

# Effect of background serum lithium concentrations on the accuracy of lithium dilution cardiac output determination in dogs

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**Objectives**—To assess the effect of increasing serum lithium concentrations on lithium dilution cardiac output (LiDCO) determination and to determine the ability to predict the serum lithium concentration from the cumulative lithium chloride dosage.

**Animals**—10 dogs (7 males, 3 females).

**Procedure**—Cardiac output (CO) was determined in anesthetized dogs by measuring LiDCO and thermodilution cardiac output (TDCO). The effect of the serum lithium concentration on LiDCO was assessed by observing the agreement between TDCO and LiDCO at various serum lithium concentrations. Also, cumulative lithium chloride dosage was compared with the corresponding serum lithium concentrations.

**Results**—44 paired observations were used. The linear regression analysis for the effect of the serum lithium concentration on the agreement between TDCO and LiDCO revealed a slope of -1.530 (95% confidence interval [CI], -2.388 to -0.671) and a y-intercept of 0.011 ( $r^2 = 0.235$ ). The linear regression analysis for the effect of the cumulative lithium chloride dosage on the serum lithium concentration revealed a slope of 2.291 (95% CI, 2.153 to 2.429) and a y-intercept of 0.008 ( $r^2 = 0.969$ ).

**Conclusions and Clinical Relevance**—The LiDCO measurement increased slightly as the serum lithium concentration increased. 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. The serum lithium concentration can be reliably predicted from the cumulative lithium dosage if lithium chloride is administered often within a short period. (*Am J Vet Res* 2002;63:1048–1052)

**L**ithium dilution cardiac output (LiDCO) determination is a newer method of measuring cardiac output (CO) that has been used in people<sup>1,2</sup> and has recently been validated in dogs.<sup>3</sup> It belongs to the group of CO measurements known as indicator dilution methods. The most common indicator dilution method is thermodilution cardiac output (TDCO) determination. These methods measure CO by inject-

ing an indicator substance into the venous blood and measuring the amount of dilution of this indicator over time, as detected from an arterial site.

The LiDCO method involves injecting lithium chloride into a central venous catheter and measuring the diluted lithium concentration at a peripheral arterial catheter site with a sensor that is selective for lithium. Recent work has validated this method as being accurate, compared with TDCO determination in humans,<sup>1,2</sup> horses,<sup>4</sup> pigs,<sup>5</sup> and dogs.<sup>3</sup> In a study<sup>3</sup> on the use of LiDCO in dogs, 2 doses of lithium were assessed, a high dose and low dose. Excellent agreement was indicated between the 2 doses. Results of the study on dogs also indicated that LiDCO agrees quite favorably with TDCO.

The manufacturers of the LiDCO measurement system have stated that an increase in the serum lithium concentration will decrease the accuracy of the system. They have determined a theoretic serum lithium concentration of 0.2 mmol/L to be the value beyond which the LiDCO system would substantially differ from the true CO as a result of the background buildup of serum lithium.<sup>4</sup> The high background serum lithium concentration would reduce the ability of the LiDCO system to differentiate the next lithium chloride injection from the prevailing serum lithium concentration. Thus, with the frequent assessment of CO by LiDCO measurements within a short period, it may be possible for the background serum lithium concentration to increase substantially. Therefore, a cutoff value would be expected for the background lithium chloride concentration, above which significant error is introduced. The authors are unaware of published data that establish this cutoff value to be optimal at 0.2 mmol/L, and we considered that there would be a gradual increase in error that possibly could be accounted for prior to or above this value.

The primary objective of this study was to determine the effect of increasing serum lithium concentrations on the LiDCO measurements, particularly when the serum lithium concentration reaches or exceeds 0.2 mmol/L. A secondary objective was to determine the ability of the cumulative lithium chloride dosage to predict the serum lithium concentration.

## Materials and Methods

The experimental design that follows was previously used to indicate the agreement between CO measurements obtained by LiDCO and TDCO determination.<sup>3</sup> The study reported here involves the analysis of additional data collected at the time of this previous study.

**Animals**—Ten crossbred dogs were used in our study. All dogs were anesthetized and instrumented as previously

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described.<sup>3</sup> In brief, the dogs were premedicated with butorphanol tartrate<sup>b</sup> (0.4 mg/kg, IM). Anesthetic induction was accomplished with thiopental<sup>c</sup> (20 mg/kg, IV), and the dogs then were intubated and initially maintained on halothane<sup>d</sup> at 1.5%. Dogs were ventilated<sup>e</sup> at a rate of approximately 10 breaths/min and to a volume calculated at 10 to 15 ml/kg.

