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Correlation, agreement and concordance of cardiac output estimated by transthoracic ultrasound and transesophageal Doppler with pulmonary artery thermodilution in anesthetized cats

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Abstract

Objective—To characterize the correlation, agreement and concordance of cardiac output (CO) measured with transthoracic ultrasound and the correlation and concordance of aortic blood flow (ABF) minute distance (MD) measured by transesophageal Doppler with CO measured by pulmonary artery thermodilution (PATD) in cats.

Study design—Experimental study.

Animals—A group of six healthy male neutered cats, aged 2e8 years and weighing 5.3 ± 0.3 kg.

Methods—Cats were anesthetized with isoflurane in oxygen. CO was measured by PATD (CO_{PATD}) and transthoracic echocardiography (CO_{ECHO}). ABF MD was measured using an esophageal Doppler flow probe aligned with descending ABF. All measurements were made under three conditions: dexmedetomidine (20 μg kg^{-1}) intravenously; atipamezole (200 μg kg^{-1}) intramuscularly and atropine (20 μg kg^{-1}) intravenously as needed to achieve a minimum heart rate of 140 beats $minute^{-1}$; and dopamine (20 μg kg^{-1} $minute^{-1}$) intravenously in that order. Correlation between CO_{PATD} and CO_{ECHO}, and CO_{PATD} and Doppler MD was evaluated using repeated measures correlation. Agreement between CO_{PATD} and CO_{ECHO} was evaluated

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Authors' contributions

BHP: study design, data acquisition, data analysis, data interpretation, manuscript preparation. VNR: data analysis, data interpretation, manuscript preparation. MCB: data acquisition, manuscript preparation. ASC: data acquisition, data analysis, data interpretation, manuscript preparation. LSB: study design, manuscript preparation. JAS: study design, data acquisition, data interpretation, manuscript preparation.

Conflict of interest statement

The authors declare no conflict of interest.

using Blande–Altman method. Differences between consecutive pairs of CO measurements were calculated for concordance analysis.

Results—Correlation between CO_{PATD} and CO_{ECHO} and between CO_{PATD} and MD was significant ($p < 0.001$), with correlation coefficients greater than 0.92. A bias of > 27% and upper limits of agreement of 66% were found between CO_{PATD} and CO_{ECHO}. Concordance rate with CO_{PATD} was 76–80% for CO_{ECHO} and 72% for MD.

Conclusions and clinical relevance—Echocardiographic methods for the measurement of CO showed poor agreement and concordance with PATD. MD showed poor concordance with PATD. As such, these methods cannot be used as an alternative to PATD nor can they appropriately track changes in CO in anesthetized cats.

Keywords

cats; cardiac output; Doppler; echocardiography; thermodilution; ultrasound

Introduction

Cardiac output (CO) is the volume of blood pumped by the heart in 1 minute (Vincent 2008). Measurement of CO in anesthetized cats is used to characterize the hemodynamic effects of drugs or drug combinations, other interventions (e.g. mechanical ventilation, pneumoperitoneum, surgery) or disease states. Currently, pulmonary artery thermodilution (PATD) is considered to be the gold standard for CO measurement (Arya et al. 2022). An *in vitro* model has shown thermodilution to have acceptable accuracy when measuring flows within the range of expected CO in cats (Dyson et al. 1984). PATD has also resulted in CO measurements similar to those obtained with radioactive microspheres in anesthetized cats (Arvidsson et al. 1983). Cardiac catheterization required for PATD has risks, including arrhythmias, air embolism if the balloon used to facilitate placement ruptures, and pulmonary artery rupture among others (Frazier & Skinner 2008). In the authors' experience, placement of PATD catheters in cats requires fluoroscopic guidance, resulting in additional logistical limitations.

Other indicator dilution techniques have been used for determination of CO in cats. Transpulmonary thermodilution was shown to have good agreement with PATD in one study but a large bias in another study (Beaulieu et al. 2009; Kutter et al. 2015). Lithium dilution was reported to have good agreement with PATD but resulted in a loss of 4.6 mL of blood per measurement, making it impractical when serial measurements are required (Beaulieu et al. 2005). Transpulmonary ultrasound dilution has been used but has not been validated against a gold standard technique in cats (Martin-Flores et al. 2018; Zatroch et al. 2019). Moreover, the commercially available equipment for transpulmonary ultrasound dilution was recently discontinued by the manufacturer (https://www.transonic.com/discontinued-items; accessed on July 24, 2024). Although these techniques are less invasive than PATD, they require arterial catheterization.

Cardiac ultrasound can be used to noninvasively measure CO. Historical studies in cats measured the change in left ventricular (LV) dimensions between systole and diastole,

and applied equations developed in humans for the estimation of ventricular volume. The resulting estimates of CO correlated poorly to measurements by PATD (Allen & Nymeyer 1983; Dyson et al. 1985). More recently, ultrasound calculations of CO based on luminal diameter measurements of the LV outflow tract and calculation of the velocity time integral (VTI) from Doppler waveforms obtained at the level of the LV outflow tract was shown to be highly positively correlated with PATD CO measurements in dogs (Uehara et al. 1995). Although this technique was reported to produce repeatable measurements in cats (Biermann et al. 2012), it has not been compared with the gold standard (i.e. PATD) in this species.

