

Lithium Dilution Cardiac Output Measurement in Oleic Acid-Induced Pulmonary Edema

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Objective: To determine whether lung injury influences the accuracy of lithium dilution cardiac output (CO) measurement.

Design: Animal experimental study.

Setting: Animal experimental laboratory.

Participants: Swine (n = 23) weighing 26.4 ± 2.47 kg (mean \pm SD).

Interventions: The animals were anesthetized and tracheotomized, then a pulmonary artery catheter was inserted into the right jugular vein, and a catheter (18G) was placed in the femoral artery. After median sternotomy and pericardiotomy, a left ventricular catheter (18G) was directly inserted. CO was measured by giving a bolus injection of lithium chloride into either the right atrium or the left ventricle in each animal. After control measurements, permeability pulmonary edema was initiated by infusing oleic acid into the central vein (injury). About 2 hours after oleic acid

infusion, CO measurements were repeated in the same manner as the control measurement had been taken.

Measurements and Main Results: Under each condition, right atrium lithium injection was similar to left ventricle lithium injection. The mean of these differences at injury (-0.06 ± 0.55 L/min) was the same as that at control (-0.05 ± 0.36 L/min).

Conclusions: Although the variability of lithium dilution CO measurement after oleic acid-induced pulmonary edema was greater than that of the control, this technique was acceptable even in cases of lung injury.

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KEY WORDS: cardiac output (CO), indicator dilution, lithium dilution, thermodilution, critical care, lung injury, oleic acid, pulmonary edema, measurement technique, pulmonary artery catheter

THE LITHIUM DILUTION TECHNIQUE for the measurement of cardiac output (LiDCO) (LiDCO, Ltd, London, UK) was introduced by Linton et al^{1,2} in 1993 and has been developed further more recently. The LiDCO system has been approved by the Food and Drug Administration and is now in use in several hospitals in the United States. In this method of cardiac output (CO) measurement, lithium chloride is injected into the atrium through a central venous catheter, and CO can be determined from the arterial lithium dilution curve, without a pulmonary artery catheter. In a previous animal study, this method was more accurate than that of conventional thermodilution in comparison with direct electromagnetic flowmetry (the laboratory gold standard).³ A peripheral vein, which is more easily accessed than a central vein, could be used for the indicator injection port.^{4,5} Because there are some objections regarding the use of a pulmonary artery catheter,⁶ this method could be considered as an alternative one that does not involve the use of a pulmonary artery catheter for management of critically ill patients.

The accuracy of the LiDCO method depends on the loss of lithium in the lungs being negligible; Band et al⁷ reported that this loss was clinically insignificant. In clinical situations, the pulmonary capillary permeability becomes greater than normal as a result of raised left atrial pressure, residual effects of recent cardiopulmonary bypass, and adult respiratory distress syn-

drome. If there is a significant loss of lithium after an increase in pulmonary capillary permeability, this loss could affect the CO values measured by the LiDCO technique. To the authors' knowledge, no previous studies have investigated the reliability of the LiDCO technique after acute lung injury. The present study was conducted to assess the reliability of the LiDCO technique by comparing the CO values before and after injection of lithium chloride into the right atrium or left ventricle using a pulmonary edema model in swine.

MATERIALS AND METHODS

This study was approved by the Committee on Animal Research, Hamamatsu University School of Medicine, Hamamatsu, Japan. Twenty-three swine (mean body weight \pm SD, 26.4 ± 2.47 kg) were studied. After administration of ketamine, 10 mg/kg intramuscularly, general anesthesia was induced by inhalation of 5% sevoflurane in oxygen at 6 L/min using a standard animal mask. After tracheostomy, anesthesia was maintained with 4% end-tidal sevoflurane and 100% oxygen via mechanical ventilation. A peripheral venous catheter (20G) was placed in the dorsal ear vein, and lactated Ringer's solution was infused at a rate of 10 mL/kg/h. After induction, pancuronium bromide was administered to ensure proper control of ventilation. Lead II of an electrocardiogram was monitored with subcutaneous electrodes in the legs.