**Instrumentation**—The instrumentation used has been previously described.<sup>3</sup> In brief, catheters were positioned in the dorsal pedal artery and right atrium to perform LiDCO determination and in the pulmonary artery to perform TDCO determination. A venous occlusion catheter was positioned in the caudal vena cava to temporarily reduce preload and CO.

**Measurement of CO**—A thermodilution cardiac computer<sup>f</sup> was used to perform the TDCO measurements. The operation of the TDCO computer and Swan Ganz catheter and the method of determining TDCO have been previously described.<sup>3</sup> In brief, the injectate used was 5% dextrose in water, which was placed in an ice bath (approx 0 C) in syringes loaded to 5 or 10 ml. To perform a TDCO determination, the injectate was administered at end expiration over 2 to 3 seconds. The volume of the injectate used was the lowest of the 2 volumes that would give at least a 0.5 C temperature change from baseline. The TDCO measurement used in each analysis was the mean of 3 consecutive observations within 10% of each other.<sup>3</sup>

A LiDCO computer<sup>g</sup> was used to perform LiDCO measurements. The operation of the LiDCO computer and the sensor and the method of determining LiDCO have been previously described.<sup>3</sup> In brief, a known amount of lithium chloride was injected into the right atrium via the right atrial catheter, and the lithium concentration in the blood withdrawn from the dorsal pedal artery was measured by a sensor sensitive to lithium.

**Experimental protocol**—It is relevant to briefly review the experimental design used in the previous work as it relates to our study reported here.<sup>3</sup> Multiple determinations of CO, by both TDCO and LiDCO methods, were obtained within each CO rate. The final LiDCO and TDCO measurements obtained within an induced CO rate were considered for analysis for the present study. Thus, 4 to 10 determinations of CO were analyzed in each dog. The initial 4 determinations of CO were obtained following the maneuver to vary the rate of CO. Determinations of CO beyond these initial 4 determinations involved maintaining CO relatively constant; that is, no effort was used to vary CO.<sup>3</sup> The various rates of CO induced have been previously described.<sup>3</sup> In brief, this involved changing the plane of anesthesia or infusion of dobutamine or occluding the caudal vena cava. The order of induction of various rates of CO was randomly determined for each dog.

The CO determinations were obtained only after dogs achieved a stable hemodynamic plane following application of the preceding maneuver designed to alter CO. This stable plane was achieved by waiting for at least 15 minutes and often as long as 60 minutes. Hemodynamic stability was assessed as previously described.<sup>3</sup>

Prior to the first determination of LiDCO and after each TDCO determination, a blood sample was obtained from the catheter inserted in the dorsal pedal artery. An aliquot of the sample was used to determine hemoglobin and sodium concentrations for the performance of a LiDCO measurement. Another aliquot of the sample was used for subsequent determination of the serum lithium concentration by use of a flame photometer.<sup>h</sup> A blood sample for serum lithium concentration was also obtained after the last CO determination.

As dictated by the previous study,<sup>3</sup> the LiDCO determination always preceded the TDCO determination.

Furthermore, the LiDCO determination involved the use of either a high or low dose of lithium chloride that was randomly assigned. The high dose was a volume of lithium chloride injectate that would produce a signal amplitude on the LiDCO cardiac computer between 0.5 to 0.7  $\mu\text{m}$ , and the low dose was a volume of lithium chloride injectate that would produce a signal amplitude between 0.2 to 0.3  $\mu\text{m}$ .

**Statistical analysis**—To determine the effect of increasing background serum lithium concentration on the LiDCO measurement, an analysis of the effect of increasing background serum lithium concentration on the agreement between TDCO and LiDCO measurements was undertaken. All data from each dog were considered for statistical analysis. The LiDCO determination, in our experimental design, included both low- and high-dose lithium chloride. Because a previous study<sup>3</sup> indicated that high- and low-dose LiDCO are equivalent, the LiDCO data were pooled for all CO comparisons. The TDCO and LiDCO measurements obtained closest to the time of the collection of a blood sample for measurement of serum lithium concentration were used to determine the variability in the agreement between TDCO and LiDCO as a function of the background serum lithium concentration.

