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A validation study comparing Cheetah monitor cardiac output to thermodilution cardiac output in patients with severe mitral regurgitation

Ludmil Mitrev[1,4]✉, Michael Rosenbloom[2], Georges Kaddissi[3], Ahmed Awad[1], Janah Aji[3], Jeffrey Ogbara[3], Keyur Trivedi[1] & Noud van Helmond[1]

Monitoring cardiac output (CO) is helpful in the perioperative management of the patient with severe mitral regurgitation (MR). We assessed the accuracy and precision of the Cheetah CO monitor in patients with moderate or severe MR undergoing right and left heart catheterization as part of their pre-operative evaluation for mitral valve surgery. Cheetah CO was obtained concurrently with thermodilution CO (TD CO). Bias data was non-normally distributed; therefore, a non-parametric equivalent to Bland and Altman limits of agreement was used. Additionally, the proportions of differences between the experimental and reference method that were ≤ 0.5 L/min, ≤ 1 L/min, and >1 L/min were calculated. Twenty-seven subjects were enrolled and completed the study. The median difference between Cheetah and TD CO measurements was – 0.82 L/min, and the 5th and 95th centiles were – 6.05 L/min and 3.25 L/min, respectively. Of all differences, 25.9%, 51.9%, and 48.1% were ≤ 0.5 L/min, ≤ 1 L/min, and > 1 L/min. No proportional bias was present. We conclude that the Cheetah CO measurements in patients with moderate to severe MR cannot be used interchangeably with TD CO due to a large bias and imprecision.

Keywords Mitral regurgitation, Cardiac output, Non-invasive cardiac output monitoring, Cheetah monitor

The Cheetah monitor (Baxter Healthcare Corporation Inc., Deerfield, IL, USA) is a non-invasive monitor that estimates cardiac output (CO) based on transthoracic bioreactance. It is of practical importance to know the extent to which the CO estimation provided by the device can be used interchangeably with thermodilution CO (TD CO) in patients with significant mitral regurgitation (MR). Cold right heart bolus TD CO is well-established as an accurate and precise method of CO measurement in patients with MR, but a pulmonary artery catheter is not always available and non-invasive methods that perform with an acceptable degree of accuracy and precision could be useful in the care of patients with MR while avoiding the procedural risk associated with right heart catherization[1–3]. The bioreactance signal that the Cheetah monitor utilizes is determined by measuring blood flow-dependent changes in the phase shifts between an oscillating electrical current applied across the thorax and the resulting voltage signal; this signal is directly proportional to aortic blood flow[4]. However, in the specific context of MR, it is mechanistically conceivable that the directionally similar blood flow through the mitral valve may confound bioreactance measurements of CO through the aorta.

Left and right heart catheterization is standard of care in the pre-operative evaluation of patients with severe MR. While left heart catheterization (LHC) assesses peak and mean pressure gradients across the aortic valve, the state of the patient's coronary vasculature, and provides an angiographic assessment of left ventricular performance, right heart catheterization (RHC) can be performed to measure the various pressures from superior vena cava to the pulmonary artery, to obtain mixed venous blood sampling, and estimate CO using the modified Fick method. The modified Fick method is commonly used in clinical practice but may be flawed

[1]Department of Anaesthesiology, Division of Cardiac Anaesthesia, Cooper University Healthcare, One Cooper Plaza, Camden 08103, NJ, USA. [2]Department of Cardiothoracic Surgery, Cooper University Healthcare, One Cooper Plaza, Camden 08103, NJ, USA. [3]Department of Cardiology, Cooper University Healthcare, One Cooper Plaza, Camden 08103, NJ, USA. [4]Department of Anaesthesiology, Division of Cardiothoracic and Vascular Anaesthesia, Cooper University Healthcare, One Cooper Plaza, Camden 08103, NJ, USA. ✉email: mitrev-ludmil@cooperhealth.edu

	Study participants (*N* = 26)
Age in years, mean (SD)	**64.6 (9.1)**
Gender, n (%)	
Female	12 (46)
Male	14 (54)
Body mass index in kg/m^2, mean (SD)	25.9 (4.4)
Body surface area in m^2, mean (SD)	1.9 (0.2)
Mitral regurgitation severity, n (%)	
Moderate	7 (27)
Moderate/Severe	3 (12)
Severe	16 (62)

Table 1. Baseline demographic and clinical characteristics. SD, standard deviation.

