fluid challenge, which hampers our capacity to strictly evaluate its accuracy to predict fluid responsiveness. However, the study was performed during routine care in which clinicians could decide whether to administer or not a fluid challenge based on the result of the postural manoeuvre. Third, fluid responsiveness was adjudicated based on both the change in CCO_{PCA} observed during PLR and the change in CO_{TPTD} in patients who received a fluid challenge. However, using only transpulmonary thermodilution measurements would have limited the amount of data in the context of an observational study, by excluding all postural manoeuvres not followed by a fluid challenge. Furthermore, CCO_{PCA} (rather than transpulmonary thermodilution) has the advantage of utilizing the same root signal (i.e. the AP waveform) to estimate CCO bias, yet with a different computational methodology. Also, all hemodynamic studies were immediately preceded by a CCO_{PCA} calibration by transpulmonary thermodilution, ensuring minimal drift in CCO values. Fourth, we acknowledge that fluid responsiveness predicted using CCO_{PCA} during PLR is associated with a false negative rate of approximately 10%, which may have hampered our estimation of the diagnostic performance of CCO_{MBA}.[14] Fifth, no TTE was performed as part of the protocol, which may have led to the identification of other variables associated with increased bias between methods and the comparison of CCO measurements with left ventricular outflow tract velocity by velocity-time integral.

5. Conclusions

In this single-centre, observational study, non-calibrated CCO_{MBA} showed a non-constant bias but an adequate ability to track changes in CCO_{PCA} during hemodynamic studies evaluating fluid responsiveness. In the specific context of our centre, the device showed excellent diagnostic and predictive performance to predict preload dependence in a medical ICU population receiving norepinephrine, with an optimal threshold of 14% during a postural manoeuvre to predict fluid responsiveness.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and with local regulations. The study obtained ethics approval from the Comité Scientifique et Ethique des Hospices Civils de Lyon, under the reference number 23-5040. All included patients or their next-of-kin received information regarding the study. Due to the non-interventional design of the study, the ethics comity waived the obligation for signed consent.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

LB and IN collected and analyzed the data, interpreted the results, and drafted the manuscript. LC, MM, FD, MG and HY collected the data, and revised the manuscript for important intellectual content. GD collected the data, interpreted the results, and revised the manuscript for important intellectual content. LB and JCR designed the study, interpreted the results, and revised the manuscript for important intellectual content. All authors read and approved the manuscript submitted for publication.

Consent to participate

All participants or their next-of-kin received all required information regarding study procedures. Due to the non-interventional design of the study, the ethics comity waived the obligation for signed consent.

Consent for publication

Not applicable.

Data availability statement

Source datasets are not publicly available due to ethical reasons. Further enquiries can be directed to the corresponding author.

Acknowledgements

The authors are grateful to all patients and their families who participated to the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccrj.2024.04.003.

