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Transpulmonary cardiac output in dogs

Comparison of cardiac output measurements using transpulmonary thermodilution and conventional thermodilution techniques in anaesthetized dogs with fluid overload

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Abstract

Objective To evaluate the agreement between cardiac output (CO) values obtained using a transpulmonary thermodilution technique (TPTDCO) and conventional thermodilution technique (TDCO) in anaesthetized dogs with fluid overload.

Study design Prospective experimental study.

Animals Six healthy Beagle dogs aged 7–8 years.

Methods Dogs were anaesthetized with sevoflurane in oxygen, and catheters were inserted for TPTDCO and TDCO measurement. After instrumentation, baseline CO was measured using each technique at a central venous pressure (CVP) of 3–7 mmHg. Dogs were subsequently

administered lactated Ringer's solution and 6% hydroxyethyl starch to induce fluid overload. CO measurements were obtained using each technique at CVP values of 8–12 mmHg, 13–17 mmHg, 18–22 mmHg and 23–27 mmHg. Agreements between CO measurements obtained with the respective techniques were analysed using Dunnett's test, Pearson's correlation coefficient and Bland–Altman analysis.

Results Thirty pairs of CO values were obtained, ranging from 1.45 L minute^{-1} to 4.69 L minute^{-1} for TPTDCO and from 1.30 L minute^{-1} to 4.61 L minute^{-1} for TDCO. TPTDCO and TDCO values correlated strongly ($r^2 = 0.915$, $p < 0.001$). The bias and mean relative bias between TPTDCO and TDCO were 0.26 ± 0.30 L minute^{-1} (limits of agreement − 0.29 to 0.81 L minute^{-1}) and 9.7%, respectively.

Conclusions and clinical relevance TPTDCO and TDCO measurements obtained in anaesthetized dogs during fluid overload exhibited good agreement. Accordingly, transpulmonary thermodilution provides an accurate measurement of CO in dogs with fluid overload.

Keywords cardiac output, dog, fluid overload, thermodilution, transpulmonary.

Introduction

The maintenance of optimal cardiac output (CO) is an important goal of haemodynamic management in anaesthetized and critically ill patients. Currently, thermodilution (TD) is the standard clinical method of measuring CO. However, this technique requires the placement of a pulmonary artery (PA) catheter through the right atrium and ventricle, which increases the risk for possible complications such as inhibition of tricuspid valve movement and embolism of the PA (Perel et al. 1987; Rooke et al. 1995), as well as morbidity and mortality, in humans (Connors et al. 1985; Linton et al. 2000; Sandham et al. 2003), dogs (Schregel et al. 1991), and other animals (Shih et al. 2009). In addition, PA catheter-guided therapy was not found to

improve survival or organ function or reduce intensive care unit stay durations among human patients (Harvey et al. 2005; Wheeler et al. 2006). In recent years, concern regarding the safety of PA catheters used for the conventional TD technique has increased, and less invasive alternative techniques for CO measurement are being developed (Corley et al. 2003).

The pulse-induced contour cardiac output (PiCCO) system provides real-time continuous CO monitoring via pulse contour analysis. In human medicine, the PiCCO system has been used to monitor CO during general anaesthesia and intensive care since the late 1990s and is considered a reliable CO measurement technique (McLuckie et al. 1996; Tibby et al. 1997; Sakka et al. 1999; Holm et al. 2001; Della Rocca et al. 2002; Pauli et al. 2002; Schiffman et al. 2002). The PiCCO system also allows the measurement of extravascular lung water (EVLW) and the pulmonary vascular permeability index (PVPI) (Katzenelson et al. 2004; Easley et al. 2009). To improve accuracy, pulse contour CO (PulseCO) values are periodically calibrated using CO measurements obtained via the PiCCO system transpulmonary thermodilution cardiac output (TPTDCO) technique. TPTDCO employs a central venous catheter for thermal indicator injection, and a thermistor-tipped catheter placed in the femoral artery to detect thermal dilution. In humans, the use of PA catheters has been associated with an increased rate of complications, especially arrhythmia, relative to the use of central venous catheter-guided therapy (19.4% *versus* 8.4%, respectively) (Wheeler et al. 2006). Therefore, TPTDCO facilitates CO measurement while reducing or eliminating the complications and morbidity associated with PA catheterization.