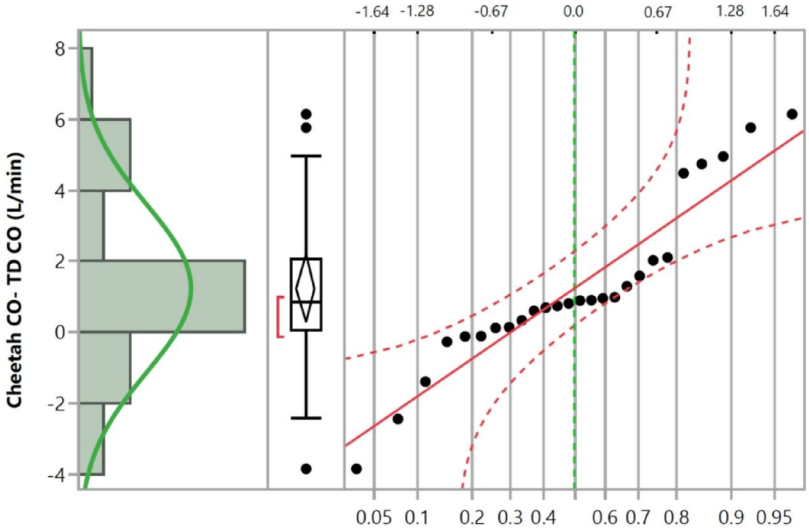


Fig. 1. Normal quantile plot with outlier boxplot of the differences between Cheetah and TD CO measurements.

due to its dependence on correctly estimating oxygen consumption[5]. Since TD CO can be obtained in patients who are undergoing right heart catheterization, the primary aim of this study was to assess the bias and limits of agreement between Cheetah CO and TD CO. A secondary aim was to assess the bias and limits of agreement between Fick CO and TD CO in these patients. TD CO was the method of reference in both cases. The trending ability of the Cheetah monitor was not assessed due to the short procedure time and the lack of significant hemodynamic changes during cardiac catheterization.

Results

In total, 26 participants enrolled and completed the study. Similar numbers of women and men participated, and most participants (62%) had severe mitral regurgitation (Table 1).

Most subjects had no or mild tricuspid regurgitation; only two had moderate tricuspid regurgitation. Two subjects (11%) had severely depressed ejection fraction (EF) and 6 (22%) had moderately depressed EF, with the remained having normal EF. All study subjects were breathing spontaneously and were in steady state during all measurements. They received on average 1.4 milligrams midazolam and 66.4 micrograms fentanyl for conscious sedation during the catheterization procedure.

Primary aim

Distribution of differences between Cheetah and TD CO measurements

Differences between Cheetah and TD CO measurements in a normal-quantile plot followed a non-linear path (Fig. 1). A Shapiro-Wilk test indicated a non-normal distribution (P =.038).

Correlation between Cheetah and TD CO measurements

Spearman correlation analysis indicated a weak to moderate correlation ($\rho = 0.393$, P =.048) between Cheetah and TD CO measurements (Fig. 2).

