

**Lithium-thermal double indicator dilution:
a new method of extravascular lung water measurement
in the critically ill?**

Thesis submitted for Doctor of Medicine (Res) degree

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Declaration Statement

This thesis is the result of my own independent work, except where otherwise stated. Any assistance received has been acknowledged in the text and a bibliography is appended.

A handwritten signature in black ink, consisting of a stylized capital letter 'B' followed by a series of connected loops and a final upward stroke.

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Abstract

There is evidence to suggest that therapy targeted at normalising extravascular lung water volume (EVLW) can improve outcomes from critical illness. Indocyanine green-thermal double indicator dilution (ICG-thermal) is considered the clinical reference standard of EVLW volume measurement but is no longer commercially available. The accuracy and reliability of the only clinically available technology (single-thermal indicator dilution) has been questioned in several studies. This thesis incorporates two clinical studies and one laboratory study designed to assess the measurement of EVLW and intrathoracic blood volumes using a prototype lithium-thermal double indicator dilution technique.

The proof of concept study suggested our hypothesis that intrathoracic blood volume (ITBV), which is required for the calculation of EVLW volume, could be determined using lithium indicator dilution, was valid. Peri-operative trends and absolute values of ITBV were consistent with those obtained using ICG-thermal in a similar patient study group. The median absolute value of ITBV measured at baseline using indocyanine green (1417 [\pm 208] ml) was similar to that obtained using lithium indicator dilution 1542 (\pm 601) ml.

EVLW volume measured by three indicator dilution techniques was then compared to post-mortem gravimetry in porcine models of acute lung injury. Sepsis and acute lung injury were associated with increased EVLW volume, (9.2 [\pm 3.0] ml kg⁻¹), compared to sham operated animals (6.6 [\pm 0.45] ml kg⁻¹) in keeping with previous studies. The Li-thermal (Bias-1.8 [\pm 13.1] ml kg⁻¹) and ICG-thermal (Bias-1.0 [\pm 6.6] ml kg⁻¹) techniques demonstrated acceptable accuracy, but wide limits of agreement suggested poor reliability.

The single-thermal technique systematically over-estimated EVLW, with unacceptably wide limits of agreement (Bias +8.5 [\pm 14.5] ml kg⁻¹). In this laboratory investigation, the double indicator methods appeared more reliable than the single-thermal technique. However none could be considered ideal.

Results of the final clinical study suggested EVLW volume measurement in man with the Li-thermal method was clearly erroneous (Bias -7.6 [\pm 7.4] ml kg⁻¹) and compared poorly to simultaneous measurements made using the ICG-thermal method (Bias +13.2 [\pm 14.4] ml kg⁻¹). A considerable over-estimation of mean transit time (MTT) when compared to the ICG-thermal technique (Bias 12.8 [\pm 13] sec) was observed, a likely consequence of using an external lithium ion electrode instead of an intra-arterial catheter. Manual analysis of the dilution curves suggested considerable variability when compared to the automated analysis. The poor accuracy of MTT, and consequently ITBV measurements in the clinical study, may partly be due to software analysis of the lithium dilution curves. Thoracic blood volumes derived from measurement of ICG transit time are reliable. However, EVLW calculations based on the thermal indicator transit time are likely to be inaccurate.

The findings of these clinical and laboratory investigations demonstrate poor agreement between both the prototype Li-thermal and the single thermal measurements of EVLW volume and the ICG-thermal method. Trans-pulmonary lithium indicator dilution measurements of ITBV and EVLW volume using an external lithium ion electrode are not sufficiently accurate to safely guide clinical interventions in individual patients. Consequently we decided not to further develop the lithium-thermal technique of EVLW volume measurement.

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Glossary of terms

Extravascular lung water volume

Water within the lung tissue and interstitium but outside of the vasculature. The normal range, indexed to body weight, is 3-7mls kg⁻¹.

Intrathoracic blood volume

The volume of blood within the thoracic cavity. The normal range, indexed to body surface area, is 800-1000mls m⁻².

Intrathoracic water volume

The total volume of fluid, including blood, within the thoracic cavity.

Lithium indicator dilution

Lithium chloride is injected via a central venous catheter and detected by an external sensor attached to a peripheral arterial catheter. The resultant indicator dilution curve allows calculation of cardiac output.

Indocyanine green-thermal double indicator dilution

Cold saline measures total intrathoracic water volume whilst indocyanine green binds to plasma proteins allowing measurement of intrathoracic blood volume. Calculation of extravascular lung water volume is therefore possible by subtraction.

Gravimetry

Post mortem reference technique of extravascular lung water volume measurement.

Single thermal indicator dilution

Mathematical analysis of a cold saline indicator curve allows derivation of thoracic fluid volumes and extravascular lung water volume.

Mean Transit Time

The mean time taken for an indicator to pass from the point of injection to the point of detection as measured on the classical indicator dilution curve

LiDCO

Trade name of lithium indicator dilution

COLD-Z

Trade name of indocyanine green-thermal double indicator dilution

PiCCO

Trade name of single-thermal indicator dilution

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Peer reviewed publications associated with this work

Original Research

Maddison B, Best T, Wolff C, Jones P, Hinds C, Pearse R. Transpulmonary lithium indicator dilution: a new method of intrathoracic blood volume measurement. *Critical Care* 2007; **11** (Suppl 2): 295

Maddison B, Giudici R, Calzia E, Wolff C, Hinds C, Radermacher P, Pearse RM. Extravascular lung water volume measurement by a novel lithium-thermal indicator dilution method: comparison of three techniques to post-mortem gravimetry. *Intensive Care Med* 2008; **34** (11): 2106-2111

Maddison B, Wolff C, Findlay G, Radermacher P, Hinds C, Pearse RM. Comparison of three methods of extra-vascular lung water volume measurement in patients after cardiac surgery. *Critical Care* 2009; **13**:R107

Review Articles

Maddison BJ, Best T, Pearse RM. Measurement of extravascular lung water. *Yearbook of Intensive Care and Emergency Medicine* 2007 (Springer-Verlag)

Copies included in the appendix

Chapter 1

Review of the relevant literature

1.1 Accumulation of extravascular lung water in the critically ill

The predominant constituent of the lung is water, with the gas exchanging air spaces (alveoli) protected by various barriers (alveolar membranes) and fluid drainage (lymphatic flow). There is continuous fluid flux within this system that ensures the alveoli remain clear of fluid thereby allowing efficient gas exchange. Consequently there is always an amount of water within the lung interstitium. Whilst in the normal range of 3 to 7 ml kg⁻¹ (water content of the pulmonary interstitium),¹ this fluid is of minor significance to the patient or attending physician. As these protective mechanisms of the lung begin to fail either through injury, increased vascular pressures or both, the amount of fluid within the interstitium increases, termed interstitial oedema. When these compensatory mechanisms are overwhelmed there is sudden catastrophic movement of fluid into the alveoli by a more rapid process termed alveolar flooding.² This is more commonly known as pulmonary oedema with physiological impairment becoming apparent when the lung water volume exceeds 10 ml kg⁻¹ (Table 1.1).³⁻¹³ Both interstitial oedema and pulmonary oedema are therefore terms that can be used to describe the accumulation of extravascular lung water (EVLW).

Pulmonary oedema is a common and serious clinical feature of a wide range of medical conditions and can pose a considerable clinical problem, such that mechanical ventilation may be required. It may result from an increase in pulmonary capillary permeability (acute

lung injury, ALI) or from an increase in pulmonary capillary pressure (hydrostatic or cardiogenic pulmonary oedema).¹⁴ Resolution of pulmonary oedema depends on the active removal of salt and water from the distal air spaces across the lung epithelial barrier,¹⁵ a mechanism frequently impaired in cases of lung injury.¹⁶

Authors ^{Ref}	Type of Oedema	EVLW)ml kg ⁻¹ , (Mean ± SD	Dilution Method
Slutsky and Brown ¹³	Cardiogenic (chronic)	16.3 ± 1.8	Double indicator
	Cardiogenic (acute)	10.7 ± 1.3	Double indicator
Bindels et al ³	Cardiogenic	13.7 ± 1.5	Double indicator
Sibbald et al. ¹²	Cardiogenic	10.2 ± 3.1	Double indicator
	ALI/ARDS	15.8 ± 4.6	Double indicator
Sibbald et al. ¹¹	Cardiogenic	9.3 ± 3	Double indicator
	ALI/ARDS	14.5 ± 4.9	Double indicator
McAuley et al ⁷	ALI/ARDS	14.2	Single indicator
Boussat et al ⁴	ALI/ARDS	17.3 ± 8	Double indicator
Michard et al ⁸	ALI/ARDS	11.3 ± 5.4	Single indicator
Martin et al ⁶	ARDS	15	Single indicator
Michelet et al ⁹	ARDS	11.2 ± 6.0	Double indicator
Patroniti et al ¹⁰	ARDS	12.3 ± 3.4	Double indicator
Groeneveld and Verheij ⁵	ALI (pneumonia)	9	Double indicator
	ALI (extrapulmonary)	7.8	Double indicator

Table 1.1 Reported values for extravascular lung water (EVLW) in patients with cardiogenic pulmonary oedema and in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS)

The clinical features of pulmonary oedema include hypoxemia and dyspnoea, along with those of the associated underlying medical condition. Diagnosis and recognition of pulmonary oedema or increased extravascular lung water volume is generally based on subjective clinical criteria including history, respiratory rate, jugular venous pressure and

auscultation of the chest combined with chest radiography. However, clinical assessment of the extent and severity of pulmonary capillary leak and EVLW accumulation is often difficult and inconsistent, particularly in critically ill patients and those who are mechanically ventilated. Evidence suggests that neither impaired oxygenation, nor chest radiographic appearances provide a reliable indication of EVLW volume.¹⁷⁻²¹ Traditional methods of reducing EVLW volume include the use of loop diuretics and vasodilator drugs.²² Such treatment is usually coupled with oxygen therapy with or without continuous positive airway pressure (CPAP) or mechanical ventilation with positive end-expiratory pressure (PEEP) to relieve respiratory distress and improve arterial oxygen partial pressure (PaO₂).^{23,24} The choice of these interventions is very much at the discretion of the clinician. Pharmacological therapy is titrated to achieve subjective clinical improvement with associated recovery of the PaO₂ to normal or above normal limits, rather than aiming for a quantitative EVLW volume target. The critically ill patient may often also require fluid resuscitation to correct hypovolaemia and maintain oxygen delivery to the major organs. However, in the presence of increased pulmonary capillary permeability or impaired myocardial function, the administration of large volumes of intravenous fluid may be associated with a significant increase in EVLW volume thereby worsening the overall condition of the patient. Effective fluid resuscitation involves a fine balance between the consequences of excessive EVLW volume and inadequate tissue oxygen delivery, both of which may result in poor outcome.^{25,26} However there is some evidence to suggest that fluid restriction can positively influence the course of illness and improve the outcome of patients with Acute Respiratory Distress Syndrome (ARDS).²⁷ Thus, balancing optimal cardiac preload and circulating volume with intravenous fluid therapy against the threat of worsening pulmonary oedema is a clinical dilemma that requires reliable monitoring tools.

1.2 Clinical relevance of extravascular lung water volume measurement

In a large retrospective analysis of 373 critically ill patients, the mortality rate was approximately 65% in patients with EVLW volume greater than 15 ml kg^{-1} , compared to approximately 33% in patients with EVLW volume less than 10 ml kg^{-1} i.e. patients with pulmonary versus interstitial oedema.²⁸ Univariate logistic regression analysis of this data demonstrated EVLW at baseline as well as simplified acute physiology score (SAPS) II and acute physiology and chronic health evaluation (APACHE) II scores ($r^2=0.05$, $p<0.0001$) were all significant predictors of mortality. The authors further analysed SAPS II and APACHE II scores. Combination of SAPS II and APACHE II scores increased r^2 to 0.136, but the improvement over SAPS II alone was not significant. The addition of baseline EVLW further increased r^2 to 0.149 ($p=0.021$ for the improvement), suggesting that EVLW contributes independently to prognosis. Three randomised control trials have investigated the use of EVLW volume to guide treatment. Fluid and diuretic therapy guided by EVLW volume, when compared to pulmonary artery occlusion, resulted in a reduction in the duration of invasive ventilation, a less positive fluid balance and shorter ICU stay.²⁹ Moreover the use of EVLW volume measurement to guide clinical management during critical illness showed reduction in the duration of mechanical ventilation and intensive care unit stay.^{26,30}

1.3 Importance of EVLW volume measurement

A recent multicentre randomised trial³¹ conducted in patients with acute lung injury demonstrated that fluid restriction and diuresis improved lung function and shortened the duration of mechanical ventilation and intensive care stay. Despite EVLW volume not

being targeted in this trial the results emphasise the potential value of EVLW measurement as a tool to guide such a therapeutic strategy.^{2,32} This is consistent with the considerable body of evidence highlighting improved outcome, reduced ventilator and ICU days with EVLW targeted therapy.^{26,28-30} In the current NHS economic climate, where cost effectiveness as well as quality of care is important, providing EVLW volume monitoring in all critically ill patients using reliable technology could be considered a routine standard of care. As there is some uncertainty surrounding the validity of the technology currently available for this purpose, it seems logical to seek a reliable, user friendly technique to accurately measure these thoracic fluid volumes.

1.4 Gravimetric technique of extravascular lung water volume measurement

The gravimetric technique of EVLW volume measurement is a laboratory research tool first described by Hemingway in 1950³³ and later adapted by Pearce.³⁴ This method was used by several groups in the 1950's and 60's to examine the physiology, pharmacology and measurement of pulmonary oedema.³³⁻³⁵ EVLW is calculated from a number of measurements, as described in section 2.4, allowing estimation of the wet:dry mass ratio of the lung. Whilst the gravimetric technique remains the reference standard to which new techniques should be compared, this method is limited by its complexity and the fact that only a single, post-mortem measurement can be made on any given subject.