Four exclusion criteria were used to reject LiDCO measurements. The first criterion limited our study to the clinically relevant range of CO (< 5 L/min), and all LiDCO measurements above this limit were removed from the analysis. The second criterion involved errors in methods during the experiment, including procedural errors. Each LiDCO determination required entering into the LiDCO cardiac computer, prior to a measurement, the baseline hemoglobin and serum sodium concentrations and the dose of lithium chloride to be injected. Omissions of any of these 3 values constituted a procedural error. The third criterion involved all paired observations obtained during hemodynamic instability (ie, hemodynamic stability was not maintained after the maneuver used to alter CO). Hemodynamic instability was defined as a variation of > 20% in the TDCO determinations within a CO rate.<sup>3</sup> The fourth criterion excluded all paired observations for which the lithium sensor had been used for > 8 CO determinations. The effect of persistent use of a lithium sensor on accuracy has been previously discussed.<sup>3</sup>

For the analysis of the effect of the cumulative lithium chloride dosage on the serum lithium concentration, all data from each dog were considered for statistical analysis. Exclusion criteria were not placed on the data for this analysis, because TDCO and LiDCO measurements were not relevant to this objective. The serum lithium concentration that was determined at the end of each CO rate was compared with the cumulative dosage of lithium chloride that had been administered up to that point. The cumulative lithium chloride dosage was expressed as dose divided by the weight of the dog in kilograms.

Linear regression analysis<sup>i</sup> was used to assess the effect of increasing serum lithium concentration on the agreement between TDCO and LiDCO measurements. Linear regression analysis was also used to assess the effect of the cumulative lithium chloride dosage on the serum lithium concentration, to enable the estimation of the background serum lithium concentration from the cumulative dosage of lithium chloride administered.

## Results

Ten dogs were used (7 male, 3 female), with a mean weight of 36.2 kg and range of 30.5 to 45.4 kg. The range of serum lithium concentrations was 0.02 to 0.47 mmol/L, with a mean of 0.17 mmol/L. The range of CO induced in these dogs was 1.10 to 12.80 L/min. The mean amount of time from the first to the last CO

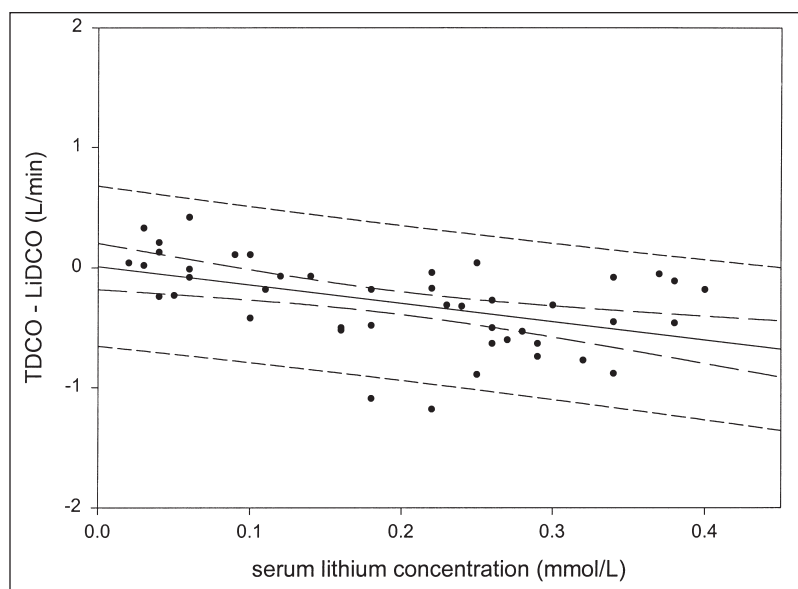


Figure 1—Linear regression plot of the difference between thermodilution cardiac output (TDCO) and lithium dilution cardiac output (LiDCO) determinations versus the serum lithium concentration in 10 dogs, for cardiac output range of 1.13 to 4.55 L/min. There are 44 paired observations representing a serum lithium concentration of 0.02 to 0.40 mmol/L. The analysis resulted in a slope (solid line) of  $-1.530$  (95% confidence interval [CI]; large-dash lines),  $-2.388$  to  $-0.671$ ) and a y-intercept of  $0.011$  ( $r^2 = 0.235$ ). The linear regression equation is  $y = -1.530x + 0.011$ . Notice the 95% CI (small-dash lines) of the predictive values for the regression equation.

