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Reliability of lithium dilution cardiac output in anaesthetized sheep

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Editor's key points

- Sheep models are often used for cardiovascular research.
- Cardiac output (CO) measurement using lithium dilution (CO_{LD}) has not been validated in sheep.
- Cardiac output measured by lithium dilution was compared with an ultrasonic flow probe.
- Lithium dilution may be similar in terms of precision error to thermodilution, but did not require a pulmonary artery catheterization.

Background. Cardiac output (CO) measurement with lithium dilution (CO_{LD}) has not been fully validated in sheep using precise ultrasonic flow probe technology (CO_{UFP}). Sheep generate important cardiovascular research models and the use of CO_{LD} has become more popular in experimental settings.

Methods. Ultrasonic transit-time perivascular flow probes were surgically implanted on the pulmonary artery of 13 sheep. Paired CO_{LD} readings were taken at six time points, before and after implantation of a left ventricular assist device (LVAD) and compared with CO_{UFP} recorded just after lithium injection.

Results. The mean CO_{LD} was 5.7 litre min^{-1} (range 3.8–9.6 litre min^{-1}) and mean CO_{UFP} 5.9 litre min^{-1} (range 4.0–9.2 litre min^{-1}). The bias (standard deviation) was 0.3 (1.0) litre min^{-1} [5.1 (16.9)%] and limits of agreement (LOA) were −1.7 to 2.3 litre min^{-1} (−28.8 to 39.0%) with a percentage error (PE) of 34.4%. Data to assess trending [rate (95% confidence intervals)] included a 78 (62–93)% concordance rate in the four-quadrant plot (n=27). In the half moon polar plot (n=19), the mean polar angle was +5°, the radial LOA were −49 to +35° and 68 (47–89)% of data points fell within 22.5° of the mean polar angle. Both tests indicated moderate to poor trending ability.

Conclusion. CO_{LD} is not precise when evaluated against CO_{UFP} in sheep based on the statistical criteria set, but the results are comparable with previously published animal studies.

Keywords: anaesthesia, veterinary; data interpretation, statistical; measurement techniques, cardiac output; measurement techniques, lithium dilution; sheep

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Lithium dilution is a minimally invasive method of measuring cardiac output (CO) at the bedside. Because of its documented good precision,[1] lithium dilution cardiac output (CO_{LD}) is often used clinically in combination with arterial-pressure-waveform transformation to provide real-time cardiovascular monitoring utilizing the LiDCO*plus*™ system (LiDCO Ltd, Cambridge, UK).

The aortic flow probe is the gold-standard method for CO measurement, but because of its extreme invasiveness (i.e. requiring a thoracotomy for placement); it is only used in animal laboratory settings. Therefore, clinical validation in humans of a new CO monitoring technique is usually performed using thermodilution as the reference method. Several studies have been conducted comparing lithium dilution to thermodilution in both humans and animal species including cats, dogs, pigs, horses, and ponies.[1–6] However, only Kurita and colleagues[1 17] have compared the accuracy of lithium dilution with that of the flow probe, and they showed that in pigs, lithium dilution performed better than thermodilution. Subsequently, a number of animal and human studies have used lithium dilution as the reference method to measure CO.[8–11]

To the authors' knowledge, lithium dilution has not been validated fully in the sheep, a commonly used animal for cardiovascular research. Thus, the aim of our study was to compare CO_{LD} with the gold-standard method. An anaesthetized sheep model was used in which an ultrasonic flow probe was surgically placed on the pulmonary artery. The sheep model was concurrently being used to evaluate a left ventricular assist device (LVAD) which is described elsewhere.[12 13] A second objective of this study was to evaluate the ability of CO_{LD} to perform with the LVAD on and running at a continuous speed that is typical for clinical use. Preliminary results from this article have been published as an abstract.[14]

