

# Transpulmonary ultrasound dilution is an acceptable technique for cardiac output measurement in anesthetized pigs

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## OBJECTIVE

To evaluate cardiac output (CO) measurements using transpulmonary ultrasound (TPUD) technology and compare results with those of the gold standard, pulmonary arterial catheter thermodilution (PACTD), in 6 healthy anesthetized pigs during acute hemodynamic changes caused by manipulation of the blood volume.

## ANIMALS

6 healthy male Landrace pigs.

## PROCEDURES

Over a period of 1 week, pigs were anesthetized with isoflurane, mechanically ventilated, and underwent instrumentation in dorsal recumbency. They were subjected to sequential experimental states during which the blood volume was manipulated so that the animals transitioned from normovolemia to hypovolemia (20% and 40% of blood volume depletion), back to normovolemia (autologous blood transfusion), and then to hypervolemia (following colloid bolus). During each volume state, CO measurements were compared between TPUD and PACTD.

## RESULTS

The mean  $\pm$  SD relative bias between TPUD and PACTD was  $7.71\% \pm 21.2\%$  with limits of agreement  $-33.9\%$  to  $49.3\%$ , indicating TPUD slightly underestimated CO values, compared with values obtained with PACTD. The mean  $\pm$  SD of the bias between the 2 methods was  $0.13 \pm 0.5$  L/min. Only 5 of 36 (13.9%) TPUD CO measurements had an absolute value of relative bias  $> 30\%$ . The percentage error calculated for TPUD was 29.4%.

## CLINICAL RELEVANCE

Results suggested that TPUD measurements have acceptable agreement with PACTD measurements. Moreover, TPUD exhibits promising potential in being used interchangeably with PACTD for future hemodynamic research involving swine as species of interest.

Cardiac output (CO) is defined as the volume of blood pumped by the heart per minute and maintains blood flow and oxygen delivery to the heart and other vital organs.<sup>1</sup> Moreover, optimum organ perfusion is determined by perfusion pressure as well as CO. This is why an accurate quantification of CO is beneficial during the perioperative management of critical patients.<sup>2</sup> With CO monitoring, the primary goals are detecting hemodynamic alterations, diagnosing their underlying causes, and guiding therapeutic decisions to optimize oxygen delivery to the tissues.<sup>3</sup>

Invasive CO monitoring with pulmonary arterial catheter thermodilution (PACTD) is referred to as the “gold standard” in animals.<sup>4-6</sup> A special thermistor-tipped Swan-Ganz catheter is inserted into the

pulmonary artery (PA), and a cold saline bolus is injected in the right atrium, to decrease the blood temperature in the PA. With the use of the indicator dilution principle, PACTD utilizes the temperature change as the indicator, and the mean decrease in temperature is inversely proportional to the CO.<sup>7</sup> This method is rarely employed in clinical settings due to the inherent risks of invasive catheterization such as thromboembolism, cardiac arrhythmias, hemorrhage, valvular injury, and infection.<sup>8</sup>

Complications arising from PACTD have led to the development of minimally invasive (MI) technologies. These newer techniques aim at producing continuous, cost-effective, and reliable hemodynamic data during various physiologic states using fast response time.<sup>9,10</sup> In the past decade, remarkable advances

have been made in veterinary medicine through the validation of several MI CO monitoring methods such as lithium dilution (LiD),<sup>4,11</sup> transesophageal echocardiography,<sup>12</sup> and transpulmonary pulse contour analysis.<sup>13,14</sup> Transpulmonary ultrasound dilution (TPUD) is another unique MI technology that utilizes central venous and arterial catheters and isotonic saline as an indicator. Blood ultrasound velocity ranges between 1,560 and 1,585 m/s depending on total blood protein, temperature, and ion concentration in plasma. In contrast, the ultrasound velocity in isotonic saline is only 1,533 m/s.<sup>15,16</sup> After injection of the saline bolus into venous circulation, change in blood velocity is measured by the ultrasound sensors. Dilution curves and Stewart Hamilton equation calculate the CO.<sup>15</sup>

