Critically ill patients routinely require hemodynamic monitoring to assess CO, tissue perfusion, and oxygen delivery. Assessing CO is essential for determination of oxygen delivery, which is an important variable in determining optimal endpoints of resuscitation. Cardiac output is the amount of blood that the heart pumps per minute and is an indicator of the volume of blood available for perfusion. Cardiac index is the CO indexed to BSA and is a more accurate value for comparing CO in animals of varying sizes.

**Objective**—To assess the agreement between cardiac output (CO) measured by use of arterial pressure waveform analysis (PulseCO) and lithium dilution (LiDCO) in conscious dogs with systemic inflammatory response syndrome (SIRS).

**Animals**—14 dogs with naturally occurring SIRS.

**Procedures**—Pulse power analysis was performed on critically ill patients with a PulseCO monitor. All measurements were obtained with an indwelling arterial line and in accordance with the manufacturer’s instructions. Intermittent measurements of CO were obtained with the LiDCO method to validate the PulseCO measurements at initial calibration (baseline; time 0) and at 4, 8, 16, and 24 hours. The 2 methods for measuring CO were compared by use of Bland-Altman analysis. An error rate for the limits of agreement between the 2 methods of < 30% was defined as being acceptable.

**Results**—Bland-Altman analysis did not indicate good agreement between measurements obtained by use of the PulseCO and LiDCO methods, despite no significant change in cardiac index (CI) over time as measured with the LiDCO method. The percentage error for the overall difference in CI values between the PulseCO and LiDCO measurements was 122%, which indicated that the PulseCO method was not an acceptable means of CO measurement when compared with the LiDCO method for this patient population.

**Conclusions and Clinical Relevance**—Agreement between the PulseCO and LiDCO methods for measurement of CO was not acceptable at 4- and 8-hour intervals after calibration in conscious dogs with naturally occurring SIRS. (Am J Vet Res 2009;70:1365–1373)

**Abbreviations**

- BSA  Body surface area
- CI  Cardiac index
- CO  Cardiac output
- LIDCO  Cardiac output measured by use of lithium dilution
- PulseCO  Cardiac output measured by use of arterial pressure waveform analysis
- SIRS  Systemic inflammatory response syndrome
- SV  Stroke volume
- SVR  Systemic vascular resistance

In humans, low CO states are associated with increases in morbidity and mortality rates, and there is poor agreement between measured CO and estimated CO as determined on the basis of clinical assessment. For veterinarians, CO and oxygen delivery have been difficult to monitor in clinical settings and are commonly estimated by use of a number of variables. These may include a combination of heart rate and rhythm, pulse rate and quality, capillary refill time, rectal temperature, serum lactate concentration, arterial blood pressure, urine output, and acid-base status. The use...
of a combination of these indirect indices has been associated with inaccurate estimates of CO in human adults and children. In a recent study that used dogs with naturally occurring SIRS, few correlations were found between results of physical examination, laboratory data, and measured CI. Analysis of results from that study indicates that none of these commonly measured variables correlate well with measured CI. However, that portion of the study was underpowered, so it is possible that significant correlations could be found in larger studies.

Because of the relative simplicity of measuring blood pressure, it is frequently used as a surrogate for blood flow measurement. However, there is often a tenuous relationship between arterial pressure and blood flow because, mathematically, the relationship between blood flow and arterial pressure requires reference to the vascular resistance. Clinicians rely heavily on pressure measurements as an index of perfusion despite available data indicating that there is virtually no correlation between changes in pressure and changes in blood flow. In a study in which healthy dogs were anesthetized for ovariohysterectomy to determine whether changes in mean arterial pressures were caused by changes in CO or SVR, investigators found that changes in mean arterial pressure do not reflect corresponding changes in CI. The inability to accurately estimate global CO has led to the development of a number of methods for measurement of CO. In addition, there remains a need for a reliable, safe, and validated method for continuous measurement of CO in dogs in a clinical setting. Continual measurement of CO is optimal in critically ill patients because of their dynamic state and constant potential variation in hemodynamic stability. Although intermittent monitoring has been validated in veterinary medicine, these results may not reflect the true status of a patient over time, and appropriate therapeutic measures cannot be instituted on the basis of intermittent CO measurements.

Traditionally, measurement of CO in clinical settings has been performed via the thermodilution method. Because of the invasiveness and complications associated with the thermodilution method, there is interest in the development of alternate methods for measurement of CO. These include use of magnetic flowmetry, indocyanine dilution, partial carbon dioxide rebreathing, transesophageal or transthoracic continuous wave Doppler ultrasonography, and thoracic bioimpedance, which are frequently too invasive, technically demanding, or impractical to perform in conscious patients.

