Comparison of the accuracy of the lithium dilution technique with the thermodilution technique for measurement of cardiac output

T. KURITA, K. MORITA, S. KATO, M. KIKURA, M. HORIE AND K. IKEDA

Summary
A new indicator dilution technique for measurement of cardiac output is described. Lithium chloride is injected via a central venous catheter and its dilution curve measured in arterial blood using a lithium-selective electrode. We assessed the lithium dilution cardiac output measurement (LiDCO) and a conventional thermodilution cardiac output measurement (ThDCO) by comparing the results of both with cardiac output determined by electromagnetic flowmetry (EMCO) under controlled laboratory conditions in 10 swine. They were monitored with a pulmonary artery catheter, femoral artery catheter and electromagnetic flowmeter placed around the ascending aorta. LiDCO, ThDCO and EMCO measurements were determined at baseline, in a hyperdynamic state produced by administration of dobutamine, at a second baseline and finally in a hypodynamic state induced by propranolol during deep anaesthesia. Data were analysed by linear regression analysis and the comparison method described by Bland and Altman; bias and precision of both LiDCO and ThDCO compared with EMCO were calculated by the method of Sheiner and Beal. The correlation coefficient between LiDCO and EMCO (0.95) was higher than that between ThDCO and EMCO (0.87). The precision value of LiDCO (0.04) was significantly less (i.e. better) than that of ThDCO (0.09). The results of this study indicated that LiDCO was more reliable compared with conventional ThDCO. (Br. J. Anaesth. 1997; 79: 770–775).

Key words

The thermodilution technique using a pulmonary artery catheter has been widely used clinically for measurement of cardiac output. With this technique, insertion of a pulmonary artery catheter involves an invasive procedure associated with several risks and complications.1–3 A recent report indicated that pulmonary artery catheterization is associated with an increase in mortality and cost of care.4 Errors in measurement may be introduced by rewarming of the injectate caused by handling before injection and by heat transfer during passage through the pulmonary artery catheter.5–9 Thermodilution may overestimate cardiac output during a low cardiac output state, probably because of excessive heat exchange secondary to slow passage of injectate.10 11 A less invasive method is available using a lithium dilution technique that uses lithium chloride as the indicator. A preliminary clinical study of this technique has been reported by Linton, Band and Haire.12 Lithium chloride, injected into the right atrium via a central venous catheter, is measured by a sensor attached to the peripheral arterial catheter, and cardiac output can be measured without a pulmonary artery catheter. Lithium does not normally exist in the human body, does not bind to plasma or tissue proteins and is excreted almost entirely in urine.13–15 There have been no studies comparing the lithium dilution technique with the thermodilution technique under controlled hypodynamic or hyperdynamic laboratory conditions. Accordingly, we assessed the reliability of lithium dilution and thermodilution techniques by comparing both with cardiac output determined by electromagnetic flowmetry under controlled hypodynamic and hyperdynamic states.

Materials and methods
EXPERIMENTAL PROCEDURE
After obtaining approval from the Institutional Ethics Committee, we studied 10 swine (body weight 10–15.5 kg). After administration of ketamine 5–7 mg kg\(^{-1}\) i.m., general anaesthesia was induced by inhalation of 4% sevoflurane in oxygen 5 litre min\(^{-1}\) using a standard animal mask. After induction, the trachea was intubated with a cuffed tracheal tube, and anaesthesia was maintained with 3% end-tidal sevoflurane and 100% oxygen with mechanical ventilation (Harvard apparatus dual phase control pump, GI3, South Natick, MA, USA). A peripheral venous cannula (20-gauge) was...
inserted in the dorsal ear vein and lactated Ringer’s solution was infused at a rate of 10 ml kg⁻¹ h⁻¹. After induction, vecuronium or pancuronium was administered. End-tidal carbon dioxide was maintained at 4.7–5.3 kPa. Lead II of the electrocardiogram (ECG) was monitored with subcutaneous electrodes introduced into the legs. After median sternotomy and pericardiotomy, the probe of an electromagnetic flowmeter (Electromagnetic blood flowmeter, MFV3200, Nihon Kohden, Tokyo, Japan) was placed around the ascending aorta for continuous measurement of cardiac output. The probe attachment was varied in order to fit the diameter of each particular aorta (FB120T, FB130T, FB140T, FB150T, FB160T, lumen diameter range 12–16 mm, Nihon Kohden). The electromagnetic flowmeter system was calibrated initially and before each change in haemodynamic state. The position of the probe of the electromagnetic flowmeter was checked after the swine was killed with potassium chloride i.v. under deep anaesthesia with 5% inspired sevoflurane.