The TPUD has been previously studied in dogs,<sup>16</sup> horses,<sup>17-19</sup> sheep,<sup>20-22</sup> and alpacas.<sup>23</sup> It is well established that swine are used for medical research due to their similar cardiac physiology as humans.<sup>24</sup> There has been limited research using TPUD in pigs as a pediatric animal model and further applying the data to human pediatric patients.<sup>15,25</sup> However, to the authors' knowledge, no veterinary studies have evaluated TPUD's efficacy in CO monitoring of pigs during acute changes in hemodynamics caused due to manipulation of blood volume. Hence, the aim of the present study was to evaluate the performance of TPUD against the gold standard, PACTD, in measuring CO during different blood volume states in anesthetized pigs. We hypothesized that TPUD will have acceptable agreement with PACTD in this scenario.

## Materials and Methods

### Animals

The study protocol was approved by the University of Florida Institutional Animal Care and Use Committee (protocol No. 201609273). Six purpose-bred male Landrace pigs were enrolled in this study. All pigs were 8 to 10 months old, and the mean  $\pm$  SD body weight was 20.1  $\pm$  0.5 kg. They were determined healthy on the basis of a thorough physical examination, CBC, and serum biochemical analyses. The pigs were housed and cared for in accordance with Association for Assessment and Accreditation of Laboratory Animal Care International guidelines.

### Anesthetic induction and standard monitoring

For each pig, food, but not water, was withheld for 15 hours before anesthetic induction. Accurate body weights were obtained on the day of the experiment. Ketamine (10 mg/kg, IM) was used solely as the premedication. General anesthesia was then induced with 5% isoflurane in oxygen delivered via a face mask and circle system connected to anesthesia machine until endotracheal intubation was successfully achieved. The endotracheal tube was then secured, and anesthesia was maintained with isoflurane.

A 22-gauge catheter was aseptically placed in an auricular vein for temporary vascular access, and

the pigs were then positioned in dorsal recumbency. A multiparametric monitor was used to continuously monitor the lead II ECG tracing, pulse oximetry, esophageal temperature, and anesthetic gas concentrations. An isoflurane vaporizer dial was adjusted as necessary to maintain the end-tidal isoflurane concentration around 1.6%, which is approximately 1.2 times the minimum alveolar concentration of isoflurane reported for pigs.<sup>26</sup> Esophageal temperature was maintained between 37 and 39 °C using a forced-air warming device and circulating warm water blankets.

Neuromuscular blockade was initiated with the atracurium bolus of 1 mg/kg, IV, and the efficiency of the blockade was monitored by a supramaximal train-of-four electrical stimulus of the common peroneal nerve. Atracurium dosing was repeated as necessary on the basis of a return of twitches during the train-of-four function on the nerve stimulator. Each pig underwent volume-controlled ventilation, with tidal volume held constant at 12 mL/kg and the respiratory frequency adjusted between 12 and 20 breaths/min to maintain the arterial partial pressure of carbon dioxide between 35 to 45 mm Hg.

### Instrumentation and need for arterial line

The left and right femoral arteries were carefully dissected, and a 5-F femoral arterial line was placed in each artery and secured. The arterial line in the right femoral artery was used for periodic arterial blood gas analysis, recording invasive blood pressures, and during CO measurements by TPUD. A saline (0.9% NaCl) solution-filled pressure transducer system was calibrated, and the transducer was zeroed and placed at the level of the manubrium at the time of each data recording. The arterial line in the left femoral artery was used for withdrawal of blood during controlled hemorrhage.