A previous study conducted in dogs suggested that the PiCCO system might serve as a less invasive method of monitoring CO in cases of severe bleeding and hypovolaemic shock (Friedman et al. 2002). Recently, Morgaz et al. (2014) reported that the PiCCO system appears to accurately monitor CO in dogs, as values determined using the TPTDCO technique agreed with those determined using the conventional TD technique (TDCO) under different

haemodynamic conditions induced by norepinephrine infusion (1 μg kg^{-1} $minute^{-1}$) and an excessive dose of sevoflurane [end-tidal sevoflurane concentration (F_E´Sevo) 4.6%]. However, although the administration of a large volume of fluid is often required for haemodynamic stabilization in anaesthetized or critically ill patients, to the present authors' knowledge, no reports have described the accuracy of TPTDCO and PulseCO with the PiCCO system in dogs with fluid overload. Therefore, we hypothesized that TPTDCO and PulseCO values would correlate with conventional TDCO values in dogs with fluid overload. Although the novel CO measurement techniques developed for use in humans might be valuable in veterinary medicine, the accuracy and suitability of these technologies must be evaluated in individual species. Proper validation studies require a comparison of the new method with an established method over a wide range of haemodynamic function, with appropriate statistical analyses. The present study aimed to compare the agreement between TPTDCO or PulseCO and TDCO values in anaesthetized dogs with fluid overload.

Materials and methods

Animals

Six Beagle dogs (three non-pregnant females and three males, all intact) were used. The, mean ± standard deviation (SD) age of the dogs was 7.3 ± 0.5 years (range: 7–8 years). Their mean ± SD weight was 13.8 ± 3.6 kg (range: 9.0–19.2 kg). The dogs received care according to the principles of the Guide for the Care and Use of Laboratory Animals prepared by Rakuno Gakuen University. The Animal Care and Use Committee of Rakuno Gakuen University approved this study (VH23B14). The dogs were judged to be in good to excellent health based upon the results of a physical examination, ultrasonographic cardiac function analysis, complete blood cell count and serum biochemical analysis. Approximately 1 month before the experiment, the minimum alveolar concentration (MAC) of sevoflurane was determined in all dogs using a tail clamp technique (Steffey & Mama 2007; Yamashita et al. 2008; Itami et al.

2013). The MAC was measured as the F_{E}'Sevo in gas sampled from the thoracic portion of the trachea (Yamashita et al. 2008) and was determined in triplicate.

Anaesthesia

All dogs were anaesthetized with sevoflurane (Sevoflo; DS Pharma Animal Health Co. Ltd, Japan) in oxygen administered using a mask and were then orotracheally intubated. Dogs were positioned in left lateral recumbency and anaesthesia was maintained at an F_{E}'Sevo value 1.3-fold of the individual predetermined sevoflurane MAC via delivery by a circle rebreathing system and anaesthesia machine (Beaver 20; Kimura Medical Instrument Co., Japan) with an out-of-circuit vaporizer (Sevotech III; Datex Ohmeda KK, Japan) and oxygen flow of 2 L $minute^{-1}$. The dogs were mechanically ventilated (12 breaths $minute^{-1}$, inspiratory:expiratory ratio of 1:2) with a time-cycled ventilator (Nuffield Anaesthesia Ventilator Series 200; Penlon Ltd, UK) to maintain an end-tidal partial pressure of carbon dioxide ($P_{E}'CO_2$) of 35–40 mmHg (4.7–5.3 kPa). The end-tidal gas was sampled from the Y-piece by a side-stream system, and $P_{E}'CO_2$ and F_{E}'Sevo were monitored using a veterinary patient monitoring system (BP-508V; Omron Colin Co., Japan). The monitor was calibrated immediately prior to each experiment with a calibration kit (AG Calibration Gas and Adaptor Set; Omron Colin Co.).

Instrumentation

A 22 gauge, 2.5 cm catheter (Supercath; Medikit Co., Japan) was placed in each cephalic vein. After the hair had been clipped and the skin over the right jugular vein aseptically prepared, approximately 0.5 mL of 2% lidocaine (Xylocaine; AstraZeneca KK, Japan) was injected intradermally before a 6 Fr catheter introducer (Catheter Introducer; Medikit Co.) was inserted. A 5 Fr Swan–Ganz triple lumen catheter (TC-504; Nihon Koden Co., Japan) equipped with an injectate temperature sensor (PV4046; PULSION Medical Systems AG, Germany) was inserted through the introducer and advanced into the right atrium and PA under pressure

126 waveform guidance.

127 The interior surface of the femoral region of the left pelvic limb was also clipped and
128 aseptically prepared for arterial catheter placement. The catheter site was desensitized with
129 approximately 0.5 mL of infiltrated 2% lidocaine and a small incision made, after which a 4 Fr
130 arterial PiCCO catheter (16 cm PiCCO Catheter PV2014L16; PULSION Medical Systems
131 AG) was inserted into the left femoral artery using a guide wire and dilator (Seldinger
132 technique) and advanced towards the iliac artery.