1.5 Indicator dilution techniques of extravascular lung water volume

measurement

The indicator dilution technique was originally developed as a method for measuring cardiac output. The most significant contributions to our understanding of this technique for the measurement of extravascular lung water were made in the 1920's by Stewart and Hamilton (see section 1.5.1.1).^{36,37} In 1955, the first measurements of pulmonary blood volume (PBV) in man were performed by Kunieda and Fujimoto using sequential injections of Evans blue dye.³⁸ This work was subsequently repeated using other indicators including indocyanine green and radio-iodinated human serum albumin.³⁹⁻⁴¹ The double indicator dilution method of EVLW volume measurement was first performed using a radioisotope by Chinard in a series of experiments in the 1950s.⁴² Subtraction of intrathoracic blood volume (ITBV), measured by one non-diffusible intravascular indicator, from total intrathoracic water volume (ITWV) measured by another which freely diffuses out of the vascular compartment, allows derivation of EVLW volume (see equation 1.1). This work eventually led to the development of a bedside technique which was introduced into clinical practice in the 1980's.

$$EVLW = ITWV - ITBV$$

Equation 1.1 Derivation of extravascular lung water volume

EVLW, Extravascular lung water; ITBV, Intrathoracic blood volume; ITWV, Intrathoracic water volume

1.5.1 Principles of indicator dilution

The perfect indicator would be stable, non-toxic and easily measured. It would distribute uniformly throughout the physiological compartment under investigation but not be lost from the system of interest during passage from the point of injection to the site of detection. It would then dissipate rapidly to avoid any error resulting from recirculation. For the purposes of thoracic volume measurements, the most important criteria may include:

1. Motion of the indicator is representative of the motion of the test fluid
2. Indicator volume is small enough not to alter the distribution of the test fluid
3. The indicator completely leaves the test system
4. Flow of the test fluid is constant during the period of evaluation
5. The whole test compartment is in a dynamic equilibrium allowing the indicator to penetrate the entire compartment and leave within the duration of a single circulation

Perhaps not surprisingly, the perfect indicator does not exist although a number of different substances have been used for this purpose. The most common practical disadvantages include poor stability, difficulties with measurement of indicator concentration and recirculation or accumulation. Although the difficulties with recirculation may be overcome by extrapolation of the concentration-time curve (Figure 1.1), accumulation of the indicator usually limits the maximum number of accurate measurements. Consequently, most indicators are only suitable for laboratory studies.

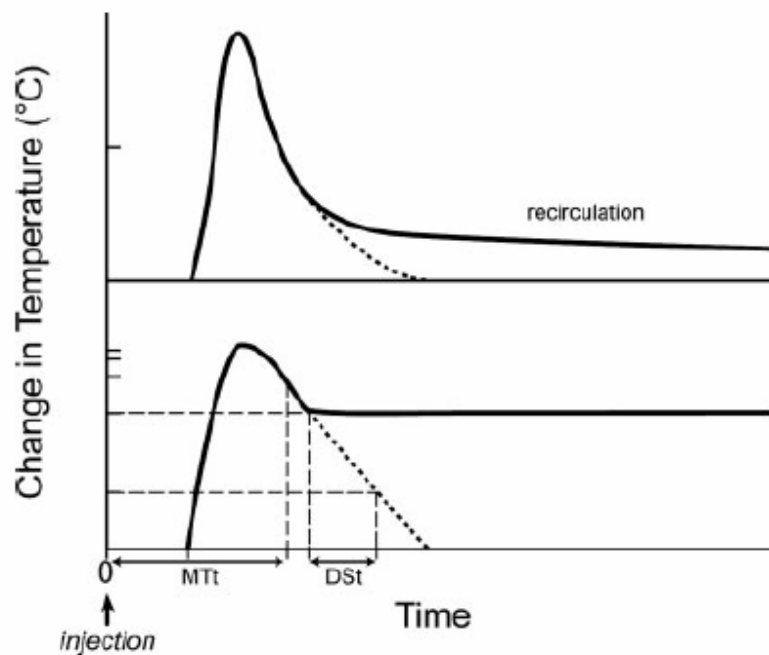


Figure 1.1 Relationship between concentration and time for an indicator injected as a bolus into a central vein and measured in a major artery

Top figure illustrates indicator recirculation. Bottom figure is the natural logarithm of the top curve extrapolated at the point the curve becomes exponential. MTt, mean transit time; DSt, downslope time

There are two principles of indicator dilution which are particularly relevant to the measurement of all thoracic fluid volumes especially EVLW volume, ITBV, ITWV and PBV, namely the Stewart-Hamilton and Newman hypotheses.

1.5.1.1 Stewart-Hamilton hypothesis

The first principle of thoracic fluid measurement using indicator dilution was formulated by Stewart in 1921 who performed a series of experiments using a hypertonic saline indicator.³⁷ As blood flowed past the sampling point, the change in electrical conductance of blood generated a detectable output signal. These studies allowed Stewart to identify and

describe the relationship between cardiac output, the volume throughout which an indicator is distributed, and the mean time taken for the indicator to pass from the point of injection to the point of detection (mean transit time, equation 1.2).

$$V = CO \times MTT$$

Equation 1.2 Stewart hypothesis

V, the volume throughout which an indicator is distributed; CO, cardiac output; MTT, mean time taken for the indicator to pass from the point of injection to the point of detection (mean transit time)

Hamilton subsequently developed the principles described by Stewart to allow the measurement of cardiac output using the indicator dilution technique to generate an arterial dye concentration versus time curve (Fig. 1.1).³⁶ Cardiac output was shown to be inversely proportional to the area under the curve (equation 1.3). The great importance of the work of Stewart and Hamilton relates to the use of the principles they described in many of the best known clinical methods of cardiac output measurement.

$$M = Q \int C(t). dt$$

Equation 1.3 Stewart-Hamilton hypothesis

If an indicator is injected rapidly into the right atrium, it will appear downstream in the pulmonary artery in a concentration that varies with time, C(t). As all the injected indicator (M) must leave the system, M is equal to the sum of the concentrations at each interval (t) multiplied by flow (Q), which is assumed to be constant.

1.5.1.2 Newman Hypothesis

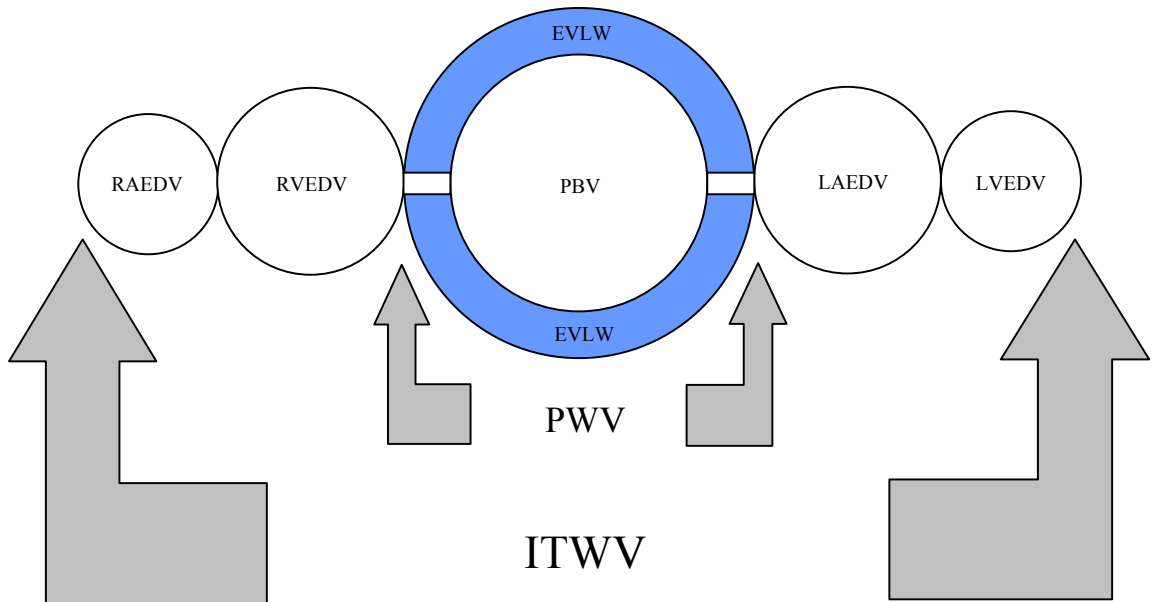
The second principle of thoracic fluid measurement using indicator dilution was described by Newman in 1951 and explains the relationship between cardiac output, the volume of the largest chamber (C) in the path of the indicator and the decay curve rate constant of the semi-logarithmic plot of indicator concentration against time. This has also been termed the downslope time (DSt) (equation 1.4).⁴³

$$C = \frac{CO}{DSt}$$

Equation 1.4 Newman Hypothesis

C, the volume of the largest chamber in the path of the indicator; CO, cardiac output; DSt, rate constant of the decay curve of the semi-logarithmic plot of indicator concentration against time, which has also been termed downslope time

These principles illustrate the fact that the conformation of the trans-pulmonary indicator dilution curve is influenced by the various intra-thoracic compartments (Figure 1.2). The volume of some of these compartments may therefore be estimated through the use of indicators with different properties.



$$ITBV = RAEDV + RVEDV + PBV + LAEDV + LVEDV$$

$$GEDV = RAEDV + RVEDV + LAEDV + LVEDV$$

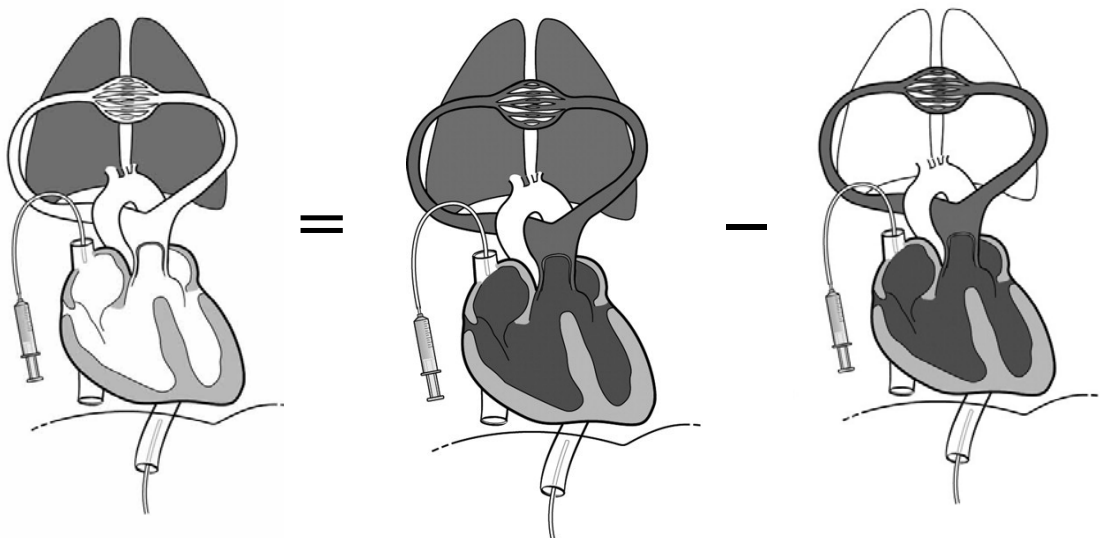
$$EVLW = ITWV - ITBV$$

Figure 1.2 Relationship between the intra-thoracic compartments which influence measurements taken from the trans-pulmonary indicator dilution curve

RAEDV, right atrial end-diastolic Volume; RVEDV, right ventricular end-diastolic volume; PWV, pulmonary water volume; PBV, pulmonary blood volume; LAEDV, left atrial end-diastolic volume; LVEDV, left ventricular end-diastolic volume; EVLW, extravascular lung water volume; ITWV, intrathoracic water volume; ITBV, intrathoracic blood volume; GEDV, global end diastolic blood volume

1.5.2 Double indicator dilution techniques

Although this technique has been performed with various pairs of indicators, the general principle is the same with each. One indicator should diffuse into and out of the thoracic water compartment within the duration of one circulation time. In clinical practice, a cold saline thermal indicator is generally used for this purpose. The second indicator must distribute throughout the ITBV compartment but not diffuse into the ITWV compartment.



$$\text{EVLW} = \text{ITWV} - \text{ITBV}$$

Figure 1.3 Derivation of EVLW using double indicator dilution

EVLW, extravascular lung water volume; ITWV, intrathoracic water volume; ITBV, intrathoracic blood volume

In most cases this indicator is non-diffusible because of strong plasma protein binding e.g. indocyanine green. Both indicators should be injected simultaneously to avoid any error due to alterations in cardiac output. According to Stewart's equation, the difference in mean

transit time (MTT) of the two indicators will allow estimation of the difference in distribution volumes which in turn represents EVLW volume (equation 1.5).

$$EVLW = COx(MTT_{Thermal} - MTT_{Non-diff})$$

Equation 1.5 EVLW calculated using differences in MTT

EVLW, extravascular lung water volume; CO, cardiac output; $MTT_{thermal}$, Mean transit time of thermal indicator; $MTT_{non-diff}$, Mean transit time of non-diffusible indicator

The most widely used double indicator method of EVLW volume measurement is the indocyanine green-thermal double indicator dilution (ICG-thermal) technique. A major assumption is made that the thermal indicator, normally ice cold saline, diffuses completely throughout the pulmonary and intrathoracic water volumes and is equal to the thermal volumes measured by this method. Measurements made using this technique appear to correlate well with those made using the gravimetric method in dogs.^{44,45} In a study of nine human organ donors, the ICG-thermal double indicator dilution technique was compared to gravimetric studies with good agreement between the two techniques, although one subject was excluded because the ICG-thermal double indicator dilution technique grossly underestimated EVLW volume (figure 1.4).⁴⁶ Subsequent macroscopic examination revealed significant acute lung injury in this patient.

In a more detailed study, Roch et al compared the ICG-thermal method to gravimetry in a pig model of direct and indirect acute lung injury.⁴⁷ The methods compared well in the animals with indirect acute lung injury. However in the direct injury model the ICG-thermal method underestimated EVLW volume, especially at higher volumes.

