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Effect of norepinephrine dosage and calibration frequency on accuracy of pulse contour-derived cardiac output

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Abstract

Introduction: Continuous cardiac output monitoring is used for early detection of hemodynamic instability and guidance of therapy in critically ill patients. Recently, accuracy of pulse contour-derived cardiac output (PCCO) has been questioned in different clinical situations. In this study we examined agreement between PCCO and trans-cardiopulmonary thermodilution cardiac output (CO_{TCP}) in critically ill patients with special emphasis on norepinephrine (NE) administration and time interval between calibrations.

Methods: This prospective, observational study was performed on seventy-three patients (mean age 63 ± 13 years sd) requiring invasive hemodynamic monitoring on a non-cardiac surgery intensive care unit. PCCO was recorded immediately before calibration by CO_{TCP}. Bland-Altman analysis was performed on data subsets comparing agreement between PCCO and CO_{TCP} according to NE dosage and time interval between calibrations up to 24 hours. Further, central artery stiffness was calculated by pulse-pressure-to-stroke-volume relationship.

Results: 330 data pairs were analyzed. For all data pairs mean CO_{TCP} (± SD) was 8.2 ± 2.0 l/min. PCCO had a mean bias of 0.16 l/min with limits of agreement of -2.81 to 3.15 l/min (percentage error of 38%) when compared to CO_{TCP}. Whereas bias between PCCO and CO_{TCP} was not significantly different between NE dosage categories or time categories elapsed between calibrations, interchangeability (percentage error <30%) between methods was only present in the high NE dosage (≥0.1µg/kg/min) subgroup, as percentage error was 40%, 47%, and 28% in no NE, NE < 0.1 and NE ≥ 0.1µg/kg/min subgroup, respectively. PCCO was not interchangeable to CO_{TCP} in subgroups of different calibration interval. The high NE dosage group showed significantly increased central artery stiffness.

Conclusions: This study shows that NE dosage, but not time interval between calibrations, has an impact on agreement between PCCO with CO_{TCP}. Only in the measurements with high NE dosage (representing the minority of measurements), PCCO was interchangeable to CO_{TCP}.

Introduction

Cardiac output monitoring in high-risk patients has gained increasing interest as early detection of hemodynamic instability can reduce morbidity in these patients [1-3]. Several studies, evaluating goal-directed protocols, reported improved outcome due to immediate treatment in order to prevent or resolve organ ischemia [4,5]. The PiCCO*plus* system (Pulsion Medical Systems, Munich, Germany) allows continuous cardiac output measurement by pulse contour analysis (PCCO). Calibration of PCCO is performed by intermittent trans-cardiopulmonary thermodilution cardiac output (CO_{TCP}). It has been demonstrated that PCCO agrees with pulmonary artery thermodilution cardiac output [6-8] and with CO_{TCP} [9,10] in cardiac surgery patients. However, the reliability of PCCO has been questioned in clinical scenarios like acute hemorrhage and subsequent norepinephrine (NE) administration [11], changes in vascular tone [12], increased intra-abdominal pressure [13] or time interval between calibration [14]. Therefore the clinician needs to consider these confounders when interpreting PCCO values and prompting therapeutic decisions.

The present prospective observational study investigated in a large group of critically ill patients whether agreement between PCCO with CO_{TCP} is affected by different NE-dosages or the time interval elapsed between calibrations. According to the literature we generated the following two hypotheses: i) Increasing NE dosage results in decreased agreement between PCCO and CO_{TCP}; ii) Increasing time interval between calibrations of PCCO results in decreased agreement between PCCO and CO_{TCP}.

Only rare data is available about the usage of PCCO calibrations in clinical practice. Therefore, we retrospectively evaluated whether NE dosage or severity of disease (APACHE II score) had an influence on calibration frequency on our ICU.

Materials and methods

Patients

In this prospective observational study, critically ill patients equipped with invasive hemodynamic monitoring by the PiCCO*plus* system (Version 6.0) on our non-cardiac ICU between September 2007 and July 2008 were included. The study was approved by our institutional review board in compliance with the Helsinki Declaration (Ethics committee of the University Hospital Schleswig-Holstein, Campus Kiel). Patients and/or relatives gave their informed consent for the patients' data to be used in the analysis. Invasive hemodynamic monitoring was performed according to the judgement of the attending physician on the ICU. Exclusion criteria were cardiac arrhythmias, a permanent pacemaker or any other mechanical cardiac support and known valvular heart disease.