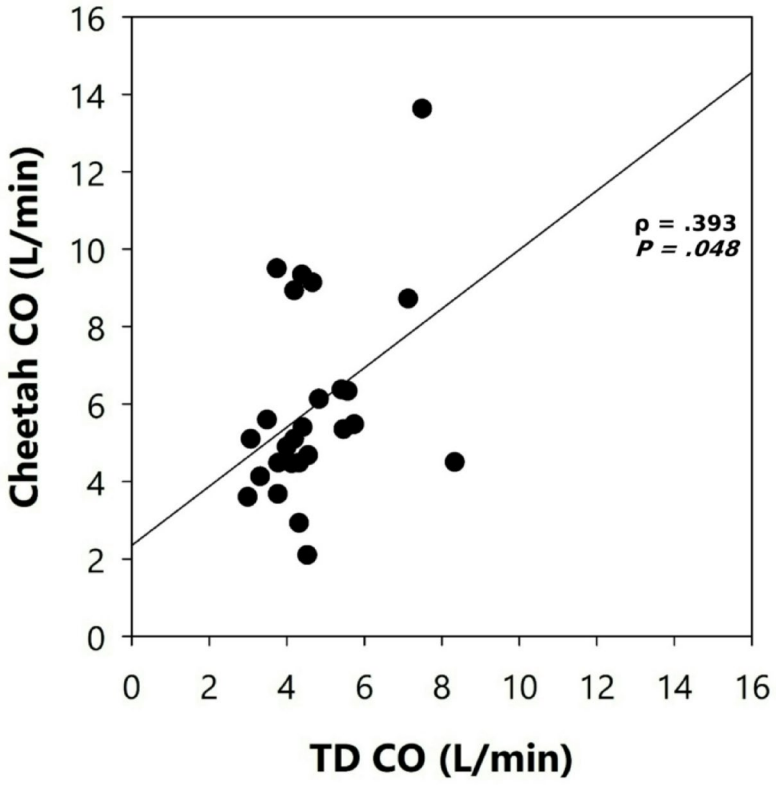


Fig. 2. Scatterplot of Cheetah and TD CO measurements. CO, cardiac output; TD, thermodilution.

Agreement between Cheetah and TD CO measurements
A difference plot between Cheetah and TD CO measurements indicated poor agreement between Cheetah and TD CO measurements (Fig. 3). The median difference between Cheetah and TD CO measurements was 0.86 L/min. The 5th and 95th centile were − 3.34 L/min and 6.01 L/min, respectively. Of all differences, 23.1%, 53.8%, and 46.2% were 0.5 ≤ L/min, ≤ 1 L/min, and > 1 L/min, respectively. There was no evidence of proportional bias (ρ = − 0.138, *P* =.496). The repeated precision of the TD reference was 4%, whereas the precision of Cheetah CO measurements was 2%, indicating that differences between measurement techniques were likely not attributable to repeatability variation.

Secondary aim

Distribution of differences between Fick and TD CO measurements
Differences between Fick and TD CO measurements in a normal-quantile plot followed a non-linear path (Fig. 4). A Shapiro-Wilk test indicated a non-normal distribution (*P* =.017).

Correlation between Fick and TD CO measurements
Spearman correlation analysis indicated a moderate correlation (ρ = 0.670, *P* <.001) between Fick and TD CO measurements (Fig. 5).

Agreement between Fick and TD CO measurements
A difference plot between Fick and TD CO measurements indicated moderate agreement between Fick and TD CO measurements (Fig. 6). The median difference between Fick and TD CO measurements was − 0.18 L/min. The 5th and 95th centile were − 1.52 L/min and 3.36 L/min, respectively. Of all differences, 45.4%, 63.6%, and 36.4% were 0.5 ≤ L/min, ≤ 1 L/min, and > 1 L/min, respectively. There was no evidence of proportional bias (ρ = 0.003, *P* =.984).

Discussion

Our study found poor agreement between Cheetah and TD CO in patients with moderate to severe MR, and moderate agreement between the modified Fick CO and TD CO. The median difference between Cheetah and TD CO measurements was 0.86 L/min, whereas the median difference between Fick and TD CO measurements was − 0.18 L/min. The differences between the measurements were not normally distributed, which could have been the result of a small sample. We therefore did not use classic Bland and Altman limits of agreement of ±1.96 standard deviations, but a non-parametric equivalent, namely the 5th and 95th centiles of the differences between the method of interest and the reference method (Cheetah and Fick CO vs. TD CO, respectively). These