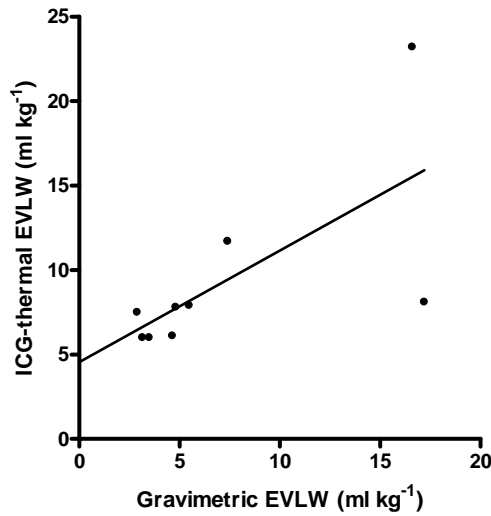


Figure 1.4 Relationship between ICG-thermal double indicator dilution technique measurements of EVLW and those made by gravimetry in human organ donors ($r^2=0.95$, $p<0.001$). From Mihm FG, et al.⁴⁶

EVLW, extravascular lung water volume

In another study using a porcine model of endotoxin induced lung injury, a similar double indicator dilution technique was compared with gravimetric measurements.⁴⁸ In this study, a deuterium oxide (²H₂O) indicator was used in preference to cold saline whilst indocyanine green was used as the non-diffusible indicator. Once again findings suggested a good correlation under baseline conditions. However, the double indicator dilution technique underestimated EVLW volume at higher values when compared to the gravimetric reference method.

It therefore seems that the indocyanine green-thermal double indicator dilution technique consistently underestimates EVLW volume at higher values, as might be the case for example, in patients with acute lung injury. This underestimation may be explained by redistribution of pulmonary blood flow away from areas in which alveoli are flooded

thereby limiting indicator diffusion and the detection of oedema in these regions during just one trans-pulmonary transit.⁴⁷⁻⁵⁰ Positive end-expiratory pressure (PEEP) during mechanical ventilation may also be associated with an underestimation of EVLW volume.⁵¹ In addition, studies have suggested that underestimation of EVLW by ICG-thermal dilution may be more frequent at higher cardiac output^{52,53}, although these findings may be explained by technical problems with specific devices.⁵⁴

Devices have been produced commercially that allow indocyanine green-thermal double indicator dilution measurements at the bedside. Despite yielding EVLW volume figures with good reproducibility⁵⁵, the clinical use of this equipment has proved unpopular, not least because of the financial cost of indocyanine green, and the technical difficulty acquiring reliable ICG indicator dilution curves. These monitors have now been withdrawn from production, although consumables are still available on a limited basis for one device (COLD-Z, Pulsion Medical Systems, figure 1.5).



Figure 1.5 COLD-Z, Pulsion Medical Systems, Munich, Germany

1.5.3 Single indicator dilution techniques

Currently the only commercially available method of EVLW volume measurement is the trans-pulmonary (single) thermal indicator technique (PiCCO, Pulsion Medical Systems, Munich, Germany, see figure 1.6). Estimation of EVLW by this technique was first proposed around 25 years ago.^{56,57} Intrathoracic thermal volume is calculated using a cold saline indicator in an identical fashion to the double indicator dilution technique described above. However, rather than using a second non-diffusible indicator to measure ITBV, this value is calculated by using additional mathematical analysis of the thermal indicator dilution curve. By applying the principle described by Newman⁴³, it is possible to calculate the volume of the single largest mixing chamber traversed by an indicator, in this case, the pulmonary water volume. By subtracting pulmonary water volume from intra-thoracic water volume, global end diastolic volume (GEDV) may be calculated. An important assumption is then made that there is a constant relationship between ITBV and GEDV that can then be used to derive EVLW.⁵⁸



Figure 1.6 PiCCO, Pulsion Medical Systems, Munich, Germany

This relationship was derived following structural regression analysis of the first two ICG-thermal dilution measurements in a derivation population of 57 critically ill patients that had suggested a constant relationship between ITBV and GEDV ($ITBV = 1.25 \times GEDV - 28.4$). An early study of the trans-pulmonary single thermal versus the indocyanine green-thermal double indicator dilution techniques suggested very poor correlation.⁵⁹ A total of 84 comparisons in 18 patients demonstrated that the single-thermal technique significantly over-estimated EVLW volume when compared to the ICG-thermal technique ($p < 0.05$). However, a subsequent study in a population of 209 critically ill patients, suggested reasonable agreement between the corresponding values of ITBV and EVLW volume using the two methods. Single-thermodilution ITBV ($ITBV_{single}$) and EVLW ($EVLW_{single}$) were calculated and compared to the ICG-thermal dilution derived values ($ITBV_{ICG-thermal}$ & $EVLW_{ICG-thermal}$). Linear regression analysis yielded a correlation of $ITBV_{single} = 1.05 \times ITBV_{ICG-thermal} - 58.0 \text{ ml m}^{-2}$ ($r = 0.97$, $p < 0.0001$). $EVLW_{single}$ was calculated using $ITBV_{single}$ and revealed the correlation $EVLW_{single} = 0.83 \times EVLW_{ICG-thermal} + 1.6 \text{ ml kg}^{-1}$ ($r = 0.96$, $p < 0.0001$). The authors noted that the single-thermal method over-estimated EVLW at low $EVLW_{ICG-thermal}$ volume and underestimated EVLW at values greater than 12 ml kg^{-1} .⁵⁸

There are several potential sources of error associated with this single thermal indicator approach to EVLW volume measurement. In common with the indocyanine green-thermal double indicator dilution technique, equilibration between the temperature of the saline bolus and body temperature may result in significant loss of indicator along the pathway between the injection point in the superior vena cava and the measurement point in the femoral artery thereby reducing the signal amplitude. Moreover, because the tip of the

femoral artery catheter is not placed at the level of the diaphragm, part or all of the volume of the abdominal aorta will be included in the measurement. This results in a falsely high estimate of ITBV and therefore a falsely low value for EVLW volume. Also, because a thermal indicator will not equilibrate fully with flooded alveoli in one trans-pulmonary circulation, it is likely that high EVLW volumes will be underestimated with this technique. The assumption that the relationship between GEDV and ITBV is constant, regardless of clinical circumstances, is also questionable. Although some studies support the existence of a relationship between these two variables, there is evidence that it is affected by changes in cardiac output and circulating volume.⁶⁰⁻⁶²

Three studies have compared the trans-pulmonary single thermal indicator dilution technique to the gravimetric method and all suggested a reasonable correlation between the two methods.^{61,63,64} However, trans-pulmonary single thermal indicator dilution consistently overestimates EVLW volume when compared to the gravimetric method. Rossi et al identified considerable bias and wide limits of agreement (5.4 ml kg⁻¹, LOA ±2.8) between the two techniques in a porcine model of endotoxin induced acute lung injury. The authors suggested that the accuracy of the single thermal technique could be improved by adjusting the algorithm so that $ITBV = 1.52GEDV + 49.7$.⁶¹ Similar problems were observed in a study by Kirov et al in an oleic acid model of acute lung injury in sheep. They too reported significant bias and limits of agreement (4.9 ml kg⁻¹ ±5.1) despite using data derived from a modified algorithm, $ITBV = 1.34GEDV$.⁶⁴

A number of studies suggest that the accuracy of EVLW volume estimation by the single thermal indicator technique could be improved by revising the mathematical relationship

between ITBV and GEDV.⁶⁰⁻⁶² Michard et al evaluated a range of clinical factors that might influence EVLW volume measurements made by trans-pulmonary single thermal indicator dilution.⁶⁵ When compared with the indocyanine green-thermal double indicator dilution technique, the reliability of measurements was not affected by height, weight, cardiac output or the dose of vasoactive agents. However, PaO₂:FiO₂ ratio, tidal volume and PEEP significantly affected the agreement between the two techniques in the measurement of EVLW volume.

Although trans-pulmonary thermal single indicator dilution is a practical bedside method of EVLW volume measurement, there is considerable doubt over the accuracy of EVLW volume measurement by this method.⁶⁶ Nevertheless EVLW volume determined using this method does appear to have prognostic significance.^{6,25}

1.6 Determination of extravascular lung water using imaging techniques

1.6.1 Chest radiography

Pulmonary oedema is normally diagnosed by clinical examination and chest radiography. The classical appearance of cardiogenic pulmonary oedema is bilateral diffuse pulmonary infiltrates, with upper lobe blood diversion and air bronchograms (figure 1.7) which can be difficult to distinguish from non-cardiogenic pulmonary oedema or acute lung injury (figure 1.8). Some studies have identified a group of patients in whom chest radiographs are abnormal but lung water measurements are within the normal range, illustrating the difficulty in distinguishing excess lung water from pulmonary infiltrates due to other causes

or regions of atelectasis.²⁰ Halperin et al. evaluated the portable chest radiograph against the ICG-thermal technique in twelve patients admitted to intensive care with a diagnosis of respiratory failure.¹⁷ They concluded that the chest radiograph allowed diagnosis of excessive EVLW but only when EVLW volume reached a threshold of 35% above normal. However, the absence of any signs of pulmonary oedema on the chest radiograph almost ruled out excessive EVLW volume. A similar study by Laggner et al. evaluated EVLW volume estimation in fifty three critically ill patients by the chest radiograph in comparison to the ICG-thermal technique.¹⁹ They found reasonable agreement between the two methods ($r = 0.83$, $p < 0.001$). Nevertheless, even as a non-quantitative method, the chest radiograph remains an unreliable indicator of the presence of pulmonary oedema largely because interpretation is influenced by a range of confounding factors.¹⁸



Figure 1.7 Chest radiograph showing cardiogenic pulmonary oedema



Figure 1.8 Chest radiograph showing non-cardiogenic pulmonary oedema in a patient with acute lung injury

1.6.2 Computed tomography (CT)

Whilst computed tomography can generate excellent images of thoracic structures, the quantification of EVLW volume is more difficult because the associated changes are non-specific. The computation of gas and tissue lung volumes from CT densities is based on several assumptions:

1. A linear correlation between physical density and attenuation of electromagnetic radiation.
2. The approximation of the physical density of non-aerated lung tissue (including lung parenchyma, blood, and water) to the physical density of water.
3. Any nominal CT volume unit identified in the lung consists only of gas and lung tissue as opposed to infective cellular debris, pus, etc.

In a small study of patients with acute lung injury, quantitative computed tomography measurements of lung oedema appeared to correlate well with those made using the ICG-thermal technique.⁶⁷ Fourteen mechanically ventilated patients with acute respiratory distress syndrome underwent a spiral CT of the thorax. Pulmonary thermal volume (PTV), EVLW and pulmonary blood volume (PBV) were measured with the indocyanine green-thermal double indicator dilution method. EVLW volume correlated well with lung weight measured by CT ($R=0.91$, $p < .0001$). Unfortunately, because of the risks associated with radiation exposure and transfer of critically ill patients, in addition to financial costs and limited availability, it is impractical to make repeated EVLW volume measurements by CT.

1.6.3 Magnetic Resonance Imaging (MRI)

MRI allows detailed three-dimensional imaging of tissue without the use of ionizing radiation. Knowledge of the signal produced by proton density and T1 weighted images allows calculation of the relative proton density within tissue. Because lung parenchyma contains insignificant amounts of fat and other hydrogen-bound complexes, the proton density measured by MRI principally reflects water content. Early attempts at proton MRI of the adult lung proved challenging. The low proton density of the lung resulted in a poor signal, whilst blood flow, cardiac pulsation and respiration caused considerable artefact. However, recent improvements in MRI technology have allowed more rapid image acquisition and electrocardiograph-respiratory gating. This allows co-ordination of stationary image capture within the cardiac and respiratory cycles with a substantial improvement in the clarity of the images acquired. MRI may therefore be used in the assessment of a variety of lung conditions including pulmonary oedema.⁶⁸ Qualitative and quantitative assessments of lung water content have been performed using MRI in both the normal adult lung^{69,70} and animal models of pulmonary oedema, where comparisons have been made with the gravimetric technique.⁷¹ The use of contrast agents has allowed measurement of total intravascular volume and the simultaneous determination of total lung water using a multi-spin-echo sequence. This provides a measurement of EVLW volume which correlates well with the gravimetric technique.⁷²

An alternative approach to the radiological imaging of lung water is the use of sodium MRI.⁷³ This approach utilizes the distribution of sodium ions to quantify EVLW. The concentration of sodium ions in extracellular fluid is greater than ten times that of

intracellular fluid. The majority of sodium ions within the lung will therefore be situated within plasma, the interstitium or the alveoli. The use of contrast agents allows the plasma signal to be suppressed. Generation of an extravascular lung sodium image is then possible and this indicates the presence and distribution of EVLW. The signal intensity appears to correlate well with EVLW volume measured by the gravimetric method.⁷³ However, at present it seems unlikely that either sodium MRI or the more basic MRI assessment of pulmonary oedema will be integrated into routine clinical practice for similar reasons to those already mentioned with regard to CT scanning.

1.6.4 Ultrasonography

Ultrasonography is considered a poor technique for imaging the lung because ultrasound waves are reflected by air within the lung, creating reverberation artefact.⁷⁴ Nevertheless, this technology can be used to provide an indication of lung water content. The ‘comet-tail’ is a form of artefact which arises when there is a marked difference in acoustic impedance between an object and its surroundings.⁷⁵ In the presence of increased EVLW volume, the comet-tail sign may be seen to originate from water-thickened interlobular septa and fan out across the lung surface. This sign may be detected with either radiological or cardiac ultrasound equipment (figure 1.9a).

