Comparison of arterial pressure waveform analysis with the lithium dilution technique to monitor cardiac output in anesthetized dogs

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Objective—To assess agreement between arterial pressure waveform–derived cardiac output (PCO) and lithium dilution cardiac output (LiDCO) systems in measurements of various levels of cardiac output (CO) induced by changes in anesthetic depth and administration of inotropic drugs in dogs.

Animals—6 healthy dogs.

Procedure—Dogs were anesthetized on 2 occasions separated by at least 5 days. Inotropic drug administration (dopamine or dobutamine) was randomly assigned in a crossover manner. Following initial calibration of PCO measurements with a LiDCO measurement, 4 randomly assigned treatments were administered to vary CO; subsequently, concurrent pairs of PCO and LiDCO measurements were obtained. Treatments included a light plane of anesthesia, deep plane of anesthesia, continuous infusion of an inotropic drug (rate adjusted to achieve a mean arterial pressure of 65 to 80 mm Hg), and continuous infusion of an inotropic drug (7 μg/kg/min).

Results—Significant differences in PCO and LiDCO measurements were found during deep planes of anesthesia and with dopamine infusions but not during the light plane of anesthesia or with dobutamine infusions. The PCO system provided higher CO measurements than the LiDCO system during deep planes of anesthesia but lower CO measurements during dopamine infusions.

Conclusions and Clinical Relevance—The PCO system tracked changes in CO in a similar direction as the LiDCO system. The PCO system provided better agreement with LiDCO measurements over time when hemodynamic conditions were similar to those during initial calibration. Recalibration of the PCO system is recommended when hemodynamic conditions or pressure waveforms are altered appreciably. (*Am J Vet Res* 2005;66:1430–1436)

The ability to measure and monitor **cardiac output (CO)** is essential for making therapeutic decisions in many critical and high-risk human surgical patients. Thermodilution has been the most commonly used technique to measure CO.[1] However, in veterinary medicine, it is limited in use as a clinical research tool, mainly as a result of the invasive nature of pulmonary artery catheterization, expertise required, and cost of the equipment.

A hemodynamic monitor[a] has recently been introduced as a new commercial system for measuring CO.[2] This new monitor incorporates **arterial pressure waveform–derived cardiac output (PCO)** and **lithium dilution cardiac output (LiDCO)** systems as a single unit.[b] The LiDCO system measures CO by use of a lithium chloride indicator dilution system. This technique is now well established and has been validated in humans,[3,4] horses,[5,6] pigs,[7] and dogs.[8] The main advantages of the LiDCO system over thermodilution are the avoidance of pulmonary artery catheterization with its associated hazards and simpler instrumentation. Furthermore, a catheterized peripheral vein can be used to inject the lithium indicator,[9,10] eliminating the need for central venous catheterization in patients that do not warrant it. However, repeated lithium injections increase background serum lithium concentrations and can overestimate CO.[11] This limits the number of LiDCO measurements and precludes continuous CO monitoring with this system alone.

The PCO system was developed to meet the need for continuous and noninvasive CO monitoring in the clinical setting. For operation, the PCO monitor is connected to a primary direct blood pressure monitor that provides an analog signal where 1 V equals 100 mm Hg. The analog arterial pressure trace undergoes a 3-step transformation by the PCO algorithm to derive the estimation of CO.[2] A nominal stroke volume is determined and converted to an estimation of the CO by multiplying it with heart rate and a calibration factor on the basis of the actual CO value (determined by use of standard methods such as the LiDCO system or thermodilution technique). After a 1-point calibration with the LiDCO system, the PCO monitor displays a beat-by-beat value for CO. By combining the PCO and LiDCO systems as a single unit, monitoring CO in the clinical setting becomes more convenient.

Because the PCO algorithm is dependent on the pressure waveform and mathematic equations that incorporate blood pressure in its calculations, it is appropriate to question whether the monitoring system can accurately track CO changes when there are

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substantial alterations of the pressure waveform or hemodynamic parameters. Initial reports[2,c,d] on the clinical use of the PCO monitor in human patients have been positive and encouraging. In humans, the PCO algorithm closely tracked the CO measured by either the LiDCO system[e] or thermodilution technique[12] and did not require recalibration for at least 8 hours in surgical patients recovering in the intensive care unit. However, the hemodynamic changes from the point of calibration to predetermined time points in the reported studies might not have been substantial for many patients recovering in the intensive care unit. During clinical anesthesia, considerable hemodynamic fluctuations commonly occur intraoperatively, and for optimum use as a CO monitor, a system should be adaptable to such fluctuations. It is also possible that the algorithm developed on the basis of a human pressure waveform might not work as well with a canine arterial waveform. To our knowledge, there is no report describing the use of the PCO system to measure CO in dogs under anesthesia. The study reported here was undertaken to assess the agreement between the PCO system and routine LiDCO system to measure various levels of CO induced by changes in anesthetic depth and by the administration of inotropic drugs in healthy dogs under isoflurane anesthesia.