Hemodynamic measurements

In all patients a central venous catheter and a thermistor-tipped arterial catheter (Pulsiocath, Pulsion Medical Systems, Munich, Germany), inserted via femoral artery, were present upon enrolment. The PiCCO device uses pulse contour analysis according to a modified algorithm originally described by Wesseling and colleagues [15] to determine PCCO and is described in more detail elsewhere [9]. This algorithm enables continuous calculation of stroke volume by measuring the systolic portion of the aortic pressure waveform and dividing the area under the curve by the aortic compliance. Therefore, the PiCCO device needs to be calibrated by CO_{TCP}. Calibrations were regularly performed by an ICU physician at a defined time-point (8:00 AM) with the patient in supine position during a time period without acute hemodynamic instability using 3 subsequent boluses of 15 ml ice-cold saline injected into the central venous line, as proposed by the manufacturer [9]. During

measurement, neither treatment provoking hemodynamic changes nor change of ventilation variables was performed. The dosage of vasopressors was kept constant. Our institutional guideline suggests calibration every eight hours or before any major change in therapy is initiated. Therefore, additional calibrations by the attending ICU physician were allowed at any time. All hemodynamic data, including PCCO, central venous pressure, mean arterial blood pressure, pulse pressure (systolic minus diastolic aortic pressure) and heart rate were recorded immediately before and after calibration by CO_{TCP}. Global end-diastolic volume index and systemic vascular resistance index were derived upon thermodilution. Stroke volume was calculated as CO_{TCP} divided by heart rate. The pulse-pressure-to-stroke-volume relationship was used to examine the influence of NE dosage on central arterial stiffness as reported previously [16]. Our ICU is equipped with a patient data management system (PDMS, CareSuite®, Picis Inc., Wakefield, MA, USA) electronically storing hemodynamic variables, including all single thermodilution calibrations and ventilatory variables minute by minute.

Statistical analysis

Statistical analysis was performed using the statistics software R (R Foundation, Vienna, Austria [17]) and GraphPad Prism 5.01 (Graphpad Sofware Inc., San Diego, CA, USA). Data are reported as mean ± standard deviation (SD) unless otherwise specified. NE subgroups were defined as no-NE, low dose-NE (<0.1 µg/kg/min), and high dose-NE (≥0.1 µg/kg/min) according to the SOFA score [18]. Subgroups of time interval elapsed after the latest calibration were defined <2 hours, 2-4 hours, 4-8 hours, 8-16 hours and 16-24 hours. Data subsets for hemodynamic variables, PP/SV ratio and calibration interval were compared by unpaired two-tailed *t*-test. Comparison of PCCO and CO_{TCP} was performed by using Bland-Altman statistics for

multiple observations per individual [19] calculating mean difference between methods (bias) ± 2 standard deviations (limits of agreement (LoA)). Bias between subgroups was compared with *t*-test. The percentage error was calculated as reported by Critchley and colleagues [20] and interchangeability between methods was assumed as a percentage error below 30%. The precision of the reference technique (CO_{TCP}) was analyzed according to Cecconi et al. from the 3 consecutive bolus injections for calibration [21]. To test whether PCCO reflects changes (Δ) in cardiac output, the ΔPCCO (PCCO – preceding CO_{TCP}) was analyzed against ΔCO_{TCP} (actual CO_{TCP} – preceding CO_{TCP}) by linear regression analysis including first pair measurements of each patient. Influence of NE dosage and severity of medical condition (APACHE II score) on calibration frequency was analyzed using Spearman correlation for nonparametric data. A $p<0.05$ was considered statistically significant.

Results

Seventy-three patients were included in this study. The median (IQR) APACHE II score of all patients was 24 [20 – 29] at time of inclusion. Detailed patient characteristics are described in table 1.

We obtained 330 data pairs. In 265 out of 330 data pairs, patients received mechanical ventilation with a mean tidal volume of 8 ± 1 ml/kg, a mean FiO_2 of 0.6 ± 0.1, a mean peak airway pressure of 23 ± 6 cmH_2O, and a mean positive end-expiratory pressure of 9 ± 3 cmH_2O. In the remaining 65 data pairs, patients breathed spontaneously and received oxygen via face mask. Calibration interval was 9 ± 7 hours (range: 1 – 24 hours). The precision of the three bolus injection - CO_{TCP} values was 7%, according to Cecconi [21].

Concerning the effect of NE dosage on the agreement between PCCO and CO_{TCP}, 27 data pairs were excluded from further analysis because of additional dobutamine or epinephrine administration. In 161 out of 303 data pairs NE was administered in a dosage ranging from 0.01 to 4.29 µg/kg/min. Hemodynamic data and calibration interval of different NE subgroups are presented in table 2.

Bias between NE-subgroups did not differ significantly. However, PCCO was interchangeable with CO_{TCP} only during high NE-dosage, and not at low or no-NE dosage. Results of the Bland-Altman analysis are presented in table 3 and plots are given in figure 1.