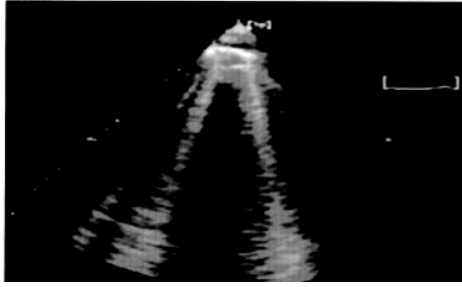


Figure 1.9a Typical comet tail artefacts as seen by ultrasound demonstrating increased extravascular lung water

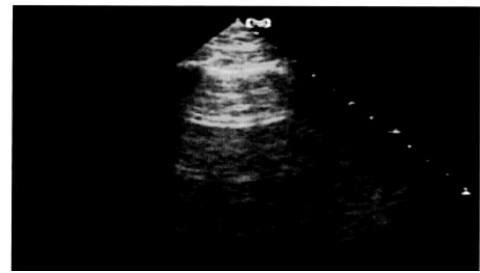


Figure 1.9b Normal subject, with regular, parallel, roughly horizontal hyperechogenic lines due to the lung-chest wall interface

In one study of critically ill patients, multiple comet-tail artefacts were identified by ultrasonography of the lungs in eighty-six out of ninety-two patients with radiographic evidence of acute lung injury, cardiogenic pulmonary oedema, or exacerbation of chronic interstitial lung disease.⁷⁶ A smaller study of twenty cardiac surgical patients demonstrated that there was a positive linear correlation between the comet-tail score and EVLW volume determined by trans-pulmonary thermal indicator dilution, as well as pulmonary artery occlusion pressure and chest radiograph lung water score.⁷⁷ Further work suggested that the comet-tail score has a linear relationship with a radiographic extravascular lung water volume score⁷⁸ and may be useful in distinguishing pulmonary oedema from other forms of lung disease.⁷⁹ However, whilst chest ultrasound may be a simple and quick method of EVLW volume assessment, this approach does not appear to have any advantage over chest radiography in terms of diagnostic accuracy, but does allow differentiation of other lung pathologies, for example, pleural effusion and consolidated lung tissue.

1.6.5 Ultrasound velocity and electrical impedance dilution

Krivitski et al described a novel technique whereby EVLW volume may be estimated by ultrasonographic blood velocity measurement and electrical impedance dilution.^{80,81} In an animal study, changes in systemic arterial sound velocity and electrical impedance during the intravenous injection of hypertonic and isotonic sodium chloride solution were used to calculate lung permeability and provide an estimate of EVLW volume.⁸⁰ These measurements were comparable to those made using the gravimetric technique. This technique has also been used to monitor changes in EVLW volume during haemodialysis.⁸¹ Although the indexed measurements were similar to those from the animal study, they do not seem to be consistent with clinical changes associated with haemodialysis.

1.6.6 Positron Emission Tomography (PET)

PET is a nuclear imaging technique that involves the use of radioactive isotope markers which emit positrons during the process of spontaneous decay. Emitted positrons, having annihilated electrons, produce gamma rays which are emitted and detected to generate a three-dimensional image. Continuous intravenous infusion of water labelled with O¹⁵ and subsequent inhalation of C¹¹ labelled carbon monoxide allows the quantitative measurement of total thoracic water and ITBV. EVLW volume is then determined by subtraction. This technique correlates well with both the indocyanine green-thermal double indicator dilution and gravimetric techniques in dogs.⁸²

1.7 Measurement of extravascular lung water using other techniques

1.7.1 Dual-isotope technique

Iodine¹³¹ labelled iodo-antipyrine and ^{99m}Tc labelled erythrocytes have been used to measure EVLW volume in rabbits with acute lung injury.⁸³ These radioactive tracers were injected into 10 rabbits with normal lungs and 11 rabbits with injured lungs. Blood samples were drawn and the animals were sacrificed. The lungs were removed, weighed and homogenized for gravimetric analysis. Samples of blood and lung homogenate were also assayed for ¹³¹I and ^{99m}Tc. Extravascular lung water volume measurement determined by the dual isotope technique correlated well the gravimetric method but appears to be restricted to the research setting.

1.7.2 Impedance plethysmography

Attempts have been made to monitor changes in intrathoracic blood volume and extravascular lung water volume by impedance plethysmography. Accumulation of lung water leads to a decrease in internal thoracic impedance, which is measured non-invasively using cutaneous electrodes placed over the right lung.⁸⁴ Internal thoracic impedance can decrease by as much as 12% before clinical signs become apparent. This technique has been successfully used to anticipate the onset of clinically evident pulmonary oedema by between 30 and 60 minutes. This technique however does not allow quantification of EVLW volume and appears to only detect alveolar flooding, not interstitial oedema. Consequently it would be of minimal benefit to the critical care physician in guiding therapeutic interventions designed to reduce EVLW volume.

1.8 Discussion

Increased extravascular lung water volume is a recognised feature of critical illness, in particular acute lung injury. Increased extravascular lung water volume has been identified in critically ill patients with acute lung injury using a variety of indicator dilution techniques.^{4-6,8,10,25} The research and indicator dilution clinical reference methods for EVLW volume measurement, namely the gravimetric and ICG-thermal techniques, are either not suitable, or not commercially available for clinical use. The variety of imaging techniques discussed in this chapter are either impractical for repeated measurements (CT, MRI & PET scanning) or provide non-quantitative information (chest radiography or ultrasonography). Alternative methodologies are restricted to the research environment (dual-isotopes) or are not sufficiently precise (impedance plethysmography). The only commercially available practical device for measuring EVLW volume at the bedside is the single-thermal indicator dilution technique (PiCCO[®], Pulsion Medical Systems, Munich, Germany). The accuracy and validity of this method may be affected by number of common confounders.^{60-62,64} Indeed, a recent study investigating the use of salbutamol infusions to control EVLW volume, was criticised because single-thermal indicator dilution technology was employed to measure EVLW volume.^{85,86}

1.9 Hypothesis

A possible solution to the need to measure EVLW volume could be trans-pulmonary lithium indicator dilution. By combining this measurement with thermodilution, EVLW volume could be calculated without relying on the assumptions made when using thermodilution alone. There are several reasons why this could be a more practical and reliable approach than previously described technologies. Lithium chloride appears to satisfy many criteria for an ideal indicator to measure a vascular compartment (see page 25), principally because it remains within the vasculature during one trans-pulmonary circulation time.⁸⁷⁻⁸⁹ This indicator has been incorporated into a commercially available device for cardiac output monitoring developed by LiDCO™ (LiDCOplus™ version 4.0, LiDCO Ltd, Cambridge, UK) and has been widely used in clinical practice for several years.⁹⁰ No side effects of the administration of lithium by this route have been reported. The device is widely available and utilises routine invasive monitoring (central venous and arterial catheters) to obtain cardiac output data via an external sensor. Accurate, reliable and repeatable cardiac output determination is essential for the successful measurement of EVLW volume. Lithium indicator dilution measurement of cardiac output has been validated in several laboratory and clinical studies.^{87,91,92} In anaesthetised pigs, cardiac output measured by lithium indicator dilution correlated more closely with measurements made by electromagnetic aortic flowmetry than did thermodilution.⁹¹ The first study of lithium indicator dilution in man was performed in nine patients immediately following cardiac surgery.⁹² Twenty two comparisons made with bolus thermodilution using the pulmonary artery catheter, revealed a mean bias of -0.30 l min^{-1} (SD 0.50). This study was repeated in 40 patients, most of whom had undergone cardiac surgery. A total of 200

comparisons were made, with a mean bias of -0.25 l min^{-1} (SD 0.46).⁸⁷ The evidence in animal and human studies suggests a good correlation between lithium dilution and thermodilution using the pulmonary artery catheter.

Using an adapted version of the LiDCO cardiac output measurement technology, where the mean transit time of the lithium indicator bolus is measured, it should be possible to derive ITBV. Simultaneous detection of a thermal signal with the subsequent incorporation of a thermistor would then allow calculation of EVLW. This adaptation of existing technology could potentially allow safe, reliable and practical measurement of EVLW volume at the bedside.

1.10 Thesis aims

1. To undertake a proof of concept study to measure intrathoracic blood volume by lithium indicator dilution for the first time
2. To compare the measurement of extravascular lung water using the new lithium-thermal double indicator dilution technique to the reference standard of gravimetric analysis in an animal model of acute lung injury
3. To compare the proposed lithium-thermal double indicator dilution technique to the current clinically available alternatives in an animal model of acute lung injury
4. To compare the proposed lithium-thermal double indicator dilution technique to the current clinically available alternatives in man
5. To develop the lithium-thermal double indicator dilution technique into a practical and reliable method of EVLW measurement in clinical practice

absorption at 805 nm. Because there is minimal light absorption by water, oxygenated and de-oxygenated haemoglobin at this wavelength, generation of the characteristic dye dilution curve by an intravascular fibreoptic tipped catheter is possible (figure 2.2). ICG has a half-life of 3-4 minutes in healthy volunteers and is taken up from the plasma almost exclusively by the hepatic parenchymal cells and is secreted entirely into the bile.⁹³ Consequently the half life of ICG will be prolonged in hepatic failure. There is no effect of renal failure on half life.

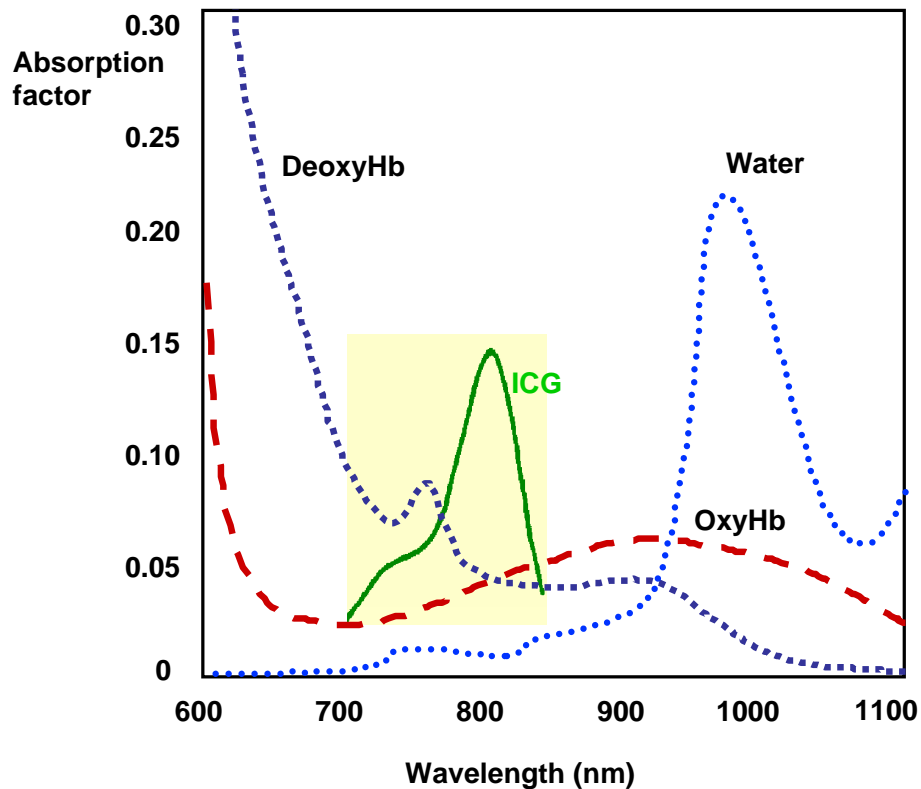


Figure 2.2 Near infrared absorption spectra of water, deoxygenated haemoglobin (deoxyHb), oxygenated haemoglobin (oxyHb) and indocyanine green (ICG)

In order to measure the changes in blood concentration of ICG, an 8.5 French gauge femoral arterial introducing sheath (Arrow; Reading, PA) is inserted by the Seldinger technique. A 3FG thermistor-tipped fibreoptic catheter (PV 2024; Pulsion Medical Systems; Munich, Germany) is then inserted into the descending aorta via the femoral artery sheath and connected to the COLD-Z[®] system (see figures 2.3 & 2.4).

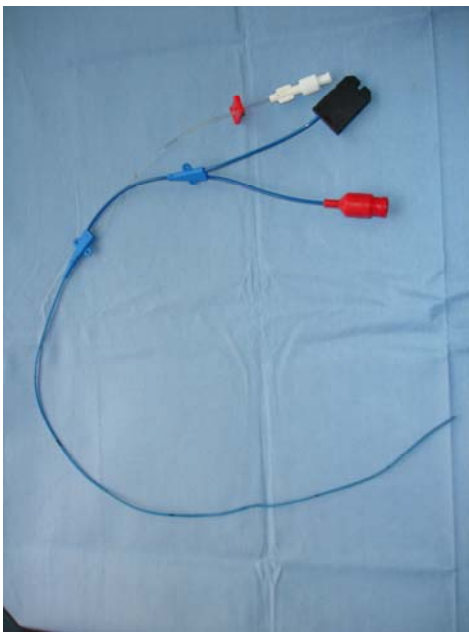


Figure 2.3 ICG-thermal catheter

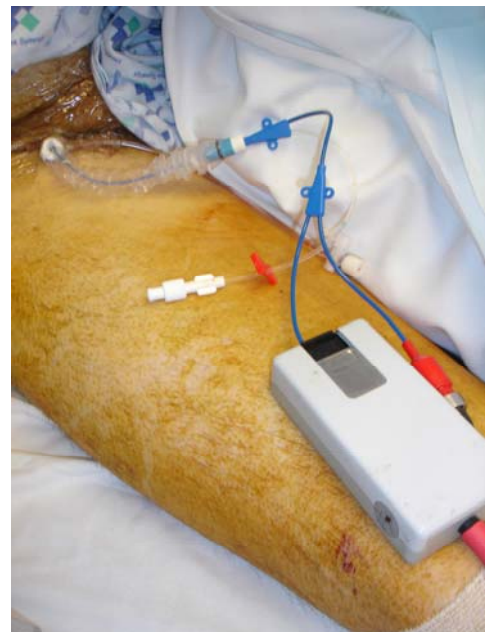


Figure 2.4 ICG-thermal catheter sited in right femoral artery

Correct positioning of the catheter is essential in order to accurately identify the ICG concentration change. The catheter is inserted to 35cm and then slowly withdrawn until a strong pulsatile signal is observed on the monitor (figure 2.5). The catheter tip must be positioned as close to the diaphragm as possible in order to avoid over or underestimation of ITBV. A pulsatile signal also indicates the catheter is positioned in an area of good blood flow within the aorta and is not abutting the vessel wall, which would result in signal

damping. Signal damping may affect both the ICG absorption and the thermal signals. Once the COLD-Z[®] system output is stable, the indicators can be injected (figure 2.6).



Figure 2.5 Strong pulsatile signal indicated by green ‘opt signal’ and good baseline calibration (red 0.01).