Materials and Methods

Animals—The University of Guelph Animal Care Committee approved this study. Six healthy crossbred dogs, 1.8 ± 0.8 (mean ± SD) years of age and weighing 27.5 ± 4.9 kg, were used. Health status was based on a general physical examination and measurement of Hct, serum total protein concentration, and BUN concentration. A detailed cardiac examination prior to recruitment into the study included echocardiography (performed by a certified cardiologist) to ascertain normal cardiac size and contractility, valvular competence, and absence of cardiac shunts

Anesthesia and instrumentation—Following overnight withholding of food, dogs were induced with propofol[f] (6 mg/kg, IV, to effect), intubated, placed in lateral recumbency, and maintained on isoflurane[g] in 100% oxygen with controlled ventilation to maintain end-tidal CO_2 between 35 to 45 mm Hg. An ear vein was used to administer crystalloid fluids at 3 mL/kg/h along with the inotropic drugs. Body temperature was maintained at 36.5° to 38.5°C by use of heated air blankets[h] and electric water heating pads.

A multichannel patient monitor[i] was used to monitor airway gases and all physiologic parameters except direct blood pressure, which was measured by use of a monitor[j] that produced a 1-V analog signal for 100 mm Hg pressure. Prior to each experiment, all pressure transducers[k] and pressure channels were calibrated with a mercury manometer and zero was set at the midsagittal level. The airway gas monitor was calibrated with a commercial gas mixture[l] prior to each experiment. Heart rate and rhythm were monitored by use of a standard lead II ECG and body temperature via an esophageal temperature probe.[i] A 19-gauge, 12-inch catheter[m] was inserted into a jugular vein and advanced to the level of the right atrium to measure right atrial pressure, with correct placement confirmed by observing the characteristic waveform on the patient monitor.

Both dorsal pedal arteries were catheterized percutaneously by use of 20-gauge, 1.88-inch catheters.[n] The dependent artery was connected to a lithium sensor[o] and the LiDCO monitor,[a] while the other was connected to the blood pressure monitor[j] to provide the arterial pressure waveform analog signal to the PCO monitor[p] and used for blood sample collection. Thus, concurrent PCO measurements were achieved during LiDCO measurements. The cephalic vein was connected to an extension tube[q] for the purpose of preloading the required lithium chloride for an uninterrupted bolus injection of the lithium indicator during LiDCO measurements. On recovery, acepromazine[r] (0.02 mg/kg, IV), butorphanol[s] (0.2 mg/kg, IV), and meloxicam[t] (0.1 mg/kg, IV) were administered.

Experimental design—All dogs were anesthetized twice, with a minimum interval of 5 days, to allow randomly assigned crossover use of either dopamine[u] or dobutamine[v] as the inotrope for each experiment. The assigned inotropic drugs were diluted in 5% dextrose before each experiment and administered by use of a syringe pump. Following induction, dogs were maintained at 1.5% to 1.8% **end-tidal isoflurane concentration (Et-iso)** for at least 30 minutes to allow instrumentation and ensure stability of hemodynamic parameters (Et-iso, end-tidal CO_2 concentration, mean arterial pressure, and heart rate did not fluctuate more than 5% for at least 10 minutes). The PCO monitor was then calibrated against LiDCO measurements with no treatments in use (baseline). The calibration factor determined at baseline was used for all subsequent PCO measurements during treatments. Following calibration, 4 treatments were randomly administered to induce hemodynamic changes and concurrent pairs of CO measurements were obtained by both systems. The 4 treatments consisted of the following: a light plane of anesthesia (1.3% to 1.8% Et-iso); a deep plane of anesthesia (2.7% to 3.3% Et-iso); continuous infusion of the assigned inotrope at a rate adjusted to achieve a mean arterial pressure of 65 to 80 mm Hg (1.5% to 2.0% Et-iso); and continuous infusion of the assigned inotrope at 7 µg/kg/min (1.5% to 2.0% Et-iso).

Steps for preparing the lithium sensors, checking for a suitable sensor voltage and stable baseline signal, were as described in the operation manual.[b] A lithium chloride[w] dose of 0.15 mmol (1 mL) was used for all LiDCO measurements throughout this study with a sensor constant of 10.5. A cephalic vein was used for injection of the lithium indicator, as previously validated in dogs.[10] For each CO measurement, 2 mL of arterial blood was aspirated anaerobically for immediate blood gas,[x] sodium,[y] and hemoglobin[z] measurements. The required sodium and hemoglobin values were entered into the LiDCO monitor. Lithium chloride was preloaded into the required extension tube. Once a stable baseline was achieved on the LiDCO monitor, the ventilator was arrested at end expiration and 6 mL of saline (0.9% NaCl) solution was used to flush the lithium chloride into the vein. The event marker on the PCO monitor was activated immediately after the injection and again when the LiDCO monitor signaled the end of LiDCO measurement. The concurrent beat-to-beat PCO measurements during the period that LiDCO measurements were taken were retrieved later from the PCO monitor, and CO was taken as the mean value for that period. Hemodynamic and respiratory parameters were recorded immediately before the lithium chloride injection and immediately after obtaining the LiDCO measurement. If instability of the hemodynamic parameters or baseline signal on the LiDCO monitor was observed during measurements, an interval of at least 5 minutes was allowed before attempting to obtain another paired CO measurement for the treatment level. A plane of hemodynamic stability was ensured (as described previously) within 20 to 60 minutes after initiation of each treatment.

Physiologic parameters for each treatment were taken as the mean value of the measurements immediately before and immediately after obtaining the LiDCO measurement. **Systemic vascular resistance (SVR)** was calculated separately on the basis of CO obtained from PCO and LiDCO measurements (SVR_P and SVR_L, respectively), where SVR (dyn•sec•cm^{-5}) = (mean arterial pressure [mm Hg] – right arterial pressure [mm Hg])/CO (L/min) × 80.