Alternatively, CO can also be estimated in a minimally invasive manner with the use of a transesophageal Doppler probe (Singer et al. 1989). This technique involves the transesophageal Doppler monitor (EDM) probe to be positioned in the thoracic esophagus; the cursor is aligned with descending aortic blood flow. It provides real-time velocity time waveforms by spectral analysis of the Doppler shift representative of blood flow velocities. The VTI, called stroke distance (SD), represents the distance the blood ejected by the LV travels down the aorta with every heartbeat and serves as the surrogate of stroke volume. A correlate of CO, called minute distance (MD), is the distance that blood travels down the aorta in 1 minute and is obtained by multiplying the SD with heart rate (HR). SD and MD have been shown to correlate well with invasively measured stroke volume and CO in dogs (Gunn et al. 2006; Paranjape et al. 2023), but this has yet to be evaluated in cats.

The aims of this study were to evaluate the correlation, concordance and agreement between CO measured by PATD and transthoracic echocardiography, and the correlation and concordance between CO measured by PATD and MD measured by transesophageal Doppler in anesthetized cats. It was hypothesized that CO measured by cardiac ultrasound has good correlation, concordance and agreement with CO measured by PATD and that MD measured by transesophageal Doppler has good correlation and concordance with CO measured by PATD.

Materials and methods

The ARRIVE 2.0 reporting guidelines were followed.

Animals

A group of six male neutered Domestic Short Hair purpose-bred research cats, aged 2–8 years and weighing 5.3 ± 0.3 kg (mean ± standard deviation), were used in this study. Cats were deemed healthy based on lack of historical evidence of disease and a normal physical examination prior to the study. Cats were housed together in a room; hiding places (cat carriers and cardboard boxes) and toys were provided. The room was on a 12:12 hours light:dark cycle. Temperature, humidity and ventilation were maintained within the United States Department of Agriculture's Animal Welfare Act and Animal Welfare Regulations requirements for cats (https://www.aphis.usda.gov/sites/default/files/AC_BlueBook_AWA_508_comp_version.pdf; accessed June 2024). Cats were fed commercial dry food (Laboratory Feline Diet 5003; LabDiet, MO, USA) once daily and had access to water *ad libitum*. Cats were fasted overnight before the study but had access to water until removed from the room before anesthesia. The study was approved

by the Institutional Animal Care and Use Committee at the University of California, Davis (protocol 22837).

Experimental protocol

Measurements were obtained after three pharmacological interventions aimed at changing CO. Dexmedetomidine (20 μg kg^{-1}, Dexdomitor; Zoetis Inc., NJ, USA) was administered intravenously (IV) to decrease CO. Atipamezole (200 μg kg^{-1}, Antisedan; Zoetis Inc.) was then administered intramuscularly (IM) to increase CO. In addition, if HR had not increased to 140 beats $minute^{-1}$ or more within 10 minutes, atropine (0.02 mg kg^{-1}, Atropine Sulfate Injection; Hikma, NJ, USA) was administered IV. Lastly, an IV infusion of dopamine (20 μg kg^{-1} $minute^{-1}$, Dopamine hydrochloride injection; Hikma) was administered to further increase CO. The order of treatments was not randomized. Measurements were obtained 10, 20 and 30 minutes after each treatment was administered to allow the calculation of measurement precision and obtain additional data as the effect of treatments changed over time. For the atipamezole treatment, if atropine was administered, the 10 minutes measurement was postponed until HR had increased to 140 beats $minute^{-1}$ or higher. For the dopamine treatment, the infusion was continued until all measurements had been obtained.

Anesthesia and instrumentation

Cats were administered dexmedetomidine 25 μg kg^{-1} subcutaneously (SC). Once sedation was appropriate, a 22 gauge, 45 mm catheter (Introcan Safety IV; B Braun Medical Inc., PA, USA) was inserted in a cephalic vein. Lactated Ringer's solution (Baxter Healthcare Corp., IL, USA) was administered IV via the catheter at a rate of 5 mL kg^{-1} $hour^{-1}$. Oxygen (3 L $minute^{-1}$) was delivered via a facemask and anesthesia was induced with propofol (Rapanofal; Ivaoes Animal Health, FL, USA), up to 4 mg kg^{-1} IV, titrated to effect. When a cat was at an appropriate depth of anesthesia (characterized by loss of palpebral reflex, eyes in an eccentric position and relaxed jaw tone), the trachea was intubated with a cuffed 4.5 mm internal diameter endotracheal tube. The endotracheal tube was connected to a Bain breathing system, the cuff was inflated and isoflurane was administered to maintain a light surgical depth of anesthesia (based on the aforementioned signs for tracheal intubation), with an oxygen flow rate of 2 L $minute^{-1}$. Cats were placed on a warming pad (HotDog; Augustine Surgical, MN, USA) set at 42 °C. Buprenorphine (20 μg kg^{-1}, Buprenorphine HCl; Par Pharmaceutical, NY, USA) and cefazolin (25 mg kg^{-1}, Cefazolin for injection; Hikma) were administered IV. Adhesive electrodes were placed on both thoracic limb paws and on the left pelvic limb paw and connected to a monitor (CARESCAPE B650; GE Healthcare, Finland) for display of lead II electrocardiogram (ECG) and measurement of HR. An inflatable cuff was placed around a pelvic limb distal to the hock and connected to a monitor (petMAP; CardioCommand, FL, USA) for measurement of arterial blood pressure. A 5 French, 7.5 cm introducer (Percutaneous Sheath Introducer; Arrow International, NC, USA) was inserted in a jugular vein using a modified Seldinger technique. A 5 French, 75 cm PATD catheter (Swan-Ganz TD; Edwards Lifesciences, CA, USA) was placed via the introducer under fluoroscopic guidance so that its tip was positioned within the pulmonary artery. The distal port of the catheter was connected to a pressure transducer (Meritrans DTXPlus; Merit Medical, Singapore) and monitor (CARESCAPE B650), and the catheter position was adjusted so that pulmonary artery waveforms could be observed. The

thermistor was connected to the same monitor for measurement of body temperature and CO by PATD (Argueta & Paniagua 2019).