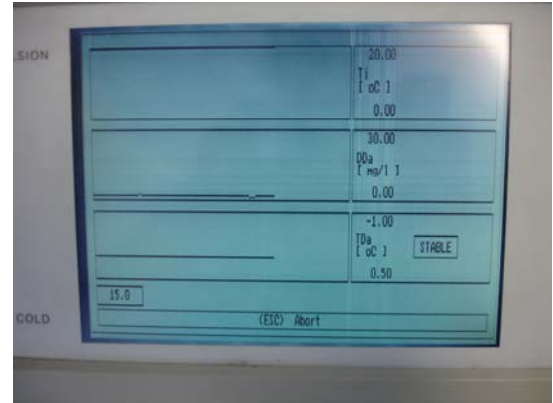


Figure 2.6 Signal stable with good catheter position and no baseline fluctuation (DDa & TDa).

The solution for injection consists of $0.1\text{-}0.3 \text{ mg kg}^{-1}$ of ICG mixed in 10-20 ml of iced saline. This solution is injected as a bolus into the superior vena cava via the distal port of a central venous catheter (figure 2.7). The COLD-Z[®] system is connected to the central venous catheter via a thermistor which detects the start of the injection, (allowing measurement of MTT) and measures the injectate temperature, allowing calculation of cardiac output (CO). The dilution curves for ICG and ice cold saline are generated simultaneously in the descending aorta, from the thermistor-tipped fiberoptic catheter signals. CO is derived from the thermal indicator dilution curve, based on the Stewart-Hamilton formula (equation 2.1).^{36,37}

$$CO = \frac{VI.(TB - TI).60.K}{AUC}$$

Equation 2.1 Calculation of cardiac output using the thermal dilution curve

CO, cardiac output; VI, volume of injectate; TB, blood temperature; TI, injectate temperature; AUC, area under the curve; K, scaling factor

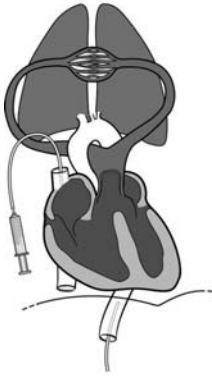


Figure 2.7 Thermistor attached to central venous catheter via three-way tap and COLD-Z machine via black data cable

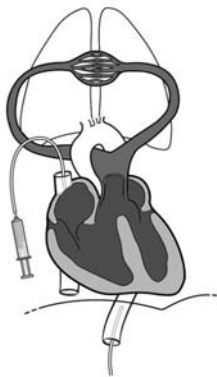


Figure 2.8 COLD-Z machine and equipment set-up around bed space

The ICG and thermal dilution curves are analysed to yield the mean transit time (MTT) of the indicators and the exponential downslope time (τ) (figure 1.1). CO and MTT are multiplied to calculate the volume between the point of injection and the point of detection. Multiplication of CO with the downslope time yields the volume of the largest mixing chamber between the point of injection and the point of detection. Mathematical analysis of the ICG dilution curve allows calculation of ITBV, PBV and GEDV. Mathematical analysis of the thermal dilution curve allows calculation of ITTV and consequent derivation of EVLW (figure 2.9).

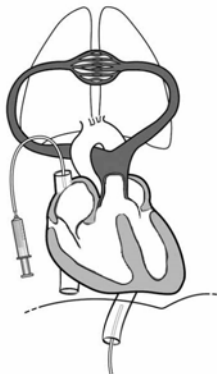


$$ITTV = CO \times MTT_{thermal}$$



$$ITBV = CO \times MTT_{ICG}$$

$$EVLW = ITTV_{(thermal)} - ITBV_{(ICG)}$$



$$PBV = CO \times \tau_{ICG}$$

$$GEDV = ITBV_{(ICG)} - PBV_{(ICG)}$$

Figure 2.9 Thoracic fluid derivation using ICG-thermal double indicator dilution

CO, cardiac output; MTT, mean transit time; ITTV, intrathoracic thermal (water) volume; ITBV, intra-thoracic blood volume τ , downslope time; PBV, pulmonary blood volume; GEDV, global end-diastolic volume; ICG, indocyanine green

2.2 Single Indicator Dilution

The only commercially available device for EVLV volume and thoracic blood volume measurements using single indicator dilution is transpulmonary thermal indicator dilution (PiCCO[®] system, Pulsion Medical Systems, Munich, Germany). A thermistor-tipped arterial catheter (5 French gauge, PV2015L20, Pulsion Medical Systems, Munich, Germany) is inserted into the descending aorta via the femoral artery and connected to the PiCCO[®] system.

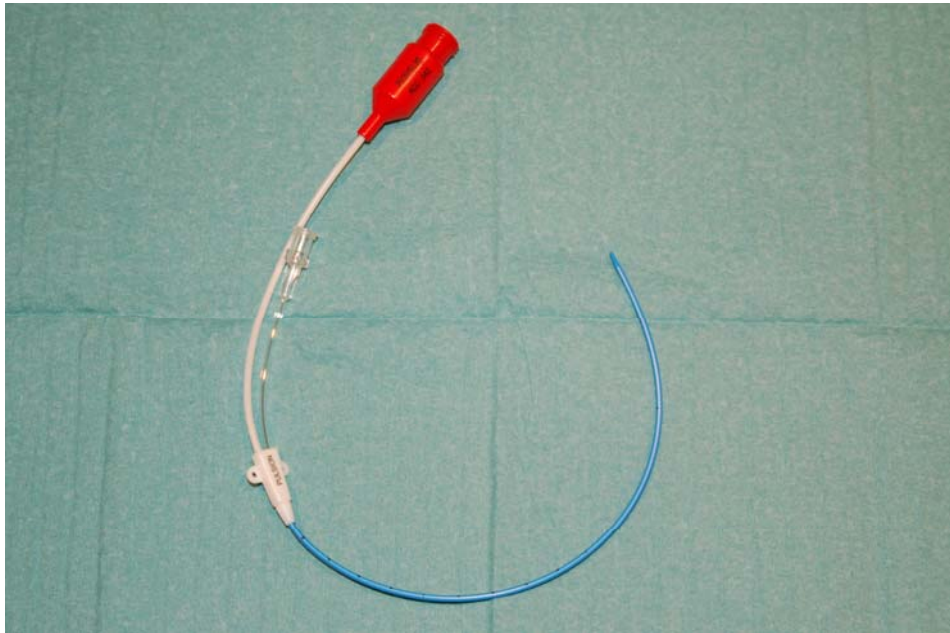
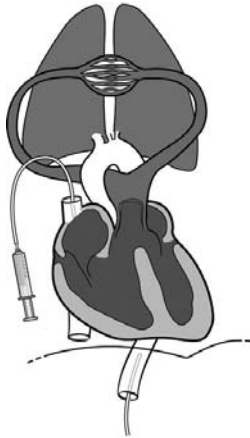
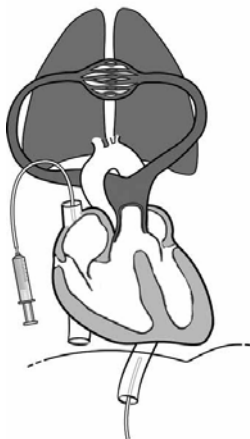


Figure 2.10 PiCCO catheter

Ice cold saline (0-6°C) is injected as a bolus into the superior vena cava via the distal port of a central venous catheter, also connected to the PiCCO[®] system in an identical fashion to the COLD-Z[®] system (figure 2.7). In common with the COLD-Z[®] system the thermistor allows detection of the start of the injection, thus allowing the measurement of MTT, and also measures the injectate temperature allowing calculation of CO. The temperature change in the descending aorta is detected by the thermistor-tipped catheter and the thermodilution curve constructed. CO is calculated from the indicator dilution curve once again using the Stewart-Hamilton formula (see equation 2.1).^{36,37} To determine ITBV, PBV and GEDV, the thermal dilution curve is analysed to yield the thermal indicator MTT and its exponential downslope time (τ) (figure 1.1). EVLW volume is then calculated (figure 2.11). Measurements are taken in triplicate and averaged.



$$ITTV = CO \times MTT_{thermal}$$



$$PTV = CO \times \tau_{Thermal}$$

$$GEDV = ITTV - PTV$$

$$ITBV = 1.25 \times GEDV$$

$$EVLW = ITTV - ITBV$$

Figure 2.11 Calculation of extravascular lung water (EVLW) volume using the transpulmonary single thermal indicator dilution technique

CO, cardiac output; MTT, mean transit time; τ , downslope time; PTV, pulmonary thermal (water) volume; GEDV, global end-diastolic volume; ITTV, intrathoracic thermal (water) volume; ITBV, intra-thoracic blood volume

2.3 Lithium Indicator Dilution

A small dose of lithium chloride (0.15-0.30mmol) is injected via a central or peripheral venous line, the former being preferable.⁹⁴ The resulting arterial lithium concentration–time curve is generated by drawing blood over a single use lithium ion sensitive electrode attached to a peripheral arterial catheter (figure 2.12). The electrode is connected to the arterial catheter via a three-way tap. A small battery powered peristaltic pump is used to create a constant blood flow of 4.25 ml min⁻¹ through the sensor and over the tip of the electrode (figure 2.13).

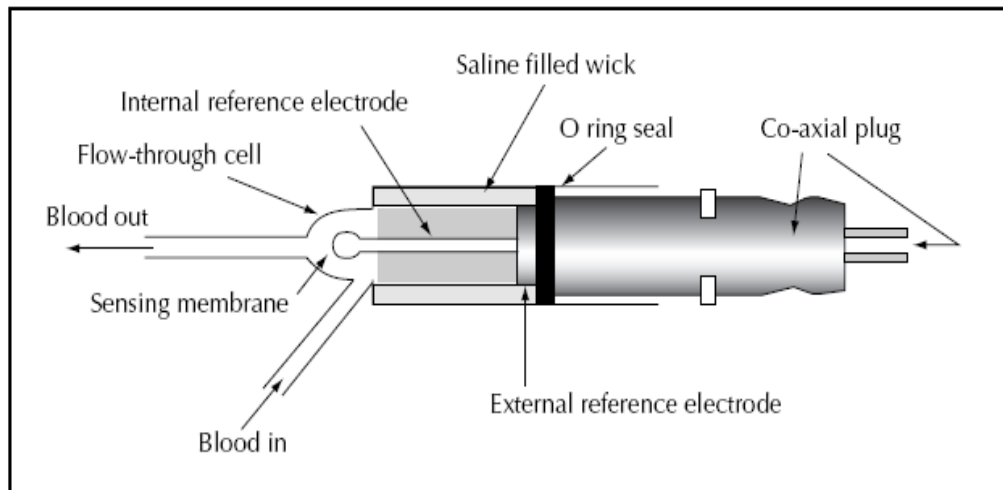


Figure 2.12 Lithium ion sensitive electrode. Reproduced with the kind permission of Dr M. Jonas

The electrode contains a reference material which provides a constant ionic environment and supports a membrane which is selectively permeable to lithium ions (figure 2.12). The potential difference across the membrane is related via the Nernst equation to the plasma lithium concentration. A correction for sodium concentration is therefore required because this is the main determinant of potential difference at baseline. A correction for packed cell volume is applied because lithium is distributed solely in plasma. A wick soaked in

heparinised saline prior to use, creates an electrical connection between blood and the remote reference electrode.



Figure 2.13 Lithium ion sensitive electrode (bottom right) and battery operated peristaltic pump.

The use of non-depolarising muscle relaxants may interfere with lithium measurements because the quaternary ammonium ion is also sensed by the electrode causing positive baseline drift. This may prevent calibration of the monitor for 15-120 minutes after drug administration depending on the dose and type of non-depolarising muscle relaxant. The more potent the drug, for example pancuronium, the less the interference because the equipotent dose contains fewer molecules. Because the continuous measurement of CO is derived by arterial waveform analysis, muscle relaxants may be used freely once calibration has been performed. In common with most other methods of cardiac output measurement, the presence of intra cardiac shunts will also result in erroneous measurements. The pharmacokinetics of intra-venous lithium have been described.⁹⁵ No side effects have been reported upon the administration of lithium by this route. The dose of lithium required for calibration can be used on ten successive occasions in a 40 kg anephric patient without exceeding the therapeutic range for oral lithium therapy. Consequently, lithium toxicity

does not limit use. The manufacturer does not recommend the administration of intravenous lithium chloride to patients who weigh less than 40kg, are pregnant or receiving oral lithium therapy, although the technology has been used in children.

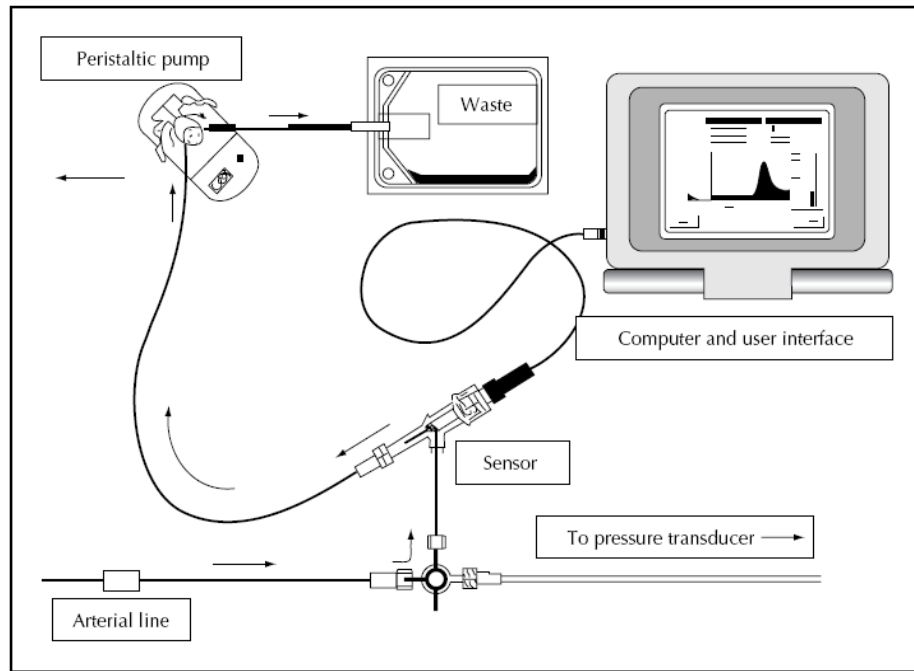


Figure 2.14 Configuration of the lithium sensor and peristaltic pump during the calibration process. Reproduced with the kind permission of Dr M. Jonas.