Methods

Animals

The study was approved by the Commission of Animal Experimentation of the Canton of Bern, Switzerland (No. 52/09). Thirteen female adult random-bred sheep were fasted overnight, but given free access to water. The sheep were premedicated with i.m. midazolam (0.2 mg kg^{-1}) and methadone (0.2 mg kg^{-1}). After 1 h, i.v. access via the jugular vein (13 G 10.5 cm Intranule, Vygon, Ecouen, France) was established and anaesthesia was induced with midazolam (0.2 mg kg^{-1}), ketamine (3.5 mg kg^{-1}), and either propofol or alphaxalone (1–3 mg kg^{-1}). The trachea was intubated orally with an 11 mm cuffed tube. Anaesthesia was maintained with a minimal concentration of 1.6% isoflurane in oxygen and fentanyl (5 μg kg^{-1} bolus; then 5–10 μg kg^{-1} h^{-1} infusion). The minimum alveolar concentration for isoflurane in sheep is 1.6%.[15] Pancuronium (0.1 mg kg^{-1}) was administered to provide neuromuscular block during the thoracotomy. Anaesthetic depth was adjusted and judged to be adequate before administration of pancuronium. If the heart rate or arterial pressure increased in response to surgical stimulation, additional fentanyl was given and the rate of infusion increased. Norepinephrine (0.1–1.0 μg kg^{-1} min^{-1} infusion) was used intermittently to maintain mean arterial pressure ~60 mm Hg, and amiodarone (2 mg kg^{-1}) was used as an anti-arrhythmic. The intercostal nerves were blocked with bupivicaine 0.5% (up to 2 mg kg^{-1}) at the thoracotomy site. The lungs were ventilated mechanically using a Primus anaesthesia machine (Dräger Medical GmbH, Lübeck, Germany) with a tidal volume of 8–10 ml kg^{-1} and positive-end-expiratory pressure set at 5 cm H_2O. Respiratory rate was adjusted to achieve normocapnia (end-tidal CO_2 of 4.6–6.0 kPa). The inspired fraction of oxygen was titrated up from 60% to maintain an Sa_{O_2} of 90–95%. An orogastric tube decompressed the sheep's rumen. A Datex S/5 monitor (Datex Ohmeda Ltd, Hatfield, UK) provided continuous monitoring of the electrocardiogram, arterial and central venous pressures, pulse oximetry, end-tidal CO_2, circuit gas concentrations (oxygen and isoflurane), and spirometry. Rectal temperature was maintained between 36 and 37°C with a circulating-warm-air blanket (WarmTouch™, Mallinckrodt Medical, Covidien, Dublin, Ireland). Intravascular volume was maintained with continuous i.v. administration of lactated Ringer's solution and a 6% hetastarch solution (initially 5 ml kg^{-1} h^{-1}, each) and adjusted individually based on monitoring parameters (central venous pressure, urine output, salivation, and blood loss) to achieve normovolemia. Severe intra-operative blood loss was compensated for by autologous blood transfusion with a cell saver (AutoLog, Medtronic, Inc., Minneapolis, MN, USA). At the end of the experiment, the animals were euthanized under general anaesthesia with an i.v. lethal dose of potassium chloride (20 mmol).

Surgical preparation

Once anaesthesia was established, a 30 cm 7 Fr double-lumen central venous catheter (Arrow Int., Teleflex Medical, Reading, PA, USA) was placed percutaneously into the left external jugular vein. Its distal port was used for central venous pressure measurement and injection of lithium chloride. A second 7 Fr double-lumen catheter was surgically placed in the left carotid artery to measure arterial pressure, to sample arterial blood for gas analysis, and to attach the lithium sensor and pump.

A left thoracotomy, described elsewhere,[12 13] was used to enter the thorax and an appropriately sized PAU-Series transit-time ultrasonic flow probe (A20 or A24, Transonic Systems, Inc., Ithaca, NY, USA) was placed around the main pulmonary artery to measure reference CO. The flow probe has a reported accuracy or precision error [i.e. 95% confidence intervals (CIs)], of 10%.[16] A study in six anaesthetized pigs using the A-series probe showed excellent correlation ($r>0.98$) with both aortic and pulmonary artery placement against calibrated-roller-pump right-heart bypass and no significant difference between the two placement methods.[17] In the sheep, the ascending aorta is very short and oval, making probe placement technically difficult. In another study involving chronically implanted flow probes in sheep, the pulmonary artery was chosen for similar anatomical reasons.[18]

The output of the flow meter (CO_{UFP}) was continuously acquired at a sample rate of 200 Hz using a model 416 iWorx data recorder and Labscribe2 software (iWorx, Dover, NH, USA). Offset (zero value when submerged in warm water bath) was checked before each experiment to ascertain that deviation from zero was within specification values.