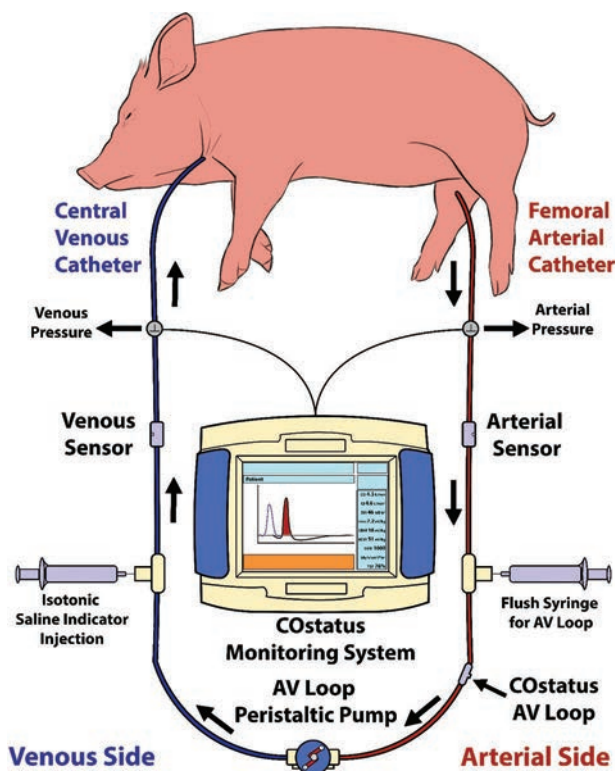
### Instrumentation for CO monitoring by PACTD (PACTD<sub>CO</sub>)

The left and right external jugular veins were carefully dissected, and an 8-F introducer (Arrow Percutaneous Sheath Introducer; Teleflex) was inserted in each jugular vein and secured. The introducer sheath in the left jugular vein was used for TPUD measurements. A 7-F thermodilution PA catheter (Swan-Ganz Catheter; Edwards Lifesciences Corp) was advanced through the introducer in the right jugular vein until its distal pressure sensing lumen was located in the PA. Correct placement of the thermodilution catheter was determined on the basis of observation of characteristic pressure waveforms and pressure values after it was connected to the PACTD monitor (Cardiac output-IntelliVue; Phillips Healthcare). For PACTD<sub>CO</sub>, a 10-mL bolus of chilled (3 to 5 °C) 5% dextrose solution was periodically injected into the central venous port of the thermodilution catheter. The temperature of the injected dextrose solution was measured by an in-line thermistor that was located between the syringe and injection port of the PA catheter. All hemodynamic data were transferred

to a bioamplifier (PowerLab; AD instruments), which sent continuous real-time data to a laptop computer equipped with software (ChartPro; AD Instruments) to record it.

### Instrumentation for CO monitoring by TPUD (TPUD<sub>CO</sub>)

The set up for TPUD (Figure 1) included the use of a central venous catheter and a femoral arterial line to create an arteriovenous (AV) loop between these 2 catheters. With the formation of this extracorporeal circuit, blood was put through a peristaltic pump to provide stable blood flow during measurements. Ultrasound velocity sensors and flow sensors were also a part of this circuit. Periodic flushing of the AV loop was performed with heparin (1 U/mL)



**Figure 1**—Graphical representation of the set up for transpulmonary ultrasound dilution (TPUD) using a cardiac output (CO) multiparameter monitor (COstatus; Transonic Systems Inc) to measure CO in 6 healthy, anesthetized, purpose-bred male Landrace pigs during acute hemodynamic changes caused by manipulation of the blood volume. An extracorporeal arteriovenous (AV) loop is connected to an indwelling femoral arterial catheter and central venous catheter. Blood is directed via a peristaltic pump. Ultrasound velocity sensors and flow sensors are also present on the circuit. Periodic flushing of the AV loop is performed with heparinized flush to prevent thrombosis formation, and 0.9% saline bolus (1 mL/kg body weight) prewarmed to body temperature is used as an indicator. After the arterial sensor detects the changes in the blood ultrasound velocity, a dilution curve is generated on the monitor and cardiac output values are displayed. The figure is modified and reproduced from the *British Journal of Anaesthesia*,<sup>27</sup> with permission of Elsevier, all rights reserved.