Coefficient of correlation *r* (95% confidence interval) between ΔPCCO and ΔCO_{TCP} was 0.46 (0.25 - 0.64; p<0.001) for all, 0.19 (-0.23 – 0.55; p=0.36) for no NE, 0.37 (-0.09 – 0.70; p=0.11) for NE <0.1 µg/kg/min, and 0.78 (0.53 - 0.91, p<0.001) for NE ≥0.1 µg/kg/min subgroups, respectively.

In the NE ≥ 0.1 µg/kg/min subgroup a significant (p<0.05) higher pulse-pressure-to-stroke-volume relationship (arterial stiffness) was observed compared to no NE or NE < 0.1 µg/kg/min subgroups, respectively (figure 2).

Mean bias between PCCO and CO_{TCP} did not depend on time elapsed from the preceding calibration. However, in none of the subgroups agreement between PCCO and CO_{TCP} met defined criteria for interchangeability as percentage error was above 30 % in all respective interval subgroups. The time related effect on agreement is presented in table 3. Individual bias during each interval, as well as mean bias ± limits of agreement are plotted in figure 3.

On our ICU, we recorded a mean (± SD) time interval since the preceding calibration of 9 ± 6 hours. In 151 (46%) recordings, time interval exceeded the recommended 8

hours interval. In 14 (4%) recordings, time interval was as long as 24 hours. Time interval did not correlate with NE dosage or APACHE II score (r = -0.04, p=0.48 and -0.01, p=0.41), respectively.

Discussion

In the present study, we demonstrated an influence of NE dosage on agreement of PCCO as only during high NE dosage criteria of interchangeablity with CO_{TCP} were met. Time elapsed between calibrations did not affect agreement between methods.

Goal-directed therapy in high-risk patients has shown to improve outcome [4,5]. One essential observation in these studies was that the earlier treatment was started the better the outcome. Therefore continuous cardiac output monitoring in critically ill patients is needed. However, PCCO needs to be validated in a large number of patients and during relevant conditions to gain more insight into mechanisms influencing this variable. The present study compared PCCO and CO_{TCP} in 73 ICU patients suffering from several comorbidities. Most previous studies compared PCCO with CO_{TCP} in small series of patients during cardiac surgery [6,8,9,22]. Data from larger patient samples, however, are scarce. The percentage error between PCCO and CO derived by a thermodilution method varied between 26% and 50% in earlier studies [14,23]. Critchley et al. have defined a percentage error of less than 30% to indicate interchangeability [20]. Accordingly, we found an acceptable agreement of PCCO with CO_{TCP} only in data subsets obtained with high-NE dosage, although a percentage error of 28% is reasonably still high. However, the results of the present study tend to refuse our first hypothesis. Increasing NE dosage does not seem to be associated with decreased agreement between PCCO and CO_{TCP}, but rather with improved interchangeability. PCCO further showed a better performance in tracking changes in cardiac output during increased NE dosage as coefficient of correlation

between ΔPCCO and ΔCO_{TCP} was higher. The vascular tone seems to be an important issue regarding the agreement of PCCO methods with a reference method such as trans-cardiopulmonary thermodilution. Rodig et al. described an increased bias between PCCO and CO measured by thermodilution after administration of phenylephrine. The observed change of SVR > 60% between calibrations may explain their findings [12]. A recent publication, applying the same PCCO software used in our study, concluded that agreement was not influenced by changes in SVR due to better adaptation of the newer algorithm [14]. In the present study SVR was not different between NE subgroups. Therefore, we hypothesize that despite a comparable SVR, a differing compliance of the vascular tree between subgroups of different NE dosages may explain the different level of agreement. A higher NE dosage may result in an increased central arterial stiffness and therefore reduced arterial compliance [24] as recently reported by Wittrock and coworkers [16]. In agreement to these findings, high NE dosage resulted in significantly higher pulse-pressure-to-stroke-volume relationship as an indicator of arterial stiffness. The increasing arterial stiffness is leading to a more rigid vascular system and subsequently may result in better agreement between methods. It is conceivable in this context, that the vasculature on high NE has less oscillatory capacity which limits changes in arterial compliance and consequently the deviation from the compliance obtained upon calibration. In clinical routine, however, many patients may be treated with either a low dose or no NE, and according to our results PCCO is not interchangeable with CO_{TCP} in these patients.

Our results do not show a time related effect on agreement between PCCO and $CO_{TCP,}$ thus denying the second hypothesis. Percentage error was above 30% in all calibration interval subgroups. The manufacturer recommends recalibration every eight hours. Godje et al. reported an overall acceptable agreement up to 44 hours,

however, they did not indicate the bias and percentage error of subsets regarding different calibration intervals [9]. Hamzaoui et al. reported a percentage error below 30% only within the first hour after calibration of PCCO but up to 37% within a six hours calibration interval [14]. The authors concluded that PCCO is stable during a one hour period and even changes in SVR do not alter agreement. These results would prompt to hourly recalibration. Considering our results, time elapsed from preceding calibration is not determining the level of agreement as individually good agreement was observed up to 24 hours and individually poor agreement occurred within a period of two hours after calibration. Moreover, we found acceptable agreement in patients with high NE dosage, thus higher arterial stiffness, who had mean calibration period of nine and ten hours.