As the sheep were enrolled in multiple study protocols,[12 13] they were heparinized and a CentriMag™ Rotary Blood Pump (Levitronix GmBH, Zürich, Switzerland) was surgically implanted. The CentriMag™ is a magnetically levitated centrifugal-flow pump designed to work as an active cardiac bypass in heart failure patients. It is a device that consists of a blood pump that is connected via cannulas to the left ventricular apex (inflow) and the aorta (outflow). The pump operates as a direct drive motor and can therefore be controlled very accurately. Even under sudden changes in loading conditions, the speed is maintained within 1% of its set value because of the built-in feedback controller.[13]

Lithium dilution

CO_{LD} was measured by flushing 0.225–0.3 mmol of lithium chloride (Interdelta SA, Givisiez, Switzerland) with 20 ml of NaCl 0.9% into the distal port of the central line using the park-and-ride system (LiDCO Ltd, Cambridge, UK), 7 s after the injection button was pressed on the LiDCO*plus*™ computer. Timing of the injection was randomized throughout the respiratory cycle and all measurements were performed by the same investigator (S.A.). Haematocrit and sodium concentrations were obtained just before each lithium dilution measurement.

Data collection protocol

Sets of paired CO readings were taken at six time points: T1—before implantation of the LVAD; T2—after implantation of the LVAD but before any experiments involving its use; T3—with the LVAD running at a continuous speed of 2000 r.p.m.

and T4 to T6—following separate experiments with the LVAD, but with the device switched off and clamped so that no blood circulated through the device. At each time point (T1–6), two sets of readings were taken, 5 min apart, to allow time for clearance of the lithium injectate from the circulation. CO_{LD} measurements were visually inspected and stored on a computer using LiDCO*view* Pro software. The criteria for curve rejection included: a signal amplitude of <0.1 mM, abnormal curve shape, sensor drift or cardiac arrhythmias. Rejected measurements were not repeated in order to limit increases in background serum lithium concentrations.

Markers indicating exact timing of roller pump action and lithium injection were placed in the Labscribe2 software in order to facilitate later data analysis. Based on these markers, each individual lithium measurement was compared with the average of CO_{UFP} calculated using 20 sequential heart cycles recorded just after lithium injection.

Statistical analysis

Patient characteristic data are presented as mean [standard deviation (SD)]. Precision and percentage error were based on 95% CI rather than 1 SD. Agreement between CO_{LD} and CO_{UFP} was assessed using a modified Bland and Altman plot adjusted for repeated measures.[19] Bias was calculated as the difference between the two readings ($CO_{UFP} - CO_{LD}$). Limits of agreement (LOAs) were calculated as the mean bias $\pm 1.96 \times$ SDs of the bias, after correcting for repeated measures. Percentage error was calculated from the LOA divided by the mean CO for the study {$100 \times$[$1.96 \times$ SD of the bias/(mean CO_{UFP}+mean CO_{LD}/2)]}. The current benchmark for an acceptable percentage error, when the reference method is thermodilution (precision of $\pm 20\%$), is $<28.4\%$.[20] However, CO_{UFP} had a precision of $\pm 10\%$.[16] Using the Critchley errorgram[20] to correct for different precisions in the reference method, if the precision of CO_{LD} needs to be $< \pm 20\%$, then the revised acceptable percentage error is set at $<22.4\%$.[20]

In addition to accuracy, trending ability was assessed using concordance analysis and polar plot methodology.[21 22] The change in CO was calculated from consecutive readings such that $\Delta CO = COa - COb$. The central exclusion zones used to minimize statistical noise were set at 0.5 and 0.35 litre min^{-1}, respectively. For comparisons against thermodilution, a reference method with a quoted precision of $\pm 20\%$, Perrino and colleagues[23] found that the optimum central exclusion zone was 15% or 0.75 litre min^{-1} for a mean CO of 5 litre min^{-1}. Other authors have used smaller exclusion zones of 0.5 litre min^{-1}.[20] In the present study, the precision of the reference method was $\pm 10\%$, thus a smaller 0.5 litre min^{-1} exclusion zone could be legitimately used. Furthermore, when using the polar method of trend analysis, the radial lengths are derived from the average of the two CO readings (test and reference) rather than the hypotenuse of the right angle triangle they form in Cartesian space, hence introducing a 1–1.4 scaling factor. Therefore, the exclusion zone used in the polar diagram was reduced to 0.35 litre min^{-1} from 0.5 litre min^{-1}.