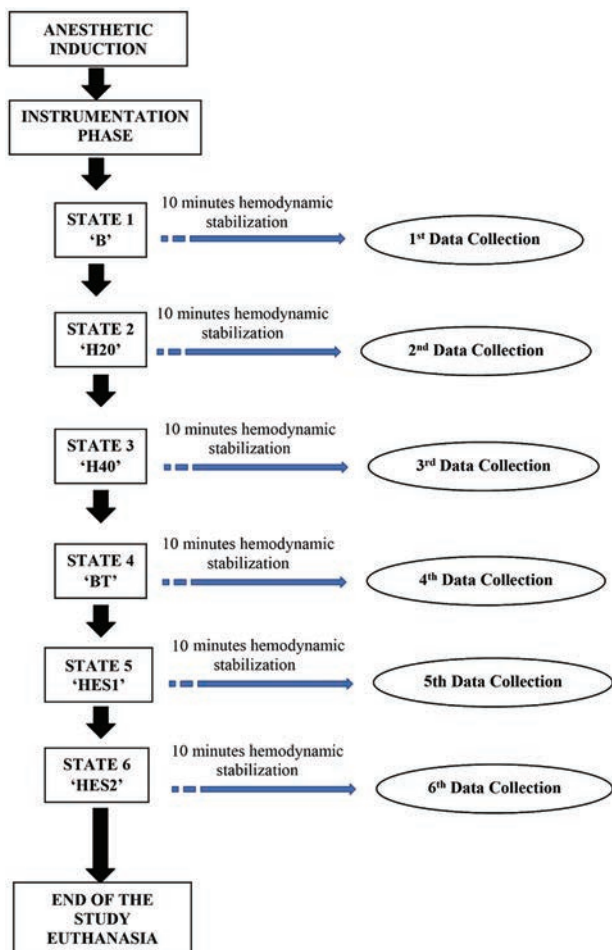
to prevent thrombosis. Indicator 0.9% saline bolus (1 mL/kg) prewarmed to body temperature was injected into the venous limb, and the venous flow sensor measured the exact amount of injected indicator and the ultrasound velocity of the used saline. As the injected saline bolus circulated through the body, it caused a transient dilution of blood proteins. This temporary hemodilution was detected by the arterial flow sensor as a decrease in ultrasound velocity. A curve was then generated that represented the extent of this dilution over time. With this ultrasound dilution curve, CO was calculated by the TPUD monitor (COstatus, Transonic Systems Inc).

### Experimental design and different volume states

After instrumentation, each pig was subjected to sequential nonrandomized blood volume states (Figure 2). First, baseline data collection was performed (state 1: normovolemia; B). Following this, controlled hemorrhage was induced by withdrawing blood from the left femoral line over a period of 15 minutes until 20% (state 2: moderate hypovolemia; H20) and 40% (state 3: severe hypovolemia; H40) of the estimated total circulating blood volume was removed. The total circulating blood volume for pigs was considered as 70 mL/kg of body weight.<sup>28</sup> The blood that was withdrawn was stored in blood collection bags containing an anticoagulant. The bags were placed on a weighing scale and continuously weighed as they were being filled to ensure that only the calculated amount of blood was removed during hypovolemia states. The next step involved transfusing the total volume of blood removed during states 2 and 3 (state 4: normovolemia; BT) via the left jugular introducer over a period of 15 minutes. In the next state, a 500-mL bolus of 6% hydroxyethyl starch was administered through the left jugular introducer over a period of 15 minutes, and data were collected 10 minutes after the bolus was finished (state 5: hypervolemia; HS1). Last recordings were performed 30 minutes after state 5 data were collected, and this was referred to as a separate state (state 6: hypervolemia; HS2). Once all data were acquired, each pig was humanely euthanized with pentobarbital overdose (1 mL/10 kg body weight).

### PACTD<sub>CO</sub> and TPUD<sub>CO</sub> data collection

At least 10 minutes were given for hemodynamic stabilization before any data were recorded under each state. At each data point, PACTD<sub>CO</sub> represented the mean of 3 consecutive measurements, and TPUD<sub>CO</sub> represented the mean of 2 consecutive measurements. If there was more than 10% variation between PACTD<sub>CO</sub> data value or TPUD<sub>CO</sub> data during the collection, then an extra reading was obtained. At least 3 minutes were given between each CO measurement for both techniques. The order of the 2 techniques was randomized using a coin toss. Each researcher was assigned to record data from either PACTD or TPUD during the study and hence was blinded to the measurements from the other technique at all times.