References

[1] Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med 2014;40:1795–815.
[2] Gruenewald M, Meybohm P, Renner J, Broch O, Caliebe A, Weiler N, et al. Effect of norepinephrine dosage and calibration frequency on accuracy of pulse contour-derived cardiac output. Crit Care 2011;15:R22.
[3] Mukkamala R, Kohl BA, Mahajan A. Comparison of accuracy of two uncalibrated pulse contour cardiac output monitors in off-pump coronary artery bypass surgery patients using pulmonary artery catheter-thermodilution as a reference. BMC Anesthesiol 2021;21:189.
[4] Khanna AK, Nosow L, Sands L, Saha AK, Agashe H, Harris L, et al. Agreement between cardiac output estimation by multi-beat analysis of arterial blood pressure waveforms and continuous thermodilution in post cardiac surgery intensive care unit patients. J Clin Monit Comput 2022;37(2):559–65.
[5] Saugel B, Heeschen J, Hapfelmeier A, Romagnoli S, Greiwe G. Cardiac output estimation using multi-beat analysis of the radial arterial blood pressure waveform: a method comparison study in patients having off-pump coronary artery bypass surgery using intermittent pulmonary artery thermodilution as the reference method. J Clin Monit Comput 2020;34:649–54.
[6] Le Gall A, Vallée F, Joachim J, Hong A, Matéo J, Mebazaa A, et al. Estimation of cardiac output variations induced by hemodynamic interventions using multi-beat analysis of arterial waveform: a comparative off-line study with transesophageal Doppler method during non-cardiac surgery. J Clin Monit Comput 2022;36:501–10.
[7] Greiwe G, Peters V, Hapfelmeier A, Romagnoli S, Kubik M, Saugel B. Cardiac output estimation by multi-beat analysis of the radial arterial blood pressure waveform versus intermittent pulmonary artery thermodilution: a method comparison study in patients treated in the intensive care unit after off-pump coronary artery bypass surgery. J Clin Monit Comput 2020;34:643–8.
[8] 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;15:85–91.
[9] Peyton PJ, Chong SW. Minimally invasive measurement of cardiac output during surgery and critical care: a meta-analysis of accuracy and precision. Anesthesiology 2010;113:1220–35.
[10] Joosten A, Desebbe O, Suehiro K, Murphy LS, Essiet M, Alexander B, et al. Accuracy and precision of non-invasive cardiac output monitoring devices in perioperative medicine: a systematic review and meta-analysis. Br J Anaesth 2017;118:298–310.
[11] von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008;61:344–9.
[12] Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. BMJ 2015;351:h5527.
[13] Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916;17:863–71.
[14] Monnet X, Rienzo M, Osman D, Anguel N, Richard C, Pinsky MR, et al. Passive leg raising predicts fluid responsiveness in the critically ill. Crit Care Med 2006;34:1402–7.
[15] Yonis H, Bitker L, Aublanc M, Perinel Ragey S, Riad Z, Lissonde F, et al. Change in cardiac output during Trendelenburg maneuver is a reliable predictor of fluid responsiveness in patients with acute respiratory distress syndrome in the prone position under protective ventilation. Crit Care 2017;21.
[16] R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2008.
[17] Bates D, Maechler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. J Stat Software 2015;67:1–48.
[18] Carstensen B, Gurrin L, Ekstrøm CT, Figurski M. MethComp: analysis of agreement in method comparison studies. 1.30.0 ed.. 2020.
[19] Barton K. MuMIn: multi-model inference. https://CRAN.R-project.org/package=MuMIn; 2020.
[20] Thiele C, Hirschfeld G. Cutpointr: improved estimation and validation of optimal cutpoints in R. J Stat Software 2021;98:1–27.
[21] Carstensen B, Simpson J, Gurrin LC. Statistical models for assessing agreement in method comparison studies with replicate measurements. Int J Biostat 2008;4:16.
[22] Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307–10.
[23] Cecconi M, Rhodes A, Poloniecki J, Della Rocca G, Grounds RM. Bench-to-bedside review: the importance of the precision of the reference technique in method comparison studies–with specific reference to the measurement of cardiac output. Crit Care 2009;13:201.
[24] Aya HD, Ster IC, Fletcher N, Grounds RM, Rhodes A, Cecconi M. Pharmacodynamic analysis of a fluid challenge. Crit Care Med 2016;44:880–91.
[25] Cannesson M, Le Manach Y, Hofer CK, Goarin JP, Lehot JJ, Vallet B, et al. Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a "gray zone" approach. Anesthesiology 2011;115:231–41.
[26] Rodig G, Prasser C, Keyl C, Liebold A, Hobbhahn J. Continuous cardiac output measurement: pulse contour analysis vs thermodilution technique in cardiac surgical patients. Br J Anaesth 1999;82:525–30.
[27] Hamzaoui O, Monnet X, Richard C, Osman D, Chemla D, Teboul JL. Effects of changes in vascular tone on the agreement between pulse contour and transpulmonary thermodilution cardiac output measurements within an up to 6-hour calibration-free period. Crit Care Med 2008;36:434–40.
[28] Teboul JL, Saugel B, Cecconi M, De Backer D, Hofer CK, Monnet X, et al. Less invasive hemodynamic monitoring in critically ill patients. Intensive Care Med 2016;42:1350–9.
[29] Kouz K, Michard F, Bergholz A, Vokuhl C, Briesenick L, Hoppe P, et al. Agreement between continuous and intermittent pulmonary artery thermodilution for cardiac output measurement in perioperative and intensive care medicine: a systematic review and meta-analysis. Crit Care 2021;25:125.
[30] de Courson H, Ferrer L, Cane G, Verchere E, Sesay M, Nouette-Gaulain K, et al. Evaluation of least significant changes of pulse contour analysis-derived parameters. Ann Intensive Care 2019;9:116.