determination for each dog was 5.5 hours, with a range of 3 to 7 hours. The mean number of injections of lithium chloride per dog was 32.1, with a range of 12 to 44. This included both low- and high-dose lithium chloride injections.<sup>3</sup>

To assess the accuracy of the serum lithium concentration determination methodology, 2 controls were utilized, 1 at the low end and 1 at the high end of the human therapeutic range. This analysis resulted in determining the coefficient of variations for the 2 control samples, each performed 10 times on separate days. The low control sample had a mean ( $\pm$  SD) concentration of  $0.69 \pm 0.1$  mmol/L and a coefficient of variation of 2%. The high control sample had a mean concentration of  $2.12 \pm 0.03$  mmol/L and a coefficient of variation of 1%.

A total of 74 paired observations of TDCO and LiDCO measurements and the corresponding serum lithium concentration were determined. Implementation of exclusion criteria resulted in the following paired observations being removed from the analysis. Six observations were excluded for LiDCO measurements  $> 5$  L/min. Methodologic errors resulted in 7 observations being excluded, including 3 for incorrect input of sodium and hemoglobin values, 3 for obstruction of the dorsal pedal arterial catheter, and 1 for failure of the flow regulator pump battery during determinations. Hemodynamic instability resulted in 3 observations being excluded. Lithium sensors used for  $> 8$  CO measurements resulted in 14 observations being excluded. Thus, 44 paired observations were used for the analysis of the effect of increasing background serum lithium concentration on the agreement between LiDCO and TDCO measurements. The range of LiDCO measurements used in the analysis was 1.13

to 4.55 L/min. The range of corresponding serum lithium concentrations used in the analysis was 0.02 to 0.40 mmol/L.

Values obtained by LiDCO determination increased as background serum lithium concentration increased. The linear regression analysis of the effect of the serum lithium concentration on the agreement between TDCO and LiDCO measurements revealed a slope of  $-1.530$  (95% confidence interval [CI],  $-2.388$  to  $-0.671$ ) and a y-intercept of  $0.011$  ( $P < 0.001$ ,  $r^2 = 0.235$ ; Fig 1). The linear regression equation was therefore expressed as:

$$y = -1.530x + 0.011$$

Using this equation, the estimated mean difference (95% CI) between TDCO and LiDCO determinations when a serum lithium concentration was measured at 0.1, 0.2, 0.3 or 0.4 mmol/L was  $-0.142$  ( $-0.787$  to  $0.503$ ),  $-0.295$  ( $-0.940$  to  $0.350$ ),  $-0.448$  ( $-1.093$  to  $0.197$ ), or  $-0.601$  ( $-1.246$  to  $0.044$ ) L/min, respectively.

The linear regression analysis of the effect of the cumulative lithium chloride dosage on the serum lithium concentration indicated a slope of  $2.291$  (95% CI,  $2.153$  to  $2.429$ ) and a y-intercept of  $0.008$  ( $P < 0.001$ ,  $r^2 = 0.938$ ; Fig 2). The linear regression equation therefore was expressed as:

$$y = 2.29x + 0.008$$

Using this equation, the estimated (95% CI) serum lithium concentration when a cumulative dosage of lithium chloride was calculated at 0, 0.05, 0.10, 0.15, 0.20, or 0.25 mmol/kg was  $0.008$  ( $-0.047$  to  $0.062$ ),  $0.122$  ( $0.067$  to  $0.177$ ),  $0.237$  ( $0.182$  to  $0.291$ ),  $0.351$  ( $0.296$  to  $0.406$ ),  $0.466$  ( $0.411$  to  $0.521$ ), or  $0.580$  ( $0.526$  to  $0.635$ ) mmol/L, respectively.