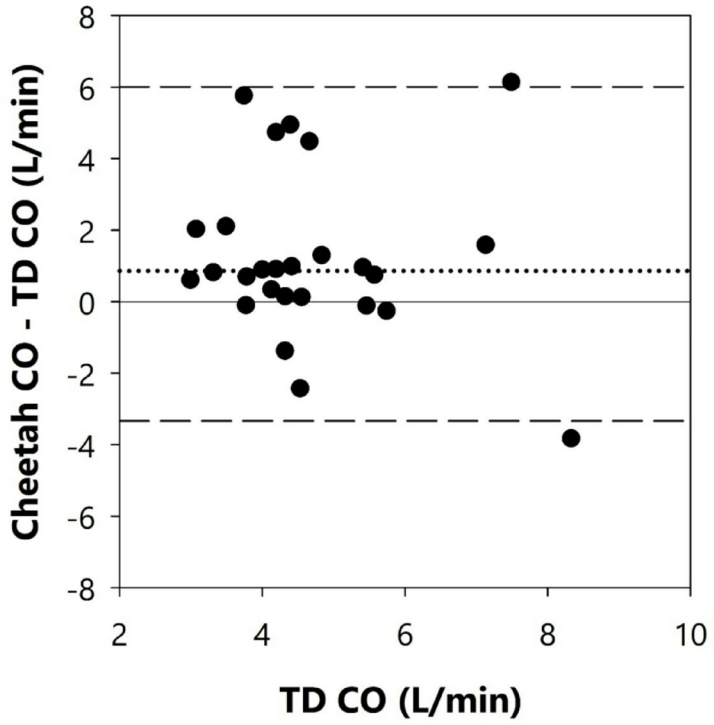


Fig. 3. Difference plot of Cheetah and TD CO measurements. The dotted line indicates the median difference between Cheetah and TD CO measurements, whereas the dashed lines indicate the 5th and 95th percentiles. CO. cardiac output; TD, thermodilution.

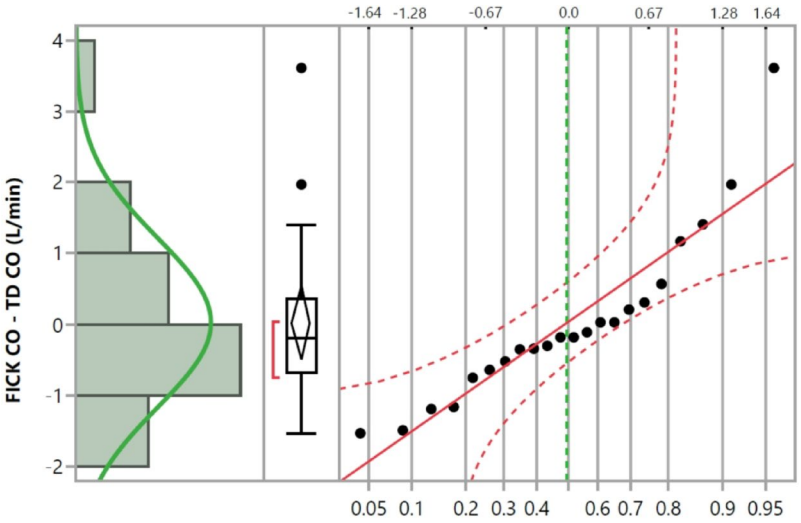
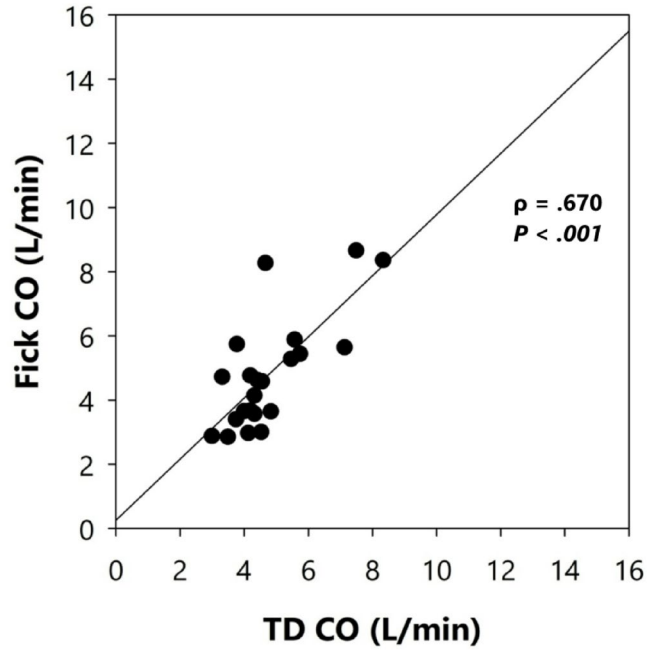