133 Measurements of TPTDCO and TDCO

134 TPTDCO was measured using a PiCCO system (PiCCOplus monitor, Version 6.0; PULSION
135 Medical Systems AG). To measure TPTDCO, a distal port of the PA catheter was retracted to
136 the cranial vena cava and used as the indicator injection site. A 3 mL bolus of ice-cold 5%
137 dextrose (5% w/v glucose injection; Terumo Co., Japan) was used as an indicator. Following
138 TPTDCO measurements, PulseCO was recorded when the artery pressure waveform stabilized
139 after indicator administration. TDCO was measured using a multi-parameter patient
140 monitoring system (DS-7210; Fukuda Denshi Co., Japan). To measure TDCO, distal and
141 proximal Swan–Ganz catheter ports were advanced into the PA and right atrium, respectively.
142 The same indicator was injected through the proximal port of the catheter in the right atrium.
143 Changes in blood temperature were measured using the arterial PiCCO catheter tip thermistor
144 in the left femoral artery for TPTDCO and the Swan–Ganz catheter tip thermistor in the PA for
145 TDCO. The order of TPTDCO and TDCO measurements was randomized. Fluid
146 administration was stopped while TPTDCO and TDCO were measured. All CO measurements
147 were performed at end-expiration without inducing apnoea. Each CO measurement technique
148 was repeated until three consecutive values with a difference of < 10% were obtained.

149 Measurement of other cardiovascular variables

150 Central venous pressure (CVP) was determined using a distal port of the Swan–Ganz catheter

placed at the cranial vena cava and connected to a pressure transducer kit that included pressure resistance tubing (CDX-A90; Cobe Laboratories, Inc., Japan) and a multi-parameter patient monitoring system. Right atrial pressure (RAP), pulmonary arterial pressure (PAP) and PA occlusion pressure (PAOP) were determined using the respective ports of the PA catheter at standard positions while connected to the same system. Systolic (SAP), mean (MAP) and diastolic (DAP) arterial pressures were measured using the arterial PiCCO catheter placed at the femoral artery and connected to a pressure transducer (PiCCO Monitoring Kit PV8215; PULSION Medical Systems AG) and the PiCCOplus monitor. These pressure transducers were calibrated to a zero reference at the level of the manubrium, and the catheters were also flushed periodically with heparinized 0.9% sodium chloride. EVLW and PVPI were recorded using a PiCCO system during the TPTDCO measurement. In addition, the oesophageal temperature (T), heart rate (HR) and electrocardiogram (lead II) were recorded (BP-508V; Omron Colin Co.).

Experimental protocol

Following instrumentation, the dogs were stabilized for approximately 30 minutes. Baseline values of cardiovascular variables (TPTDCO, PulseCO, TDCO, RAP, PAP, PAOP, SAP, MAP, DAP and HR) were determined at a CVP of 3–7 mmHg. The order of data collection (TPTDCO and TDCO) was randomized. Subsequently to the determination of baseline values, infusions of lactated Ringer's solution (LRS) (Solulact; Terumo Co.) and 6% hydroxyethyl starch (HES) (Salinehes; Fresenius Kabi Japan Co., Japan) administered through the catheters placed in the right and left cephalic veins were initiated. LRS and HES were administered initially at infusion rates of 90 mL kg^{-1} $hour^{-1}$ and 30 mL kg^{-1} $hour^{-1}$, respectively, and controlled to achieve CVP ranges of 8–12 mmHg, 13–17 mmHg, 18–22 mmHg and 23–27 mmHg. Cardiovascular variables were measured at each CVP range.

After the completion of cardiovascular measurements at a CVP of 23–27 mmHg, the LRS and

HES infusions were discontinued, and the dogs were treated with an intravenous (IV) injection of furosemide (2 mg kg^{-1}; Lasix 10 mg mL^{-1}; Nichi-Iko Pharmaceutical Co. Ltd, Japan) and an infusion of human atrial natriuretic peptide, carperitide (0.1 μg kg^{-1} $minute^{-1}$; Hanp, 1000 μg vial; Daiichi Sankyo Co. Ltd, Japan) diluted in distilled water for infusion until the CVP had returned to a normal range (3–7 mmHg). Sevoflurane was subsequently discontinued, lack of bleeding at the catheter insertion sites was confirmed, and the dogs were allowed to recover from anaesthesia. After extubation, the dogs were monitored for food and water intake over a 24 hour period, after which the experiment was ended.