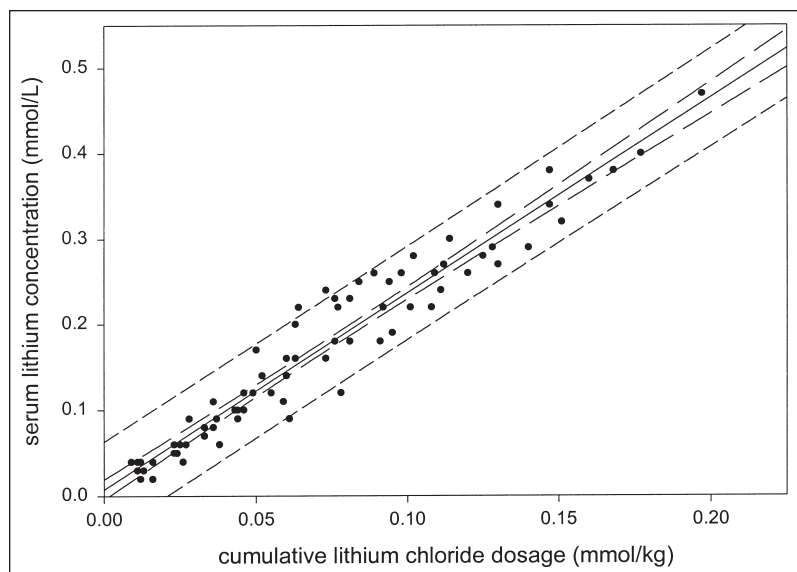


Figure 2—Linear regression plot of the serum lithium concentration versus the cumulative dosage of lithium chloride in 10 dogs. There are 74 paired observations representing a serum lithium concentration of 0.02 to 0.47 mmol/L. The analysis resulted in a slope (solid line) of 2.291 (95% CI [large-dash lines], 2.153 to 2.429) and a y-intercept of 0.008 ( $r^2 = 0.969$ ). The linear regression equation is  $y = 2.291x + 0.008$ . Notice the 95% CI (small-dash lines) of the predictive values for the regression equation.

## Discussion

The linear regression analysis of the effect of increasing background serum lithium concentration on the agreement between TDCO and LiDCO determinations revealed that the mean difference between TDCO and LiDCO determinations became greater as the serum lithium concentration increased. This occurred because the LiDCO determinations begin to overestimate the CO as the serum lithium concentration increases. As the background serum lithium concentration increases, the lithium sensor and computer have greater difficulty differentiating the next dose of lithium chloride from the background concentration. The resulting indicator dilution curves become smaller, which results in a smaller area under the curve, the denominator in the CO equation. Accumulation of the indicator represents a problem with all indicator dilution methods for measuring CO. However, this problem is less evident with TDCO measurements as the body readily dissipates the indicator (temperature).

The linear regression analysis (Fig 1) of the relation between serum lithium and the agreement between TDCO and LiDCO measurements revealed the expected negative slope ( $-1.530$ ) as a result of the gradually increasing serum lithium concentration. The y-intercept was virtually zero, which would indicate that there is no error present when the serum lithium concentration is zero. This would be expected and supports the view that it is the background serum lithium concentration that is creating this error. However the  $r^2$  value for the linear regression analysis was 0.235, indicating a weak association. The low  $r^2$  value may be attributable to uncontrolled variables within the 2 tests. For example, LiDCO was performed as a single determination, whereas TDCO was repetitively performed until 3 consecutive observations were within

10%, which were then averaged into 1 determination. This would reduce the error with the TDCO measurement. Had the reported LiDCO value been similarly determined as the mean of 3 consecutive observations within 10%, the resultant LiDCO measurement may have been closer to the TDCO values. Overall this may have resulted in less variability in LiDCO measurements. However, the manufacturer recommends only a single determination of LiDCO as performed here.

The critical serum lithium concentration, beyond which the measure of CO is no longer reliable, has been set by the manufacturer of LiDCO at 0.2 mmol/L. The average error introduced into the LiDCO system when the serum lithium concentration increased was not clinically relevant, but the 95% CI observed were wide, which could achieve clinical relevance. No attempt was made from the analysis to create a cutoff value to suggest a serum lithium concentration beyond which a clinically relevant degree of error would be introduced. Clinical relevance will vary with the individual clinician and clinical situation. Clinical relevance may be defined as a difference between the measured value and the real value that is of such a magnitude as to change a clinical decision.<sup>6</sup>

The data indicate that the cumulative lithium chloride dosage can predict the serum lithium concentration when multiple injections are performed over a short period. This finding allows the operator to estimate the serum lithium concentration that has been introduced from previous lithium chloride injections when the injections occurred over a short period. The operator can also estimate the "real CO" on the basis of the observed LiDCO measurement and the estimated error introduced by the estimated serum lithium concentration. If the determinations are performed over a long period (eg, days), then the estimated serum lithi-

um concentration will be greater than the true serum lithium concentration.