Statistical analyses—All 48 pairs of CO measurements were analyzed for differences between the PCO and LiDCO systems of measurement by use of a mixed model[aa] on log-transformed data. Our goal was to check for any significant confounding treatment, dog, time, total lithium chloride received, and carryover of previous treatment effects. All nonsignificant ($P > 0.05$) factors were removed from the model, and the difference of least squares means (adjusted for multiple comparisons[13]) was applied to check for differences between the PCO and LiDCO measurements within each treatment. A multivariate analysis[aa] with similar steps to check for confounders was used to calculate the Pearson correlation coefficient between the PCO and LiDCO measurements. Agreement between the PCO and LiDCO measurements was compared by use of the Bland-Altman technique.[14] In addition, 95% content tolerance intervals with 95% confidence were constructed.[15] Other physiologic parameters were analyzed for treatment difference by use of a 2-way ANOVA for a randomized complete blocked design.[aa] A Dunnett test was applied for comparison to baseline calibration values, and a Tukey test was used for comparison among treatment levels. For all statistical procedures, residual analyses were conducted to assess whether assumptions for ANOVA were met (model adequacy, normality, and equal variances). A Shapiro-Wilk test was used to check for normality, and data were log transformed when necessary. Significance was considered at values of $P < 0.05$.

Results

All 48 pairs of CO measurements were collected successfully from the 6 dogs. The measurements were summarized and presented as mean ± SD values according to the treatments (**Table 1**). All LiDCO measurements for the 4 treatment levels within the same experiment day were achieved with < 8.0 (5.8 ± 0.94) mL of lithium chloride. The duration of each experiment (from induction to recovery) ranged from 3 to 4.7 (3.7 ± 0.5) hours. Dogs recovered smoothly from anesthesia with no adverse effects.

No difference in measurements was found between experimental days during calibration and light and deep planes of anesthesia. Compared with the baseline blood pressure (systolic, mean, and diastolic arterial pressures) at calibration, the deep plane of anesthesia induced lower blood pressure, whereas dopamine infusions induced higher blood pressure. Pulse waveforms were visibly different with the treatments (**Figure 1**). Dobutamine infusions induced higher heart rate, systolic arterial pressure, and hemoglobin concentrations but lower SVR_L (on the

Table 1—Mean ± SD estimates of cardiac output, obtained by use of the pulse contour cardiac output (PCO) system or the lithium dilution cardiac output (LiDCO) system, and values of physiologic parameters in 6 anesthetized dogs under various conditions.

		Anesthetic conditions					
Parameter	**Baseline calibration**	**Light plane**	**Deep plane**	**Dopamine adjusted***	**Dopamine (7 μg/kg/min)**	**Dobutamine adjusted***	**Dobutamine (7 μg/kg/min)**
Temperature (°C)	37.6 ± 0.5	37.4 ± 0.4^{a}	37.6 ± 0.3^{a}	37.7 ± 0.4^{a}	37.5 ± 0.4^{a}	37.6 ± 0.5^{a}	37.7 ± 0.3^{a}
End-tidal isoflurane (vol %)	1.57 ± 0.15	1.64 ± 0.16^{a}	2.99 ± 0.24†^{b}	1.72 ± 0.17^{a}	1.72 ± 0.13^{a}	1.77 ± 0.14^{a}	1.8 ± 0.11†^{a}
Arterial carbon dioxide tension (mm Hg)	36.8 ± 1.8	36.9 ± 1.5^{a}	37.9 ± 3.0^{a}	37.0 ± 3.2^{a}	37.1 ± 3.6^{a}	36.6 ± 2.4^{a}	36.0 ± 1.8^{a}
Arterial oxygen tension (mm Hg)	546.9 ± 40.2	541.0 ± 42.8^{a}	540. 2 ± 17.1^{a}	554.7 ± 24.6^{a}	565.9 ± 25.6^{a}	546.4 ± 33.3^{a}	552.8 ± 26.4^{a}
Sodium (mmol/L)	147 ± 3	147 ± 3^{a}	146 ± 3^{a}	145 ± 4^{a}	145 ± 4^{a}	150 ± 3^{a}	150 ± 2^{a}
Hemoglobin (g/dL)	13.3 ± 1.5	13.2 ± 1.4^{a}	13.1 ± 1.4^{a}	14.1 ± 1.5^{ab}	13.8 ± 1.5^{ab}	15.1 ± 1.7†^{bc}	15.8 ± 1.3†^{c}
Right atrial pressure (mm Hg)	4 ± 2	4 ± 1^{a}	8 ± 2†^{b}	5 ± 1^{a}	5 ± 2^{a}	3 ± 1^{a}	3 ± 1^{a}
Heart rate (beats/min)	88 ± 12	97 ± 12^{abc}	105 ± 12^{bc}	87 ± 16^{ab}	78 ± 19^{a}	129 ± 34†^{c}	127 ± 22†^{c}
Systolic arterial pressure (mm Hg)	92 ± 7	101 ± 17^{b}	60 ± 7†^{a}	143 ± 18†^{cd}	172 ± 54†^{d}	124 ± 17†^{bc}	123 ± 16†^{bc}
Mean arterial pressure (mm Hg)	62 ± 13	67 ± 12^{b}	45 ± 4†^{a}	84 ± 7†^{bc}	93 ± 28†^{c}	69 ± 8^{b}	69 ± 7^{b}
Diastolic arterial pressure (mm Hg)	50 ± 10	55 ± 10^{bcd}	38 ± 3†^{a}	66 ± 7†^{cd}	72 ± 21†^{d}	52 ± 9^{bc}	49 ± 6^{b}
LiDCO (L/min)	2.8 ± 0.60	3.23 ± 0.83^{ab}	1.44 ± 0.33†^{a}	4.07 ± 0.41†^{b}	4.19 ± 1.19†^{b}	6.62 ± 2.12†^{c}	6.19 ±1.67†^{c}
PCO (L/min)	2. 8 ± 0.60	3.30 ± 1.14^{a}	2.07 ± 0.55^{a}	3.16 ± 0.69^{a}	2.91 ± 0.75^{a}	5.57 ± 2.08†^{b}	5.73 ± 1.59†^{b}
SVR_L (based on LiDCO; dyn•sec•cm^{-5})	1,754 ± 551	1,620 ± 353^{b}	2,126 ± 407^{c}	1,567 ± 124^{b}	1,737 ± 423^{bc}	857 ± 237†^{a}	893 ± 241†^{a}
SVR_P (based on PCO; dyn•sec•cm^{-5})	1,754 ± 551	1,679 ± 591^{abc}	1,500 ± 325^{abc}	2,085 ± 430^{cd}	2,493 ± 694^{d}	1,041 ± 309^{ab}	959 ± 243^{a}
Mean (PCO + LiDCO)/2 (L/min)	2.8 ± 0.60	3.26 ± 0.92^{a}	1.75 ± 0.41^{a}	3.62 ± 0.42^{a}	3.55 ± 0.95^{a}	6.09 ± 2.06†^{b}	5.96 ± 1.44†^{b}