A pulmonary artery catheter (5 F, 4 lumen, Nihon Kohden) was inserted into the right jugular vein, and a double-lumen catheter (16–18-gauge) was placed in the femoral artery. Arterial pressure was monitored via one lumen of the femoral artery catheter, and blood samples were obtained from the other lumen for measurement of plasma concentrations of lithium. Heparin 100 u. kg⁻¹ was administered in order to avoid blood clotting on the membrane surface of the lithium sensors, thus avoiding deterioration of the sensors. By warming with heating lamps, blood temperature of the swine was maintained in the range 36.5–37.5°C. In all experiments it took less than 1.5 h from induction of anaesthesia to the first baseline measurements. After baseline measurements were obtained, haemodynamic status was changed from baseline to a hyperdynamic state (20–40% increase in cardiac output monitored with EMCO) by continuous infusion of dobutamine at a rate of 10 μg kg⁻¹ min⁻¹, and then returned to baseline. Next, the status was changed from baseline to a hypodynamic state (20–40% decrease in cardiac output) by administration of propranolol 0.5–2.0 mg and increase in end-tidal sevoflurane concentration to 4–5%. After obtaining haemodynamic stability for at least 10 min, cardiac output was measured. ThDCO was determined by a thermodilution computer (Cardiac Output Computer, MTC6210, Nihon Kohden) using 5 ml of ice-cold 5% glucose injected into the right atrium. During apnoea at the end of expiration, 0.67 ml of a lithium chloride solution (0.15 mol litre⁻¹) was injected (dose = 0.1 mmol) as a bolus into the right atrium via the atrial port of the pulmonary artery catheter. The same investigator performed all injections. To ensure that the injection bolus dose was exactly 0.67 ml, the deadspace of this catheter (0.39 ml) had previously been filled with more than 0.4 ml of lithium chloride solution until a small amount of indicator leakage had come out from the tip of the catheter, and had a small peak appeared on the recording curve of the concentration–time course. The primary circulation curve was discriminated from the secondary (or recirculation) curve by the method of Linton, Linton and Band, based on the theory of using a log-normal analysis to determine the integral of the primary curve. Cardiac output was then calculated using the following formula by Linton, Band and Haire:

\[
\text{Cardiac output (litre min}^{-1}) = \frac{[\text{dose of lithium chloride (mmol)} \times 60]}{[\text{area under curve (mmol litre}^{-1} \text{s)} \times (1-\text{PCV})]}
\]

where area under the curve = the integral of the primary curve and PCV = packed cell volume. Division by (1–PCV) converts plasma flow to blood flow as lithium is distributed only in the plasma fraction of blood. PCV was measured as the value of haematocrit (Kubota Hematocrit KH-120A, Tokyo, Japan) before cardiac output measurement in each haemodynamic state.

**STATISTICAL ANALYSIS**

The linear regression equations between ThDCO and EMCO, and between LiDCO and EMCO were calculated by simple linear regression analysis using the least squares method. As recommended by Bland and Altman, the difference (ThDCO–EMCO) compared with (ThDCO+EMCO)/2, and the difference (LiDCO–EMCO) compared with (LiDCO+EMCO)/2 were plotted and

