



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

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3 Transpulmonary cardiac output in dogs

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

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16

17 **Abstract**

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

21 **Study design** Prospective experimental study.

22 **Animals** Six healthy Beagle dogs aged 7–8 years.

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

26 administered lactated Ringer's solution and 6% hydroxyethyl starch to induce fluid overload.
27 CO measurements were obtained using each technique at CVP values of 8–12 mmHg,
28 13–17 mmHg, 18–22 mmHg and 23–27 mmHg. Agreements between CO measurements
29 obtained with the respective techniques were analysed using Dunnett's test, Pearson's
30 correlation coefficient and Bland–Altman analysis.

31 **Results** Thirty pairs of CO values were obtained, ranging from 1.45 L minute⁻¹ to
32 4.69 L minute⁻¹ for TPTDCO and from 1.30 L minute⁻¹ to 4.61 L minute⁻¹ for TDCO.
33 TPTDCO and TDCO values correlated strongly ($r^2 = 0.915$, $p < 0.001$). The bias and mean
34 relative bias between TPTDCO and TDCO were 0.26 ± 0.30 L minute⁻¹ (limits of agreement
35 -0.29 to 0.81 L minute⁻¹) and 9.7%, respectively.

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

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

41

42 **Introduction**

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

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

55 The pulse-induced contour cardiac output (PiCCO) system provides real-time continuous CO
56 monitoring via pulse contour analysis. In human medicine, the PiCCO system has been used to
57 monitor CO during general anaesthesia and intensive care since the late 1990s and is
58 considered a reliable CO measurement technique (McLuckie et al. 1996; Tibby et al. 1997;
59 Sakka et al. 1999; Holm et al. 2001; Della Rocca et al. 2002; Pauli et al. 2002; Schiffman et al.
60 2002). The PiCCO system also allows the measurement of extravascular lung water (EVLW)
61 and the pulmonary vascular permeability index (PVPI) (Katzenelson et al. 2004; Easley et al.
62 2009). To improve accuracy, pulse contour CO (PulseCO) values are periodically calibrated
63 using CO measurements obtained via the PiCCO system transpulmonary thermodilution
64 cardiac output (TPTDCO) technique. TPTDCO employs a central venous catheter for thermal
65 indicator injection, and a thermistor-tipped catheter placed in the femoral artery to detect
66 thermal dilution. In humans, the use of PA catheters has been associated with an increased rate
67 of complications, especially arrhythmia, relative to the use of central venous catheter-guided
68 therapy (19.4% *versus* 8.4%, respectively) (Wheeler et al. 2006). Therefore, TPTDCO
69 facilitates CO measurement while reducing or eliminating the complications and morbidity
70 associated with PA catheterization.

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

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

89 **Materials and methods**

90 **Animals**

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

101 2013). The MAC was measured as the FE´Sevo in gas sampled from the thoracic portion of the
102 trachea (Yamashita et al. 2008) and was determined in triplicate.

103 Anaesthesia

104 All dogs were anaesthetized with sevoflurane (Sevoflo; DS Pharma Animal Health Co. Ltd,
105 Japan) in oxygen administered using a mask and were then orotracheally intubated. Dogs were
106 positioned in left lateral recumbency and anaesthesia was maintained at an FE´Sevo value
107 1.3-fold of the individual predetermined sevoflurane MAC via delivery by a circle rebreathing
108 system and anaesthesia machine (Beaver 20; Kimura Medical Instrument Co., Japan) with an
109 out-of-circuit vaporizer (Sevotech III; Datex Ohmeda KK, Japan) and oxygen flow of
110 2 L minute⁻¹. The dogs were mechanically ventilated (12 breaths minute⁻¹,
111 inspiratory:expiratory ratio of 1:2) with a time-cycled ventilator (Nuffield Anaesthesia
112 Ventilator Series 200; Penlon Ltd, UK) to maintain an end-tidal partial pressure of carbon
113 dioxide (PE´CO₂) of 35–40 mmHg (4.7–5.3 kPa). The end-tidal gas was sampled from the
114 Y-piece by a side-stream system, and PE´CO₂ and FE´Sevo were monitored using a veterinary
115 patient monitoring system (BP-508V; Omron Colin Co., Japan). The monitor was calibrated
116 immediately prior to each experiment with a calibration kit (AG Calibration Gas and Adaptor
117 Set; Omron Colin Co.).

118 Instrumentation

119 A 22 gauge, 2.5 cm catheter (Supercath; Medikit Co., Japan) was placed in each cephalic vein.
120 After the hair had been clipped and the skin over the right jugular vein aseptically prepared,
121 approximately 0.5 mL of 2% lidocaine (Xylocaine; AstraZeneca KK, Japan) was injected
122 intradermally before a 6 Fr catheter introducer (Catheter Introducer; Medikit Co.) was inserted.
123 A 5 Fr Swan–Ganz triple lumen catheter (TC-504; Nihon Kodan Co., Japan) equipped with an
124 injectate temperature sensor (PV4046; PULSION Medical Systems AG, Germany) was
125 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

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

164 Experimental protocol

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

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

176 HES infusions were discontinued, and the dogs were treated with an intravenous (IV) injection
177 of furosemide (2 mg kg⁻¹; Lasix 10 mg mL⁻¹; Nichi-Iko Pharmaceutical Co. Ltd, Japan) and
178 an infusion of human atrial natriuretic peptide, carperitide (0.1 µg kg⁻¹ minute⁻¹; Hanp,
179 1000 µg vial; Daiichi Sankyo Co. Ltd, Japan) diluted in distilled water for infusion until the
180 CVP had returned to a normal range (3–7 mmHg). Sevoflurane was subsequently discontinued,
181 lack of bleeding at the catheter insertion sites was confirmed, and the dogs were allowed to
182 recover from anaesthesia. After extubation, the dogs were monitored for food and water intake
183 over a 24 hour period, after which the experiment was ended.