*Dose was adjusted to achieve a mean arterial pressure of 65 to 85 mm Hg. †Significantly ($P < 0.05$) different from baseline calibration value.
$^{a-d}$Between treatments, values with different superscript letters are significantly ($P < 0.05$) different.

basis of LiDCO measurements), compared with baseline (Table 1). Only the deep plane of anesthesia induced a higher right atrial pressure, compared with baseline. None of the parameters during the light plane of anesthesia were different from baseline. Based on LiDCO measurements of CO, the deep plane of anesthesia induced lower CO, whereas dopamine and dobutamine infusions induced higher CO, compared with baseline. Based on PCO measurements of CO, the difference in CO was detected only during dobutamine infusions and SVR_P changes were not detected.

Overall, the PCO and LiDCO systems of CO measurement were not significantly ($P = 0.553$) different; significant ($P < 0.001$) interactions were found between the systems of CO measurement and treatment effects. Significant differences were found between the 2 systems of CO measurement during the deep plane of anesthesia ($P < 0.001$), dopamine at adjusted doses ($P = 0.001$), and dopamine infusion at a dose of 7 µg/kg/min ($P < 0.001$). Significant differences were not detected between the 2 systems of CO measurement during the light plane of anesthesia ($P = 0.728$), dobutamine infusion at adjusted doses ($P = 0.125$), and dobutamine infusion at a dose of 7 µg/kg/min ($P = 0.291$). The Pearson coefficient of correlation (r) between PCO and LiDCO measurements after correcting for the confounding treatment and dog effects was 0.6289 ($P = 0.002$).

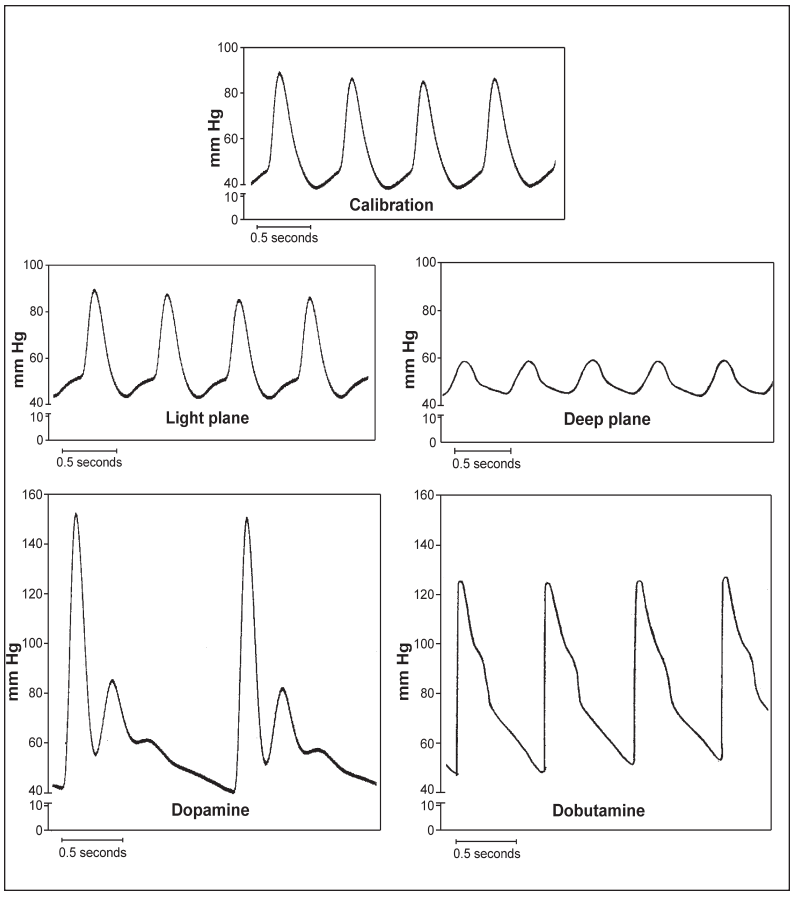

Figure 1—Traces of typical arterial pressure waveform images during calibration, light plane of anesthesia, deep plane of anesthesia, dopamine infusion, and dobutamine infusion.