A pulmonary artery catheter (5F, 4-lumen; Nihon Kohden, Tokyo, Japan) was inserted into the right jugular vein, and a catheter (18G) was placed in the femoral artery. After median sternotomy and pericardiotomy, a left ventricular catheter (18G) was directly inserted. The position of the left ventricular catheter was checked after the swine had been killed with potassium chloride under deep anesthesia with 5% inspired sevoflurane. A lithium sensor was attached to the femoral artery for measurement of the lithium concentration. Heparin (100 U/kg) was administered to avoid blood coagulation on the membrane surface of the lithium sensors, and deterioration of the sensors was prevented. By warming with heat lamps, the blood temperature of the swine was maintained in the range of 38.5°C to 40.0°C.

After hemodynamic stability had been maintained for at least 10 minutes, CO was determined. The LiDCO technique was performed by giving a bolus injection of lithium chloride into the right atrium through the atrial port of the pulmonary artery catheter (LiD-RA) or into the left ventricular catheter (LiD-LV). During apnea at the end of expiration, the same person administered lithium chloride. The interval between

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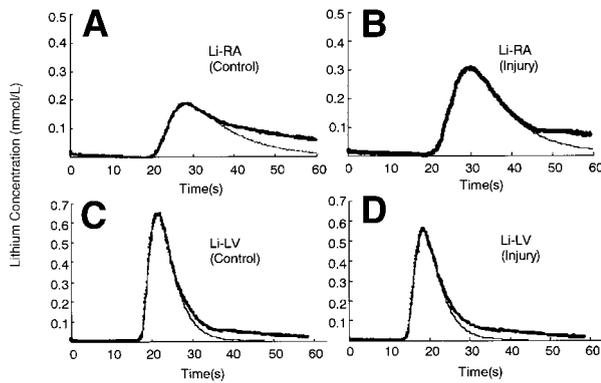


Fig 1. (A and B) Lithium dilution curves for lithium chloride injected into the right atrium of the control (A) and after injury (B). (C and D) Lithium dilution curves for lithium chloride injected into the left ventricle of the control (C) and after injury (D). The bold lines show the data points recorded from the lithium ion selective electrode. The regular lines are the least-squares lognormal derived using the points from 0 to 10% down from the peak on the washout limb. The data points deviate from the lognormal as the lithium ion starts to recirculate.

LiD-RA and LiD-LV was kept as short as possible. The paired measurement of CO was made in each animal. After the control measurement was obtained, 0.1 mL/kg of oleic acid was administered into the right atrium over 1 hour to produce the pulmonary edema model. About 2 hours after oleic acid administration and after obtaining hemodynamic stability, CO measurements were determined using the same method used to record the controls.

The LiDCO system was used for the measurements of CO using lithium dilution. CO was measured by injecting 1 mL of an isotonic solution of lithium chloride (0.15 mol/L) while withdrawing arterial blood from the femoral arterial catheter at 4 mL/min past the lithium sensor. A roller pump was used to regulate the blood flow from the femoral arterial catheter. Lithium chloride solution, 1 mL, was injected as a bolus into the right atrium through the atrial port of the pulmonary artery catheter or into the left ventricular catheter during apnea at the end of expiration. The same person performed all injections. To ensure that the bolus injection dose was exactly 1 mL, the deadspaces of the central venous lumen of the pulmonary artery catheter (0.39 mL) and the left ventricular catheter were filled with lithium chloride solution until a small amount of indicator leakage was observed and a small peak appeared on the recording curve of the concentration time course.