A minimally invasive CO monitoring technique is the LiDCO method, which uses the established indicator-dilution technique to define CO, with lithium chloride used as the indicator. Results for the LiDCO method were compared with results for bolus thermodilution in 40 human patients in a high-dependency postoperative cardiac unit and a general intensive care unit. In that study, overall agreement between the two methods was good (r² = 0.94), which indicated that LiDCO was at least as accurate as bolus thermodilution with significantly less scatter. Cardiac output was measured in anesthetized pigs with LiDCO, thermodilation, and an electromagnetic flow probe placed around the ascending aorta. Correlation between LiDCO and electromagnetic flowmetry (r² = 0.95) was higher than between thermodilution and electromagnetic flowmetry (r² = 0.87) for CO values that ranged from 0.2 to 2.8 l/min. The LiDCO method is not a criterion-referenced standard for measurement of CO; however, in dogs, it is comparable to CO measurements obtained via the thermodilution method. The LiDCO data are used to calibrate a pressure waveform method (ie, PulseCO) that determines the CO through auto-correlation from a nonlinear transformation of the input analogue arterial pressure. However, it is unclear when and for what conditions this recalibration should be performed. Theoretically, this combination should provide a beat-by-beat measurement of CO, with little clinical risk. This combined technique is theoretically ideal because it will measure CO continuously for a period before recalibration with the LiDCO method is necessary, whereas the LiDCO method alone only measures CO intermittently.

It has been thought that PulseCO measurements remain reliable without recalibration for at least 8 hours after cardiac surgery and without recalibration for 4 hours in critically ill human patients. The LiDCO and PulseCO methods have been compared in anesthetized dogs and in dogs with rapid iatrogenically induced increases and decreases in CO.

To the authors’ knowledge, there have not been any reports comparing LiDCO and PulseCO measurements at 4- and 8-hour intervals without recalibration in conscious, critically ill dogs with naturally occurring disease. We hypothesized that there would be good agreement between CO measurements obtained by the use of the PulseCO and LiDCO methods at 4- and 8-hour intervals in that patient population. Thus, the purpose of the study reported here was to assess the accuracy of CO measurement by use of the PulseCO when compared with the LiDCO system in dogs with SIRS.

Materials and Methods

Animals—Fourteen client-owned dogs with naturally occurring disease that had been admitted to the Critical Care Unit of the Colorado State University Veterinary Medical Center were enrolled in the study. Seven dogs were spayed females, 6 were castrated males, and 1 was a sexually intact female. Breeds included mixed-breed dog (n = 4), Collie (2), Siberian Husky (1), Rottweiler (1), Labrador Retriever (1), Springer Spaniel (1), Australian Cattle Dog (1), Shetland Sheepdog (1), Irish Wolfhound (1), and Golden Retriever (1). Mean age was 8.5 years (range, 0.3 to 13.0 years). Body weight ranged from 12 to 43.8 kg (mean, 28 kg). Informed client consent was obtained prior to enrollment of each dog in the study. The study protocol was approved by the Colorado State University Institutional Animal Care and Use Committee.

All dogs enrolled in the study met the following inclusion criteria: weight > 10 kg, preexisting catheters inserted in an artery and a vein (jugular or cephalic), and evidence of SIRS. Criteria for SIRS were based on results of physical examination and hematologic analysis conducted at the time of admission and included 3...
or more of the following variables: respiratory rate > 40 breaths/min, heart rate > 120 beats/min, rectal temperature < 38°C or > 40°C, WBC count < 3,000 or > 18,000 cells/µL, or band cells > 10%. The underlying disease process was recorded for each dog and included sepsis (n = 4), hemoabdomen (4), sterile peritonitis (gastric perforations without bacterial growth on culture; 2), traumatic injury (2), intestinal foreign body obstruction (1), and cardiopulmonary arrest (1).

**Instrumentation**—The preexisting arterial catheter was connected to a lithium sensor and the LiDCO monitor, as described by the manufacturer. The preexisting venous catheter was used for the purpose of preloading the required amount of lithium chloride for an uninterrupted IV bolus injection of the lithium indicator solution during LiDCO measurements. Heart rate and rhythm were monitored continuously by use of a standard lead II ECG. Body temperature was monitored intermittently via a rectal thermometer.