In the four-quadrant plot, a concordance rate of >90–95% indicates good trending ability. In the polar plot, good alignment in calibration between the two methods exists if the mean polar angle deviates $<5^\circ$ from the polar axis of zero-degrees. Trending ability is considered good if $>95\%$ of data points lie within radial limits of 30° around the mean polar angle. Here, again the boundary limits for data concordance were scaled down from 30° to 22.5° around the mean polar angle of 5° because of the smaller precision error of the reference method used (i.e. $\pm 10\%$ rather than $\pm 20\%$), although the acceptance criteria for the precision error of the test method was still set at $\pm 20\%$.

We also chose to display the polar data on a semicircular or half moon plot with both upward and downward CO changes shown together in the same half-circle. Besides showing all the ΔCO data together, it also saves space.

After zone exclusion of some data points, the sample sizes used for the trend analyses became small. To increase the sensitivity and specificity of the trend analyses, we calculated the CI of the derived concordance rates. If one treats trend analysis data as binomial as there are two outcomes, do or do not concord, then the SD of the concordance rate is $\sqrt{[np(1-p)]}$, where n is the number of data sets and p is the proportion that concord. This SD is then converted to a percentage by multiplying it by $100/n$. For the trend data to have sufficient power to be predictive, the upper confidence interval should be less than the 95% acceptance threshold for good trending ability.

Statistical analysis was performed using MedCalc 12.3.0 (MedCalc Software, Mariakerke, Belgium). The four quadrant and polar plots were drawn using SigmaPlot (Systat Software, Inc., San Jose, CA, USA).

Results

Thirteen sheep were used. Two died because of uncontrollable haemorrhage (Sheep 2 and 3) during implantation of the LVAD. Data from the pilot study (Sheep 1) and one sheep with severe arrhythmias (Sheep 6) were excluded. As a result, data from nine sheep were included. Mean body weight was 71 (9) kg.

A total of 73 pairs of CO data were collected, of which 26 pairs were rejected (Table 1), leaving 47 pairs for analysis. The comparison statistics are presented in Table 2 and Figure 1.

Data to assess trending were limited to 27 of 38 possible data pairs in the four-quadrant plot and 19 of 38 possible data pairs in the polar plot after excluding central zone data (Fig. 1). The concordance rate [proportion (95% CI)] for the 27 data pairs was 78 (62–93)% in the four-quadrant plot. In the half moon polar plot and based on the 19 data pairs with mean CO changes >0.35 litre min^{-1}, the mean polar angle was $+5^\circ$, the radial LOA were -49 to $+35^\circ$ and 68 (47–89)% of data points fell within 22.5° (revised for a reference precision of $\pm 10\%$) of the mean polar angle.

Discussion

Our data provide evidence that the precision error of lithium dilution measurements in sheep is greater than previously thought (i.e. in excess of 20%) and when trending changes in

Table 1 Total number of measurements per sheep and reasons for rejecting

Sheep no.	Total measurements	Good measurements	Rejected positive drift of lithium sensor	Rejected unusual shape of lithium curve	Rejected technical failure
4	8	5	2	1	
5	4	3		1	
7	6	3	1	2	
8	8	6			2
9	8	6		1	1
10	10	8	2		
11	11	7		3	1
12	6	3		3	
13	12	6	3	3	

Table 2 Summary of the bias and comparison statistics for all of the data and additionally for the subgroups before and after LVAD implantation. The data after LVAD implantation were further subdivided into points where the LVAD was off and clamped [LVAD in (off)] and where the LVAD was on and running at a continuous speed of 2000 rpm [LVAD in (on)]. CO_{LD}, cardiac output measured by lithium dilution; CO_{UFP}, cardiac output measured by the flow probe around the main pulmonary artery; LOA, limits of agreement; PE, percentage error. The bias and LOA percentages are based on the mean CO_{UFP}