Statistical analysis

Using the statistical software package Statcel3 (OMS Publishing, Inc., Japan), an analysis of variance (ANOVA) and Dunnett's test for repeated measures were used to analyse changes in cardiovascular measurements. Relationships between TPTDCO and TDCO values were evaluated using linear regression and Pearson's correlation coefficient. Relationships between PulseCO and TDCO values were also evaluated. A coefficient of concordance (r) was calculated as an additional measure of agreement between TPTDCO and TDCO values (Shoukri & Pause 1999). Agreement between TPTDCO and TDCO was determined using the method reported by Bland and Altman (Bland & Altman 1986, 1999, 2007; Critchley & Critchley 1999). For each observation, bias was calculated as the difference between TPTDCO and TDCO (TPTDCO – TDCO). The limits of agreement were reported as the mean bias ± 1.96 SD. Relative bias was calculated as follows: (TPTDCO − TDCO)/([TPTDCO + TDCO]/2) × 100 (Shoemaker et al. 1994). Statistical significance was set at $p < 0.05$.

Results

The mean ± SD sevoflurane MAC in the dogs was 2.52 ± 0.39% (range: 2.15–2.96%). Consequently, anaesthesia was maintained with an FE´Sevo of 3.28 ± 0.50% (1.3 MAC)

throughout the study. The total LRS volume administered to the dogs was 2728 ± 659 mL (range: 1915–3541 mL) at infusion rates of 60–120 mL kg^{-1} $hour^{-1}$. The total HES volume administered to the dogs was 930 ± 180 mL (range: 745–1156 mL) at infusion rates of 10–40 mL kg^{-1} $hour^{-1}$. An average of 133 ± 35 minutes elapsed before the dogs returned to a normovolaemic state. No complications at the femoral catheter site and no adverse effects other than oedema of the face and muzzle were observed in any dog. In all dogs, oedema resolved by the next day of the experiment and no further medication was necessary.

Normothermia was achieved in all dogs throughout the study. Data from five ranges of CVP were analysed (Table 1). HR increased and systemic vascular resistance (SVR) decreased significantly from baseline values, beginning at a CVP of 8–12 mmHg ($p < 0.05$ and $p < 0.01$, respectively). There were no significant changes in SAP, MAP, DAP, EVLW or PVPI during IV fluid administration.

Thirty comparison pairs of data were collected in the six dogs. TPTDCO, TDCO and PulseCO values exhibited significant parallel increases in response to fluid administration ($p < 0.05$), although values reached a plateau at a CVP of 13–17 mmHg and beyond. There were no significant differences in CO values between the TPTDCO and PulseCO techniques ($p = 0.656$). Additionally, the correlation coefficient (r) and decision coefficient (r^2) for correlations between TPTDCO and TDCO values were strong ($r = 0.957$ and $r^2 = 0.915$, respectively). The correlation coefficient and decision coefficient for correlations between PulseCO and TDCO values were similarly robust ($r = 0.943$ and $r^2 = 0.890$, respectively).

The following linear regression equations were calculated (Fig. 1):

TPTDCO value =1.0756 (TDCO value) + 0.0845

PulseCO value = 1.0477 (TDCO value) + 0.2187

The mean TPTDCO/TDCO bias was 0.26 ± 0.30 L $minute^{-1}$ (limits of agreement: − 0.29 to 0.81 L $minute^{-1}$). The mean PulseCO/TDCO bias was 0.18 ± 0.71 L $minute^{-1}$ (limits of

agreement: −0.69 to 1.05 L minute^{-1}) (Fig. 2). There was a proportional error between TPTDCO and TDCO values, with a mean relative bias (TPTDCO – TDCO) of 9.7 ± 10.9%. There was also a proportional error between PulseCO and TDCO values, with a mean relative bias (PulseCO – TDCO) of 6.5 ± 26.6%, and two of the 30 pairs of values greatly deviated from the limits of agreement. The linear regression equation and mean relative bias were therefore calculated without these two pairs.

Discussion

Frequently, it is necessary to infuse large amounts of fluid in order to maintain a stable haemodynamic status during anaesthesia or intensive care in conditions such as sepsis or severe burns. In our canine model of increasing preload (from normal to excessively high CVP), TPTDCO measured via the PiCCO system and TDCO were shown to measure CO similarly, producing values that correlated strongly. However, TPTDCO values were slightly higher and a proportional error was observed between the methods.

Conventional TDCO was selected as a reference method because it has been validated for use in dogs (Yamashita et al. 2007) and is the most frequently used technique for measuring CO in canine cardiovascular research. In the present study, the bias, precision and accuracy of the TPTDCO measurement technique were analysed simultaneously by comparing the values obtained with TDCO values at varying degrees of excessive fluid administration.