**Measurement of CO**—The PulseCO® is a beat-to-beat CO monitor that calculates SV from the arterial pressure waveform by use of an autocorrelation algorithm. The algorithm is not dependent on waveform morphology; rather, it calculates nominal SV from a pressure-volume transformation of the entire waveform. The nominal SV is converted to actual SV by calibration of the algorithm with LiDCO.24

A lithium-sensitive electrode was situated in a flow-through cell. The electrode consisted of polyurethane with a central lumen. The electrode was primed and then attached to the arterial monometer line via a 3-way stopcock. When the stopcock was opened, blood flowed into the sensor assembly at a rate (4 mL/min) controlled by a peristaltic, battery-powered pump. The flow-through cell was designed with an eccentric inlet so that blood swirled past the tip of the electrode, which contained a membrane selectively permeable to lithium. The voltage across the membrane was related to the plasma lithium concentration by use of the Nernst equation. A correction was applied for the sodium concentration. A wick, which was soaked (1.8% NaCl), was placed in the blood-filled section of the flow-through cell. The sodium ion–sensitive electrode represented the reference. Voltage was measured by use of an isolated amplifier, digitalized, and analyzed online.20 For each CO measurement, the computer required the sensor constant (provided by the manufacturer), injected dose of lithium chloride, and hemoglobin and sodium concentrations in the patient’s serum.25

Isotonic lithium chloride (0.002 to 0.004 mmol/kg) was injected as a bolus via the central or peripheral venous route, and a concentration-time curve was generated with the arterial ion-selective electrode attached to the arterial line manometer system.24 Although the central venous site was recommended by the manufacturer, the cephalic vein can be used in dogs, which eliminates the need for central venous catheterization and allows the assessment of CO in patients for which a central venous catheter is contraindicated, such as those with a coagulopathy and a high risk of thromboembolism.25

The LiDCO computer received the lithium concentration from the sensor, constructed and analyzed the dilution curve, and determined the CO.23 The CO was calculated from the lithium dose and the area under the concentration-time curve prior to recirculation by use of the following equation:

\[
CO = \frac{(\text{lithium dose} \times 60)}{\text{area} \times (1 – \text{PCV})}
\]

where area is the integral of the primary curve, and PCV is calculated as hemoglobin concentration divided by 34. A correction for PCV was necessary because lithium was distributed into the plasma. The voltage response of the lithium ion–sensitive electrode represented the percentage change of ion concentration, and because lithium is not typically present in plasma, extremely small doses can be used.24 The PulseCO monitor calculated continuous CO (after LiDCO calibration) by use of an analysis of the arterial blood pressure trace. The arterial blood pressure trace underwent a 3-step transformation that incorporated pulse power analysis.20 In the first step, the arterial pressure waveform was transformed into a volume-time waveform on the basis of the curvilinear relationship between pressure and volume (ie, compliance) as follows:

\[
\text{Change in V/change in P} = k \times 250 \times e^{-k \times p}
\]

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.22 This can be used to determine CO when the relationships are constant. However, arterial compliance changes as arterial pressure changes.24 The vessel walls stiffen as pressure and volume increase and become less compliant. This can be plotted as a curvilinear relationship, which appears to be similar among subjects.28

In the second step, an estimate of SV was calculated. The value of the derived arterial blood volume was subtracted from the volume trace. This generated a sine-like waveform, which yielded an estimate of change around the mean value. By squaring the values of the sine-like curve, a double waveform was generated. The square root of the mean of this double waveform, known as the root mean square, yielded an estimate of the nominal SV.24

In the final step, heartbeat duration was calculated by moving 1 version of the volume waveform successively, step by step, relative to another until maximum reinforcement was achieved. This time period represented the duration of the cardiac cycle.24 The final value was scaled on the basis of calibration to a value derived by dilution of the lithium indicator, which provided the actual SV.28 The PulseCO algorithm used the duration of the cardiac cycle (ie, interval between systolic pressure waves) to calculate heart rate and multiplied this by the derived nominal SV to calculate CO. Some authors have suggested18,26 that this system should be minimally affected by changes in arterial compliance,
wave morphology, pulse wave reflection, or the degree of damping.

Experimental protocol—All subjects included in the study were conscious dogs with naturally occurring SIRS. All dogs had been stabilized and instrumented prior to the first measurement obtained by use of the LiDCO system. The PulseCO monitor was then calibrated against the LiDCO measurements.