This study also examined the clinical usage of calibrations by using PiCCO technology. Our institutional guidelines recommend a recalibration of the PiCCO system every 8 hours (3 times a day) as well as before and after any major change in therapy. We found that in only 54% of recordings institutional guidelines of recalibration were met. We did not observe a correlation of calibration frequency with APACHE II score or NE dosage, indicating that calibration of PCCO may not be dependent on severity of critical illness. These findings were surprising, since recalibration may increase agreement between methods [13]. However, our results indicate that time interval elapsed between calibrations may not to be the most important factor determining PCCO accuracy; moreover therapy during calibrations seems to be important.

There are some limitations to our study. To avoid additional risk due to a more invasive methodology of cardiac output measurement we used the PiCCO integrated trans-cardiopulmonary thermodilution instead of pulmonary artery thermodilution

method as reference technique to PCCO as previously described [13,14]. The calibration interval was not strictly standardized in order to measure the effect of NE dosage on calibration frequency on our ICU.

Conclusions

This study demonstrates further limitations of the PCCO method for determination of continuous cardiac output. Only during high NE dosage (≥ 0.1 µg/kg/min) PCCO was interchangeable to CO_{TCP}. Therefore, accuracy of PCCO measurement relies on important clinical circumstances.

Key messages

- During clinical conditions PCCO and CO_{TCP} measurements cannot be used interchangeably in patients without or on low dose of vasopressors.
- Acceptable agreement between the methods was only observed during increased dose of norepinephrine, representing the minority of measurements. Even then, the limits of agreement are rather large.
- The time interval between calibrations of PCCO does not improve the reliability of PCCO within a period of 24 hours.

Abbreviations

Δ, delta, change of CO between actual and preceding calibration; APACHE II, Acute Physiology and Chronic Health Evaluation II score; CI, cardiac index; CO_{TCP}, trans-cardiopulmonary thermodilution cardiac output; CVP, central venous pressure; GEDI, global end-diastolic volume index; HR, heart rate; ICU, intensive care unit; IQR, inter quartile range; LoA, limits of agreement; MAP, mean arterial pressure; NE, norepinephrine; PCCO, pulse contour cardiac output; PE, percentage error; PP/SV,

pulse pressure/stroke volume ratio; *r,* coefficient of correlation; SD, standard deviation; SOFA, Sepsis-related Organ Failure Assessment score; SV, stroke volume; SVRI, systemic vascular resistance index.

Competing interests

BB is member of the advisory board of Pulsion Medical Systems. MG, PM, JR, AC, OB, NW, JS and MS declare that they have no competing interests.

Authors' contributions

MG conceived of the study design, carried out statistical analysis and drafted the manuscript. PM, OB and JR helped to draft the manuscript. AC supported statistical analysis. NW, JS and MS coordinated the study. BB conceived of the study design, coordinated the study and helped with statistical analysis and drafting the manuscript. All authors read and approved the final manuscript.

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References

1. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M: **Early goal-directed therapy in the treatment of severe sepsis and septic shock.** *N Engl J Med* 2001, **345:**1368-77.
2. Eisenberg PR, Jaffe AS, Schuster DP: **Clinical evaluation compared to pulmonary artery catheterization in the hemodynamic assessment of critically ill patients.** *Crit Care Med* 1984, **12:**549-53.
3. Kern JW, Shoemaker WC: **Meta-analysis of hemodynamic optimization in high-risk patients.** *Crit Care Med* 2002, **30:**1686-92.
4. McKendry M, McGloin H, Saberi D, Caudwell L, Brady AR, Singer M: **Randomised controlled trial assessing the impact of a nurse delivered, flow monitored protocol for optimisation of circulatory status after cardiac surgery.** *Bmj* 2004, **329:**258.
5. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED: **Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445].** *Crit Care* 2005, **9:**R687-93.
6. Buhre W, Weyland A, Kazmaier S, Hanekop GG, Baryalei MM, Sydow M, Sonntag H: **Comparison of cardiac output assessed by pulse-contour analysis and thermodilution in patients undergoing minimally invasive direct coronary artery bypass grafting.** *J Cardiothorac Vasc Anesth* 1999, **13:**437-40.
7. Bein B, Worthmann F, Tonner PH, Paris A, Steinfath M, Hedderich J, Scholz J: **Comparison of esophageal Doppler, pulse contour analysis, and real-time pulmonary artery thermodilution for the continuous measurement of cardiac output.** *J Cardiothorac Vasc Anesth* 2004, **18:**185-9.
8. Felbinger TW, Reuter DA, Eltzschig HK, Moerstedt K, Goedje O, Goetz AE: **Comparison of pulmonary arterial thermodilution and arterial pulse contour analysis: evaluation of a new algorithm.** *J Clin Anesth* 2002, **14:**296-301.
9. Godje O, Hoke K, Goetz AE, Felbinger TW, Reuter DA, Reichart B, Friedl R, Hannekum A, Pfeiffer UJ: **Reliability of a new algorithm for continuous cardiac output determination by pulse-contour analysis during hemodynamic instability.** *Crit Care Med* 2002, **30:**52-8.
10. Felbinger TW, Reuter DA, Eltzschig HK, Bayerlein J, Goetz AE: **Cardiac index measurements during rapid preload changes: a comparison of pulmonary artery thermodilution with arterial pulse contour analysis.** *J Clin Anesth* 2005, **17:**241-8.