The Bland-Altman plot revealed that the PCO monitor always read higher than the LiDCO monitor during deep anesthesia but lower than the LiDCO monitor during dopamine infusions (**Figure 2**). The PCO monitor read lower than the LiDCO monitor during dobutamine infusions at adjusted doses, but this difference was not significant. Because there were significant treatment interactions, the bias and precision statistics on log-transformed data were computed separately for each treatment (**Table 2**). Upper and lower limits of agreement were computed on the basis of mean ± 2 SD of bias,[14] whereas the tolerance limits were computed on the basis of mean ± 3 SD of bias to adjust for the sample size (n = 6).[15] These values were back transformed (antilog) to obtain the PCO-to-LiDCO measurement ratio.[14] Mean bias and tolerance limits varied depending on the treatment levels. Based on the limits of agreement (mean ± 2 SD of bias), the PCO monitor always read higher than the LiDCO monitor during deep anesthesia but lower than the LiDCO monitor during dopamine infusions. In this study, the power to detect 30% or more difference between PCO and LiDCO measurements was 92.5%.

Table 2—Mean bias, agreement, and tolerance limits between PCO and LiDCO systems by treatment.

	Anesthetic conditions					
Ratio parameter	**Light plane**	**Deep plane**	**Dopamine adjusted***	**Dopamine (7 µg/kg/min)**	**Dobutamine adjusted***	**Dobutamine (7 µg/kg/min)**
Mean bias (PCO/LiDCO)	1	2.26	0.54	0.44	0.65	0.83
Upper limit of agreement	1.82	4.12	0.98	0.81	1.18	1.51
Lower limit of agreement	0.55	1.24	0.3	0.24	0.36	0.46
Upper limit of tolerance	2.45	5.5	1.32	1.09	1.59	2.04
Lower limit of tolerance	0.4	0.92	0.22	0.18	0.26	0.34

Values are computed on the basis of log-transformed data and back transformed (antilog) for expression as a ratio. Power to detect 30% or more difference between PCO and LiDCO is 92.5%.

Limit of agreement = Mean ± 2 SD bias. Limit of tolerance = Mean ± 3 SD of bias to adjust for sample size of n = 6.

See Table 1 for remainder of key.

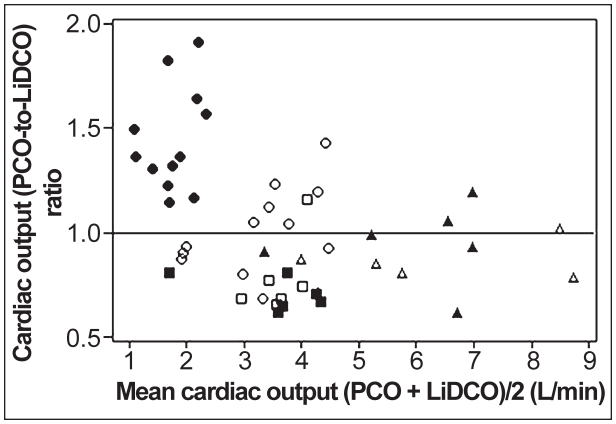

Figure 2—Bland-Altman plot of cardiac output measurements obtained by use of the pulse contour cardiac output (PCO) and lithium dilution cardiac output (LiDCO) systems on the basis of 48 pairs of cardiac output measurements from 6 dogs during light plane anesthesia (open circles), deep plane anesthesia (closed circles), infusion of the adjusted dose of dopamine (open squares), infusion of dopamine at a dose of 7 µg/kg/min (closed squares), infusion of the adjusted dose of dobutamine (open triangles), and infusion of dobutamine at a dose of 7 µg/kg/min (closed triangles). Bias is expressed as the PCO-to-LiDCO measurement ratio.

Discussion

Under the conditions of our study, the PCO monitor provided directional tracking of CO measurements but poor accuracy when the hemodynamic conditions were altered appreciably from those during the initial calibration with the LiDCO system (baseline). The agreement between PCO values obtained via the PCO system was better when the hemodynamic status was constant (light anesthesia), even when the PCO measurement was obtained at varying times up to 3 hours after calibration.

The concepts of deriving CO based on the arterial pressure waveform can be traced to as early as 1904; however, many attempts have met with limited success.[1,16] In general, agreement between systems that were based on pressure waveform analysis and clinical standards, such as thermodilution, has been poor, particularly when there are large changes in SVR.[17] Because the PCO system to derive CO is dependent on the pressure waveform, concerns for its accuracy centered on the validity of this algorithm with waveform variation associated with vascular tone changes. Significant changes in SVR, such as during infusion of drugs, hypovolemia, or hypothermia, may influence the assumptions underlying this algorithm and thus its accuracy. This study was designed to simulate only some of these changing conditions during anesthesia, specifically with changes of anesthetic depth and infusions of inotropic drugs.