2.4.1 Cardiac Output derivation

Cardiac output is calculated from the lithium dose and the area under the concentration time curve prior to recirculation.

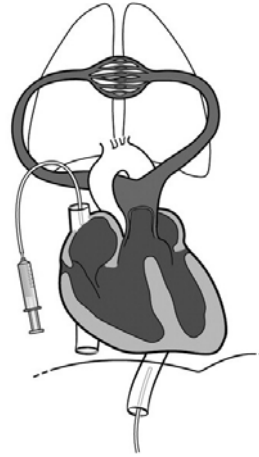
$$CO = \frac{LiCl_{dose} \times 60}{AUC \times (1 - PCV)}$$

Equation 2.2 Cardiac output derivation using lithium indicator dilution

CO, cardiac output; AUC, area under the concentration time curve; PCV, packed cell volume

2.4.2 Intrathoracic blood volume derivation

Accurate ITBV measurement by lithium indicator dilution relies on accurate cardiac output determination and MTT measurement combined with reliable software analysis of the dilution curve. The timing of the lithium bolus injection is standardised by a countdown timer on the monitor. Intrathoracic blood volume derivation using lithium indicator dilution relies on identifying the indicator MTT and applying the Stewart hypothesis (Equation 1.2). This measurement assumes that lithium remains confined to the intravascular compartment during one trans-pulmonary circulation time. Although lithium ions quickly leave the intravascular compartment, two studies suggest that this loss does not cause any significant error within the short time that elapses between injection and detection.^{87,89} Kurita et al induced acute lung injury with oleic acid in pigs having cannulated both the right and left ventricles. Lithium chloride was injected into the right and then left ventricle and an indicator dilution curve was constructed by a lithium ion sensitive electrode attached to a femoral arterial catheter. There was no difference in CO measured by injection into either ventricle.⁸⁹ Band et al performed a similar study in patients with cannulae sited in both right and left atria during cardiac surgery. Lithium indicator dilution curves were recorded following injection into either the right or left atria. They concluded that loss of lithium into the lungs following injection into the right atrium was clinically insignificant.⁸⁷



$$ITBV = CO \times MTT_{Li}$$

Figure 2.15 Calculation of ITBV using lithium indicator dilution

ITBV, intra-thoracic blood volume; CO, cardiac output; MTT_{Li} , lithium indicator mean transit time;

Because the lithium electrode is attached to a peripheral artery (normally the radial artery) and externally placed, measured MTT will include the time taken for the indicator to transit the arterial circulation from the margin of the thorax to the radial artery catheter, as well as through the external tubing to the electrode. This is represented by equation 2.3:

$$MTT_{ITBV} = MTT_{Li} - (T_{arm} + T_{electrode})$$

Equation 2.3 Derivation of physiological MTT using lithium indicator dilution

MTT_{ITBV} , physiological MTT; MTT_{Li} measured lithium MTT; T_{arm} indicator transit time from thoracic border to radial arterial catheter; $T_{electrode}$ time through external tubing to the electrode

As the volume of the arterial catheter and extension tubing is constant and flow through this system is regulated by a peristaltic pump at a constant speed of 4.25 ml min^{-1} this component of measured MTT is constant. In bench studies, this value has been found to be 13.3 seconds. The indicator transit time from the margin of the thorax to the radial arterial

catheter has been investigated, but not in the context of post operative cardiac surgical patients. Published data suggests transit of the indicator from the margin of the thorax to the wrist would be highly unlikely to result in a delay of more than 2.0 seconds. However, the variability of this component of the transit time has not been investigated. Consequently the measured MTT may vary not only due to changes in ITBV but also changes in the peripheral circulation. This adjustment will be discussed further in the subsequent chapters.

$$MTT_{Li} = MTT_{ITBV} + (T_{arm} + 13.3 \text{ sec})$$

Equation 2.4 Derivation of measured Lithium MTT

MTT_{Li} , measured lithium MTT; MTT_{ITBV} , physiological MTT; T_{arm} indicator transit time from thoracic border to radial arterial catheter

2.4 Gravimetry

The laboratory study involves a modified post-mortem gravimetric method to calculate extra-vascular lung water volume.^{34,61,96} Immediately prior to animal sacrifice, 60 ml of central venous blood is taken for determination of the haemoglobin concentration, haematocrit and wet:dry mass ratio of blood. The lungs are removed immediately post mortem, drained of blood, and weighed. An amount of water equal to the weight of the lungs is added to induce haemolysis. The lungs and the added water are then homogenized using a commercial blender and a homogenizer. Half of the homogenate is used to determine its wet:dry mass ratio and the other half centrifuged at 30,000g for one hour at 4°C to obtain a supernatant. The supernatant is separated and the haemoglobin concentration and wet:dry mass ratio determined. The dry weights of the blood, homogenate and supernatant are determined after three days incubation in a heat chamber at 85°C. EVLW is then calculated according to the formula described in figure 2.16.

$$[1] \quad Fw_s = \frac{Ww_s - Wd_s}{Ww_s}$$

$$[2] \quad Fw_h = \frac{Ww_h - Wd_h}{Ww_h}$$

$$[3] \quad Qr = Qh \times \frac{Hb_s}{Hb_b} \times \frac{Fw_h}{Fw_s} \times Hct$$

$$[4] \quad Qb = Qr + \left[Qr \left(\frac{1 - Hct}{Hct} \right) \right]$$

$$[5] \quad Fw_b = \frac{Ww_b - Wd_b}{Ww_b}$$

$$[6] \quad EVLW = Qh \times Fw_h - Qb \times Fw_b - Qwt$$

Figure 2.16 Formulae used in gravimetric determination of EVLW

Qlb = weight of removed lungs; Qwt = weight of added water; Wwb = wet weight of blood; Wdb = dry weight of blood; Fwb = fraction water of blood; Wwh = wet weight homogenate; Wdh = dry weight homogenate; Fwh = fraction water of homogenate; Wws = wet weight supernatant; Wds = dry weight supernatant; Fws = fraction water supernatant; Hct = haematocrit; Qb = residual blood content in lungs; Qr = Red cell mass of lung; Qh = total weight of homogenate; Hb_s = haemoglobin concentration in supernatant; Hb_b = haemoglobin concentration in blood; EVLW = extravascular lung water

Chapter 3

Measurement of intrathoracic blood volume using trans-pulmonary lithium indicator dilution: a proof of concept study

3.1 Introduction

Increased extravascular lung water (EVLW) volume during critical illness is associated with prolonged mechanical ventilation, delayed recovery and increased mortality rates.^{25,28-30} Quantification of EVLW volume allows treatment to be adjusted to regulate lung water, perhaps resulting in improved clinical outcomes.^{29,30} Neither assessment of oxygenation nor chest radiography provide a reliable indication of EVLW volume,^{17,18,20} and there is as yet no ideal method for measuring EVLW volume at the bedside.

The clinical reference standard for EVLW volume measurement is the trans-pulmonary indocyanine green-thermal double indicator dilution technique, the theoretical and methodological descriptions of which are described in sections 1.4.2 and 2.1. At present, the only commercially available method of EVLW volume measurement is the trans-pulmonary (single) thermal indicator dilution technique as described in section 1.4.3, however, there is some concern regarding the validity of this approach.⁶⁶

One solution might be to measure ITBV by the trans-pulmonary lithium indicator dilution technique. In combination with thermodilution, EVLW volume could be calculated without relying on the mathematical assumptions made when using thermodilution alone. Lithium chloride satisfies many of the criteria for an ideal indicator and ITBV measurements could be made using an adapted version of cardiac output measurement technology which has been in clinical use for several years.^{87-89,91,92} The small displacement volume of the lithium indicator minimises measurement error and, in contrast to trans-pulmonary thermal (single) indicator dilution,⁹⁷⁻¹⁰⁰ there does not appear to be any significant loss of lithium indicator between injection and sampling sites.^{87,89} The technique is straightforward and less expensive than indocyanine green indicator dilution and in combination with thermodilution would allow EVLW volume measurement by double indicator dilution using existing technology.

However, the measurement of ITBV by lithium indicator dilution has not previously been described and might be affected by a number of potential sources of error. The aims of this study were to measure ITBV using lithium indicator dilution for the first time, allowing validation of this concept and comparison with published data collected using indocyanine green indicator dilution.

3.2 Methods

3.2.1 Patients

This single centre, observational study was prospectively approved by the Local Research Ethics Committee. Patients aged over 50 years undergoing elective cardiac surgery with cardio-pulmonary bypass were eligible for recruitment according to pre-defined criteria. The peri-operative changes in ITBV and EVLW volume in this population are significant and well described.¹⁰¹⁻¹⁰⁴ Patients were screened for eligibility prior to surgery and written informed consent obtained. Exclusion criteria were refusal of consent, concurrent lithium therapy, pregnancy and weight less than 40 kg. Patients with acute arrhythmias, severe peripheral vascular disease, significant cardiac valvular regurgitation and intra-aortic balloon counterpulsation were also excluded as these conditions could affect forward flow of the lithium indicator.

3.2.2 Clinical Management

A 20G right radial arterial catheter was inserted prior to induction of general anaesthesia with propofol 2-3 mg kg⁻¹, fentanyl 3-5 µg kg⁻¹ and vecuronium 0.1 mg kg⁻¹. Anaesthesia was maintained with inhaled isoflurane and boluses of fentanyl and vecuronium as required. A right internal jugular central venous catheter was then inserted prior to surgery. Cardio-pulmonary bypass was managed by a perfusionist in consultation with anaesthetic and surgical staff. The bypass circuit was primed with two litres of Ringer's lactate solution and 15,000 international units of heparin. Packed red blood cells were administered to maintain a haemoglobin concentration above 8 g dl⁻¹. Cumulative fluid balance data was

obtained from anaesthetic and perfusionist records in theatre and nursing charts in the critical care unit. Invasive ventilation was standardised according to best practice.¹⁰⁵ Initial settings were as follows: mandatory rate of 12 breaths per minute, positive end-expiratory pressure of 5 cm H₂O and tidal volume 7 ml kg⁻¹. Patients were managed in a critical care unit following surgery, where sedation was discontinued and the tracheal tube removed by clinical staff according to local protocols.

3.2.3 ITBV measurements

Measurements were performed following induction of anaesthesia, after discontinuation of cardio-pulmonary bypass and sternotomy closure, and then two, four and 24 hours following surgery using the method described in chapter 2. Measurements were made a minimum of 25 minutes following the administration of non-depolarising muscle relaxants in order to avoid any baseline drift of the lithium sensor voltage. A lithium concentration–time curve was constructed and values of cardiac output and ITBV were calculated automatically, allowing for the proposed indicator transit time down the arm and through the external equipment (see section 2.4.2). The time of injection was standardised through the use of a visual countdown on the monitor (LiDCOplus™ version 4.0, LiDCO Ltd, Cambridge, UK).

3.2.4 Statistical analysis

Data from previous work suggested that ITBV may typically rise by 7.5ml kg⁻¹ during cardio-pulmonary bypass and that values change by between 5% and 10% during the first

24 hours after surgery.^{103,104} Assuming a type I error rate of 5% and a type II error rate of 10%, it was estimated that 20 patients would be required to detect a change in ITBV of 1.5 ml kg⁻¹ (standard deviation (SD) 2 ml kg⁻¹). Data are presented as mean (SD) where normally distributed, and median (inter-quartile range [IQR]) where not normally distributed. The significance of peri-operative changes in ITBV was tested using repeated measures analysis of variance (ANOVA) with Tukey's correction. The association between cardiac index and ITBV was tested using linear regression. Analysis was performed using GraphPad Prism version 4.0 (GraphPad Software, San Diego, USA). Significance was set at $p < 0.05$.

3.3 Results

Twenty patients were recruited in July and August 2006. The baseline characteristics of these patients are presented in table 3.1 and physiological data in table 3.2. In four patients, the arterial catheter occluded and was removed before the final 24 hour measurement could be taken. No difficulties were encountered due to baseline sensor drift caused by prior use of non-depolarising muscle relaxants.

ITBV data is presented in table 3.3 and figure 3.1. Initial ITBV values were slightly less than the quoted normal range¹⁰⁶ but changed significantly during the peri-operative period ($p < 0.0001$). Values peaked at two hours following surgery before returning to normal for many patients by the first post-operative day. Linear regression analysis indicated a weak relationship between ITBV and cardiac index ($r^2 = 0.22$, $p < 0.0001$) (figure 3.2). There was also a weak relationship between ITBV and MTT ($r^2 = 0.29$, $p < 0.0001$) (Figure 3.3).

n	20
Age	70 years [64-75]
Gender	13 male, 7 female
Weight	76 kg [67 – 86]
Parsonnet score	10 [1 – 13.5]
Duration of cardio-pulmonary bypass	99 minutes [60 – 130]
Coronary artery bypass graft	15
Aortic valve replacement	2
Coronary artery bypass graft and aortic valve replacement as combined procedure	3

Table 3.1 Baseline patient characteristics

Data presented as median [SD]

Time	Pre-bypass	Post-bypass	2 hours	4 hours	24 hours
MAP (mm Hg)	70.5 [64-75]	63.0 [58-69]	66.5 [63-76]	69.5 [63-76]	72.0 [68-78]
CVP (mm Hg)	8 [7-9]	9 [6-11]	11 [10-14]	12 [10-13]	14 [8-16]
CI (l min⁻¹ m⁻²)	1.98 (±0.45)	1.92 (±0.42)	2.22 (±0.56)	2.29 (±0.58)	2.56 (±0.94)
PaO₂ (kPa)	33.2 (±13.3)	30 (±12.0)	18.0 (±4.2)	15.9 (±3.2)	12.1 (±3.1)
PaO₂:FiO₂ (kPa)	58 (±20)	38 (±18)	42 (±10)	43 (±11)	n/a
V_T (ml)	529 (±77)	535 (±77)	536 (±73)	525 (±110)	n/a
PEEP (cm H₂O)	5 [5-5]	5 [5-5]	5 [5-5]	5 [5-5]	n/a
Peak P_{AW} (cm H₂O)	19 [17-25]	21 [19-23]	24 [19-28]	20 [15-26]	n/a
Cumulative fluid balance (ml)	0	3145 (±1141)	3325 (±1173)	3955 (±1113)	5821 (±1683)

Table 3.2 Physiological parameters.