Fig. 4. Normal quantile plot with outlier boxplot of the differences between Fick and TD CO measurements. CO. cardiac output; TD, thermodilution.

limits were wide in the case of Cheetah CO (−3.34 L/min and 6.01 L/min), and less so in the case of Fick CO (−1.52 L/min and 3.36 L/min). In either case, there was no evidence of proportional bias.

Considerable variability exists concerning the biases and limits of agreement of CO monitors relative to a reference method such as TD CO[4,6–10]. Prior studies of Cheetah CO have shown smaller biases and LOA compared to our findings. One study comparing Cheetah CO to a continuous TD CO system in intensive care patients showed that Cheetah CO had a bias of + 0.16 L/min and limits of agreement of ± 1.04 L/min[11]. Another study in intensive care patients showed a bias of −0.09L/min and limits of agreement of ± 2.4 L/min[12]. Yet another study evaluated Cheetah CO to Fick CO and TD CO in subjects with pulmonary hypertension[13]. Bias and limits of agreement of Cheetah CO compared to Fick CO were 0.21 ± 2.3 L/min. Bias and limits of



ρ = .670

P < .001

Fig. 5. Scatterplot of Fick and TD CO measurements. CO, cardiac output; TD, thermodilution.

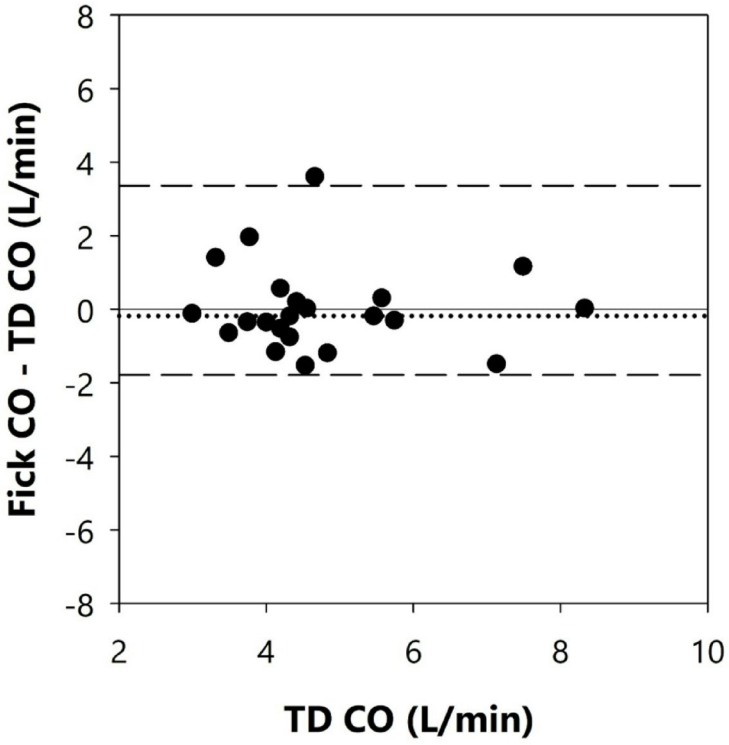


Fig. 6. Difference plot of Fick and TD CO measurements. The dotted line indicates the median difference between Fick and TD CO measurements, whereas the dashed lines indicate the 5th and 95th percentiles. CO. cardiac output; TD, thermodilution.

agreement of Cheetah CO compared to TD CO were − 0.37 ± 2.6 L/min. In the same study, the bias and limits of agreement of Fick CO against TD CO were − 0.91 ± 2.1 L/min. A meta-analysis of studies examining the bias and precision of non-invasive CO monitors found a random-effects pooled bias and limits of agreement of − 0.13 and 2.23 L min^{-1}, respectively[14]. The percentage error was 47%, and there was significant inter-study heterogeneity. However, only one of the studies in this meta-analysis compared the Cheetah CO to a method of reference (partial carbon dioxide rebreathing method)[15].