184 Statistical analysis

185 Using the statistical software package Statcel3 (OMS Publishing, Inc., Japan), an analysis of
186 variance (ANOVA) and Dunnett's test for repeated measures were used to analyse changes in
187 cardiovascular measurements. Relationships between TPTDCO and TDCO values were
188 evaluated using linear regression and Pearson's correlation coefficient. Relationships between
189 PulseCO and TDCO values were also evaluated. A coefficient of concordance (*r*) was
190 calculated as an additional measure of agreement between TPTDCO and TDCO values
191 (Shoukri & Pause 1999). Agreement between TPTDCO and TDCO was determined using the
192 method reported by Bland and Altman (Bland & Altman 1986, 1999, 2007; Critchley &
193 Critchley 1999). For each observation, bias was calculated as the difference between TPTDCO
194 and TDCO (TPTDCO – TDCO). The limits of agreement were reported as the mean
195 bias ± 1.96 SD. Relative bias was calculated as follows:
196 $(\text{TPTDCO} - \text{TDCO}) / ([\text{TPTDCO} + \text{TDCO}] / 2) \times 100$ (Shoemaker et al. 1994). Statistical
197 significance was set at $p < 0.05$.

198 **Results**

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

201 throughout the study. The total LRS volume administered to the dogs was 2728 ± 659 mL
202 (range: 1915–3541 mL) at infusion rates of $60\text{--}120$ mL kg^{-1} hour^{-1} . The total HES volume
203 administered to the dogs was 930 ± 180 mL (range: 745–1156 mL) at infusion rates of
204 $10\text{--}40$ mL kg^{-1} hour^{-1} . An average of 133 ± 35 minutes elapsed before the dogs returned to a
205 normovolaemic state. No complications at the femoral catheter site and no adverse effects other
206 than oedema of the face and muzzle were observed in any dog. In all dogs, oedema resolved by
207 the next day of the experiment and no further medication was necessary.

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

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

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

222 $\text{TPTDCO value} = 1.0756 (\text{TDCO value}) + 0.0845$

223 $\text{PulseCO value} = 1.0477 (\text{TDCO value}) + 0.2187$

224 The mean TPTDCO/TDCO bias was 0.26 ± 0.30 L minute^{-1} (limits of agreement: -0.29 to
225 0.81 L minute^{-1}). The mean PulseCO/TDCO bias was 0.18 ± 0.71 L minute^{-1} (limits of

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

232 **Discussion**

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

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

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

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

256 The rates of infusion of LRS and HES were based on data provided in a previous report in
257 which serious complications such as seizure and dyspnoea were not observed (Nelson et al.
258 2010). Neither of these complications occurred in the present study. When the Guyton curve is
259 applied, there is a shift in fluid loading towards the upper part of the venous return curve, which
260 increases the overall CO. Combined with Starling's law, CVP and CO increase in response to
261 fluid administration, but the increase in CO demonstrates a ceiling effect. The present study
262 was designed to determine whether TPTDCO was able to accurately evaluate the physiological
263 responses of excessive preload induced by fluid administration. TPTDCO values increased
264 significantly in response to fluid administration and showed a ceiling effect. Hence, high CVP
265 levels in dogs may represent a condition in the descending portion of the venous return curve,
266 and may be associated with unresponsiveness to fluid administration thereafter. Fluid infusion
267 also induces other changes in cardiovascular variables. For example, a moderate increase in
268 HR was noted. Possible reasons for this increase might include distortion of the right atrial wall
269 in response to fluid overload, leading to sinoatrial node stimulation and increased sinoatrial
270 node firing and HR (Chiba 1977). It is also likely that reflexive tachycardia occurred in
271 response to reduced SVR as blood viscosity decreases as a result of fluid infusion. The
272 increasing RAP might have also induced atrium natriuretic peptide secretion, leading to a
273 reduction in SVR (Lang et al. 1987). However, the newer volatile anaesthetics, including
274 sevoflurane, tend to preserve CO at clinically useful concentrations, facilitated by reductions in
275 SVR (Steffey & Mama 2007). A high dose of sevoflurane possibly suppressed the

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

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

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

303 The present study is subject to some limitations. The TPTDCO technique was accurate when
304 compared with TDCO, with a decision coefficient (r^2) of 0.915. However, there was a
305 proportional error of 9.7% between the methods. Despite this small bias and limits of
306 agreement, the Bland–Altman plot demonstrated considerable dispersion around the bias.
307 Similar increases in dispersion around the bias at higher CVP levels are often reported in
308 studies comparing CO measurement techniques over a wide range of haemodynamic function.
309 Such bias can be statistically remedied via a proportional and/or log transformation of the data
310 (Tibby et al. 1997). Nonetheless, a wide range of CO should be included in the design of
311 appropriate experiments to evaluate new monitors. Increasing the number of comparative pairs
312 would have improved the reliability of the statistical analysis and might have narrowed the
313 limits of agreement. Additionally, a small interval (< 3 minutes) was required to shift from
314 TPTDCO to TDCO measurements (and vice versa), and therefore, these measurements were
315 not truly simultaneous. In this study, fluid therapy was temporarily discontinued during CO
316 measurements in order to prevent a change in hypervolaemic status. All other variables were
317 kept constant during these CO measurements and therefore it is unlikely that this interval led to
318 analytical errors. A further limitation of this study refers to the small sample size (six dogs and
319 30 pairs of data points), and accordingly the possibility of a Type II statistical error cannot be
320 eliminated. However, it was possible to minimize individual variations because both control
321 and experimental data were collected in the same animal.

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

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

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

335

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340

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440

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

448

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

455

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

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