**Figure 2**—Timeline of the data collection performed in obtaining measurements of CO in the pigs described in Figure 1 with the use of TPUD versus the gold standard, pulmonary arterial catheter thermodilution (PACTD). After anesthetic induction and instrumentation, each pig underwent baseline data collection (state 1 “B”: normovolemia;). Following this, controlled hemorrhage was induced by withdrawing blood over 15 minutes until 20% (state 2 “H20”: moderate hypovolemia) and 40% (state 3 “H40”: severe hypovolemia) of the estimated total circulating blood volume was removed. The blood that was withdrawn during states 2 and 3 was transfused back to the pig over 15 minutes in the next step (state 4: “BT”: normovolemia). In the next state, a 500-mL bolus of 6% hydroxyethyl starch was administered over 15 minutes, and data were collected 10 minutes after the bolus was finished (state 5 “HS1”: hypervolemia). Last recordings were performed 30 minutes after state 5 data were collected, and this was referred to as a separate state (state 6: hypervolemia; HS2). For each pig, once all data were acquired, the pig was euthanized.

## Statistical analysis

The bias for each observation was calculated as follows:  $PACTD_{CO} - TPUD_{CO}$ . Considering the measurements represented a large physiographical range (low, intermediate, and high CO values), the bias was expressed as a percentage of the average CO values, as recommended in the literature.<sup>29</sup>

Hence, the relative bias (RB) was calculated using the following equation:

$$RB = \frac{(PACTD_{CO} - TPUD_{CO})}{[0.5 \times (PACTD_{CO} + TPUD_{CO})]} \times 100 \quad (1)$$

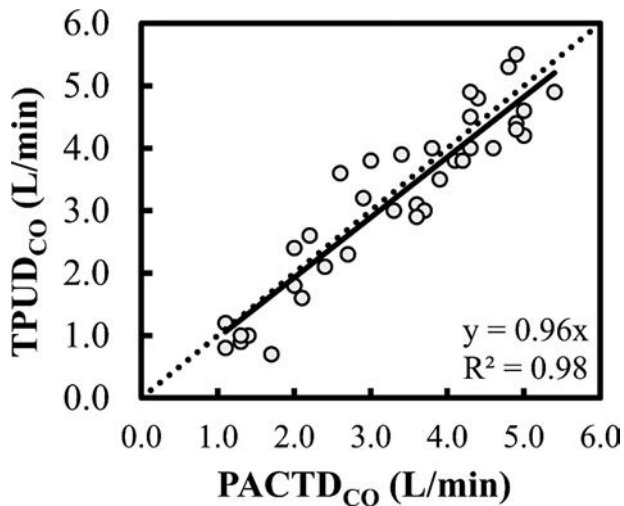
A positive RB (%) represented underprediction of  $TPUD_{CO}$  when compared with  $PACTD_{CO}$ , whereas a negative RB (%) represented overprediction of  $TPUD_{CO}$ . The limits of agreement (LOA) were reported as  $RB \pm 1.96 \times SD$  to include 95% CI. According to past literature,<sup>29</sup> the overall mean of  $RB < 30\%$  was required for an acceptable performance by the test method as compared with the reference method. In addition, the absolute value of RB for each observation was compared with the 30% value for an overall performance estimate.

Normality of the bias data was assessed using the Shapiro-Wilk and D’Agostino and Pearson tests. The relationship between  $PACTD_{CO}$  and  $TPUD_{CO}$  was measured using a linear regression analysis. Concordance between PACTD and TPUD was assessed using the Lin concordance correlation ( $\rho_c$ ), an integrated quantifier of precision and accuracy, with a value of 1 indicating perfect concordance.<sup>30</sup> The Bland and Altman (BA) method<sup>31</sup> was used to evaluate the agreement between  $PACTD_{CO}$  and  $TPUD_{CO}$ . In case the mean and SD of the bias between CO values of TPUD and PACTD were dependent on the magnitude of the original measurement, and a relationship between bias and magnitude of measurements existed (proportioning effect), then the BA analysis for nonuniform differences was conducted. Under this scenario, the bias was linearly regressed against the average bias.<sup>32</sup> Finally, a polar plot was used to analyze the agreement between  $PACTD_{CO}$  and  $TPUD_{CO}$ ,<sup>33</sup> where the distance from the center represented the absolute values of the mean change in CO ( $[\Delta PACTD_{CO} + \Delta TPUD_{CO}]/2$ ), and the angle with the horizontal ( $0^\circ$  radial) represented the disagreement. A good trending ability was characterized as data located within 10% of the mean CO. All analyses were conducted using a commercial statistical software (SAS version 9.4; SAS Institute Inc). The BA and polar plots were created with available software (Excel, Microsoft Corp; Polar Plot 2 analysis add-in; accessed October 26, 2021; <https://andypope.info/charts/polarplot3.html>). For all analyses, values of  $P < 0.05$  were considered significant.