The LiDCO measurements were obtained as described elsewhere and in accordance with the manufacturer’s specifications. Steps for preparing the lithium sensors and determining a suitable sensor voltage and stable baseline signal were performed as described in the operation manual. Throughout the study, the dose of lithium chloride used for all LiDCO measurements was 0.004 mmol/kg (0.15 mmol/mL). A preexisting catheter in a jugular or cephalic vein was used for injection of the lithium indicator. Lithium chloride was loaded into the extension tubing. Once a stable baseline for the arterial blood was achieved on the LiDCO monitor, 20 mL of saline solution was used to flush the lithium chloride into the vein, as per the manufacturer’s recommendation. This ensured that a bolus of lithium chloride was rapidly introduced into the circulation. Once the LiDCO measurement was completed and the machine calibrated for that dog, the preexisting arterial catheter was connected to the direct arterial pressure monitoring device and PulseCO monitoring was initiated. The LiDCO measurements and calibration for the PulseCO were performed at 0, 4, 8, 16, and 24 hours, with the initial calibration designated as time 0. The PulseCO measurements were recorded immediately prior to each LiDCO calibration. Hemodynamic variables were recorded immediately before the lithium chloride injection and immediately after obtaining the LiDCO measurement. When instability of the baseline signal or the minimum lithium threshold was not reached on the LiDCO monitor, an interval of at least 5 minutes was allowed before attempting to obtain another calibration measurement with the LiDCO. The current beat-to-beat PulseCO measurement during the period immediately prior to LiDCO measurement was recorded.

At the time of each measurement, the data measured or assessed and recorded included rectal temperature, heart rate, respiratory rate, capillary refill time, mucous membrane color, direct arterial blood pressure (systolic, diastolic, and mean), and urine output. For each CO measurement, 2 mL of arterial blood was aspirated anaerobically for immediate analysis. Arterial blood gas analysis with determination of sodium concentration and hemoximetry were performed on samples obtained at the time of each measurement. The required sodium and hemoglobin concentrations were entered into the LiDCO monitor. All therapeutic interventions were recorded. All data were collected solely by one of the investigators (ALB). No recommendations for changes in treatment of the dogs were made as a result of the CO measurement. The attending clinician treated each patient as deemed appropriate, which included administration of 1 or more of the following: fentanyl, morphine, hydromorphone, acepromazine, lidocaine, or procainamide. Some of the dogs also received plasma, blood or human albumin transfusions, boluses of fluid, or magnesium chloride. Many dogs were receiving supplemental oxygen. Some dogs were also being treated with positive inotropes or vaspressors, including constant rate infusions of dobutamine, dopamine, vasopressin, norepinephrine, or epinephrine.

Cardiac output was indexed to BSA for each dog to allow for comparisons among dogs of various sizes. The equation used to calculate BSA was as follows:

\[ \text{BSA} = 0.101 \times \text{kilograms of body weight}^{0.67} \]

The attending clinician treated each patient as deemed appropriate, which included administration of 1 or more of the following: fentanyl, morphine, hydromorphone, acepromazine, lidocaine, or procainamide. Some of the dogs also received plasma, blood or human albumin transfusions, boluses of fluid, or magnesium chloride. Many dogs were receiving supplemental oxygen. Some dogs were also being treated with positive inotropes or vaspressors, including constant rate infusions of dobutamine, dopamine, vasopressin, norepinephrine, or epinephrine.

Figure 1—Graphs of CI values over time as measured by use of the LiDCO (A) and PulseCO (B) methods and mean arterial pressure as measured by use of a direct arterial line (C) for each of 14 dogs with SIRS. Each symbol represents results for 1 dog. Time 0 is the calibration with LiDCO followed by the initial PulseCO measurement.
Statistical analysis—All statistical analyses were performed by use of a commercially available statistical package. To assess hemodynamic stability, CI values from the LiDCO measurements were analyzed by use of a repeated-measures ANOVA, which included time as a fixed effect. A Bland-Altman approach was used to evaluate the agreement between LiDCO and PulseCO CI values. The percentage error was calculated as the product of 2 times the SD of the differences between the 2 methods divided by the mean CI for both methods. Percentage errors were calculated without regard to time (47 pairs) and also at each time point (4, 8, 16, and 24 hours).

Results

Eleven of 14 dogs in the study survived to discharge, and 3 died or were euthanatized. Euthanasia was performed because the 3 dogs developed complications. A total of 56 paired LiDCO and PulseCO measurements were initially planned (14 dogs at time 4, 8, 16, and 24 hours). PulseCO measurements were not performed at the initial LiDCO calibration at time 0. Measurements could not be obtained at all time points because of death, euthanasia, or technical problems. Four paired measurements in 8 dogs, 3 paired measurements in 4 dogs, 2 paired measurements in 1 dog, and 1 paired measurement in 1 dog were recorded. Thus, 47 pairs of data were available at the end of data collection. All of the measurements were suitable for analysis.