An FE´Sevo 1.3 MAC was used in this study for two reasons: 1) the MAC is a useful concept for comparing the effects of inhaled anaesthetics on vital organs, and 2) the MAC corresponds to the effective dose (ED_{50}); 1.2–1.4 MAC is the dose corresponding to the ED_{95}, which is used to prevent movement in response to external stimuli such as PA catheter manipulation. Sevoflurane exerts dose-dependent cardiovascular depressant effects (Steffey & Mama 2007); for example, SVR was found to decrease with increasing depth of anaesthesia, accompanied by a dose-dependent decrease in arterial blood pressure, in dogs anaesthetized with sevoflurane at

different MAC values (Mutoh et al. 1997). Therefore, the MAC values were initially determined for individual dogs and cardiovascular measurements were determined during anaesthesia with an individual FE´Sevo 1.3 MAC in this study. This additional experimental step helped to minimize individual variability as a source of error when establishing the relationships between changes in cardiovascular variables.

The rates of infusion of LRS and HES were based on data provided in a previous report in which serious complications such as seizure and dyspnoea were not observed (Nelson et al. 2010). Neither of these complications occurred in the present study. When the Guyton curve is applied, there is a shift in fluid loading towards the upper part of the venous return curve, which increases the overall CO. Combined with Starling's law, CVP and CO increase in response to fluid administration, but the increase in CO demonstrates a ceiling effect. The present study was designed to determine whether TPTDCO was able to accurately evaluate the physiological responses of excessive preload induced by fluid administration. TPTDCO values increased significantly in response to fluid administration and showed a ceiling effect. Hence, high CVP levels in dogs may represent a condition in the descending portion of the venous return curve, and may be associated with unresponsiveness to fluid administration thereafter. Fluid infusion also induces other changes in cardiovascular variables. For example, a moderate increase in HR was noted. Possible reasons for this increase might include distortion of the right atrial wall in response to fluid overload, leading to sinoatrial node stimulation and increased sinoatrial node firing and HR (Chiba 1977). It is also likely that reflexive tachycardia occurred in response to reduced SVR as blood viscosity decreases as a result of fluid infusion. The increasing RAP might have also induced atrium natriuretic peptide secretion, leading to a reduction in SVR (Lang et al. 1987). However, the newer volatile anaesthetics, including sevoflurane, tend to preserve CO at clinically useful concentrations, facilitated by reductions in SVR (Steffey & Mama 2007). A high dose of sevoflurane possibly suppressed the

cardiovascular responsiveness to fluid administration. As a result, SAP, MAP and DAP were unaltered during fluid overload. According to the haemodynamic formula (Muir 2007), arterial pressure may not be affected by an increase in CO and decrease in SVR. A PiCCO system may be able to accurately evaluate physiological responses with excessive fluid overload, including CO, MAP and SVR. As in humans, a large amount of fluid is required to maintain arterial pressure in dogs with sepsis (Butler 2011). Therefore, monitoring CO, MAP and SVR with the PiCCO system facilitates therapeutic decisions such as whether the administration of inotropic drugs or vasoconstrictors will be clinically useful.

PulseCO measurements confer an important advantage upon patients because they provide real-time CO data, allowing clinicians to immediately observe responses to treatment. Previous studies have shown that the PulseCO must undergo recalibration at each new haemodynamic state to maintain accuracy (Gruenewald et al. 2008; Piehl et al. 2008; Shih et al. 2011). PulseCO was automatically recalibrated during each TPTDCO measurement when using the PiCCO system. In the present study, PulseCO values were recorded when TPTDCO was measured by using a chilled 5% dextrose injection at each CVP point; no significant differences in CO were observed between the TPTDCO and PulseCO values. Additionally, fluid therapy was temporarily discontinued during CO measurement to prevent the fluid temperature and fluid volume from interfering with the thermodilution method. These two interventions may have resulted in more similar PulseCO and TPTDCO values. As a result, there was a strong correlation between the PulseCO and TDCO values in the present study (r^2 = 0.890). However, the PulseCO values were slightly higher than the TDCO values; notably, proportional error was observed between the methods, and the arterial catheter failed to recognize the arterial pressure waveform signal in two pairs, which were considered outliers. This failure in these two pairs may have resulted from damping or equipment failure. The tip of the catheter site should be checked and the catheter flushed to obtain the correct arterial

pressure waveform. Further studies will be necessary to evaluate the analytical accuracy of the pulse contour at different levels of CVP in the absence of recalibration.