The finding of moderate agreement between the modified Fick CO and TD CO is consistent with previous larger studies comparing modified Fick vs. thermodilution[16,17] and suggests there is some utility to modified Fick in settings where TD CO is not available. However, TD CO better predicts mortality[16,17] and should be favored over modified Fick in clinical practice.

Weaknesses of our study include the relatively small sample size and the non-normally distributed data, necessitating the use of non-parametric methods. In their 1999 paper, Bland and Altman pointed out that such methods are "generally less reliable than those obtained using normal distribution theory."[18] In addition, 11% of patients in our study had severely depressed ejection fraction, raising the possibility of low flow states affecting the measurements. Two subjects had moderate tricuspid regurgitation (TR). This also raises the question of whether their TR could have affected the TD CO measurements.

Conclusions

The bias and the 5th and 95th centiles of the differences between Cheetah and TD CO were considerably higher and wider in our study population compared to the results of the other studies of Cheetah CO referenced herewith. We conclude that Cheetah CO cannot be used interchangeably with TD CO in patients with moderate to severe MR. An overestimation of CO by almost 1 L/min by the Cheetah monitor would be clinically significant even in subjects with high CO. This is not to say that the Cheetah monitor is not valuable in patients with no MR. Additionally, this study did not evaluate the monitor's trending ability as the RHC and LHC are short procedures and are not usually associated with major hemodynamic changes.

Methods

The Cooper University HealthCare Institutional Review Board (IRB) approved the study (IRB #19-210EX). All procedures were in accordance with the ethical standards of the local IRB and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All participants in the study provided written informed consent.

Cheetah non-invasive cardiac output monitor

The Cheetah monitor uses bioreactance to estimate cardiac output[11,12,19]. The pulsatile flow of blood in the large thoracic arteries produces phase shifts in an alternating current passed through the chest via two pairs of external electrodes, on either side of the chest above and below the diaphragm[8]. The phase shifts are measured, and stroke volume (SV) is estimated based on its correlation with the phase shifts and the thoracic voltage. The Cheetah signal effectively measures the blood volume change in the thorax between systole and diastole. The monitor has been validated in spontaneously breathing and mechanically ventilated patients, as well as in patients with arrhythmias. Unlike bioimpedance, the bioreactance method is independent from the distance between the electrodes[4]. Because the electrodes are paired, two separate signals are obtained and averaged to produce the SV estimate.

Inclusion and exclusion criteria

Subjects were enrolled if they met the following criteria:

1. Had planned RHC and LHC.
2. Were at least 18 years of age.
3. Provided written informed consent to participate in the study.
4. Had at least moderate to severe MR (echocardiographic grade 3 or 4 MR) on pre-referral transthoracic echo.
5. The subjects' height and weight was accurately documented.

Subjects were excluded if the following conditions were present:

1. Other valve pathology graded greater than moderate (aortic, tricuspid, pulmonic).
2. Did not have a pre-procedure transthoracic echocardiogram (TTE).
3. Chronic atrial fibrillation with irregular pulse.
4. Intracardiac shunt.
5. Intra-aortic balloon pump or other circulatory assist device.
6. Intubated or unconscious patients.
7. Known pregnancy.
8. Emergency heart catheterization.
9. Uncompensated congestive heart failure.
10. Current participation in an investigational drug or device study that could interfere with the study end-points.
11. Anticipated reason why TD CO could be obtained.