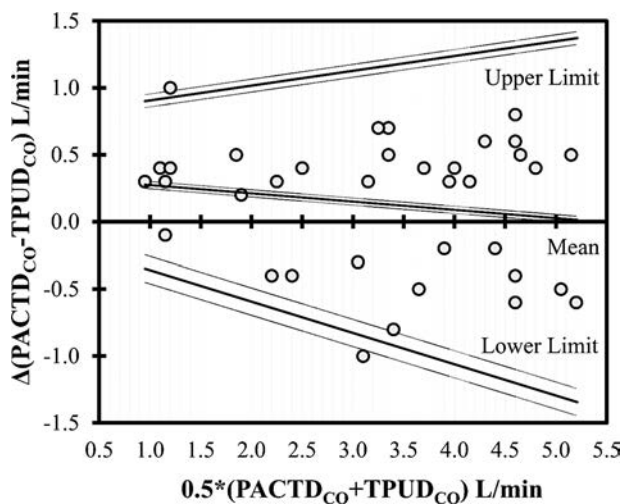
## Results

This research study was carried over a period of 1 week such that 1 pig underwent the experiment in 1 day. A total of 36 comparisons were determined between PACTD and TPUD, as there was  $< 10\%$  variation across triplicate (for PACTD) and duplicate (for TPUD) measurements for both methods. The mean  $\pm$  SD of  $PACTD_{CO}$  was  $3.34 \pm 1.31$  L/min (range, 1.1 to 5.4 L/min) and of  $TPUD_{CO}$  was  $3.21 \pm 1.39$  L/min (range, 0.7 to 5.5 L/min), respectively. The mean  $\pm$  SD of the bias between the 2 methods was  $0.13 \pm 0.5$  L/min. The RB (%) between the 2 methods was



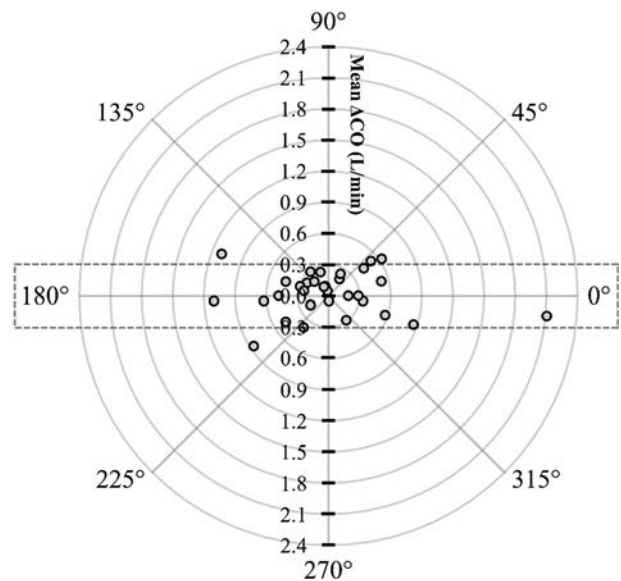


**Figure 3**—Scatter plot representing measurements of CO by TPUD (TPUD<sub>CO</sub>) and PACTD (PACTD<sub>CO</sub>) for the 6 pigs described in Figure 1 across the 6 blood volume states (36 observations) described in Figure 2. Regression analysis about the line  $Y = X$  (dashed line) resulted in a good fit (solid line) as shown by the slope (0.96) and  $R^2$  (0.98).