The disposable sensor consisted of a lithium-selective electrode in a flow-through cell. The voltage across the lithium-selective membrane was digitized on-line and recorded by a dedicated computer, which converted the voltage signal to lithium concentration and calculated CO as: $CO (L/min) = [dose \text{ of lithium chloride (mmol)} \times 60] / [area \text{ under curve (mmol} \cdot \text{s/L)} \times (1 - PCV)]$ (area under curve = the integral of the primary curve; PCV = packed cell volume). Division by $(1 - PCV)$ converts plasma flow to blood flow because the lithium ion is distributed only in the plasma fraction of blood. Packed cell volume was measured as the value of hematocrit (Kubota Hematocrit KH-120A, Tokyo, Japan) before each CO measurement. The primary circulation curve was distinguished from the secondary (or recirculation) curve by Linton's⁸ method based on the theory of lognormal analysis to determine the integral of the primary curve. After each experiment, the obtained curves were evaluated to determine whether they approximated a lognormal curve, and mean transit times (MTT) were calculated (MTT-LiD-RA, mean transit time of lithium dilution curves representing injection into the right atrium; MTT-LiD-LV, mean

transit time of lithium dilution curves representing injection into the left ventricle).⁹

The statistical data analysis was performed using StatView 4.54 (Abacus Concepts, Berkeley, CA). A paired *t*-test was performed to compare each arterial blood gas and hemodynamic parameter, LiD-RA, LiD-LV, the difference between LiD-RA and LiD-LV (Δ), the difference expressed as a percentage of the left ventricular injection value ($\Delta\%$), and MTT-LiD-RA and MTT-LiD-LV between control and injury conditions. LiD-RA and MTT-LiD-RA were compared with LiD-LV and MTT-LiD-LV under each condition by Student *t*-test. The linear regression equations of LiD-RA and LiD-LV under each condition were calculated by simple linear regression analysis using the least-squares method. As recommended by Bland and Altman,¹⁰ the difference $(LiD-RA - LiD-LV)$ was plotted against $(LiD-LV + LiD-RA)/2$ for each condition, and the means and SDs (bias and precision) of the differences were calculated. All data are expressed as mean \pm SD. A level of $p = 0.05$ was considered significant in each statistical analysis.

RESULTS

The representative dilution curves using both injection sites and those before and after injury are shown in Fig 1. All dilution curves closely approximated a lognormal curve to 50% below the peak. The arterial blood gas analysis and hemodynamic data for control and oleic acid-induced injury groups are shown in Table 1. Two hours after oleic acid administration, the pH and PaO₂ significantly decreased, and the PaCO₂, mean pulmonary artery pressure, and pulmonary artery occlusion pressure significantly increased. No significant differences were observed between the mean systemic arterial pressure of the respective groups. Table 2 shows LiD-RA, LiD-LV, differences in CO, and mean transit time of lithium dilution curves representing injection into the right atrium (MTT-LiD-RA) and mean transit time of lithium dilution curves representing injection into the left ventricle (MTT-LiD-LV) for each condition. Under both conditions, no statistical differences were observed between LiD-RA and LiD-LV, and MTT-LiD-RA was significantly greater than MTT-LiD-LV. The mean of those differences (Δ) was -0.05 ± 0.36 L/min ($\Delta\% = -1.84 \pm 9.18\%$) for the control and -0.06 ± 0.55 L/min ($\Delta\% = -0.16 \pm 12.62\%$) for the injury conditions. No significant differences in any parameter were observed between control and injury conditions.

The correlations between LiD-LV and LiD-RA in each state are shown in Fig 2. The correlation coefficient of the linear regression line between LiD-LV and LiD-RA in the control

Table 1. Arterial Blood Gas and Hemodynamic Parameters

Variable	Control	Injury	Significance
pH	7.46 \pm 0.07	7.40 \pm 0.07	$p < 0.05$
PaO ₂ (mmHg)	393.1 \pm 77.1	167.6 \pm 84.3	$p < 0.05$
PaCO ₂ (mmHg)	42.1 \pm 6.14	47.2 \pm 6.07	$p < 0.05$
MAP (mmHg)	65.1 \pm 7.01	65.9 \pm 9.87	NS ($p = 0.73$)
MPAP (mmHg)	19.6 \pm 3.10	24.1 \pm 2.76	$p < 0.05$
PAOP (mmHg)	10.0 \pm 1.83	14.1 \pm 3.22	$p < 0.05$

NOTE. Data are shown as mean \pm SD.