A canine EDM probe (K9P; Deltex Veterinary, UK), connected to a veterinary EDM system (CardioQ-EDMV^{+}; Deltex Veterinary), was used in this study. The probe is 120 cm long with a 4.02 MHz Doppler crystal at the animal end, angled 45 degrees from the longitudinal axis of the probe. The probe was lubricated with a water-soluble gel (Lubricating Jelly; McKesson Medical-Surgical, VA, USA) before insertion into the esophagus via oral route. The crystal was aligned with blood flow of the descending aorta. The probe was adjusted by gentle in, out and rotational movements until the desired signal quality was obtained. Once an appropriate signal was achieved (characterized by sharp-looking velocity time waveforms coupled with sharp and loud auditory Doppler signals; Fig. 1), the probe was left in place. When the signal quality deteriorated, it was gently repositioned to improve the signal quality before obtaining any measurements from the EDM. Before measurement capture, the EDM averages the measurements obtained from a set number of individual heart beats (cycle time) to reduce variability. Outputs from the EDM were filtered to remove artefacts caused by low-frequency signals as a result of excess heart valve or wall motion noise. In addition, the amount of amplification applied (gain) was adjusted as needed to optimize signal quality. The EDM probe was removed before each series of transthoracic echocardiographic measurements because it interfered with these measurements, and repositioned as described above immediately after the echocardiographic measurements were completed for that time point.

Measurements

Once instrumentation was completed, CO (PATD) and MD (transesophageal Doppler) were measured concurrently and immediately followed by transthoracic echocardiography.

Pulmonary artery thermodilution cardiac output measurement—For PATD, 3 mL of cold (0–5 °C) isotonic saline solution (Baxter Healthcare Corp.) or 5% dextrose in water (Baxter Healthcare Corp.) were rapidly injected via the proximal port of the PATD catheter. Measurements were repeated until three values of CO differing by less than 10% were obtained. The average of these three values was considered the CO for that time point. Isotonic saline solution and 5% dextrose in water were used in alternance at each time point to prevent hyponatremia and excessive increase in circulating volume over time, respectively.

Transesophageal Doppler measurements—Transesophageal Doppler measurements were obtained concurrently with PATD measurements. The cycle time was set at 5 heart beats for most EDM measurements but was increased to 10 heart beats when significant variation in the signal was observed on the EDM screen. Data files were retrieved from the EDM, and SD (cm) and MD (cm minute^{-1}) data were obtained. As the EDM provides beat-by-beat measurements and calculates MD by multiplying the HR with SD, all individual EDM measurements where the HR differed from the HR obtained from the ECG by more than 10 beats minute^{-1} were removed. Data points were also removed from analysis where EDM failed to correctly trace the velocity time waveform resulting in inaccurate assessment

of SD and hence MD. An average was obtained for the remaining heartbeat measurements corresponding to each data point for all the subjects and were used for statistical analysis.

Transthoracic echocardiographic measurements—All echocardiographic images were acquired by the same investigator (JAS), using an ultrasound machine and a 7–12 mHz sector array probe (Philips EPIQ Cvx; Andover, MA, USA). Transthoracic echocardiographic assessment of CO was conducted via the subcostal aortic outflow spectral Doppler profile and aortic annular diameter obtained from two different imaging planes. For the first measurement technique (US AortPS), the right parasternal long-axis five-chamber view was utilized to obtain the diameter of the LV outflow tract at the aortic annulus and the subcostal pulsed-wave Doppler tracing of aortic outflow velocity obtained with the gate positioned just beyond the valve annulus into the aortic root (Fig. 2). For the second analysis (US AortSC), the subcostal imaging plane was utilized for both the aortic annular diameter and Doppler measures (Fig. 2). Simultaneous HR assessment was performed by measuring the R–R intervals on the concomitant lead II ECG for the cine loops measured. Cross-sectional area (CSA) was later calculated from aortic annular diameter assuming that it was circular. CO was calculated by the equation CO = CSA × VTI × HR (Fig. 2) (Boon 2011). Fractional area change (US FAC) was assessed as an index of systolic function from the right parasternal short-axis view as previously described (Boon 2011). The LV area in systole and diastole were measured and used to calculate the percent fractional area change (FAC%; Fig. 2). All measurements were made in triplicate, with care to avoid arrhythmias or cardiac cycles immediately following an arrhythmia, by a single investigator (VNR) blinded to patient identification and time point using an offline echocardiographic workstation (syngo Dynamics Workplace; Siemens Medical Solutions, PA, USA).

Instruments were removed after completion of the last measurement, meloxicam (0.2 mg kg^{-1} SC, OstiLox; VetOne, ID, USA) and buprenorphine (20 μg kg^{-1}) were administered, and cats were allowed to recover from anesthesia. Cats were offered for adoption at the conclusion of the study.