Results of our study indicate that the PCO monitor is able to track CO changes in the same direction as the LiDCO system; that is, PCO measurements increase as CO increases and vice versa. However, PCO measurements always overestimated CO during the deep plane of anesthesia and underestimated CO during dopamine infusions in all instances except one. Furthermore, PCO measurements underestimated CO during dobutamine infusion, although this was not a significant finding. As a consequence, PCO measurements overestimated the decrease in SVR during deep anesthesia, overestimated the increase in SVR during dopamine infusions, and, to a lesser degree, underestimated the decrease in SVR during dobutamine infusions.

Mean bias and tolerance limits between PCO and LiDCO measurements varied depending on the treatments. During the light plane of anesthesia, the mean bias of the PCO-to-LiDCO measurement ratio was 1 (ie, PCO – LiDCO = 0), with a 95% confidence interval for a PCO-to-LiDCO measurement ratio of 0.4 to 2.45. In other words, for an individual comparison, the PCO monitor may read 60% lower to 145% higher than the LiDCO system during light planes of anesthesia. Similarly, the PCO monitor may read 8% lower to 450% higher than the LiDCO system during deep anesthesia, 82% lower to 9% higher than the LiDCO system during dopamine infusion at a dose of 7 µg/kg/min, 78% lower to 32% higher than the LiDCO system during dopamine infusion at adjusted doses, 66% lower to 104% higher than the LiDCO system during dobutamine infusion at 7 µg/kg/min, and 74% lower to 59% higher than the LiDCO system during dobutamine infusion at adjusted doses. Unfortunately, these discrepancies could be clinically important in determining patient care.

Combinations of changes in the shape of the pressure waveform and hemodynamic parameters induced by the different treatments may explain the variability in the agreement between PCO and LiDCO measurements according to treatments. Among the different treatments, the shape of the waveform and hemodynamic parameters induced by the light plane of anesthesia were similar to those during the baseline calibration, and this probably explains why no significant difference was detected between the PCO and LiDCO measurements during this treatment. During deep planes of anesthesia, the shape of the pressure waveform was different and systolic, mean, and diastolic arterial pressures were lower, compared with baseline, in all dogs.

It is interesting to note that the PCO system did not underestimate CO in the dobutamine treatments to the same degree as in the dopamine treatments. Although both inotropic drugs increased CO, changes in the shape of the waveforms and the hemodynamic parameters differed. Compared with changes from baseline calibration, dopamine induced higher systolic, mean, and diastolic arterial pressures, whereas dobutamine induced higher heart rate, systolic arterial pressure, and hemoglobin concentrations but lower SVR_L. Differences in magnitude, direction of changes in these parameters, and their impact on waveform variation may be considered as potential factors contributing to the consistent underestimation of CO during dopamine infusion. The formula used by the computer to calculate LiDCO measurements is as follows:

$$CO\ (L/min) = (\text{lithium dose [mmol]} \times 60)/(\text{area under curve [mmol} \times L^{-1} \times \text{s]} \times [1 - PCV]),$$

where PCV equals hemoglobin (g/dL) divided by

Although dobutamine tended to increase hemoglobin concentration, this was accounted for by the formula to calculate LiDCO measurements. Furthermore, if the hemoglobin concentration during dobutamine infusion increased beyond that measured at 3 minutes before each LiDCO measurement, higher LiDCO measurements would have increased the bias, which was not the case. Therefore, the hemoglobin concentration was most likely not a contributing factor. The difference in the change of peripheral vascular tone in relation to CO or stroke volume as well as heart rate induced by the 2 inotropic drugs resulted in distinctly different pressure waveforms that could have influenced the PCO measurements and therefore bias. Because blood pressure is incorporated in the PCO calculations to derive the CO, the underestimation of CO during dopamine infusion could be related to the higher blood pressure.

The PCO algorithm involves 3 steps. In the first step, the arterial pressure waveform is transformed into a volume-time waveform on the basis of the curvilinear relationship between pressure and volume (ie, compliance[b]) as follows:

$$\Delta V/\Delta P = k \times 250 \times e^{-k \cdot P},$$

where V is volume, P is blood pressure, k is the scaling or calibration factor, 250 is the arterial tree saturation (full expansion) volume in milliliters for the calibration factor of k = 1, and e is the natural logarithm.

On the basis of this equation for a given calibration factor, the change (increase) in volume decreases as pressure increases. This may explain why the PCO system underestimated CO during dopamine infusions (higher blood pressure) while overestimating CO during deep anesthesia (lower blood pressure). Similarly, because blood pressure during dobutamine infusions was lower than blood pressure during dopamine infusions, the PCO system did not underestimate the CO during dobutamine infusion to the same degree as during dopamine infusions.

In our study, the shape of the pressure waveform during deep anesthesia and the inotrope infusions was different, compared with those during calibration. The shape of an arterial waveform is a result of the interaction between flow and characteristics of the arterial wall, with pressure wave reflections being the predominant factor.[1] For example, an increase in arterial tone would decrease compliance, which results in an early return of reflected waves, causing increases in systolic and pulse pressure. Also, velocity of the pressure wave and duration of the pulse can affect reflected waves at a particular arterial site.[18] Because the occurrence and contribution of reflected waves in changing the pressure waveform may differ among the different treatments in our study, this could be another explanation for the variation in bias and tolerance limits among the different treatments.

Correlation and regression analysis have traditionally been used in many studies to compare 2 systems of measurements. However, this type of analysis has its deficiencies.[19] A large range of CO values will result in a falsely higher correlation coefficient. The correlation coefficient (r = 0.6289) in our study was estimated after correcting for dog and treatment effect, thus adjusting for CO range. If uncorrected, the correlation coefficient for our study would be 0.872, which is still lower than 0.99[12] and 0.94[f] determined in previous studies on human patients.