	Sample size	Mean CO_{LD} (litre min^{-1})	Mean CO_{UFP} (litre min^{-1})	Range (litre min^{-1})	Bias (SD) (%)	LOA (%)	PE (%)
All data	47	5.7	5.9	3.8–9.6	5.1 (16.9)	−28.8 to 39.0	34.4
LVAD out	11	6.8	6.8	4.4–9.6	0.0 (17.6)	−35.3 to 36.8	35.5
LVAD in (all)	36	5.3	5.7	3.8–9.0	5.3 (12.3)	−17.5 to 29.8	24.2
LVAD in (on)	10	5.3	5.6	4.3–8.0	5.4 (9.0)	−10.7 to 21.4	17.0
LVAD in (off)	26	5.3	5.7	3.8–9.0	7.0 (12.3)	−17.5 to 29.8	24.4

CO it lacks reliability. Comparisons were made against a pulmonary artery flow probe which has greater precision (i.e. 10%) than thermodilution (i.e. 20%).[20] The percentage error for our analysis was 34.4%, which far exceeded the revised acceptance criteria of 22.4% for flow probe comparisons. Furthermore, trend analysis using both four-quadrant and half moon polar plots returned concordance rates of 78 (62–93) and 68 (47–89)%, respectively. For good trending, more than 95% of data pairs should concord. For lithium dilution to be recommended as the method of choice for measuring CO in sheep studies, it needs to satisfy both the above criteria.

In 1997, Kurita and colleagues[1] first published animal data from anaesthetized pigs in which lithium dilution was compared with a gold standard in electromagnetic aortic flow probe and thermodilution readings over a range of COs. The authors presented their data on scatter and Bland–Altman plots. However, trending ability was not assessed and only bias with 1 − SD was quoted. At the time, their data were considered to support the use of lithium dilution because of a good predictive performance test. Since 1997, more pertinent statistical methods have been described in the literature that better address accuracy and trending ability of CO devices.[19–22] Thus, upon re-examination of their Bland–Altman plots, and using the mean CO of 1.36 litre min^{-1} reported in their paper, a percentage error against the flow probe of ~26% and against thermodilution of ~45% is calculated, which indicates that lithium dilution in the pig has a precision error in excess of 22.4%, a figure more in keeping with our sheep data and does not support the level of accuracy suggested previously. Our percentage error for CO_{LD} *vs* CO_{UFP} was 34.4% compared with 26% in their study. The latter may be an underestimate because no adjustment for repeated measures could be performed.[19] Trending ability also could not be evaluated from their paper. They assumed good trending ability from regression analysis data. In their study, the range of COs was smaller, 0.5–3.0 litre min^{-1}, compared with our study, 3.8–9.6 litre min^{-1}. This difference in ranges may have affected the percentage errors collected during the study. Some authors have shown decreased precision at high CO values.[3] Furthermore, the precision of the lithium method in the swine study may have been improved statistically by only including paired measurements that had differed by <10%. In critically ill patients, it was shown that the precision of lithium dilution was optimal when three repeated measurements were averaged.[24] We chose to use only one reading to avoid excessive increases in background lithium concentrations, and if there was a technical failure or significant difference between the measurements, the reading was discarded and not repeated. In Kurita and colleagues' study, all measurements were performed during a period of apnoea, whereas in our study measurements were taken randomly throughout the ventilatory cycle. Pilot data showed a significant decrease in CO_{UFP} while the lithium dilution was performed if the sheep was kept apnoeic. This difference may further have affected our results.