**Figure 4**—Bland-Altman plot showing nonuniform differences between PACTD<sub>CO</sub> and TPUD<sub>CO</sub> measurements for the 6 pigs described in Figure 1 across 6 blood volume states (36 observations) described in Figure 2, showing a weak relationship (slope = -0.06; intercept = 0.34) between the bias and the average CO data. Each circle represents an individual difference value, the central solid line represents the nonuniform mean bias of the differences, the upper and lower solid lines represent the upper and lower limits of agreement, and the fainter dashed lines represent the 95% CI for each. Overall, there is a good agreement between TPUD<sub>CO</sub> and PACTD<sub>CO</sub> as only 2 observations were outside the limits of agreement.

$7.71 \pm 21.2\%$  (LOA, -33.9% to 49.3%). Five of 36 (13.9%) observations had an absolute value of RB > 30%. The percentage error (PE) expressed as  $(100 \times 1.96 \times \text{SD of the bias/mean CO})$  was reported as 29.4%.



**Figure 5**—Polar plot representing changes in CO values measured by TPUD<sub>CO</sub> and PACTD<sub>CO</sub> methods for the 6 pigs described in Figure 1 across 6 blood volume states (36 observations) described in Figure 2. Dotted lines represent 10% agreement boundaries (ie, 10% = 0.33 L/min as mean CO = 3.3 L/min). The distance from the center represents the absolute values of the mean change in CO  $[(\Delta\text{PACTD}_{\text{CO}} + \Delta\text{TPUD}_{\text{CO}})/2]$ , and the angle from the horizontal 0° radial axis represents the disagreement. The plot shows good trending ability as only 4 points lie outside the limits of good agreement.

The regression about line  $Y = X$  (**Figure 3**) yielded the expression:  $\text{TPUD}_{\text{CO}} = 0.96 \times \text{PACTD}_{\text{CO}}$  ( $R^2 = 0.98$ ). A positive mean RB (7.71%) and slope (< 1) about  $Y = X$  indicated a slight underprediction of TPUD<sub>CO</sub> when compared with PACTD<sub>CO</sub>. The Lin concordance correlation coefficient between PACTD and TPUD was  $\rho_c = 0.93$  ( $P < 0.001$ ). Initial data analysis revealed that the bias (PACTD<sub>CO</sub> - TPUD<sub>CO</sub>) was nonnormally distributed. Therefore, BA analysis for nonuniform differences was conducted. The BA analysis for nonuniform differences showed a weak relationship (slope = -0.06; intercept = 0.34) between the bias and the average CO data (**Figure 4**), which indicated a consistent performance of TPUD across a broad range of CO values. Overall, there was a good agreement between TPUD and PACTD as only 2 observations were outside the LOA from the BA analysis. The polar plot (**Figure 5**) showed a good trending ability across a large physiographic range of CO values as the majority of the data points were inside the limits of good agreement (ie, 10% = 0.33 L/min as mean CO = 3.3 L/min) and only 4 points were outside these limits.

## Discussion

The use of PACTD in clinical settings is often questioned due to the invasiveness, impracticalities, and complications reported in humans and veterinary species.<sup>34-36</sup> The goal of the present study was to test the agreement of TPUD with PACTD to evaluate MI

methods that can replace PACTD during hemodynamic research in pigs. Newer CO monitoring methods that are MI are being introduced in veterinary medicine, but the data are still limited in swine regarding these techniques, especially the TPUD technology. The present study observed that TPUD had a good agreement with the gold standard, PACTD, when acute changes were made to the blood volume of pigs.

A prior study<sup>15</sup> in piglets compared TPUD with PA blood flow measured by transit time ultrasound flow probe. They reported that TPUD overestimated pulmonary blood flow with 0.040 L/min (LOA,  $\pm$  0.258 L/min) and 0.058 L/min (LOA,  $\pm$  0.136 L/min) for CO measurements in piglets with 0.5 mL/kg and 1.0 mL/kg of injection volume, respectively. Darling et al<sup>25</sup> showed that in adult healthy pigs, the bias between PACTD and TPUD was 0.3 L/min (LOA, -0.39 to 0.99 L/min), and both these methods matched equally well over the entire range of CO measured. However, the performance of TPUD during that study<sup>25</sup> was not assessed during manipulations made in the CO states, such as hemorrhagic shock or hypervolemia.