The range of CI values for all time periods in all study dogs for the LiDCO measurements was 1.41 to 5.42 L/min/m², with a mean of 3.45 L/min/m² (Figure 1). The range of CI values for all time periods in all study dogs for the PulseCO measurements was 0.97 to 12.62 L/min/m², with a mean of 3.61 L/min/m². Mean arterial pressures for all dogs were plotted. There was no significant (P = 0.61) time effect, as determined on the basis of LiDCO CI values in the dogs. In 11 dogs, CI values measured by the use of LiDCO did not vary from the median by more than 1.63 L/min/m² in each dog for all time periods and 2.0 L/min/m² in the remaining 3 dogs. In 9 dogs, mean arterial pressure did not vary by more than 16 mm Hg from the median value in the dogs, and in 5 dogs, mean arterial pressure did not vary by more than 28 mm Hg from the median value.

Bland-Altman analysis revealed an overall mean ± SD bias for the comparison of LiDCO and PulseCO values of 0.13 ± 4.28 L/min/m² (limits of agreement, –3.07 to 8.81 L/min/m²) and percentage error of 122% (Figure 2). Bias, limits of agreement, and percentage error for each specific time point were summarized (Table 1). No consistent direction of change in the PulseCO measurements, relative to the LiDCO measurements, was evident. At all time points, percentage error was > 30%, which indicated there was not acceptable agreement between the 2 methods at any time point. Bland-Altman analysis revealed a relatively large variability in the differences between the 2 methods (differences ranged from –3.07 to 8.81 L/min/m²), given the overall mean value of 3.52 L/min/m².

Discussion

The study reported here indicated that the PulseCO method does not accurately track changes in CO in conscious critically ill dogs over time. Traditional pulse contour analysis techniques for determining CO use algorithms that correlate the area under the arterial pressure curve with SV, which, when multiplied by heart rate, equals CO. However, multiple factors, including aortic compliance, reflected pressure waves, and waveform damping, prevent this from being a straightforward or linear relationship. 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 the duration of the pulse can affect reflected waves at a particular arterial site. If the SVR decreases, then reflection at the arterial-arteriolar junctions will decrease, which reduces the backward wave in the aorta. The mechanical properties of the aorta and other large arter-

Table 1—Overall mean, bias, and percentage error of PulseCO and LiDCO CI measurements obtained for 14 dogs with SIRS.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Overall mean of PulseCO and LiDCO (L/min/m²)</th>
<th>Bias (L/min/m²)*</th>
<th>Percentage error (%)/†</th>
<th>Range of differences (L/min/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>3.86 ± 0.50</td>
<td>0.10 ± 0.24</td>
<td>–0.78 to 8.04</td>
<td>0.64 – 3.79</td>
</tr>
<tr>
<td>8</td>
<td>3.40 ± 0.24</td>
<td>–0.34 ± 0.20</td>
<td>2.28 to 1.42</td>
<td>0.68 – 3.56</td>
</tr>
<tr>
<td>16</td>
<td>3.11 ± 0.30</td>
<td>–0.72 ± 1.20</td>
<td>–1.90 to 2.15</td>
<td>0.62 – 3.58</td>
</tr>
<tr>
<td>24</td>
<td>3.91 ± 0.62</td>
<td>0.50 ± 0.26</td>
<td>–1.59 to 5.22</td>
<td>0.68 – 3.56</td>
</tr>
<tr>
<td>Overall</td>
<td>3.52 ± 0.13</td>
<td>0.13 ± 0.28</td>
<td>–3.07 to 8.81</td>
<td>0.64 – 3.79</td>
</tr>
</tbody>
</table>

Time 0 is the initial calibration with LiDCO followed by the initial PulseCO measurement.

*Values reported for bias are mean ± SD. Bias was calculated as follows: (PulseCO – LiDCO) ± 2 SD. †Percentage error was calculated as 2 SD/mean CI for the 2 methods.
ies govern the pulse wave velocity and, consequently, the timing of wave reflection. Pulse contour methods must attempt to track changes in CO and SVR despite changes in ventricular ejection and wave reflection.\textsuperscript{18} The inability to adequately assess these factors in patients decreases the ability of pulse contour analysis to accurately predict CO.

As a consequence of SIRS, disruption in homeostasis caused by the production of proinflammatory mediators includes loss of vascular tone, which is believed to be secondary to excessive inducible nitric oxide synthase production and, possibly, a deficiency of vasopressin. Disruption of the endothelial permeability barrier is also a consequence of SIRS, which is a direct result of cytokine production.\textsuperscript{23,34} The SVR index is calculated by measuring the arterial blood pressure, central venous pressure, and CI,\textsuperscript{31} all of which may be affected by loss of vascular tone in dogs affected with SIRS. At higher mean CI values, it appeared that the PulseCO method overestimated the true CI of each dog. There was less bias between the 2 methods of measurement at lower and more typical mean CI values. This overestimation of PulseCO and increased bias at higher mean CI values may have been a consequence of decreased SVR in dogs with SIRS, which could have led to an overestimation of CI on the basis of the PulseCO algorithm.