Statistical analysis

Sample size was not calculated by power analysis. Power analysis for the Bland–Altman method to assess agreement, considered the primary outcome, requires knowledge of the standard deviation of the differences between measurements, and no relevant data for such differences were available in cats. Statistical analysis was conducted using commercial software (Prism 10.1.0, GraphPad, CA, USA; and MedCalc 22.016, MedCalc Software, Belgium) and a web interface for the repeated measures correlation package (rmcorr) in R (https://lmarusich.shinyapps.io/shiny_rmcorr/; accessed 25 June 2024). Normal distribution of the data was verified using the Shapiro–Wilk test. All values within a measurement method (PATD, US AortPS, US AortSC, US FAC or MD) were pooled for analysis, that is, data collected after dexmedetomidine, atipamezole ± atropine and during dopamine were analyzed together rather than separately. Correlation between PATD and US AortPS, US AortSC, US FAC and MD was examined using the repeated measures correlation package in R (Bakdash & Marusich 2017; Marusich & Bakdash 2021). Agreement between PATD measurements and measurements obtained with US AortPS and US AortSC was analyzed

using the Bland–Altman method for repeated measurements (Bland & Altman 1999). Limits of agreements within 30% of the mean CO obtained by the reference method (PATD) were considered compatible with acceptance of the alternative measurement technique (Critchley & Critchley 1999). Changes in CO were calculated as the difference between pairs of consecutive measurements (resulting in a negative value if CO increased and a positive value if CO decreased) and plotted on a four-quadrant plot to evaluate the trending ability of US AortPS, US AortSC, US FAC and MD, considering PATD as the reference for true changes in CO. Concordance rate was calculated as the ratio of the number of data points for which the direction of the change was the same in the measurement method and the PATD reference to the total number of data points and expressed in percent (Critchley et al. 2010). A 15% exclusion zone was used as data within the exclusion zone represent small changes in CO that may be owing to random factors and are not predictive of trending ability (Critchley et al. 2010). The alpha level was set at 0.05 and data are presented as mean ± standard deviation, except where specified.

Results

Because of logistical issues at the start of the study (equipment unavailable), transesophageal Doppler measurements were only performed in five cats. The total number of measurements was 54 for PATD, US AortPS, US AortSC and US FAC, and 33 for MD. The missing data for MD were related to the HR displayed by the EDM monitor not matching the HR displayed by the ECG monitor. All cats were administered atropine because HR was < 140 beats minute^{-1} 10 minutes after administering atipamezole.

As measured by PATD, CO ranged from 0.19 to 1.07 L minute^{-1}. Overall CO was 0.56 ± 0.28 L minute^{-1} for PATD, 0.72 ± 0.35 L minute^{-1} for US AortPS and 0.71 ± 0.34 L minute^{-1} for US AortSC. Overall FAC was 58.8 ± 16.2% and overall MD was 884 ± 133 cm minute^{-1}. PATD CO was 0.30 ± 0.06, 0.47 ± 0.09 and 0.91 ± 0.13 L minute^{-1} after administration of dexmedetomidine, atipamezole and atropine, and during administration of dopamine, respectively (Table 1). Correlation between PATD and other measurement techniques was significant ($p < 0.001$ for all). The coefficients of correlation [95% confidence interval (CI)] were 0.96 (0.93–0.98), 0.96 (0.93–0.98), 0.92 (0.86–0.95) and 0.92 (0.84–0.96) for PATD and US AortPS, PATD and US AortSC, PATD and FAC and PATD and MD, respectively.

Blande–Altman plots for PATD and US AortPS and US AortSC are presented in Fig. 3. Differences between replicate measurements for PATD, US AortPS and US AortSC were −0.01 ± 0.06, 0.02 ± 0.12 and 0.02 ± 0.10 L minute^{-1}, respectively. Bias (95% CI) was 29 (21–34)% and 27 (21–32)% of the overall mean PATD CO for US AortPS and US AortSC, respectively. Upper and lower limits of agreement (95% CI) were 15 (5–39)% and 72 (61–96)% and 14 (4–34)% and 66 (57–87)% of the overall mean PATD CO for US AortPS and US AortSC, respectively.

Four quadrant concordance plots for PATD and US AortPS, US AortSC, US FAC and MD are presented in Fig. 4. Concordance with PATD was 80%, 76%, 75% and 72% for US AortPS, US AortSC, US FAC and MD, respectively.

Discussion

In this study, ultrasound-based noninvasive echocardiographic methods for the estimation of CO in anesthetized cats had significant correlation, but poor agreement and inadequate concordance with the gold standard PATD. Minimally invasive transesophageal Doppler measurement of MD had strong correlation but poor concordance with PATD. Because correlation is not affected by the magnitude of the difference between measurements, only by their linear relationship, it provides limited information on whether measurement techniques yield similar estimates (Bland & Altman 1986). Agreement between two measurement techniques accounts for the magnitude of the difference in individual measurements and is considered to be more relevant than correlation; it is commonly assessed using Blande–Altman analysis (Bland & Altman 1999).

Blande–Altman analysis showed a large bias (average difference between individual measurements obtained by the two techniques being compared) of close to 30%, and limits of agreement well in excess of the 30% considered to be compatible with acceptance of the alternative measurement technique (Critchley & Critchley 1999). Precision of the measurements, assessed by the difference between replicates (measurements obtained in the same individual and same condition) was better for PATD than for US AortPS and US AortSC, providing further evidence that ultrasound measurement of CO is inferior to PATD. Agreement between PATD and FAC was not assessed because FAC measures the relative change in the surface area of the left ventricle between systole and diastole, providing an estimate of stroke volume but not an actual volume measurement. This precludes direct comparisons with PATD. Similarly, agreement between PATD and MD was not assessed because MD does not measure CO but blood flow at the level of the descending aorta. Limited agreement between these measurements is expected given that the fraction of CO directed to the brachiocephalic and subclavian arteries is excluded from the MD measurement. In addition, conversion to actual blood flow requires measurement of the diameter of the aorta, which is not possible using the equipment utilized for MD measurement.