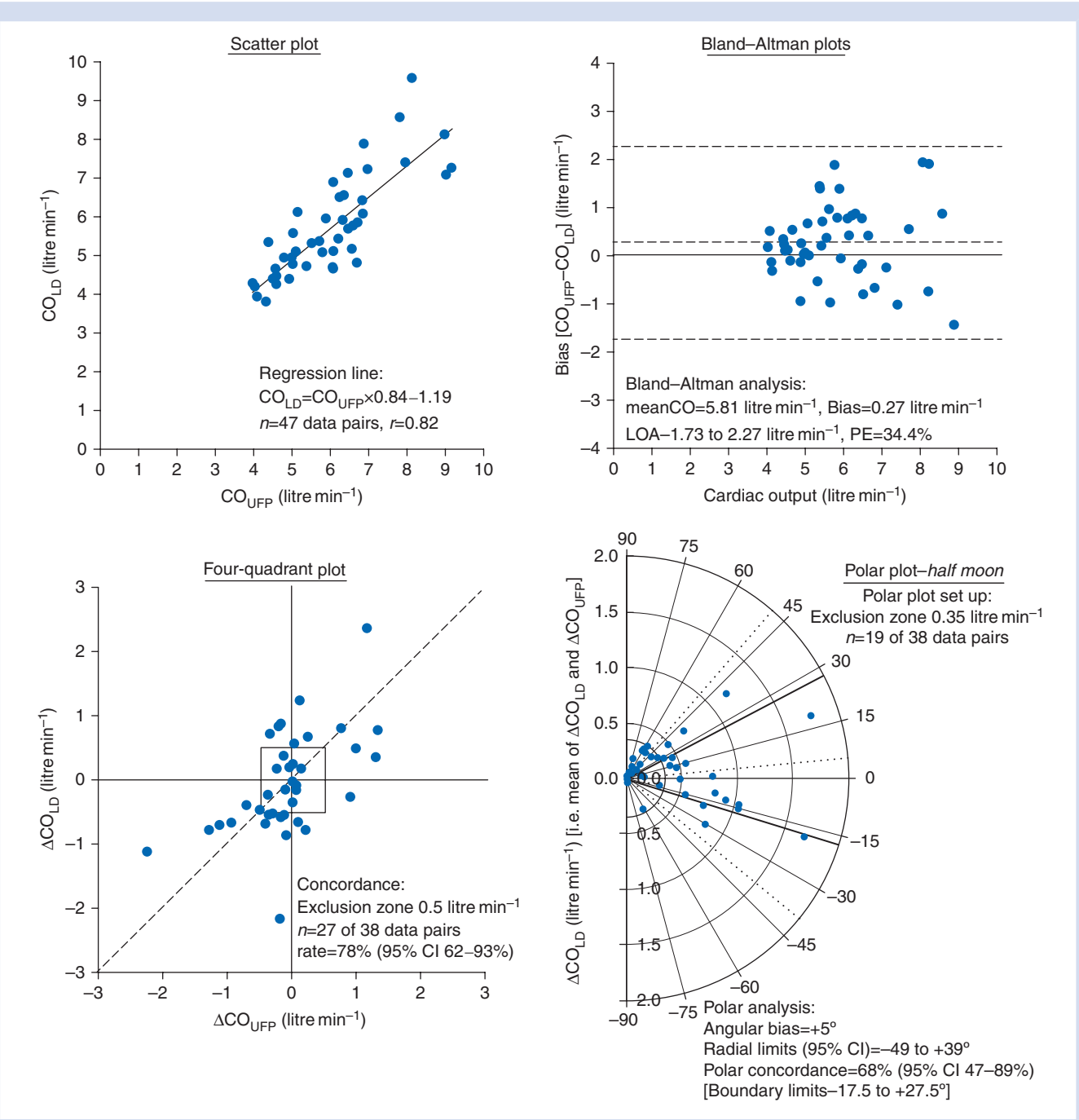

Fig 1 Four plots that summarize the validation statistics. The scatter plot shows all the data as *X*, *Y* points. A regression line is drawn with correlation coefficient (*r*). CO_{LD}, lithium dilution cardiac output; CO_{UFP}, ultrasonic flow probe cardiac output; PE, percentage error. The Bland–Altman plot has been adjusted for repeated measures. Dashed horizontal lines represent mean bias and LOA for the data (95% CI). The four-quadrant plot shows change data (ΔCO) and is used to assess trending. The dashed line is the line of identity (*Y*=*X*) and the central exclusion zone is shown as a square box. The polar plot is shown using a semi-circular or half-moon design with all the ΔCO data shown together in the same half sector. The dotted lines show the mean polar axis and two radial LOA, equivalent to the 95% confidence limits of the Bland–Altman plots. The central exclusion zone is shown by the inner half-circle.

A number of authors since Kurita and colleagues have compared lithium dilution with thermodilution in the animal laboratory.[2–6] A study of 6 horses showed that thermodilution and lithium dilution were comparable based on data analysis which included standard Bland–Altman and regression analysis. We calculated an approximate percentage error of 26%.[6] Data from 10 dogs concluded that CO_{LD} was reliable.[3] Bland–Altman analysis was also used, and again the data analysis was limited. Percentage error appeared to be 25–30%. A study of 6 cats concluded good agreement between the two

methods, with an estimated percentage error of 29%.[2] Based on these and other studies, the general consensus has been that CO_{LD} is at least as precise as thermodilution and can replace it in animal research. Since then, lithium dilution has been commonly used in veterinary practice.