Although the variables for stable hemodynamics have been subjectively defined in the study reported here by what the authors consider acceptable changes in CI measured by the LiDCO method and mean direct blood pressure, we can state that at the specified time intervals at which these variables were measured, they met our specifications for hemodynamic stability. However, these variables were not measured continuously during the time between intervals; therefore, we cannot state that these dogs had stable hemodynamics continuously throughout the study period.

Many studies have been performed to evaluate agreement between the PulseCO and thermodilution methods, with varying outcomes. Clinical studies\textsuperscript{14,18,32} performed in human cardiac and intensive care patients revealed good agreement and correlation between PulseCO and thermodilution methods over a wide range of CO values without the need for frequent recalibration. In a recent study,\textsuperscript{33} investigators concluded that the PulseCO measurements underestimate CO, compared with CO determined by use of the thermodilution method, when decreasing the SVR by infusion of prostaglandin E1, which makes use of the PulseCO unsuitable during cardiac surgery. In contrast, a study\textsuperscript{34} in which investigators compared PulseCO with thermodilution techniques in human patients undergoing off-pump coronary artery bypass grafting revealed that the PulseCO method may overestimate CO in these patients, compared with measurements made by use of the thermodilution method.

Studies have also been performed to compare PulseCO and LiDCO measurements in humans. In a study\textsuperscript{35} in which investigators compared PulseCO with LiDCO in postsurgical human patients, it was found that the correlation between the methods was good with minimal bias and clinically acceptable limits of agreement; however, these patients did not have dramatic changes in CO values during the study period.

A few studies to compare the PulseCO and LiDCO methods in dogs have been performed. A recent study\textsuperscript{21} in anesthetized dogs identified significant differences between CO derived from PulseCO methods, compared with CO derived by use of the LiDCO technique, when deep planes of anesthesia were used to induce hypotension, with a tendency toward overestimation of CO. In that study,\textsuperscript{21} investigators also found that the PulseCO system provided better agreement with the LiDCO measurements over time when hemodynamic conditions were stable. Another study\textsuperscript{22} was performed to determine the agreement and correlation between CO determined by use of PulseCO and LiDCO techniques during iatrogenic severe hemorrhagic shock and after fluid resuscitation in dogs. The authors of that study\textsuperscript{22} concluded that PulseCO determination of CO does not accurately predict rapid decreases in CO or the effects of fluid resuscitation in dogs.

Clinical acceptability of the difference between PulseCO and thermodilution measurements has been defined by some to be within 0.5 L/min.\textsuperscript{34} This criterion might be too strict because the reference method can result in inaccuracy of 10%.\textsuperscript{16} Results of a meta-analysis of studies that used bias and precision statistics to compare CO measurement techniques indicate that acceptance of a new technique should rely on agreement limits of up to ±30%.\textsuperscript{37} Validation of the PulseCO monitor in human patients resulted in an upper and lower limit of agreement of ±1.1 L/min (estimated at ±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.\textsuperscript{16} Another study\textsuperscript{32} had an upper and lower limit of agreement of ±1.87 L/min (22% to 31%) on the basis of 84 pairs of CO measurements from 21 patients within a 24-hour study period. In a recent study\textsuperscript{19} in humans, the PulseCO and LiDCO values were compared in 14 critically ill patients. Bias and limits of agreement between the 2 techniques were deemed acceptable for the first 4 hours of the study, with the percentage error being 20% at 1 hour after baseline measurement, 24% at 2 hours, and 25% at 4 hours. However, at 8 hours after baseline measurement, the error increased to 43%. The authors of that study\textsuperscript{19} concluded that agreement between lithium dilution CO and the pulse power algorithm in the PulseCO method remains acceptable for up to 4 hours in critically ill patients. Results of the study reported here contradicted this finding; however, the bias and limits of agreement found between the 2 techniques in our study were not acceptable during 4- or 8-hour intervals between recalibration. We calculated a percentage error of 147% at the 4-hour interval, 62% at 8 hours, 101% at 16 hours, and 120% at 24 hours. A difference of 3.52 L/min/m\textsuperscript{2} between techniques is not clinically acceptable because therapeutic interventions will be greatly influenced by such a difference. Arrhythmias may make pulse waveform analysis unreliable because heart rate can be miscalculated when large changes are evident in the pressure waveform. Substantial fluctuations in compliance of the arterial vascular system may change the arterial pressure waveform and affect the accuracy of pulse power.
analysis performed by PulseCO. It has been suggested that calibration every 8 hours is sufficient for accurate, continuous PulseCO monitoring in the intensive care unit setting; however, we did not find this in our study because calibration was performed at 4- and 8-hour intervals and PulseCO measurements were obtained immediately prior to recalibration. It remains possible that actual changes in CO developed in the short interval between the sequential LiDCO and PulseCO measurements, which necessitated recalibration of the PulseCO machine. However, the machine was recalibrated every 4 to 8 hours, as recommended by the manufacturer.