Data presented as mean (SD) or median [IQR]. MAP, mean arterial pressure; CVP, central venous pressure; CI, cardiac index; V_T, tidal volume; PEEP, positive end-expiratory pressure; Peak P_{AW}, peak airways pressure.

Time	Pre-bypass	Post-CPB	2 hours	4 hours	24 hours	<i>p</i>
ITBV (ml)	1542 (±601)	1942 (±562)	2318* (±524)	2268* (±889)	1873 (±658)	<0.001
ITBV (ml m⁻²)	849 (±336)	1068 (±287)	1265* (±273)	1244* (±431)	1100 (±357)	<0.001
ITBV (ml kg⁻¹)	20.9 (±9.6)	26.0 (±7.5)	31.0* (±7.4)	30.0* (±11.2)	20.0 (±12.9)	<0.001
CI (l min⁻¹ m⁻²)	1.98 (±0.45)	1.92 (±0.42)	2.22 (±0.56)	2.29 (0.58)	2.56* (±0.94)	<0.05
MTT (seconds)	25.5 (±6.3)	34.0 (±9.4)*	36.2 (±10.6)*	33.7 (±12.2)*	25.6 (±7.1)	<0.0001

Table 3.3 Lithium indicator dilution data

Data presented as mean (SD) or median [IQR]. ITBV, Intrathoracic blood volume; CI, cardiac index; MTT, mean transit time. * indicates significant changes with respect to pre-op values. ITBV is presented in three different formats (ml, ml m⁻² and ml kg⁻¹) to allow comparison with previous work.

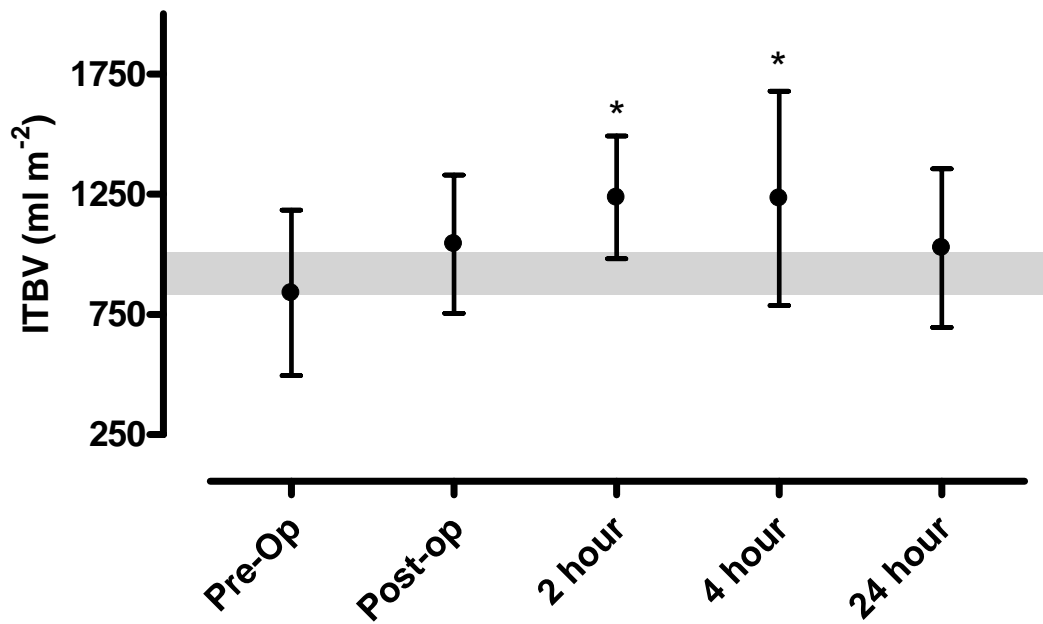


Figure 3.1 Intrathoracic blood volume (ITBV) as measured by lithium indicator dilution at different time-points

Data presented as mean (SD). Changes in ITBV highly significant ($p < 0.0001$, repeated measures ANOVA).

* indicates significant changes with respect to pre-op values. Shaded area indicates normal value of ITBV.

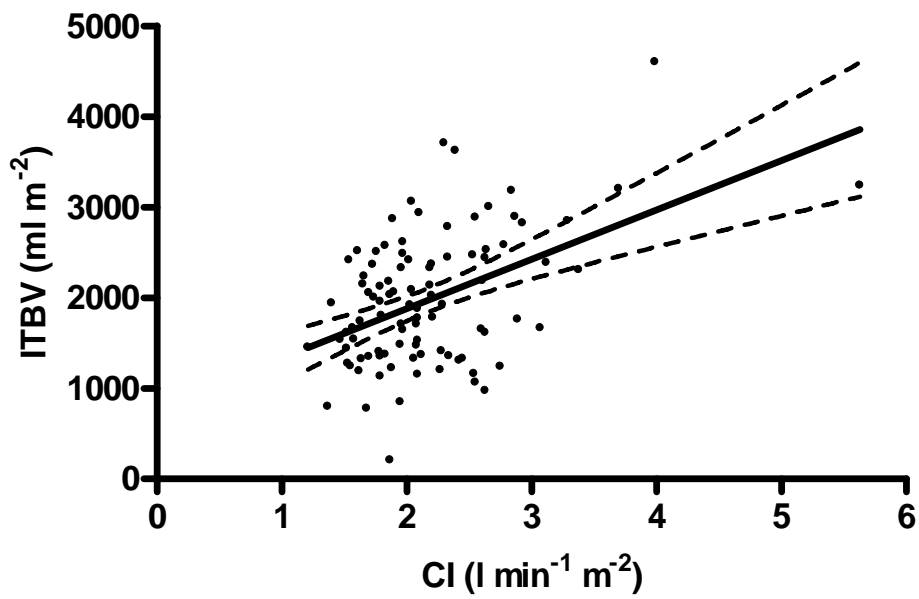


Figure 3.2 Linear regression analysis of the relationship between cardiac index (CI) and intrathoracic blood volume (ITBV). $r^2=0.22$.

Dotted lines signify 95% confidence intervals for gradient. Discussed in section 3.4.3.

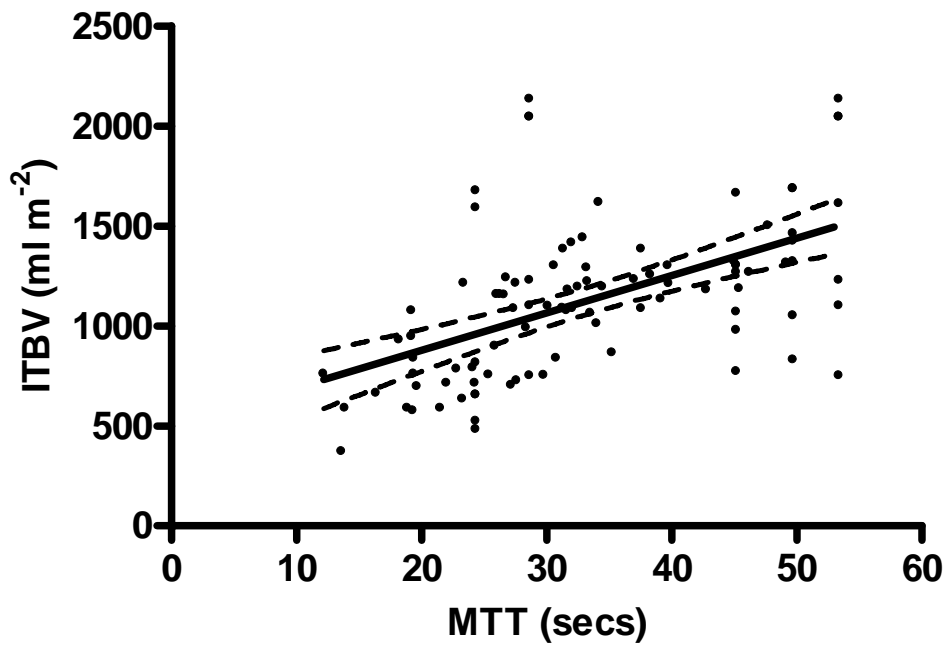


Figure 3.3 Linear regression analysis of the relationship between mean transit time (MTT) and intra-thoracic blood volume (ITBV). $r^2=0.29$

Dotted lines signify 95% confidence intervals for gradient. Discussed in section 3.4.3.

3.4 Discussion

3.4.1 Summary of findings

This proof of concept study of the use of lithium indicator dilution to measure ITBV identified significant peri-operative changes in ITBV which were consistent with previously published data.¹⁰⁴ These findings suggested that ITBV measurement by lithium indicator dilution using an external electrode is valid and that further work to develop a trans-pulmonary double indicator dilution technique utilising lithium and thermal indicators to measure EVLW volume would be worthwhile.

3.4.2 Comparison to previous work

The measurements of ITBV in this study were consistent with those taken during previous investigations.^{104,106-108} Direct comparison between studies is not straightforward because previous reports present data indexed either according to body mass, surface area or as absolute values (see table 3.3). Both peri-operative trends and absolute measurements of ITBV in this study were consistent with those taken using indocyanine green indicator dilution during and after cardiac surgery with cardio-pulmonary bypass.¹⁰⁴ The median absolute value of ITBV measured at baseline using indocyanine green was 1417 (± 208) ml which was similar to the baseline measurement of 1542 (± 601) ml obtained using lithium indicator dilution. Measurements of ITBV using lithium indicator dilution were also comparable to indocyanine green dilution measurements in healthy volunteers (741 [± 54] ml m⁻²), ventilated patients without pulmonary oedema (1410 [± 294] ml) and patients admitted to intensive care with acute respiratory failure (881 [± 64] ml m⁻²).¹⁰⁶⁻¹⁰⁸

3.4.3 Potential sources of error

Most recent studies of indocyanine green indicator dilution have utilised a spectrophotometric catheter inserted via the femoral artery so that the tip lies within the aorta close to the diaphragm and therefore at the margin of the thoracic cavity. Whilst this approach allows a direct measurement of mean indicator transit time, it is also more invasive, requiring placement of a specialised arterial catheter. In contrast, the lithium ion sensitive electrode utilised in this study was designed for external use. Whilst less invasive, the concern was that this approach may introduce measurement error due to the difference between the measured and trans-thoracic values of mean transit time. It is reassuring therefore, that whilst linear regression analysis identified highly significant relationships between ITBV and both cardiac output and mean transit time, neither relationship was sufficient in isolation to explain the observed changes in ITBV. This is important as changes in ITBV should be independent of changes in CO and MTT and not mathematically coupled. This would suggest that the assumption of a fixed time delay due to indicator transit from the margin of the thoracic cavity to the external electrode does not prevent a valid calculation of ITBV by this method.

3.4.4 Benefits of this technique

This technique was very straightforward and easy to use at the bedside. The additional cost of the consumables and lithium indicator is minimal and calibration does not inhibit ongoing clinical care. One major concern prior to this study was the potential interference

of non-depolarising muscle relaxants (NDMR) causing positive drift of the LiDCO baseline. This phenomenon was not observed during the duration of the study, probably because a potent NDMR was used for induction and maintenance of anaesthesia and the time taken to site invasive monitoring post induction and pre-bypass was sufficient to allow plasma levels of the NDMR to fall.

3.4.5 Conclusions

This initial proof of concept study confirmed the feasibility of measuring ITBV by lithium indicator dilution. In combination with thermodilution, this method could potentially provide a practical but accurate double indicator dilution method of extravascular lung water volume measurement at the bedside. Further clinical and laboratory studies are required to evaluate the accuracy of ITBV and EVLW volume measurement using this technique.

Chapter 4

Estimation of extra-vascular lung water volume measurement by lithium-thermal indicator dilution in porcine models of acute lung injury: Comparison of three techniques to post-mortem gravimetry

4.1 Introduction

The laboratory reference technique of EVLW volume measurement is post-mortem gravimetry. EVLW volume is calculated from a number of measurements allowing estimation of the wet:dry weight ratio of the lung and hence derivation of EVLW volume as described in section 2.4.³⁴ The accepted clinical reference technique for measuring EVLW volume (ICG-thermal double indicator dilution) was validated in several animal models by comparison with gravimetry.^{34,45,46} The only device currently commercially available for EVLW volume measurement (single thermal indicator dilution) was also validated in studies using comparison with gravimetry.^{61,63,64} However there appeared to be a trend to over-estimation at higher EVLW volumes perhaps due to the mathematical assumptions made in the derivation of ITBV. These assumptions may be invalid in some common clinical situations.⁶⁰⁻⁶²

The initial proof of concept study confirmed the feasibility of ITBV measurement by lithium indicator dilution in cardiac surgical patients. By combining the trans-pulmonary lithium indicator dilution measurement of ITBV with a thermodilution measurement of ITTV, derivation of EVLW volume should be possible. There is a need to confirm the accuracy of this proposed method and to compare this to the alternative technologies.

The aims of this study were to compare gravimetric EVLW volume measurements with those made by the lithium-thermal double indicator dilution, ICG-thermal double indicator dilution and single-thermal indicator techniques in porcine models of acute lung injury.

4.2 Methods

This study was performed using two porcine models designed to invoke systemic inflammatory and associated cardiovascular and respiratory responses. These were a caecal ligation and puncture model of faecal peritonitis induced septic shock and an aortic balloon occlusion model of visceral ischaemia. In line with the principles of reduction and refinement, this investigation was conducted as part of two ongoing interventional laboratory studies to minimise unnecessary animal use. The protocols of these studies were approved by the Animal Care Committee of the University of Ulm, Germany as well as the governmental animal protection authorities (Regierungspräsidium Tübingen, Germany).

All animals were fasted for 18 hours prior to each experiment with unrestricted access to water. They were premedicated, an auricular vein cannulated and anaesthetised, the details of which are given in sections 4.2.1 and 4.2.2. After orotracheal intubation, ventilator parameters were identical in both studies and set according to clinical standards: volume-controlled ventilation, tidal volume (V_T) 8 ml kg⁻¹, $P_{AW} < 40$ cmH₂O, Positive End Expiratory Pressure (PEEP) 10 cmH₂O, I:E ratio 1:1.5, respiratory rate titrated to maintain PaCO₂ at 35-45 mmHg. If the PaO₂:FiO₂ ratio decreased below 300 mmHg, the I:E ratio was increased to 1:1 and PEEP was increased to 12 cmH₂O. If the PaO₂:FiO₂ ratio decreased below 200 mmHg, PEEP was increased to 15 cmH₂O. FiO₂ was set at the minimum level needed to maintain arterial haemoglobin saturation (SaO₂) above 90%.