The present study is subject to some limitations. The TPTDCO technique was accurate when compared with TDCO, with a decision coefficient (r^2) of 0.915. However, there was a proportional error of 9.7% between the methods. Despite this small bias and limits of agreement, the Bland–Altman plot demonstrated considerable dispersion around the bias. Similar increases in dispersion around the bias at higher CVP levels are often reported in studies comparing CO measurement techniques over a wide range of haemodynamic function. Such bias can be statistically remedied via a proportional and/or log transformation of the data (Tibby et al. 1997). Nonetheless, a wide range of CO should be included in the design of appropriate experiments to evaluate new monitors. Increasing the number of comparative pairs would have improved the reliability of the statistical analysis and might have narrowed the limits of agreement. Additionally, a small interval (< 3 minutes) was required to shift from TPTDCO to TDCO measurements (and vice versa), and therefore, these measurements were not truly simultaneous. In this study, fluid therapy was temporarily discontinued during CO measurements in order to prevent a change in hypervolaemic status. All other variables were kept constant during these CO measurements and therefore it is unlikely that this interval led to analytical errors. A further limitation of this study refers to the small sample size (six dogs and 30 pairs of data points), and accordingly the possibility of a Type II statistical error cannot be eliminated. However, it was possible to minimize individual variations because both control and experimental data were collected in the same animal.

It is currently possible to measure EVLW and PVPI because the TPTDCO indicator passes through pulmonary circulation (Katzenelson et al. 2004; Easley et al. 2009). Although chest radiographs were not evaluated for pulmonary oedema, no dogs exhibited dyspnoea or cyanosis after the experiment. Therefore, TPTDCO using the PiCCO system is likely to

represent a good tool for monitoring cardiopulmonary function during fluid overload management in dogs. Furthermore, sepsis and severe burns enhance vascular permeability and lead to acute respiratory distress syndrome. Accordingly, TPTDCO is expected to be useful in future evaluations of heart and lung function in a canine model of septic shock.

In conclusion, in the present canine model of increasing preload (from normal to excessively high CVP), TPTDCO and TDCO yielded similar CO measurements with strongly correlating values. However, the TPTDCO values were slightly higher than the TDCO values and proportional error was observed between the methods. Regardless, we consider TPTDCO to be useful for evaluating the haemodynamic status of anaesthetized dogs with fluid overload.

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Figure 1 Regression plots of the comparisons between values for: a) transpulmonary thermodilution cardiac output (TPTDCO) and thermodilution cardiac output (TDCO), and b) pulse contour cardiac output (PulseCO) and TDCO collected from six anaesthetized dogs. The circles indicate correspondence at the various ranges of central venous pressure (CVP). The solid line represents $y = x$; the dashed line represents the regression line. Two of the PulseCO and TDCO pairs deviated greatly from the limits of agreement and were omitted from the calculations.

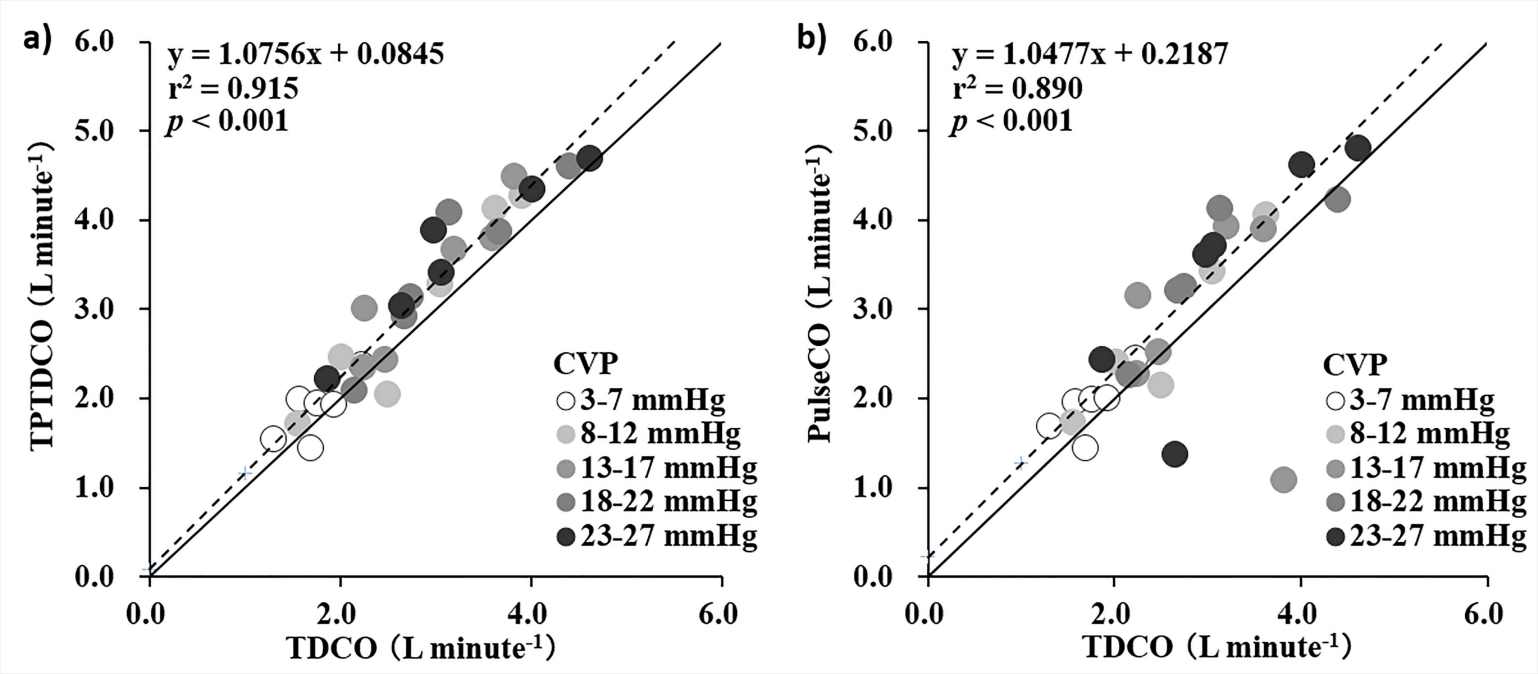
Figure 2 Bland–Altman analyses displaying agreement of the differences between techniques with the mean values from two techniques for: a) transpulmonary thermodilution cardiac output (TPTDCO) and thermodilution cardiac output (TDCO), and b) pulse contour cardiac output (PulseCO) and TDCO using 30 pairs of values collected from six anesthetized dogs. Two pairs of PulseCO and TDCO values deviated greatly from the limits of agreement (LOA) and were omitted from the calculations.