Results of a meta-analysis of studies that used bias and precision statistics to compare CO measurement techniques revealed that acceptance of a new technique should rely on agreement limits of up to ± 30%.[19] Validation of the PCO monitor on human patients resulted in an upper and lower limit of agreement of ± 1.1 L/min (estimated as ± 22%) on the basis of 80 pairs of CO measurements (from 3.3 to 8.5 L/min) from 20 patients within a study period of 8 hours,[12] whereas another study[e] had an upper and lower limit of agreement of ± 1.87 L/min (22% to 31%) on the basis of 84 pairs of CO from 21 patients within a 24-hour study period. If all 48 pairs of CO in our study were subjected to a similar calculation process, the limit of agreement would be ± 2.06 L/min (26% to 50%), which is greater than the recommended limits of agreement.

These wider limits of agreement and poorer correlation in our study are likely attributable to the greater hemodynamic changes induced by the treatments. However, species differences cannot be ruled out. The physiologic measurements (heart rate and systolic and diastolic arterial pressures) in the study by Hamilton et al[12] did not appear to be different from those during calibration, whereas significant hemodynamic changes from baseline (initial 1-point calibration) were induced in all dogs in our study. Because the PCO system depends entirely on the analog pressure waveform input, any artifact, distortion, or dampening of the waveform (eg, blood clot and partially kinked catheter) must be recognized and corrected. It is also important to have hemodynamic stability during calibration of the PCO monitor. Its reliability would be questionable during periods of arrhythmias or when the waveform is poorly defined. In our study, we took care to ensure that the direct blood pressure monitoring line was free of blood clots and bubbles and that hemodynamic stability existed during every CO measurement. The dynamic response of the arterial monitoring system was not determined for each experiment in our study, but results of a previous study[e] indicate that this factor did not influence the degree of agreement between PCO and LiDCO measurements.

The use of a peripheral vein instead of a central vein for lithium chloride injection should have little effect on the bias in our study because the LiDCO system estimates the area under the curve on the basis of the first passage of the lithium indicator before recirculation. Therefore, it should be independent of the rate of flow to the heart as long as the flow does not alter the curve appreciably to preclude extrapolation of the first pass. Furthermore, a study[10] in dogs comparing injection sites by use of the cranial vena cava versus cephalic vein showed a bias (central to peripheral) of 0.098 ± 0.168 L/min and a correlation coefficient of 0.902. Although the sample size in our study was small (n = 6), calculations based on the variance of difference between PCO and LiDCO measurements revealed a power of 92.5% to detect a 30% or greater difference between the PCO and LiDCO estimates.

Our study was not designed to address whether the accuracy of PCO measurements would drift over time. However, during the statistical model testing for the multivariate analysis to find the correlation coefficient between PCO and LiDCO measurements, time did not have a significant (P = 0.911) effect. Results from the studies[12,f] on humans indicate that PCO is accurate (in hemodynamically stable patients) without recalibration for up to 8 hours. Therefore, time per se should not affect the accuracy of PCO unless it is accompanied with significant hemodynamic changes and changes to the pressure waveform.

In conclusion, results from our study indicate that the PCO system can be used to track changes in the CO when the hemodynamics or pressure waveform are similar to those during calibration. When these conditions changed significantly from those during calibration, as they would during anesthesia and surgery, the PCO system does not appear to be adequate for accurate continuous CO monitoring. Recalibration is recommended for accurate estimation of CO when conditions are altered considerably. Further studies on the effects of blood loss, volume replacement, and hypothermia on the performance of PCO would be helpful for data interpretation in the clinical setting.