11. Bein B, Meybohm P, Cavus E, Renner J, Tonner PH, Steinfath M, Scholz J, Doerges V: **The reliability of pulse contour-derived cardiac output during hemorrhage and after vasopressor administration.** *Anesth Analg* 2007, **105:**107-13.
12. 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.
13. Gruenewald M, Renner J, Meybohm P, Hocker J, Scholz J, Bein B: **Reliability of continuous cardiac output measurement during intra-abdominal hypertension relies on repeated calibrations: an experimental animal study.** *Crit Care* 2008, **12:**R132.
14. 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.
15. Wesseling KH, Jansen JR, Settels JJ, Schreuder JJ: **Computation of aortic flow from pressure in humans using a nonlinear, three-element model.** *J Appl Physiol* 1993, **74:**2566-73.
16. Wittrock M, Scholze A, Compton F, Schaefer JH, Zidek W, Tepel M: **Noninvasive pulse wave analysis for the determination of central artery stiffness.** *Microvasc Res* 2009, **77:**109-12.
17. R Development Core Team. **R: A language and environment for statistical computing.** Vienna, Austria: R Foundation for Statistical Computing, 2009.
18. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG: **The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine.** *Intensive Care Med* 1996, **22:**707-10.
19. Bland JM, Altman DG: **Agreement between methods of measurement with multiple observations per individual.** *J Biopharm Stat* 2007, **17:**571-82.
20. 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.
21. 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.

22. Sander M, von Heymann C, Foer A, von Dossow V, Grosse J, Dushe S, Konertz WF, Spies CD: **Pulse contour analysis after normothermic cardiopulmonary bypass in cardiac surgery patients.** *Crit Care* 2005, **9:**R729-34.
23. Ostergaard M, Nielsen J, Rasmussen JP, Berthelsen PG: **Cardiac output--pulse contour analysis vs. pulmonary artery thermodilution.** *Acta Anaesthesiol Scand* 2006, **50:**1044-9.
24. Chemla D, Hebert JL, Coirault C, Zamani K, Suard I, Colin P, Lecarpentier Y: **Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans.** *Am J Physiol* 1998, **274:**H500-5.

Figure legends

Figure 1. Bland-Altman plots of different norepinephrine (NE) subgroups.
PCCO: pulse contour cardiac output, CO_{TCP}: trans-cardiopulmonary thermodilution cardiac output, PE: percentage error. Solid line – mean bias; dotted lines – limits of agreement.

Figure 2. Arterial stiffness. Pulse-pressure (PP) to stroke-volume (SV) relationship as measure of central arterial stiffness within the different norepinephrine (NE) dosage (µg/kg/min) subsets. Data are mean ± SD; * $p<0.05$ *vs*. no NE, # $p<0.05$ *vs*. NE <0.1µg/kg/min.

Figure 3. Bias in relation to time interval between calibrations. Mean bias (box) ± limits of agreement and individual bias (circles) in % of CO_{TCP} between PCCO and CO_{TCP} in subsets of different calibration intervals. Dotted lines illustrate interchangeability (± 30%).

Table 1. Patient characteristics, medical history as well as reason for instrumentation with PiCCO monitoring system.

Patients (n)	73
Age (years)	63 ± 13; (21 – 82)
Gender (male / female)	53 / 20
Weight (kg)	79 ± 14
Height (cm)	175 ± 8
APACHE II Score	24 (7 – 45)
Medical history	
None	6
Arterial hypertension	35
Chronic obstructive pulmonary disease	9
Coronary heart disease	7
Diabetes	12
Renal insufficiency	11
Reason for hemodynamic monitoring	
Hypovolemia (major surgery)	19
Hypovolemia (major trauma)	5
Peritonitis	15
Pneumonia	7
Resuscitated from cardiac arrest	5
Septic shock	22

Data are mean ± SD, absolute numbers or median (range). Multiple answers are possible.