Concordance analysis evaluates trending ability, that is, whether the direction of change in a variable obtained by a measurement technique is identical to that of a standard measurement technique (Critchley et al. 2010). This is important because there may be value in knowing the direction of change in measurement even if the measurement itself is not highly accurate. Good concordance is indicated by a 92% concordance rate or higher, meaning that the direction of the change in measurement agrees between the two techniques in at least 92% of paired measurements (Critchley et al. 2010). The highest concordance rate with PATD in this study was 80% for US AortPS, indicating that none of the noninvasive and minimally invasive techniques assessed to estimate CO in anesthetized cats had good trending ability.

The results of this study should be interpreted in view of several limitations. The sample size was small; however, conditions of the study were tightly controlled, and the group of cats expressed less variability than expected in the overall cat population (all healthy, male neutered, similar size, etc.). These factors are expected to reduce the variability in obtained measurements and to provide close to optimal conditions for good agreement

and concordance between measurement methods. In addition, the sample size was not determined by power analysis but was selected to be similar to the sample size used in similar published studies in cats (Beaulieu et al. 2005, 2009; Rezende et al. 2008; Biermann et al. 2012; Kutter et al. 2015). A sample size smaller than that calculated by power analysis may have resulted in larger than optimal 95% CIs in the Bland–Altman analysis. However, because the CIs for the upper limits of agreement in this study do not include the largest acceptable value, a larger study sample would not have changed the interpretation of the results. Measurement of CO with different methods presents a challenge in ensuring the timing of readings themselves are not a source of error. Measurements from EDM were obtained concurrently with PATD, but transthoracic echocardiographic assessment was performed last. Additionally, the EDM probe had to be removed after each measurement to avoid interference with echocardiographic measurements. Repositioning and acquisition of a good EDM signal proved challenging, especially when dopamine was administered. Many of the missing data points with EDM were because of inappropriate signal acquisition at very high HR that were particularly noticed when study subjects were administered dopamine. In addition, changes in preload owing to the injections for PATD measurement might have affected the measurements and contributed to the poor concordance. Because FAC and MD do not directly measure CO, agreement with PATD was not examined. Nevertheless, concordance of US FAC and MD with PATD was lowest among the four measurement techniques assessed, suggesting lack of usefulness in the study conditions. Moreover, the inability to estimate CO at several time points in this study further limits the applicability of MD. To ensure measurements were obtained over a wide range of CO values, CO was manipulated pharmacologically. Low, intermediate and high CO were produced by administration of dexmedetomidine, atipamezole with or without atropine, and dopamine, respectively. The effects of these drugs are not representative of all conditions causing decreases or increases in CO. For example, dexmedetomidine causes bradycardia and vasoconstriction, and these might have affected ultrasound measurements differently than other causes of low CO such as decreased myocardial contractility or low preload. A high dose of dopamine was used to promote high CO. Dynamic outflow tract obstruction was frequently observed during administration of dopamine and interfered with the estimation of CO via ultrasound-based methods. The order of CO states (low, intermediate, high) was not randomized because residual effects from the previous pharmacological intervention were deemed to be more likely to interfere with the effects of the next intervention if a different order had been used. This lack of randomization might be a source of bias and resulted in the majority of successive measurements going from lower to higher, which might have influenced concordance analysis. This is reflected in Fig. 4, with most data in the left lower quadrant of the plots, reflecting an increase in CO. Blinding of the investigator to pharmacological intervention was performed for the *post hoc* calculation of CO from the measurements obtained by transthoracic echocardiography (US AortPS, US AortSC, FAC) but not for the acquisition of these data or for the other measurements (PATD and MD). Lack of randomization of the treatment order and changes in HR and contractility would have made blinding difficult during acquisition of echocardiographic and MD data, and that PATD was considered unlikely to be influenced by the operator. Nevertheless, the lack of blinding is a potential source of bias. Arrhythmias, if present, may have caused variability in CO. As described in the methods, care was taken to avoid cardiac cycles

following arrhythmias for the calculation of echocardiographic variables. No arrhythmia was observed by the investigators during PATD and MD measurement; however, it is possible that some occurred.

In conclusion, in this study in anesthetized cats, US AortPS and US AortSC did not show adequate concordance or agreement with PATD, and FAC and MD did not show adequate concordance with PATD to be considered a valid alternative for the measurement of, or tracking changes in CO.