**LITHIUM DILUTION CARDIAC OUTPUT MEASUREMENT**

A prototype LiDCO measurement system was used (LiDCO, Ltd., London, UK). The lithium sensor consists of a flow-through cell containing a lithium-selective electrode developed for this use. The indicator is lithium chloride 0.15 mol litre⁻¹, prepared in glass ampoules by the pharmacy at St Thomas’s Hospital (London, UK). The voltage from the sensor is logarithmically related to plasma lithium concentration and is recorded via an electrically isolated preamplifier and analogue to digital converter by a Macintosh computer (PowerBook 5300CS, Apple Computer, Cupertino, CA, USA). Before they were used the sensors were calibrated by exposure to saline and then to a solution of lithium chloride 1 mmol litre⁻¹ in saline and recording the change in voltage. A roller pump (CP-136, Nissho Corporation, Osaka, Japan) was used to regulate blood flow from the femoral arterial catheter via the flow-through cell to 4 ml min⁻¹ until a stable baseline voltage was recorded. Then, during apnoea at the end of expiration, 0.67 ml of a lithium chloride solution (0.15 mol litre⁻¹) was injected (dose = 0.1 mmol) as a bolus into the right atrium via the atrial port of the pulmonary artery catheter. The same investigator performed all injections. To ensure that the injection bolus dose was exactly 0.67 ml, the deadspace of this catheter (0.39 ml) had previously been filled with more than 0.4 ml of lithium chloride solution until a small amount of indicator leakage had come out from the tip of the catheter, and had a small peak appeared on the recording curve of the concentration–time course. The primary circulation curve was discriminated from the secondary (or recirculation) curve by the method of Linton, Linton and Band, based on the theory of using a log-normal analysis to determine the integral of the primary curve. Cardiac output was then calculated using the following formula by Linton, Band and Haire:

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means (SD) of the differences were calculated. The predictive performance test described by Sheiner and Beal was performed to evaluate statistical significance of the bias (mean prediction error by which ThDCO or LiDCO overestimates or underestimates EMCO) and precision (mean squared prediction error by which ThDCO or LiDCO overestimates or underestimates EMCO) values between two different dilution techniques. One-way analysis of variance followed by the Bonferroni multiple comparison test were used to compare the changes in cardiac output at each haemodynamic state. \( P<0.05 \) was considered statistically significant, and results are expressed as mean (SD).

### Results

The value of EMCO obtained at baseline (1.41 (0.49) litre min\(^{-1}\)) was significantly lower than that in the hyperdynamic state (1.74 (0.47) litre min\(^{-1}\)), and was significantly higher than that in the hypodynamic state (0.93 (0.43) litre min\(^{-1}\)). There was no significant difference between the value of EMCO obtained at baseline (1.41 (0.49) litre min\(^{-1}\)) and that obtained at the second baseline (1.36 (0.53) litre min\(^{-1}\)). Three aberrant LiDCO readings and 20 ThDCO readings were rejected to obtain 80 readings, respectively. The correlations between ThDCO and EMCO, and between LiDCO and EMCO are shown in figure 1. The correlation

#### Table 1

<table>
<thead>
<tr>
<th>Haemodynamic State</th>
<th>Baseline 1</th>
<th>Hyperdynamic state</th>
<th>Baseline 2</th>
<th>Hypodynamic state</th>
<th>All data</th>
</tr>
</thead>
<tbody>
<tr>
<td>ThDCO</td>
<td>-0.03, 0.06</td>
<td>0.04, 0.17</td>
<td>0.09, 0.07</td>
<td>0.03, 0.08</td>
<td>0.03, 0.09</td>
</tr>
<tr>
<td>LiDCO</td>
<td>0.10*, 0.03</td>
<td>0.01, 0.02†</td>
<td>0.18, 0.06</td>
<td>0.17, 0.06</td>
<td>0.11*, 0.04†</td>
</tr>
</tbody>
</table>