The accuracy of the TPUD has been evaluated against LiD in dogs,<sup>16</sup> neonatal foals,<sup>17</sup> and juvenile horses<sup>18</sup> for measuring CO. In these studies, LiD was selected as the reference method instead of PACTD, due to the invasiveness, risks, and technical difficulties associated with the PACTD. Hence, it would be challenging to predict if TPUD would have shown similar agreement with PACTD as a reference method in these species. The  $\rho_c$  between LiD and TPUD was 0.88 in dogs, 0.83 in neonatal foals, and 0.89 in juvenile horses, suggesting TPUD had an acceptable performance. In the present analysis,  $\rho_c$  between PACTD and TPUD was 0.93 ( $P < 0.001$ ), and TPUD also demonstrated good repeatability even during acute fluctuations occurring in CO with acute changes made in the blood volume.

Based on a meta-analysis of studies using bias and precision statistics to compare CO measurement techniques, it was recommended that combining the errors of both the test and reference method, acceptance of a new method of measuring CO should rely on LOA of up to  $\pm$  30%.<sup>37</sup> In the present study, TPUD measured only 5/36 observations out of this 30% acceptable limit. The positive mean RB of  $7.71 \pm 21.2\%$  indicated that TPUD slightly underestimated CO when compared with PACTD values. Nonetheless, the PE for TPUD was 29.4%, which was within the range of 9.5% to 31.4% reported from other human and animal studies.

The benefits of using TPUD are as follows: (1) use of a nontoxic indicator (isotonic saline) and existing vascular catheters; (2) operator independency; (3) no need for calibration; and (4) easy and fast setup ( $< 10$  min). Unlike LiD, it is not associated with any blood loss. No clinically relevant changes in cerebral and systemic circulation and oxygenation have been associated with TPUD.<sup>38</sup> The ultrasound blood velocity can be affected by temperature fluctuation,<sup>39</sup> and it is recommended that the isotonic saline bolus should be warmed up to body temperature. Moreover, reducing the volume or using room temperature saline has

been shown to reduce the accuracy of TPUD.<sup>40</sup> Hence, in the present study, we used a 1-mL/kg saline bolus prewarmed to body temperature as the indicator for TPUD to avoid erroneous CO readings.

The limitations of TPUD are as follows: (1) inability to perform continuous CO measurements; (2) necessity of arterial and venous catheters; (3) need for repeated injections that can cause significant volume load in small patients with marginal hemodynamics; and (4) inaccessibility to invasive blood pressure monitoring when TPUD is in use.<sup>16</sup> Potentially, indicator loss may occur in the nonhomogenous perfused lung units. This may overestimate the CO or cause shunting of blood, thus distorting the indicator dilution curves.<sup>15,27</sup> When the blood flows through AV loop in a peristaltic pump, platelet damage and clot formation can occur. Even though we did not observe formation of clots in the extracorporeal circuit, TPUD needs further evaluation in patients with coagulopathies.

The present study had limitations. The sample size was small to follow the ethical considerations for a terminal study. However, we controlled the variables that could have affected the hemodynamic status of the pigs to minimize their influence on our results. It was critical that the influence of compensatory body mechanisms on hemodynamics in the face of hypovolemia and hypervolemia did not cause significant and long-lasting effects that were carried forward during the state of normovolemia. Hence, the sequence of the volume states was not randomized. Critically ill patients often experience considerable fluctuations in their hemodynamics, and this study did not interrogate validity of TPUD in pigs with systemic diseases. Hence, further studies are warranted to ensure that the accuracy of TPUD is maintained in such patients.

With the use of a saline bolus indicator and ultrasound sensors on an AV loop, TPUD detected blood dilution on the venous and arterial side necessary for calculation of CO. This MI method demonstrated acceptable agreement with PACTD in anesthetized pigs. The mean RB and PE with TPUD was clinically acceptable in this population. Even though TPUD could be used interchangeably with other reference methods of CO measurement in healthy pigs (eg, PACTD), further research is required to evaluate its accuracy in clinical systemically ill patients.

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The authors declare that there were no conflicts of interest.

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