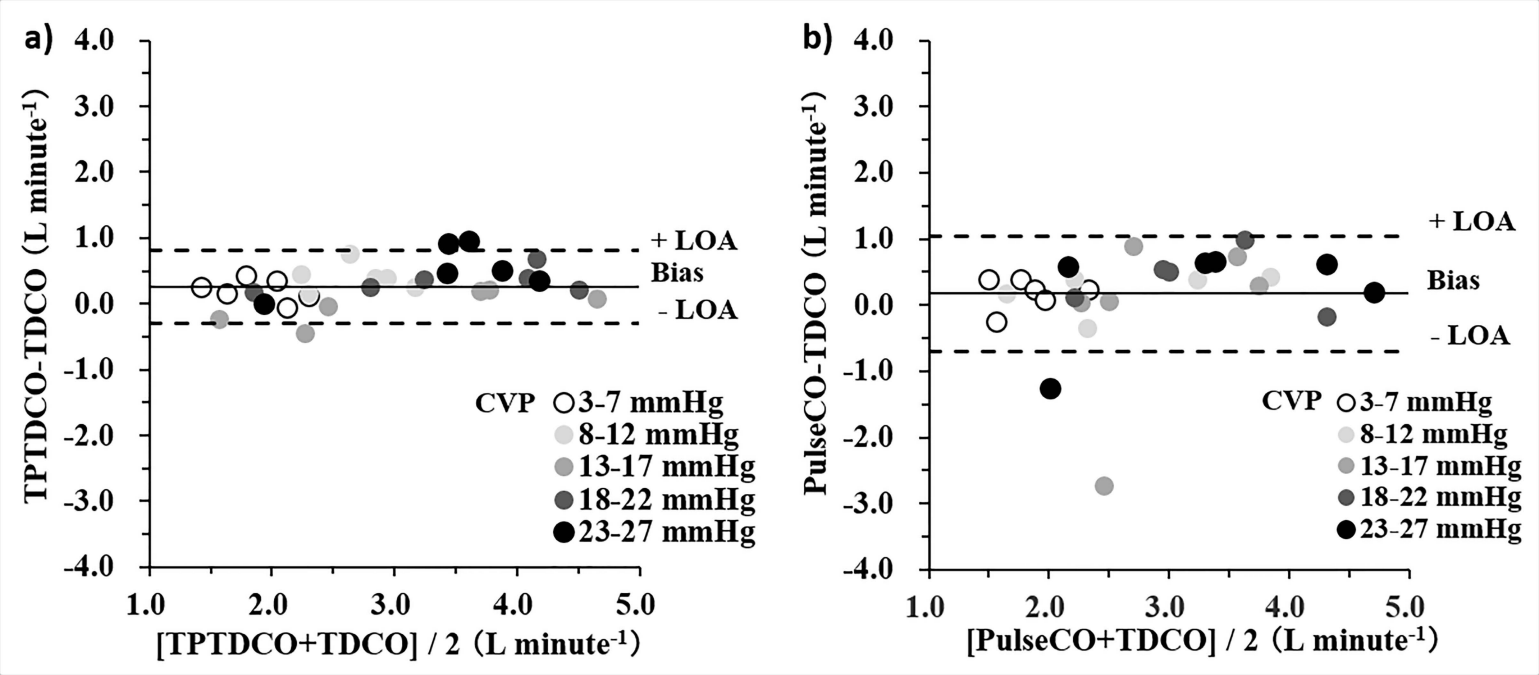
456 **Table 1** Mean ± standard deviation values for haemodynamic variables at five levels of
457 central venous pressure in six anaesthetized dogs with fluid overload