The pharmacokinetics of lithium have been determined in dogs.<sup>7,8</sup> Lithium has a narrow therapeutic range in dogs, similar to people. Its distribution is similar to sodium and can be explained by either a 2- or 3-compartment model. It has a half-life in mixed-breed dogs of 21.6 hours, whereas in Beagles it is 13.5 hours.<sup>7,8</sup> Lithium toxicosis is usually associated with chronic administration.<sup>9</sup> Evidence of lithium toxicosis was not found in any of the dogs in our study despite achieving concentrations of up to 0.47 mmol/L.

Results of an earlier study<sup>3</sup> indicated that LiDCO determination could be performed with either a low- or high-dose lithium chloride injection. In light of the present study, if one is anticipating performing multiple determinations within a short period, the low dose of lithium chloride will cause less of an increase in the background serum lithium concentration. This in turn will result in less of an overestimation of the actual CO with a LiDCO measurement. Therefore the low dose of lithium chloride should be used when performing multiple LiDCO determinations, particularly within a short period.

With the experimental design of our study, the background serum lithium concentration increased rapidly, with some dogs receiving as many as 30 to 40 injections of lithium chloride. Only a small degree of biological elimination of lithium would have occurred during the time course of our experiment (3 to 7 hours), because the half-life of lithium is longer. In the clinical setting, it is unlikely that 30 to 40 LiDCO determinations would be performed in such a short period; hence, it is also unlikely that observed high serum lithium concentrations would develop, particularly if the low dose were used. Using the regression equation that relates the cumulative lithium chloride dosage to the serum lithium concentration and using the low dose of lithium chloride, the number of injections that could be performed to reach a serum lithium concentration of 0.1, 0.2, 0.3, and 0.4 mmol/L are 16, 34, 51, and 68, respectively, if administered within the short period of 3 to 7 hours. As it is unlikely that more than 16 determinations would be performed in a clinical setting over a 7-hour period, the background serum lithium concentration is unlikely to exceed 0.1 mmol/L. Determinations on successive days would allow time for a greater amount of the lithium to be biologically eliminated from dogs.

There are several potential errors that could occur during a LiDCO determination. These include some of the errors that were encountered in the process of performing our experiment: failure to input the correct sodium and hemoglobin values in the LiDCO computer, obstruction of dorsal pedal arterial catheter, and failure of the flow regulator pump battery. Results of a previous study<sup>3</sup> indicated that the accuracy of LiDCO

determinations decreased with repeated use of a lithium sensor; thus, all data analyzed in our study are the result of a lithium sensor used for only 8 CO determinations. The manufacturer of the LiDCO system has modified the membrane of the sensor to improve its functional life span.<sup>a</sup>

Our study represents a further analysis of data collected previously by use of an experimental design that was developed to indicate the agreement between CO measurements obtained by LiDCO (2 doses) and TDCO methods at various CO.<sup>3</sup> Therefore the current design was not specific for the objectives of our study. However, the findings of our study continue to affirm that LiDCO determination is safe, accurate, easy, and inexpensive to use in dogs. Results of our study may help to increase the use of LiDCO determination in the general clinical setting. In addition, the use of linear regression equations that were developed in our study may allow users of the LiDCO method to estimate the error that will be introduced into a CO determination following multiple lithium chloride injections.

<sup>a</sup>O'Brien T, LiDCO Ltd, London, UK: Personal communication, 2000

<sup>b</sup>Torbugesic, Ayerst Veterinary Laboratories, Guelph, ON, Canada.

<sup>c</sup>Pentothal, Merial Ltd, Iselin, NJ.

<sup>d</sup>Halothane BP, Bimeda-MTC Animal Health Inc, Cambridge, ON, Canada.

<sup>e</sup>Air-Shields ventimeter ventilator, Air-Shields Inc, Hatboro, Pa.

<sup>f</sup>Edwards thermodilution cardiac output computer model COM-2, Baxter Healthcare Corp, Santa Ana, Calif.

<sup>g</sup>LiDCO cardiac monitor CM 31-01 computer, LiDCO Ltd, London, UK.

<sup>h</sup>IL 943 flame photometer, Instrumentation Laboratories, Lexington, Mass.

<sup>i</sup>SPSS software, SPSS Inc, Chicago, Ill.

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