The contribution of reflected waves to changes in the pressure waveform may have differed for the various treatments in our study. This could be an explanation for the variation between the PulseCO and LiDCO measurements. It is possible that there could be species differences that make the PulseCO less reliable in dogs than in humans. The arterial tree in dogs has greater compliance, compared with that in humans, but overall characteristic impedance is similar, which suggests that the algorithm for determination of CO should translate between species.

In our study, we ensured that the direct blood pressure line was free of clots and was not kinked during CO measurements. Most technical problems were related to the arterial catheter, such as occlusion of or slow flow rates through the catheter. These problems prevented us from obtaining LiDCO and PulseCO measurements in some patients and required catheter replacement. Arterial catheters were replaced only when the attending clinician requested continued direct arterial blood pressure monitoring, not solely for the purpose of LiDCO measurement. Minor technical problems included patient movement during a measurement or inability of the machine to contact the lithium sensor. Minor problems required replacement of the sensor or repeating the measurement, but after correction, that resulted in acceptable LiDCO measurements. However, it is still possible that technical errors may have contributed to the discrepancy detected between the 2 techniques. It is worthy of mention that in another study, 2 calibration curves were determined at each time point, and in situations in which variability exceeded 10%, the mean of the 3 measurements was used. We did not use this approach, which may explain some of the variability in our results.

In general, performing LiDCO determinations has some technical limitations, including the need for accurate measurements of serum sodium and hemoglobin concentrations. In addition, the maximum daily lithium dose of 3 mmol places a limit on the number of calibration measurements that can be made. Lithium calibration cannot be performed in patients that have received neuromuscular blockers within the past 15 to 30 minutes because these drugs react with the lithium sensor. However, these limitations did not affect our study because the dogs were not receiving neuromuscular blocking drugs and a small dose of lithium was administered at 5 time points only.

Although the safety profile for lithium is clearly established, there remains a demand for reliable, continuous CO monitoring to reduce the need for continuous lithium injections and recalibration. The manufacturer’s recommendation for a maximum total dose of 3 mmol has to be exceeded many times before toxic concentrations are reached. The toxic dose of lithium is approximately 1 mmol/L. The bolus dose of lithium for CO determination (0.15 to 0.3 mmol) is too small to have a pharmacological effect. Pharmacokinetics of lithium have been determined in dogs. The half-life of lithium is 21.6 hours in mixed-breed dogs but only 13.5 hours in Beagles. The distribution of lithium is similar to that of sodium and can be explained by a 2- to 3-compartment model. Lithium competes for binding sites with other ions, including sodium, potassium, and phosphorous. It is excreted unchanged in the urine and is primarily absorbed in the renal tubules.

Frequent administration (ie, redosing) of lithium could result in toxic effects. Chronic exposure to lithium or acute overdose can cause loss of coordination, neurotoxicosis, gastrointestinal signs, renal tubular injury, or cardiac arrhythmias; lithium can serve as a teratogen when administered during the first third of gestation. Adverse effects are enhanced in young and elderly patients or when NSAIDs, thiazide diuretics, or psychotropic medications are concurrently administered, thereby limiting the number of lithium dilutions that can be safely performed in certain patient populations. Clinical signs of lithium toxicosis have mainly been reported in humans; however, lithium toxicosis has been reported in 2 dogs. Both of those dogs had been drinking water from a swimming pool that was chlorinated with lithium hypochlorite. To our knowledge, there have been no reports of lithium toxicosis in any dogs in which the LiDCO has been performed. Toxicosis would be a concern with repeated LiDCO measurements over a short time period. However, it was suggested in another report that as many as 34 measurements could be performed within a 7-hour period without evidence of toxic effects. Lithium toxicosis was not a concern in our study because small cumulative doses were used and we adhered to the manufacturer’s recommendations.