Our data and analysis provide a clearer picture of the performance of lithium dilution in animal models, and the sheep in particular, because we used statistical methods that set clear criteria for acceptable accuracy compared with current standards (i.e. thermodilution) and criteria for good trending ability (i.e. percentage error, concordance, and polar data). Furthermore, we used a gold standard reference method (i.e. ultrasonic flow probe), unlike many previous studies.[2–6] Our data suggest that the performance of lithium dilution is similar in terms of precision error to thermodilution, but without the risks to the animal of inserting a pulmonary artery catheter.

Our study had some limitations. The power was limited to nine sheep and 47 data points. This was further reduced to 19–27 data points for assessing trending. However, our study size was in keeping with previous animal studies,[1–6] and probably had little effect on the outcomes of the Bland–Altman analysis. In respect to concordance analysis, both the four quadrant and polar plots returned statistically significant rates of 78 and 68%, respectively ($P<0.05$), that were below the acceptance rate of 95% for good trending ability. Their upper CI were 93 and 89%.

Many data points needed to be rejected and the majority, 14 of 26 were for unusual CO_{LD} curve shape. Likely causes include poor blood flow from the arterial line and dilution of lithium injectate in the arterial or venous lines. However, we followed the recommended procedures carefully, so it is unlikely that excessively long tubing on either the venous or arterial line were the cause. Blood flow from the arterial line was manually checked before each measurement and the carotid artery should have provided steady blood flow. In practice, the auricular artery is much easier to access but is very susceptible to constriction especially during periods of altered haemodynamics or hypothermia.

Eight of the 26 rejected curves were excluded because of positive drift of the lithium sensor. Known causes of sensor drift include drug interactions with neuromuscular blockers. Our protocol purposely used a single bolus of pancuronium because of its long duration of action, therefore avoiding the need for re-administration and further sensor interaction. Pancuronium has been determined to be compatible for use with the LiDCO*plus*™ system by the manufacturer and has been used in other lithium dilution validation studies.[1 7] The software is designed to detect interaction with the positively charged quaternary ammonia ion of the neuromuscular blocker, therefore sensor interactions with pancuronium should indicate a curve rejection because of positive drift. All but one of the positive drift errors occurred during T1, therefore, it is likely that a time interval longer than 30 min is necessary after administration of pancuronium before performing lithium dilution measurements in sheep.

It is also interesting to note that percentage error of the data substantially improved to 24.2% when the subgroup of data taken before LVAD implantation was removed (T1). Recent research has detected possible sensor interactions with a number of other drugs including ketamine.[25] Ketamine was used for induction of anaesthesia in this study, ~1.5 h before T1. The increase in error at T1 may have been related to ketamine administration or to the low number of curves left for analysis after removal of the rejected positive drift curves.

A secondary objective of our study was to evaluate the reliability of CO_{LD} with the LVAD on and running at continuous speed. Although the data are limited to 10 measurements, there appears to be good precision (PE of 17%), indicating that CO_{LD} may potentially be useful in patients with an implanted LVAD. Further study will be needed in humans to confirm this.

Conclusion

When evaluating the performance of a CO monitoring technique proper and up-to-date statistical methods need to be applied that include Bland–Altman and a trend analysis. Our study describes the use of such statistics to compare CO_{LD} with $CO_{UFP,}$ the gold standard. Our findings revealed that CO_{LD} measurement in sheep was not as precise as we had expected and it does not trend changes in CO sufficiently reliably, but the results are comparable with previously published animal studies.

Authors' contributions

S.M.A.F.: study design, literature search, data collection, data analysis, first draft of manuscript and final approval of manuscript. L.A.C.: literature search, data analysis, statistical analysis, generation of figures, first draft of manuscript and final approval of manuscript. A.W.: instrumentation, data collection and final approval of manuscript. H.B.: instrumentation, data collection and final approval of manuscript. T.P.: data collection, data analysis and final approval of manuscript. S.V.: study design, literature search, data collection, data analysis, first draft of manuscript, grant submission, ethical committee permission and final approval of manuscript.

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Declaration of interest

None declared.

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