Variable	Central venous pressure (mmHg)				
	3–7 (baseline)	8–12	13–17	18–22	23–27
HR (beats minute^{-1})	109 ± 16	128 ± 19*	128 ± 10*	129 ± 11*	134 ± 12†
SAP (mmHg)	113 ± 9	115 ± 17	118 ± 10	117 ± 12	117 ± 17
MAP (mmHg)	86 ± 8	84 ± 11	86 ± 6	86 ± 7	87 ± 11
DAP (mmHg)	72 ± 7	68 ± 8	70 ± 3	70 ± 5	71 ± 8
RAP (mmHg)	5 ± 3	11 ± 2†	16 ± 2†	20 ± 3†	24 ± 2†
PAP (mmHg)	15 ± 2	21 ± 2†	25 ± 1†	28 ± 3†	34 ± 3†
PAOP (mmHg)	8 ± 3	15 ± 1†	20 ± 2†	25 ± 2†	30 ± 2†
TPTDCO (L minute^{-1})	1.87 ± 0.34	2.99 ± 1.08	3.30 ± 0.84*	3.45 ± 0.91†	3.60 ± 0.91†
TDCO (L minute^{-1})	1.74 ± 0.31	2.77 ± 0.92*	2.93 ± 0.70*	3.12 ± 0.80†	3.19 ± 0.98†
PulseCO (L minute^{-1})	1.92 ± 0.34	2.75 ± 0.96	2.82 ± 1.09	3.42 ± 0.80*	3.43 ± 1.31*
SVR (dynes second^{-1} cm^{-5})	3832 ± 433	2276 ± 782†	1961 ± 452†	1760 ± 382†	1649 ± 339†
T (°C)	37.4 ± 0.4	37.7 ± 0.6	37.7 ± 0.5	37.6 ± 0.7	37.3 ± 0.5
EVLW (mL)	207.5 ± 77.7	204.8 ± 103.6	200.9 ± 93.7	225.3 ± 111.7	243.7 ± 123.6
PVPI	2.1 ± 0.2	1.9 ± 0.5	1.8 ± 0.4	2.0 ± 0.6	2.1 ± 0.7
LRS (mL)	113 ± 7	379 ± 98	918 ± 175	2,056 ± 762	2,728 ± 659
HES (mL)	36 ± 4	135 ± 38	322 ± 83	665 ± 264	930 ± 180
Time from baseline (minutes)	0	62 ± 12	110 ± 8	167 ± 8	223 ± 5

458 HR, heart rate; SAP, systolic arterial pressure; MAP, mean arterial pressure; DAP, diastolic
459 arterial pressure; RAP, right atrial pressure; PAP, pulmonary artery pressure; PAOP, pulmonary
460 artery occlusion pressure; TPTDCO, cardiac output measured by the transpulmonary

thermodilution technique; TDCO, cardiac output measured by the traditional thermodilution technique; PulseCO, pulse contour cardiac output; SVR, systemic vascular resistance; T, oesophageal temperature; EVLW, extravascular lung water; PVPI, pulmonary vascular permeability index; LRS, lactated Ringer's solution; HES, hydroxyethyl starch 6%. *$p < 0.05$; †$p < 0.01$: significant difference from baseline.


a)
y = 1.0756x + 0.0845
r² = 0.915
p < 0.001
TPTDCO (L minute⁻¹)
TDCO (L minute⁻¹)
CVP
3-7 mmHg
8-12 mmHg
13-17 mmHg
18-22 mmHg
23-27 mmHg
b)
y = 1.0477x + 0.2187
r² = 0.890
p < 0.001
PulseCO (L minute⁻¹)
TDCO (L minute⁻¹)
CVP
3-7 mmHg
8-12 mmHg
13-17 mmHg
18-22 mmHg
23-27 mmHg


a)
TPTDCO-TDCO (L minute-1)
[TPTDCO+TDCO] / 2 (L minute-1)
+ LOA
Bias
- LOA
CVP
3-7 mmHg
8-12 mmHg
13-17 mmHg
18-22 mmHg
23-27 mmHg
b)
PulseCO-TDCO (L minute-1)
[PulseCO+TDCO] / 2 (L minute-1)
+ LOA
Bias
- LOA
CVP
3-7 mmHg
8-12 mmHg
13-17 mmHg
18-22 mmHg
23-27 mmHg