Multiple injections of indicators that are not rapidly cleared from the circulation increase the potential for background interference and typically result in overestimation of CO. A study was performed to determine the effect of background lithium concentrations on repeated LiDCO measurements. The CO values increased slightly as the serum lithium concentration increased in that study. This error was not clinically relevant and was minimal at a serum lithium concentration of 0.1 mmol/L and modest at a concentration of 0.4 mmol/L. Theoretically, after frequent LiDCO determinations within a short period or a high total number of serial determinations, the serum lithium concentration may increase sufficiently to interfere with the accuracy of the LiDCO measurement, which can lead to an overestimation of CO. However, background serum lithium concentrations were unlikely to have contributed to error in the study reported here because we adhered to the guidelines for dosing recommended by the manufacturer. Background lithium concentrations were not measured in this study. Additionally, the 20-mL bolus of saline solution associated with each LiDCO calibra-
tion could have temporarily improved SV. However, this appeared unlikely to be a major factor because 20 mL of saline solution only contributed 2% of blood volume in a 10-kg dog.

In general, agreement between methods based on pressure waveform analysis and clinical standards, such as thermodilution, has been poor, particularly when there are large changes in SVR. Because the PulseCO system is dependent on the pressure waveform, concerns for its accuracy center on the validity of its algorithm, with waveform variation associated with changes in vascular tone. Substantial changes in SVR, such as during infusion of drugs, hypovolemia, or hypothermia, may influence the assumptions underlying this algorithm and thus its accuracy. Although we did not measure SVR in the study reported here, we can assume that it did not change by an appreciable amount between subsequent measurements because of the fact that there were no large changes in CI or mean arterial pressure at these time intervals in our study dogs. However, we cannot assume that SVR did not vary during the entire study period because we did not measure SVR or perform more frequent CO measurements with the LiDCO method in the interim of the 4- and 8-hour intervals. This is admittedly a limitation of the study; however, each LiDCO calibration required approximately 6 mL of blood to be extracted from the dog, which we did not believe was appropriate in these affected animals. Critically ill patients often have fluctuations in temperature and vascular resistance and may require administration of inotropic agents, vasopressors, or vasodilators. Our study did not standardize the use of infusions of colloid solutions, boluses of colloid solutions, acepromazine, inotropes, pressors, blood transfusions, antiarrhythmics, or magnesium.

For the study reported here, we concluded that there was inadequate agreement between LiDCO and PulseCO measurements in conscious, critically ill dogs despite no significant change in CI values (as measured by the LiDCO) over time. This study was designed to assess the ability of the PulseCO algorithm to maintain accuracy in a mixed group of critically ill dogs. Critically ill dogs whose CO should be monitored for clinical purposes are used, but they are rarely the patients that have been used for validation of the methods. To the authors' knowledge, this is the first study in which agreement between LiDCO and PulseCO measurements in conscious dogs with naturally occurring disease has been evaluated. This is also the first study for which disagreement between PulseCO and LiDCO values in dogs without large changes in cardiovascular variables over time has been reported. Identification and analysis of the clinical conditions associated with decreased accuracy between PulseCO and LiDCO measurements require much larger study populations, but are ultimately needed to fine-tune the current PulseCO algorithms. For the conditions of our study, the PulseCO method was unreliable and inaccurate for monitoring CI measurements, compared with measurements for the LiDCO method over time. We concluded that PulseCO calibration may need to be performed more frequently than every 4 hours in awake critically ill patients. It is possible that because of the potential hemodynamic variability in this patient population, all CO measurements made by the PulseCO method in dogs with SIRS are unreliable and this technique should not be validated for use in conscious, critically ill dogs.

c. Lithium chloride injection, 0.15 mmol/mL, CM50-001-01, Lot No. p4095, LiDCO Ltd, London, England.
d. ABL 800 Flex blood gas analyzer, Radiometer Inc, Copenhagen, Denmark.
e. OSM 3 Hemoximeter, Radiometer Inc, Copenhagen, Denmark.
f. Fentanyl citrate injection, Hospira Inc, Lake Forest, Ill.
g. Morphine sulfate injection, Baxter HealthCare Corp, Deerfield, Ill.
h. Hydromorphone HCl, Hospira Inc, Lake Forest, Ill.
i. Acepromazine maleate, VedCo Inc, St Joseph, Mo.
j. Lidocaine HCl, Hospira Inc, Lake Forest, Ill.
k. Procainamide hydrochloride extended release, TEVA Pharmaceuticals, Sellersville, Pa.
l. 25% human albumin, Buminate 25%, Baxter HealthCare Corp, Deerfield, Ill.
m. Magnesium chloride injection, American Regent Inc, Shirley, NY.
n. Dobutamine injection, Bedford Laboratories, Bedford, Ohio.
o. Dopamine HCl, Hospira Inc, Lake Forest, Ill.
p. Vasopressin injection, American Regent Inc, Shirley, NY.
q. Levoephed, Hospira Inc, Lake Forest, Ill.
r. Epinephrine injection, IMS Ltd, South El Monte, Calif.

References