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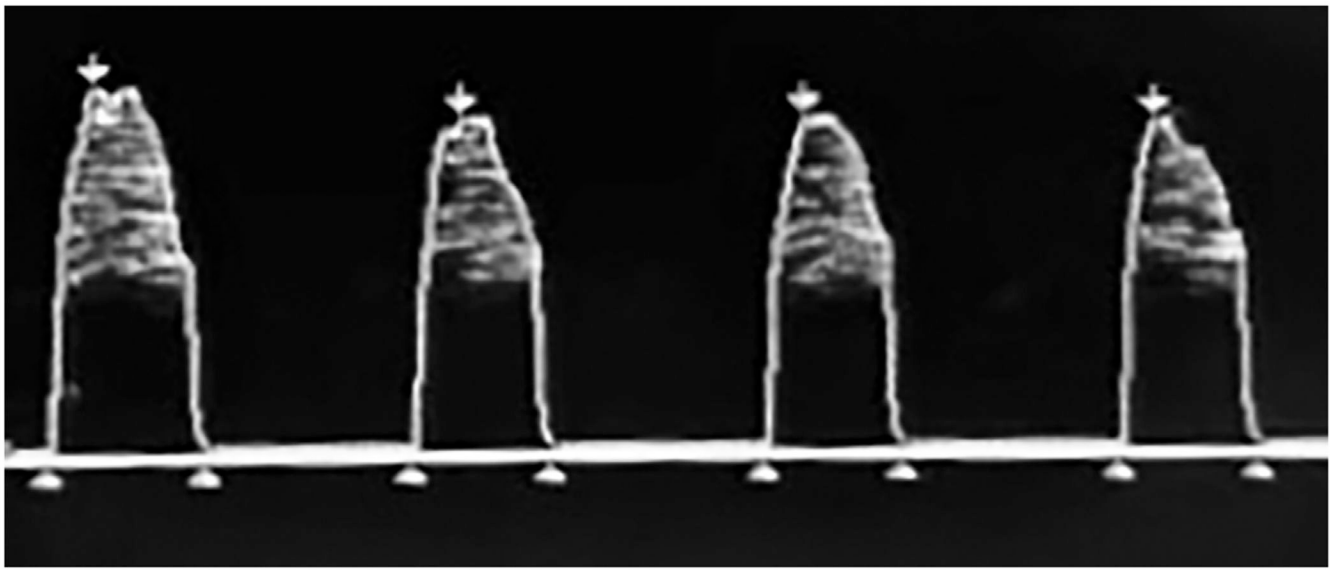

Figure 1.

Representative recording of the velocity time waveform obtained by the esophageal Doppler monitor. The top arrows indicate identification by the software of the peak velocity and the lower arrows represent the flow time (duration of time of the flow from the left ventricle during systole). The actual signal is represented by the blurry filling and the lines delineating each waveform are traced by the software and used for calculation of stroke distance as the area under the curve (velocity time integral).

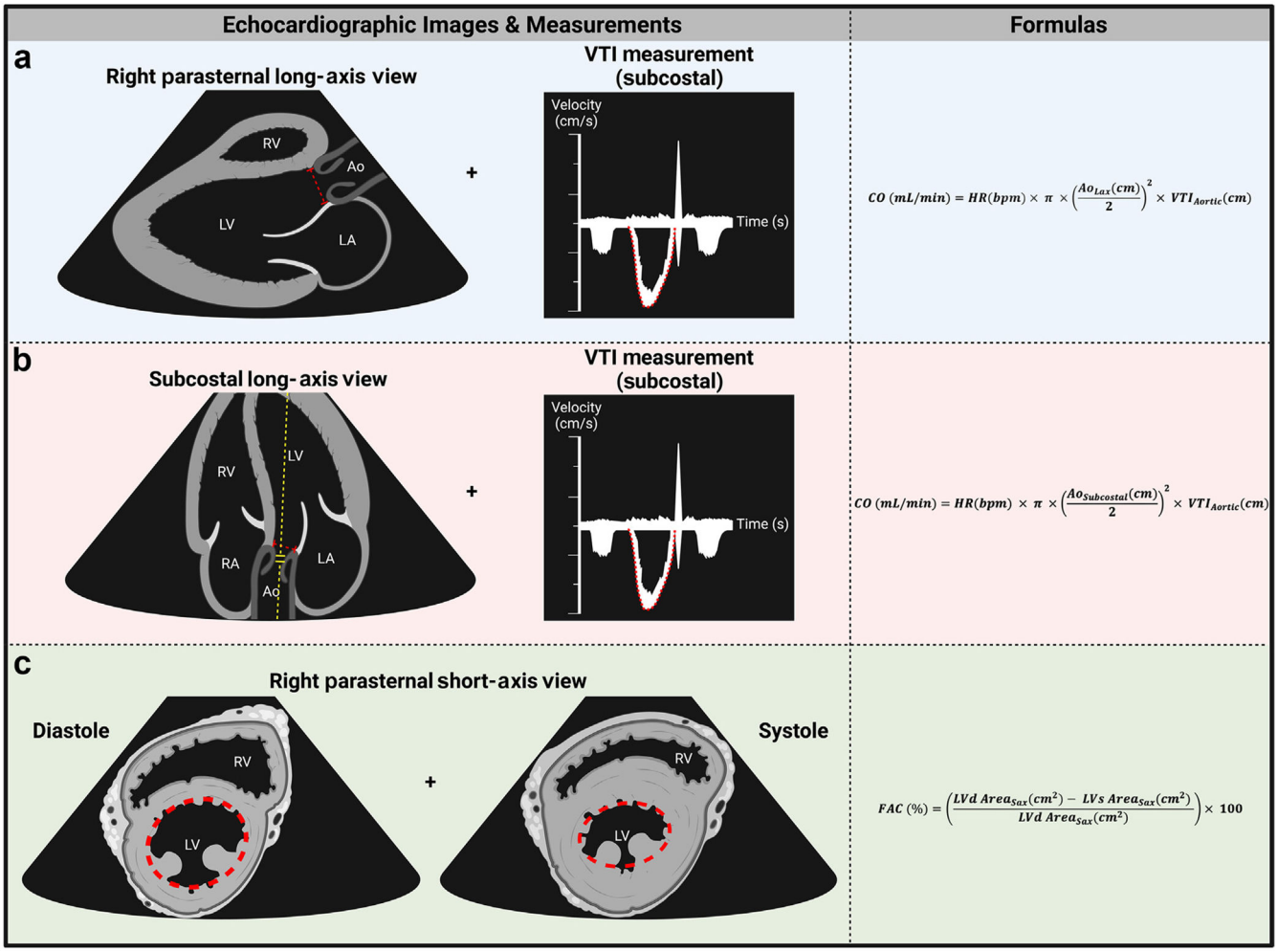

Figure 2.