Cardiac output measurements

RHC and LHC was performed using routine methods. Catheterization data were recorded using the McKesson Cardiology Station Release 13.0 (McKesson Corporation, San Francisco, CA). All system clocks were matched and time-stamped data was exported from the Cheetah monitor on a USB drive. A Swan-Ganz catheter was used during RHC to measure TD CO with intermittent cold saline bolus. The TD CO was averaged from 3, 4 or 5 boluses as determined by the interventional cardiologist on visual inspection of the thermodilution curve. The Cheetah CO values were exported from the Cheetah monitor and averaged over the same period during which the TD CO measurements were made. The modified Fick CO was obtained from aortic and mixed venous blood samples using the Fick equation:

$$\mathrm{CO} = \frac{\mathrm{VO2}}{(\mathrm{CaO2} - \mathrm{CvO2})\,\mathrm{x10}}$$

where CO = cardiac output, VO_2 = estimated O_2 consumption, CaO_2 = arterial oxygen content, CvO_2 = venous oxygen content. VO_2 was estimated as 125 millilitres O_2 x Body Surface Area (BSA). The physiologic equation for CaO_2 and CvO_2 was used:

$$\text{Oxygen content} = 1.36\ \text{x Hgb}\ [\text{mg/dl}]\ \text{x}\ \mathrm{SaO_2 or\ SvO_2}$$

where SaO_2 = arterial oxygen saturation, SvO_2 = mixed venous oxygen saturation, and Hgb = haemoglobin. Because the estimated rather than the measured VO_2 value was used, we refer to Fick CO as the "modified Fick CO".

Statistical analysis

Baseline demographic and clinical characteristics were analysed using descriptive statistics. A two-sided *P*-value < 0.05 was considered statistically significant for all analyses.

Primary aim

A previously published stepwise approach and checklist for CO monitor validation studies were used to compare the Cheetah CO measurements with the reference TD CO measurements[20]. Differences between the Cheetah and TD CO measurements were checked for normality using a normal-quantile plot and the Shapiro-Wilk test[20]. Considering these assessments indicated that the differences did not follow a normal distribution, non-parametric approaches were used for correlation analysis as well as the difference plot[18,20]. As a non-parametric equivalent to limits of agreement, the 5th and 95th centiles of the differences between Cheetah and TD CO measurements were calculated[18]. Additionally, the proportions of differences between Cheetah and TD CO measurements ≤ 0.5 L/min, ≤ 1 L/min, and >1 L/min were calculated[18]. The proportionality of differences between Cheetah and TD CO measurements was assessed by plotting a regression line in the difference plot and Spearman rank order correlation[20]. Cheetah and TD CO repeated measurement precision were calculated using the coefficient of error (CE)[20,21].

Secondary aim

Differences between Fick CO and TD CO measurements were checked for normality using a normal-quantile plot and the Shapiro-Wilk test[20]. Considering these assessments indicated that the differences did not follow a normal distribution, non-parametric approaches were used for correlation analysis as well as the difference plot[18,20]. As a non-parametric equivalent to limits of agreement, the 5th and 95th centiles of the differences between Fick and TD CO measurements were calculated[18]. Additionally, the proportions of differences between Fick and TD CO measurements ≤ 0.5 L/min, ≤ 1 L/min, and >1 L/min were calculated[18]. The proportionality of differences between Fick and TD CO measurements was assessed by plotting a regression line in the difference plot and Spearman rank order correlation[20].

Sample size calculation

In the context of Bland-Altman analysis, the use of a desired maximal width for the 95% CIs around the mean error enables sample size calculations[20]. 95%-CIs were constructed around a hypothetical mean error of 30% for different sample sizes based on a mean CO of 5.0 L/min and an SD of 0.75; a sample size (n) of 22 was needed for a total width of the CI of no more than 20%.

Data availability

The complete dataset is available from the Figshare public repository at [https://doi.org/10.6084/m9.figshare.30099667].

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Author contributions

L.M. and N.v.H. participated in study conception, design, data analysis and manuscript preparation. N.v.H. prepared all figures and tables. L.M., M.R., G.K., A.A., J.A., J.O. and K.T. participated in enrolment, data collection and manuscript editing.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to L.M.