* \( P<0.05 \) compared with bias value of ThDCO. † \( P<0.05 \) compared with precision value of ThDCO.
Dynamic changes such as slowing of heart rate, 20–22 bolus injection of ice-cold 5% glucose elicits haemodynamic changes. As it does not require the use of a pulmonary artery catheter and it is not lost in plasma or tissue proteins. 13,14 Because we stopped mechanical ventilation and maintained i.v. infusion causes small fluctuations in pulmonary blood temperature. 15,20 In a recent prospective cohort study, Connors and colleagues analysed 5735 critically ill adult patients receiving care in an intensive care unit. They compared outcome in two groups of patients (matched for severity of illness): one group had pulmonary artery catheters inserted and the other did not. They found that pulmonary artery catheterization was associated with a 24% higher mortality, longer hospital stay and increased medical costs. As the thermodilution technique uses cold as an indicator, several factors may influence cardiac output estimation by this method. Renner, Morton and Sakuma conducted an animal study to determine the accuracy and reproducibility of the thermodilution technique using 5- or 10-ml room temperature or iced injectates. Their results showed that a smaller volume of room temperature injectate impaired accuracy but not reproducibility at low cardiac outputs, and that this same volume impaired reproducibility at high cardiac outputs. 26 Thermodilution measurements obtained at specific times during the respiratory cycle are known to vary by 5–20%. Measurement errors caused by even a small cyclical variation in pulmonary blood temperature with respiration may be another factor in the variation of results in thermodilution techniques. Even if the end of expiration is used to time injection of the indicator, cardiac output is underestimated during spontaneous breathing and overestimated during continuous or intermittent positive-pressure ventilation. Variations in pulmonary artery blood temperature transiently increase after cardiopulmonary bypass, and the increased thermal noise may cause significant errors in the results of thermodilution techniques. Wetzel and Latson reported that cardiac output was underestimated during rapid volume infusion because rapid peripheral volume infusion causes small fluctuations in pulmonary artery blood temperature. In our study, ThDCO was performed using 5 ml of ice-cold 5% glucose as the indicator and was measured during apnoea at the end of expiration to reduce baseline fluctuations in pulmonary artery blood temperature.

The lithium dilution technique causes less of a problem from loss of indicator. It cannot be lost through the injection catheter and it is not lost in its passage through the lungs, nor does it bind to plasma or tissue proteins. Because we stopped mechanical ventilation and maintained i.v. infusion rates constant while cardiac output was measured, we kept fluctuations in baseline voltage by respiratory cycle or rapid volume infusion to a minimum. Lithium chloride injection did not elicit any haemodynamic changes. As it does not require the use of a pulmonary artery catheter, the lithium dilution technique is a less invasive method; measurements can be taken via in situ central venous and arterial catheters without exposing patients to any of the risks associated with the use of a pulmonary artery catheter.

Several caveats with the LiDCO system should be...
mentioned. (1) We administered heparin 100 u. kg to avoid blood clotting on the sensor because clotting would cause rapid deterioration of the electrode. The sensor used in our study was a prototype disposable one, not treated with anticoagulant. We used one sensor throughout each experiment because of limited availability of the prototype sensors and because of this, administration of heparin was essential. (2) Linton, Band and Haire reported that the sudden transition from room temperature saline to warm blood caused a transient drift in electrode potential. We observed this in our study; however, we had enough time for blood sample withdrawal (10–15 s) to stabilize the drift of the lithium sensors before measurement. (3) We observed a transient increase in baseline voltage for a few minutes starting just after administration of NaHCO₃, vecuronium or pancuronium. Although these drugs do not cause permanent unacceptable drift or deterioration of the electrode, it should be kept in mind that administration of these drugs during or immediately before the measurement time may decrease the accuracy of the lithium dilution technique. (4) The LiDCO system requires obtaining 4 ml min⁻¹ of sample blood; mean blood loss for each measurement was 2.6 ml, which was less than that in the system reported by Linton, Band and Haire (who withdrew 15–30 ml min⁻¹). Because the sensor is located outside the artery, sample volume loss may be unavoidable, but a decrease in sample volume may be realized in the future if a smaller sensor is designed or sample reinfusion is made possible.

The lithium dilution technique requires further examination concerning pharmacokinetics and the future safety of multiple injections of lithium chloride in clinical settings. As lithium has been administered orally as the carbonate salt (Li₂CO₃) in the treatment of affective disorders, pharmacokinetics and the emergence of side effects by multiple injections over a short time should be investigated to determine safety and dose limitations.

References

Accuracy of the lithium dilution cardiac output measurement