Illustration depicting echocardiographic images and assessment of cardiac output and fractional area change. Representative echocardiographic illustrations for the measurement of aortic cross-sectional area (left) and velocity time integral (VTI; right) in the right parasternal long-axis (a) and subcostal (b) views for the calculation of cardiac output (CO; mL minute^{-1}) is provided. The VTI was always obtained from the subcostal view. The position of the sample gate for measurement of VTI is illustrated in yellow. Illustrative echocardiographic images in the right parasternal short-axis view (c) depicting diastolic (left) and systolic (right) left ventricular (LV) area measurements for the calculation of LV fractional area change (FAC%) is presented.

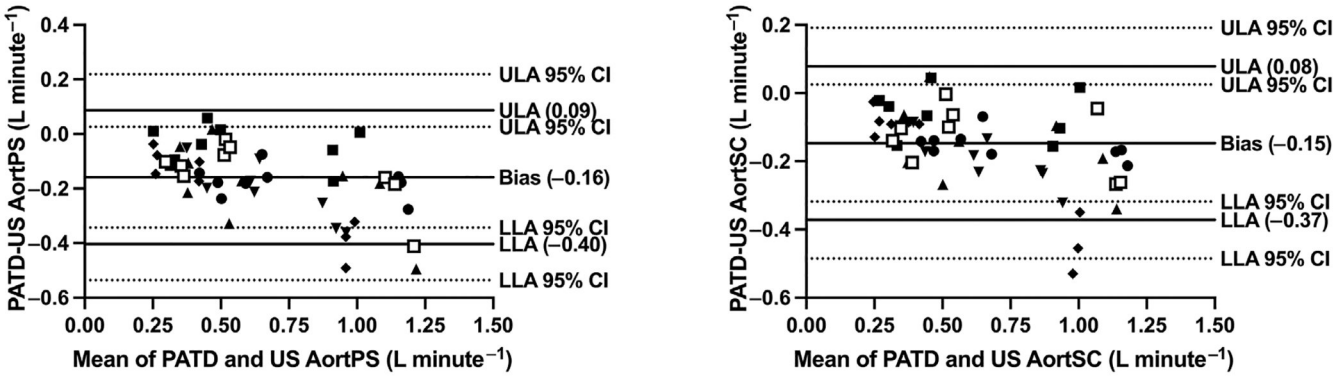

Figure 3.

Bland–Altman plots showing the agreement between cardiac output (CO) measured using pulmonary artery thermodilution (PATD) and ultrasound parasternal long-axis view (US AortPS, left) or ultrasound subcostal long-axis view (US AortSC, right). Cardiac output was measured in six cats (each represented by a different symbol) anesthetized with isoflurane in oxygen, following administration of dexmedetomidine [20 μg kg^{-1}, intravenously (IV)], then atipamezole (200 μg kg^{-1} intramuscularly) and atropine (20 μg kg^{-1} IV) as needed to produce a heart rate of 140 beats $minute^{-1}$ or higher, and lastly during IV administration of dopamine (20 μg kg^{-1} $minute^{-1}$). The order of treatments was not randomized. Three CO measurements were obtained at 10 minutes intervals after each drug administration with each measurement technique. Limits of agreement are defined as 1.96 times the standard deviation of the differences in measurement between the two techniques. Bias is the average difference in CO between the two measurement techniques. CI, confidence interval; LLA, lower limit of agreement; ULA, upper limit of agreement.