Abbreviations: MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; PAOP, pulmonary arterial occlusion pressure; NS, not significant.

Table 2. Lithium Dilution Cardiac Output Values at Injection Sites and the Differences in These Values

Variable	Control	Injury
LiD-RA (L/min)	4.12 ± 0.89	4.42 ± 1.05
LiD-LV (L/min)	4.17 ± 0.70	4.48 ± 0.89
Δ (L/min)	-0.05 ± 0.36	-0.06 ± 0.55
Δ %	-1.84 ± 9.18	-0.16 ± 12.62
MTT-LiD-RA (s)	34.1 ± 2.54	34.2 ± 3.31
MTT-LiD-LV (s)	24.5 ± 5.07	23.2 ± 5.06

NOTE. Data are shown as mean ± SD.

Abbreviations: LiD-RA, lithium dilution cardiac outputs for lithium chloride injected into the right atrium; LiD-LV, lithium dilution cardiac output for lithium chloride injected into the left ventricle; Δ, the difference between the 2 cardiac output estimations; Δ %, the difference expressed as a percentage of the left ventricular injection value; MTT-LiD-RA, mean transit time of lithium dilution curves representing injection into the right atrium; MTT-LiD-LV, mean transit time of lithium dilution curves representing injection into the left ventricle.

state (0.93, $r^2 = 0.86$) was greater than that between LiD-LV and LiD-RA in the injury state (0.87, $r^2 = 0.75$); however, this difference was not statistically significant. The differences (LiD-RA - LiD-LV) plotted against (LiD-LV + LiD-RA)/2 in each state are shown in Fig 3. The bias (the mean of the differences) at injury (-0.06) was almost the same as that at control (-0.05). The precision (the SD of the differences) at injury (0.55) was greater than that at control (0.36).

DISCUSSION

Oleic acid-induced lung injury has been established as an experimental model for permeability pulmonary edema. Previous investigators have reported that after its infusion, the amount of extravascular lung water gradually increases over the course of 120 minutes and reaches a plateau soon afterward.¹¹ Pathologic findings include alveolar flooding, epithelial damage, and microvascular thrombosis.¹² Accordingly, in the present study, the CO measurements were made 2 hours after administering oleic acid. Chinard et al¹³ injected $^{22}\text{Na}^+$ into the right atrium of anesthetized dogs and showed that its recovery in the arterial blood was similar to that of T1824 (Evans Blue, which is protein bound), showing that there was minimal loss in the lungs. It is likely that lithium behaves in the same way. When the pulmonary capillary permeability is normal, the

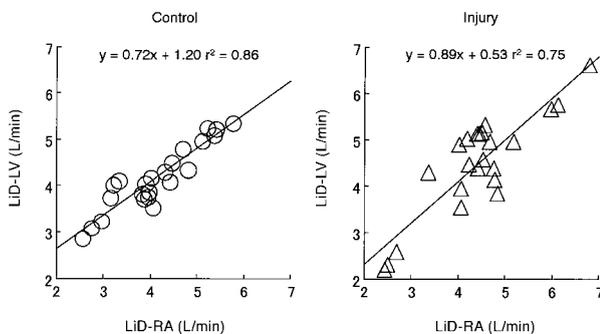


Fig 2. Linear regression between LiD-RA and LiD-LV at control (left) and at injury (right).