Table 2. Hemodynamic data and calibration interval of different norepinephrine (NE) subgroups.

	All	**no-NE**	**NE < 0.1** (µg/kg/min)	**NE ≥ 0.1** (µg/kg/min)
n	(330)	(142)	(82)	(79)
Hemodynamics				
CI (l/min·m^2)	4.3 ± 1.1	4.4 ± 1.0	4.3 ± 1.0	4.3 ± 1.2
MAP (mm Hg)	81 ± 15	88 ± 16	80 ± 11 *	76 ± 13 *
HR (bpm)	98 ± 19	94 ± 16	96 ± 18	105 ± 21 *†
CVP (mm Hg)	12 ± 5	11 ± 5	12 ± 5	13 ± 4
GEDI (ml/m^2)	791 ± 191	808 ± 213	794 ± 180	780 ± 171
SVRI (dynes·s/cm^5/m^2)	1367 ± 413	1435 ± 409	1309 ± 379	1274 ± 419
Calibration interval (min)	443 (234-784)	442 (243-761)	518 (247-821)	439 (200-914)

Data are given are mean ± SD or median (IQR). * p<0.05 *vs.* no-NE; † p<0.05 *vs.* NE < 0.1. This table presents descriptive hemodynamic data and calibration interval regarding norepinephrine (NE) dosage subgroups. Cardiac index (CI), mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), global end-diastolic volume index (GEDI), systemic vascular resistance index (SVRI).

Table 3. Results of Bland-Altman analysis PCCO vs. CO_{TCP}.

	n ($n_{all}/n_{patient}$)	**Mean** (l/min)	**Bias** (l/min)	**Limits of agreement** (l/min)	**Percentage error** (%)
All	330/73	8.1	0.16	-2.81 – 3.15	38
No NE	142/44	8.41	0.16	-3.12 – 3.44	40
NE < 0.1 (µg/kg/min)	82/38	8.50	0.06	-3.88 – 4.00	47
NE ≥ 0.1 (µg/kg/min)	79/30	7.87	0.29	-1.83 – 2.42	28 *
calibration interval 0 – 2 hours	36/25	8.00	0.25	-4.00 – 4.51	54
calibration interval 2 – 4 hours	48/35	7.78	0.12	-3.37 – 3.60	46
calibration interval 4 – 8 hours	95/41	8.21	0.09	-2.43 – 2.61	31
calibration interval 8 – 16 hours	101/47	8.19	0.21	-3.17 – 3.59	42
calibration interval 16 – 24 hours	50/28	8.06	0.23	-2.90 – 3.34	40

* interchangeability according to Critchley et al. [20]. n_{all}: number of measurements pairs for PCCO and CO_{TCP}, $n_{patient}$: number of patients, Mean: mean of all PCCO and CO_{TCP} measurements. Bias and limits of agreement were calculated according to Bland and Altman. [19].

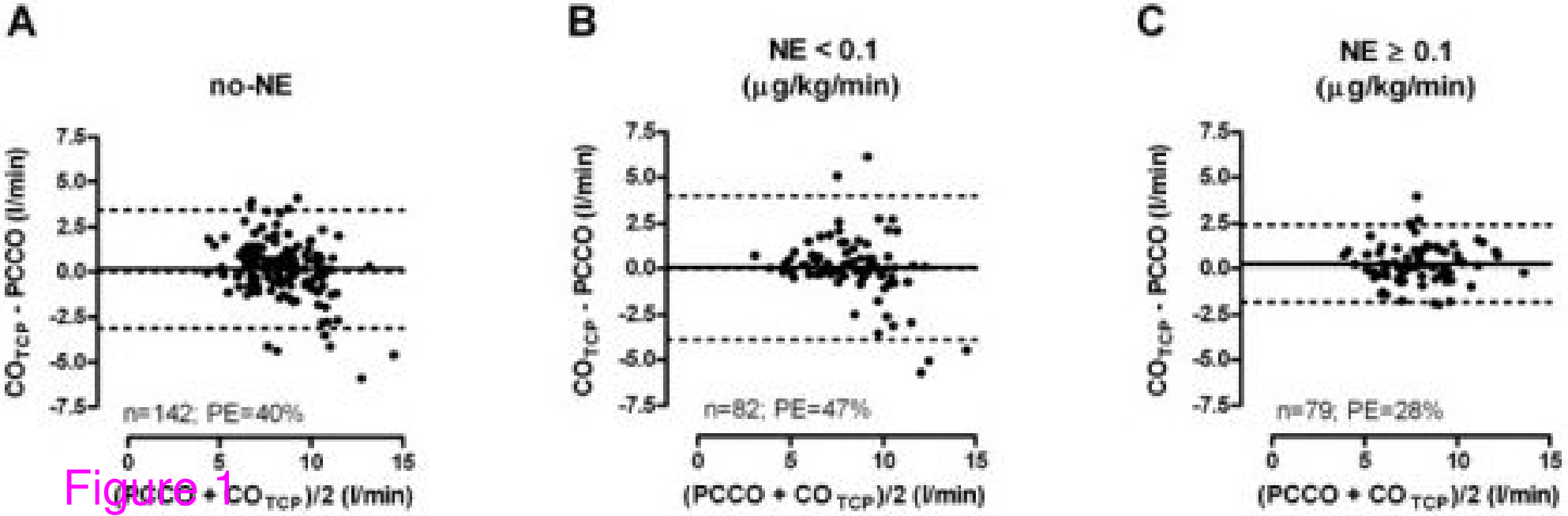
A
no-NE
B
NE < 0.1
(µg/kg/min)
C
NE ≥ 0.1
(µg/kg/min)
CO_{TCP} - PCCO (l/min)
7.5
5.0
2.5
0.0
-2.5
-5.0
-7.5
n=142; PE=40%
n=82; PE=47%
n=79; PE=28%
0
5
10
15
(PCCO + CO_{TCP})/2 (l/min)