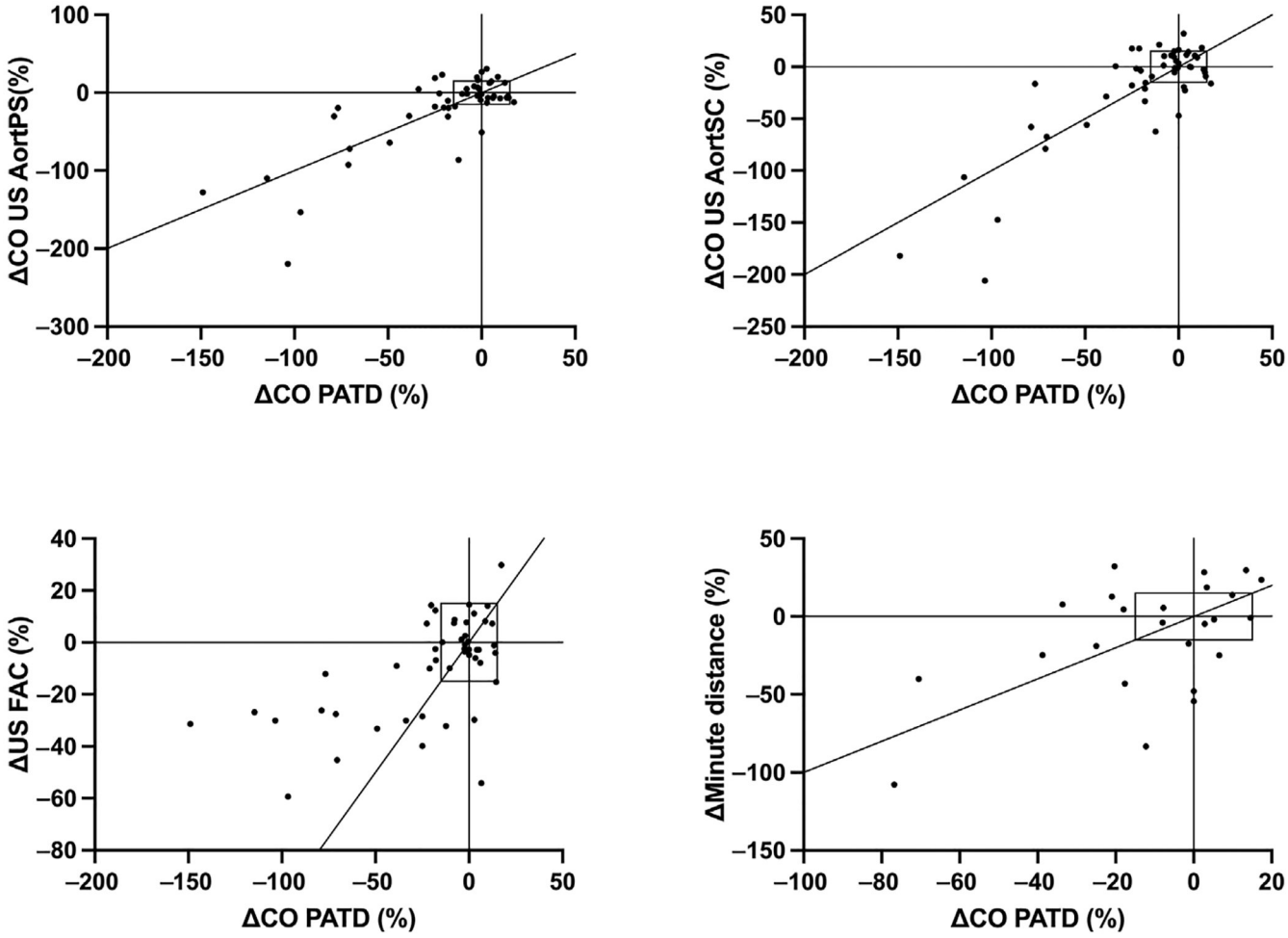

Figure 4.

Four quadrant plots showing the concordance between pulmonary artery thermodilution (PATD, considered to represent the true direction of change in cardiac output) and ultrasound parasternal long-axis view (US AortPS, top left), ultrasound subcostal long-axis view (US AortSC, top right), ultrasound fractional area change (US FAC) and transesophageal Doppler minute distance. Cardiac output (CO) was measured in six cats (each represented by a different symbol) anesthetized with isoflurane in oxygen, following administration of dexmedetomidine [20 μg kg^{-1} intravenously (IV)], then atipamezole (200 μg kg^{-1} intramuscularly) and atropine (20 μg kg^{-1} IV) as needed to produce a heart rate of 140 beats $minute^{-1}$ or higher, and lastly during IV administration of dopamine (20 μg kg^{-1} $minute^{-1}$). The order of treatments was not randomized. Three CO measurements were obtained at 10 minute intervals after each drug administration. The vertical and horizontal lines divide the plot in quadrants where the lower left quadrant contains data points where both methods showed an increase in CO, the upper right quadrant contains data points where both methods showed a decrease in CO, the upper left quadrant contains data points where the reference method showed an increase in CO and the alternative method showed a decrease in CO and the lower right quadrant contains data points where the reference method showed a decrease in CO and the alternative method showed an increase

in CO. Measurements showing concordance are contained in the lower left and upper right quadrants. Data on the oblique line would represent equal changes with the two methods. The rectangle shows a 15% change exclusion (data contained in the rectangle were not used to calculate the rate of concordance as the magnitude of change is considered too small for meaningful interpretation). **Δ**: change. Negative **Δ** values reflect an increase in CO in pairs of successive measurements and positive **Δ** values reflect a decrease in CO in pairs of successive measurements.

Table 1

Mean ± standard deviation cardiac output measured by pulmonary artery thermodilution (PATD; L minute^{-1}), transthoracic echocardiography using a parasternal view (US AortPS; L minute^{-1}) or subcostal view (US AortSC; L minute^{-1}) of the aortic annulus, fractional area change (FAC; %) using a parasternal short-axis view and minute distance (MD; cm minute^{-1}) obtained from a transesophageal Doppler in six cats anesthetized with isoflurane. Cats were administered dexmedetomidine (20 μg kg^{-1}) intravenously followed by atipamezole (200 μg kg^{-1}) intramuscularly and atropine (0.02 mg kg^{-1}) intravenously as needed to increase heart rate to 140 beats minute^{-1} or higher, followed by dopamine (20 μg kg^{-1} minute^{-1}). The order of treatments was not randomized. Measurements were obtained at 10 minute intervals for 30 minutes following each treatment.

Treatment	PATD	US AortPS	US AortSC	FAC	MD
Dexmedetomidine	0.30 ± 0.06	0.41 ± 0.10	0.41 ± 0.09	41.5 ± 7.5	612 ± 332
Atipamezole	0.47 ± 0.09	0.58 ± 0.12	0.57 ± 0.13	57.3 ± 7.8	929 ± 366
Dopamine	0.91 ± 0.13	1.17 ± 0.14	1.14 ± 0.13	77.7 ± 2.7	1664 ± 87