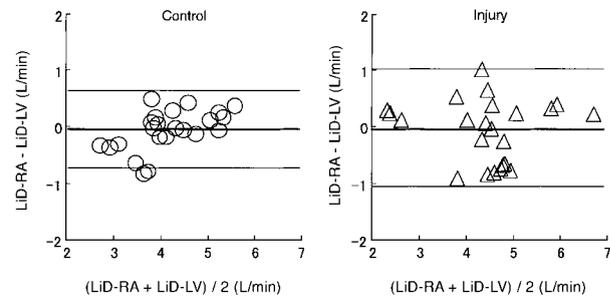


Fig 3. Difference between LiD-RA and LiD-LV plotted against mean at control (left) and at injury (right). The bold line shows the mean; regular lines indicate ± 2 SD.

extent of diffusion of lithium into pulmonary extracellular fluid may be smaller, or its diffusion back into capillary blood may be rapid when the diffusion gradient reverses. If pulmonary capillary permeability is increased, however, significant loss or unbalanced diffusion may occur.

The authors examined the accuracy of the LiDCO technique within the period during which lithium was most likely to be lost or to undergo unexpected distribution in the lung. Band et al⁷ reported in a study of cardiac surgical patients that in comparing the LiDCO technique of LiD-RA with LiD-LA, LiD-RA was greater than LiD-LA, and the mean of these differences was $3.6 \pm 4.9\%$. Band et al⁷ concluded that these differences reflected increases of pulmonary capillary permeability caused by raised left atrial pressure and the residual effects of recent cardiopulmonary bypass.

In the present study, LiD-LV was measured rather than LiD-LA because it was easier to insert a left ventricular catheter and to confirm that there was no leakage of lithium chloride solution. Given that the mixture of lithium in the left ventricle was complete and the curve-fitting procedure accurately discriminated the primary curve according to obtained dilution curves (Fig 1), the difference would result from the loss or unstable diffusion of lithium in the lung. Although the variability of LiD-RA compared with LiD-LV at injury was slightly greater than that at control (Fig 3), LiD-RA was closely correlated with LiD-LV under both conditions (Fig 2), and LiD-RA was similar to LiD-LV (Table 2). For these injection sites, no significant difference was observed between mean transit times before and after injury (Table 2). These results indicated that the loss or unstable diffusion of lithium in the lung was negligible even with the lung injury. Although the accuracy of the LiDCO technique decreased slightly with lung injury, this finding was at a clinically insignificant level.

In the present study, the thermodilution CO measurement was not compared with the LiDCO technique despite the insertion of the pulmonary artery catheter because the interval between measurements was kept as short as possible. (Changes in the measurement technique require more than a few minutes to set up.) Stetz et al¹⁴ showed that individual bolus thermodilution readings had to change by at least 22% for a real change in CO to be assumed. Average (mean of 3) bolus thermodilution readings had to change by at least 13%. From this stand-

point, it seems to be acceptable in the clinical situation that the accuracy of the lithium dilution method decreases in cases of pulmonary edema.

Limitations of the present study were that the authors did not measure the extravascular lung water, and they did not evaluate histologic analysis for the determination of lung edema. Given that oleic acid-induced lung injury might be less severe than that found in other reports,^{15,16} these results did not completely prove the performance of the LiDCO technique in cases of more severe lung injury. Because the purpose of this study was to assess the influence of lung injury on the LiDCO method, it was assumed that LiD-LV was not affected by lung injury.

In conclusion, although the accuracy of the LiDCO technique decreases slightly in the lung with pulmonary edema, it

is still at an acceptable level. Because this method does not require a pulmonary artery catheter and because a peripheral venous catheter can be used instead of a central venous catheter at the lithium injection site, measurement is obtained more easily; measurements can be taken by in-place central or peripheral venous and arterial catheters, which usually have already been established in patients requiring CO measurement, without exposing patients to any of the risks associated with pulmonary artery catheter insertion.¹⁷⁻¹⁹ Although there are some disadvantages, such as blood loss at each measurement and the possibility of toxicity by multiple injections over a short time,^{3,4} taking the results of the present study into consideration, the LiDCO technique is a viable alternative to a pulmonary artery catheter for management of CO in critically ill patients.

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