Figure 1

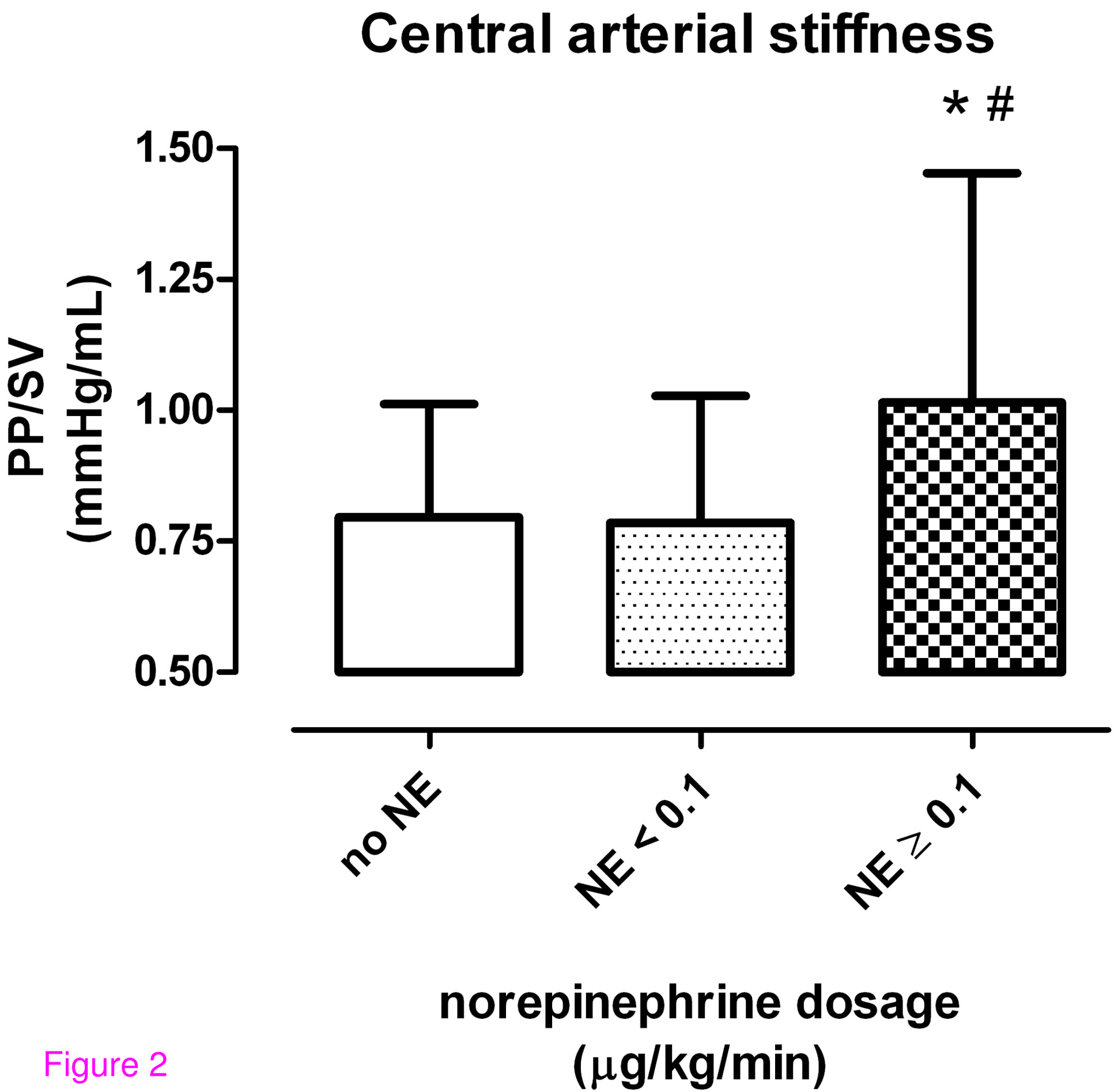
Central arterial stiffness
* #
PP/SV
(mmHg/mL)
1.50
1.25
1.00
0.75
0.50
no NE
NE < 0.1
NE ≥ 0.1
norepinephrine dosage
(μg/kg/min)