a. LiDCO plus hemodynamic monitor, LiDCO Ltd, London, UK.
b. LiDCO plus hemodynamic monitor user's manual 1.0, LiDCO Ltd, London, UK.
c. Heller LB, Fisher M, Pfanzelter N, et al. Continuous intraoperative cardiac output determination with arterial pulse wave analysis (PulseCO™) is valid and precise (oral presentation) (abstr), in *Proceedings*. 24th Annu Meet Am Soc Cardiovascular Anesthesiol Anesth Analg 2002;93:SCA1–SCA112.
d. Tallman J, Resano F, Weddington T. PulseCO—pulse contour versus continuos cardiac output comparison in off-pump coronary bypass graft surgery (oral presentation) (abstr), in *Proceedings*. 24th Annu Meet Am Soc Cardiovascular Anesthesiol 2002;96:A481.
e. Pittman JA, Sum-Ping JS, Sherwood MW, et al. Continuous cardiac output monitoring by arterial pressure waveform analysis: a 24-hour comparison with the lithium dilution indicator method (oral presentation), in *Proceedings* 24th Annu Meet Am Soc Cardiovascular Anesthesiol Anesth Analg 2002;94:71.
f. Propofol injection (10 mg/mL), Abbott Laboratories Ltd, St-Laurent, QC, Canada.
g. Isoflurane USP inhalant anesthetic, Abbott Laboratories Ltd, St-Laurent, QC, Canada.
h. Bair Hugger warming unit model 505, Augustine Medical Inc, Eden Prairie, Minn.
i. Criticare Model 1100, Criticare Systems Inc, Waukesha, Wis.
j Tektronix 414 portable patient monitor, Tektronix Inc, Beaverton, Ore.
k. Transducer set, Becton-Dickinson Critical Care System Pte Ltd, Singapore.
l. Anesthesia calibration gas, Criticare Systems Inc, Waukesha, Wis.
m. Intracath, ref 384904, Becton-Dickinson Infusion Therapy Systems Inc, Sandy, Utah.
n. BD Insyte-W 20 GA 1-88 In, Becton-Dickinson Infusion Therapy Systems Inc, Sandy, Utah.
o. Flow-through cell electrode assembly, CM10, Batch No. WO030009, LiDCO Ltd, London, UK.
p. PulseCO hemodynamic monitor, LiDCO Ltd, London, UK.
q. Park & Ride extension tube with SMARTSITE needle-free valve, LiDCO Ltd, London, UK.
r. Acepromazine 2 mg/mL, VTH, OVC, University of Guelph, Guelph, ON, Canada.
s. Torbugesic, Ayerst Veterinary Laboratories, Guelph, ON, Canada.
t. Metacam 0.5% injection, Boehringer Ingelheim Ltd, Burlington, ON, Canada.
u. Intropin, Bristol-Myers Squibb Canada, Montreal, QC, Canada.
v. Dobutamine injection USP25, 0 mg/mL, Abbott Laboratories Ltd, St-Laurent, QC, Canada.
w. Lithium chloride injection, 0.15 mmol/mL, CM40, Batch No. 165108, LiDCO Ltd, London, UK.
x. ABL 500 blood gas system, Radiometer, Copenhagen, Denmark.
y. Nova 5 electrolyte analyser, NOVA Biomedical, Waltham, Mass.
z. OSM 3 Hemoximeter, Radiometer, Copenhagen, Denmark.
aa. SAS, version 8.0, SAS Institute Inc, Cary, NC.

References

1. Mark JB, Slaughter T, Reves JG. Cardiovascular monitoring. In: Miller RD, ed. *Anesthesia*. 5th ed. New York: Churchill Livingstone Inc, 2000;1117–1206.
2. Jonas M, Tanser SJ. Lithium dilution measurement of cardiac output and arterial pulse pressure waveform analysis: an indicator dilution calibrated beat-by-beat system for continuous estimation of cardiac output. *Curr Opin Crit Care* 2002;8:257–261.
3. Linton R, Band D, O'Brien T, et al. Lithium dilution cardiac output measurement: a comparison with thermodilution. *Crit Care Med* 1997;25:1796–1800.
4. Linton RA, Jonas MM, Tibby SM, et al. Cardiac output measured by lithium dilution and transpulmonary thermodilution in a pediatric intensive care unit. *Intensive Care Med* 2000;26:1507–1511.
5. Linton RA, Young LE, Marlin DJ, et al. Cardiac output measured by lithium dilution, thermodilution, and transesophageal Doppler echocardiography in anesthetized horses. *Am J Vet Res* 2000;61:731–737.
6. Corley KTT, Donaldson LL, Furr MO. Comparison of lithium dilution and thermodilution cardiac output measurements in anesthetized neonatal foals. *Equine Vet J* 2002;34:598–601.
7. Kurita T, Morita K, Kato S, et al. Comparison of the accuracy of the lithium dilution technique with the thermodilution technique for measurement of cardiac output. *Br J Anaesth* 1997;79:770–775.
8. Mason DJ, O'Grady M, Woods PJ, et al. Assessment of lithium dilution cardiac output as a technique for measurement of cardiac output in dogs. *Am J Vet Res* 2001;62:1255–1261.
9. Garcia-Rodriguez C, Pittman J, Cassell CH, et al. Lithium dilution cardiac output measurement: a clinical assessment of central venous and peripheral venous indicator injection. *Crit Care Med* 2002;30:2199–2204.
10. Mason DJ, O'Grady M, Woods PJ, et al. Comparison of a central and a peripheral (cephalic vein) injection site for the measurement of cardiac output using the lithium-dilution cardiac output technique in anesthetized dogs. *Can J Vet Res* 2002;66:207–210.
11. Mason DJ, O'Grady M, Woods PJ, et al. Effect of background serum lithium concentrations on the accuracy of lithium dilution cardiac output determination in dogs. *Am J Vet Res* 2002;63:1048–1052.
12. Hamilton TT, Huber LM, Jessen ME. PulseCO: a less-invasive method to monitor cardiac output from arterial pressure after cardiac surgery. *Ann Thorac Surg* 2002;74:S1408–S1412.
13. Yochberg Y, Tamhane AC. Multiple comparison procedure. In: *Wiley series in probability and mathematical statistics*. New York: John Wiley & Sons, 1987.
14. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res* 1999;8:135–160.
15. Eberhardt KR, Mee RW, Reeve CP. Computing factors for exact two-sided tolerance limits for a normal distribution. *Commun Stat Simulation* 1989;18:397–413.
16. van Lieshout JJ, Wesseling KH. Continous cardiac output by pulse contour analysis? *Br J Anaesth* 2001;86:467–469.
17. English JB, Hodges MR, Sentker C, et al. Comparison of aortic pulse-wave contour analysis and thermodilution methods of measuring cardiac output during anesthesia in the dog. *Anesthesiology* 1980;52:56–61.
18. O'Rourke MF, Yaginuma T. Wave reflections and the arterial pulse. *Arch Intern Med* 1984;144:366–371.
19. Critchley LA, Critchley AJ. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit Comput* 1999;15:85–91.