Figure 2

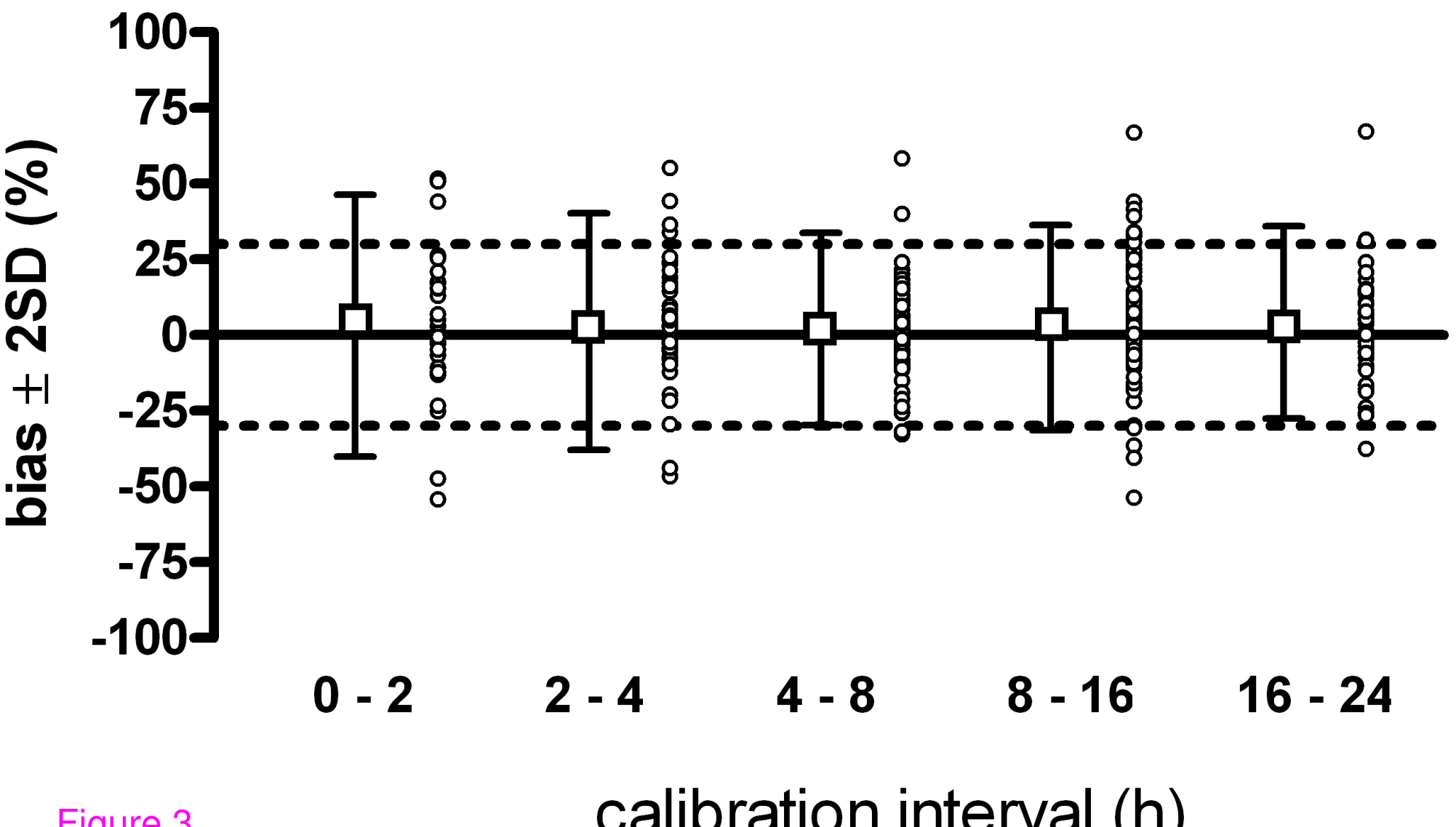
100
75
50
25
0
-25
-50
-75
-100
bias ± 2SD (%)
0 - 2
2 - 4
4 - 8
8 - 16
16 - 24
calibration interval (h)

Figure 3