4.2.1 Faecal peritonitis-induced sepsis model

Anaesthesia was induced with propofol (1-2 mg kg⁻¹) and ketamine (1-2 mg kg⁻¹) and maintained by pentobarbital infusion (0.14 mg kg⁻¹ hr⁻¹) with intermittent boluses of

buprenorphine ($30 \mu\text{g kg}^{-1}$). Muscle relaxation was achieved by a continuous intravenous alloverin infusion ($0.28 \text{ mg kg}^{-1} \text{ hr}^{-1}$). Intra-venous 6% hydroxyethylstarch was infused at $15 \text{ ml kg}^{-1} \text{ hr}^{-1}$ or at $10 \text{ ml kg}^{-1} \text{ hr}^{-1}$ if the pulmonary artery occlusion pressure was greater than 18 mmHg. A noradrenaline infusion was commenced when mean arterial pressure could no longer be maintained within 20% of baseline by volume resuscitation alone. 8.5 FG introducer sheaths were introduced into the right and left femoral arteries. A thermistor tipped catheter for single-thermal indicator dilution measurements (single-thermal, see section 4.2.5) was placed into the right femoral artery which also allowed continuous pressure monitoring, blood sampling and lithium indicator dilution measurements. A thermistor tipped fibreoptic catheter for indocyanine green-thermal double indicator dilution (ICG-thermal) measurements was placed into the left femoral artery (see section 4.2.4). Introducer sheaths were placed in the left and right jugular veins. A pulmonary artery catheter was introduced into the right jugular vein and a central venous catheter into the left. A midline laparotomy and ileostomy was performed and a number of measurement probes placed for the purposes of the interventional study. Puncture epicystostomy was performed to monitor urine output. After a delay of six hours to allow animal recovery, initial indicator dilution measurements were performed. Faecal peritonitis and septic shock was then induced by the introduction of autologous faeces (0.5 g kg^{-1}) into the abdominal cavity through indwelling abdominal tubes.¹⁰⁹ Once noradrenaline was commenced the experimental animals were randomized into one of various groups for the interventional study. The observation period continued for another 24 hours in each group during which three further indicator dilution measurements were made at twelve, eighteen and twenty four hours. The experimental animals were then sacrificed by injection of intravenous potassium chloride under deep pentobarbital anaesthesia.

4.2.2 Aortic balloon occlusion-induced ischaemia-reperfusion model

Anaesthesia was induced with propofol (3-5 mg kg⁻¹) and ketamine (1-2 mg kg⁻¹) and maintained with propofol (6-8 mg kg⁻¹ hr⁻¹) and remifentanyl infusions (15-20 µg kg⁻¹ hr⁻¹).¹¹⁰ Ringers lactate solution was infused at 10 ml kg⁻¹ hr⁻¹ for the duration of the study. Intra-venous hydroxyethylstarch was given at the anaesthetist's discretion intra-operatively and infused at 250 ml hr⁻¹ starting two hours prior to aortic occlusion until the end of the study at eight hours of reperfusion. Introducer sheaths were placed in the right and left femoral arteries for placement of balloon catheters to facilitate aortic occlusion at the level of the left subclavian artery and the aortic bifurcation. The right and left internal jugular veins were exposed for the introduction of pulmonary artery and central venous catheters respectively. The right carotid artery was exposed for placement of two introducer sheaths for the ICG-thermal and single-thermal catheters as well as arterial pressure monitoring. The lithium sensitive electrode was attached to the single-thermal catheter as per the caecal ligation induced sepsis model. Puncture epicystostomy was performed to monitor urine output. For the purposes of the interventional experiment, a delay of two hours after closure of all incisions allowed the animal to be prepared for either placebo or target drug infusions. Following this two hour delay, the aorta was occluded for 30 minutes, with the mean arterial pressure controlled to within 20% of the baseline using continuous glyceryl trinitrate, esmolol and adenosine triphosphate infusions. Noradrenaline was used to maintain mean arterial pressure during the early reperfusion period. After 8 hours the animals were sacrificed by injection of intravenous potassium chloride under deep pentobarbital anaesthesia.

4.2.3 ITBV measurement using lithium indicator dilution

ITBV was measured using lithium indicator dilution as described in section 2.3. However in the aortic balloon occlusion-induced ischaemia/reperfusion model, the external sensor was attached to the carotid arterial catheter because both femoral artery catheters were required for introducing the balloon catheters. The flow of arterial blood across the lithium sensor was regulated using a battery powered peristaltic pump. The time of injection was standardised through the use of visual instructions on the monitor. There were problems initially acquiring the indicator dilution curve with a standard five second countdown and software analysis. Initial attempts resulted in appearance of the lithium indicator dilution curve before activation of the software. Consequently in these experiments a further 10 second delay was implemented to allow data capture by the device.

4.2.4 ITBV & EVLW measurement using the COLD-Z method

ITBV, ITTV and EVLW volume measurements were made using the ICG-thermal indicator dilution technique. (COLD-Z, Pulsion Medical Systems, Munich) detailed in chapter 2, section 2.1.¹¹¹ 10ml of iced 5% dextrose solution containing 25mg ICG was injected via the central venous catheter. Changes in temperature and ICG concentration were detected using a thermistor tipped fiberoptic arterial catheter (Pulsiocath PV 2024 4F, Pulsion Medical Systems) attached to the COLD-Z monitor.

4.2.5 ITBV & EVLW measurement using the PiCCO method

ITBV, ITTV and EVLW volume measurements were made using single-thermal indicator dilution. (PiCCO, Pulsion Medical Systems, Munich) detailed in section 2.2. 10ml of iced normal saline was injected via the central venous catheter.¹¹² Changes in arterial blood temperature were detected by a thermistor tipped arterial catheter attached to the PiCCO monitor.

4.2.6 EVLW measurement using lithium-thermal double indicator dilution

EVLW volume measurement is not possible using the lithium indicator dilution technology as currently designed since only ITBV can be measured. Consequently another method must be used to measure ITTV. The calculation of EVLW volume relies on subtraction of ITBV from ITTV, but this simple mathematical principle can not be applied when these volumes are each measured by different devices. This is due to the variability in cardiac output measurement, however small, which is commonly observed between different techniques. In order to estimate EVLW using the lithium-thermal technique an alternative strategy using MTT must be adopted.

$$ITBV = CO \times MTT_{Li}$$

Equation 4.1 Derivation of ITBV using lithium indicator dilution

ITBV, intrathoracic blood volume; CO, cardiac output; MTT_{Li} lithium indicator mean transit time

$$ITTV = CO \times MTT_{thermal}$$

Equation 4.2 Derivation of ITTV using thermal indicator dilution

ITTV, intrathoracic thermal volume; CO, cardiac output; $MTT_{thermal}$ single-thermal indicator mean transit time

Consequently as $EVLW = ITTV - ITBV$, this equation can be re-written as:

$$EVLW = (CO \times MTT_{thermal}) - (CO \times MTT_{Li})$$

or

$$EVLW = CO_{Li} \times (MTT_{thermal} - MTT_{Li})$$

Equation 4.3 Derivation of EVLW using lithium-thermal double indicator dilution

EVLW, Extravascular lung water volume; ITTV, intrathoracic thermal volume; CO_{Li} , cardiac output measured by lithium indicator dilution; $MTT_{thermal}$ single-thermal indicator mean transit time; MTT_{Li} lithium indicator mean transit time

To negate the variability of cardiac output measurement, the re-written EVLW equation demonstrates that EVLW was calculated by subtracting the MTT of the lithium indicator from the MTT of the COLD-Z thermal indicator which was then multiplied by the cardiac output derived from lithium indicator dilution (see equation 4.3).

4.2.7 Cardiac output measurement

Cardiac output measurement is fundamental to the calculation of EVLW and can be measured using a number of techniques. It is unlikely that the measurements obtained using these different technologies will be identical, and that any variability could be reflected in

the calculation and subsequent comparison of thoracic fluid volumes. The accepted clinical reference standard of cardiac output measurement is thermodilution using a pulmonary artery catheter (PAC). In order to allow sensible comparison between each technique, immediately prior to each measurement point, cardiac output was measured using the PAC with three measurements taken at the end of expiration and averaged using a cardiac output computer (Sat-2; Baxter Edwards Lifesciences, Irvine, USA).

4.2.8 Post-mortem EVLW volume measurement:

Extra-vascular lung water volume was determined using the modified gravimetric method described in section 2.4.

4.2.9 Measurement time points

During the sepsis model, measurements were performed immediately prior to the introduction of autologous faeces into the abdominal cavity, then at 12, 18 and immediately prior to animal sacrifice at 24 hours. Lithium indicator dilution measurements were made a minimum of 25 minutes after discontinuation of the alloferin infusion to avoid any baseline drift of the lithium sensor voltage. During the aortic cross clamp model, measurements were made immediately prior to clamping, then at 1 and 4hrs, and then immediately prior to animal sacrifice at 8 hours after clamp release, giving a total of 4 comparisons with each technique in each model.

4.2.10 Statistical analysis

Assuming a type I error rate of 5% and a type II error rate of 10%, it was estimated that 48 comparisons in 12 animals would be required to detect a 1.0 ml kg^{-1} difference in EVLW volume between the lithium-thermal and indocyanine green-thermal double indicator dilution techniques, assuming a standard deviation of the difference between paired readings of 2 ml kg^{-1} .

ITBV and EVLW volume measurements were compared using the technique of Bland and Altman with comparisons presented as bias ($\pm 95\%$ limits of agreement [LOA]). Percentage error was calculated according to the method reported by Critchley as the limit of agreement ($\pm 2 \text{ SD}$) of the bias divided by the mean CO from the two methods under comparison.¹¹³ Data are presented as mean (SD) where normally distributed, and median (inter-quartile range [IQR]) where not normally distributed. Parametric data were compared using the unpaired t-test and non-parametric data were compared with the Mann-Whitney test. Differences in measurements of EVLW volume, ITBV and CO over time, made using the three study techniques, were compared using repeated measures analysis of variance (ANOVA) with Tukey's correction. Significance was set at $p < 0.05$.

4.3 Results

Twelve animals were included in the interventional experiments during the study period. Comparative data was obtained for all measurement techniques in ten animals, with loss of LiDCO data in one animal due to a damaged cable and another due to loss of lung tissue with the gravimetric technique. Physiological data is shown in table 4.1 illustrating changes in respiratory parameters throughout the study consistent with ALI (n=10) with tables 4.2 and 4.3 showing this data in each model. Data illustrating thoracic fluid volumes throughout the study is shown in table 4.4 and for each model is shown in tables 4.5 and 4.6.

Timepoint	Baseline	2	3	Final	p
Heart Rate (bpm)	70 (\pm 18)	114 (\pm 36)	97 (\pm 46)	95 (\pm 51)	0.12
Mean Arterial Pressure (mmHg)	94 (\pm 11)	91 (\pm 11)	87 (\pm 14)	76 (\pm 17)*	<0.05
PAC Cardiac Output (l min⁻¹)	4.3 (\pm 1.1)	5.4 (\pm 2.1)	4.4(\pm 1.4)	4.0 (\pm 1.2)	0.18
pH	7.55 (\pm 0.04)	7.45 (\pm 0.07)	7.48 (\pm 0.05)	7.46 (\pm 0.07)*	<0.01
PaO₂ (mmHg)	163 (\pm 12)	124* (\pm 21)	117* (\pm 22)	102* (\pm 33)	<0.0001
PaO₂:FiO₂ (mmHg)	465 (\pm 35)	354 (\pm 60)*	335 (\pm 64)*	263 (\pm 129)*	<0.0001
Positive End Expiratory Pressure (cm H₂O)	10 [10-10]	10 [10-10]	10 [10-10]	10 [10-12]	0.55
Peak P_{AW} (cm H₂O)	20 (\pm 2)	23 (\pm 4)	25 (\pm 5)	28 (\pm 7)*	<0.05
Cumulative fluid balance (litres)	3.4 (\pm 2)	7.4(\pm 5.7)	9.4 (\pm 7.7)	13.5 (\pm 6.5)*	<0.01

Table 4.1 Physiological data in both models combined

Data presented as mean (SD) or median [IQR]. PAC, pulmonary artery catheter. * indicates significant changes with respect to baseline values.

Timepoint	Baseline	12 hours	18 hours	24 hours	p
Heart Rate (bpm)	78 (\pm 17)	126 (\pm 32)	125 (\pm 36)	127 (\pm 40)*	<0.05
Mean Arterial Pressure (mmHg)	97 (\pm 10)	94 (\pm 13)	87 (\pm 18)	71 (\pm 20)*	<0.05
PAC Cardiac Output (l min⁻¹)	4.8 (\pm 1.1)	4.4 (\pm 0.8)	4.6 (\pm 1.4)	4.5 (\pm 1.4)	0.94
pH	7.54 (\pm 0.03)	7.50 (\pm 0.03)	7.48 (\pm 0.05)	7.44 (\pm 0.06)*	<0.002
PaO₂ (mmHg)	167 (\pm 15)	125* (\pm 27)	108* (\pm 14)	92** (\pm 16)	<0.0001
PaO₂:FiO₂ (mmHg)	477 (\pm 42)	358 (\pm 78)*	310 (\pm 39)*	234 (\pm 79)**	<0.0001
Positive End Expiratory Pressure (cm H₂O)	10 [10-10]	10 [10-10]	10 [10-10]	12 [10-12]	0.55
Peak P_{AW} (cm H₂O)	21 (\pm 2)	19 (\pm 1)	27 (\pm 4)	31 (\pm 7)*	<0.01
Cumulative fluid balance (litres)	4.8 (\pm 0.9)	11.5 (\pm 3.0)*	14.8 (\pm 4.3)*	17.8 (\pm 4.6)*	<0.0001

Table 4.2 Physiological variables for the sepsis model (n=6)

Data presented as mean (SD) or median [IQR]. PAC, pulmonary artery catheter. * indicates significant changes with respect to baseline values. ** indicates significant changes with respect to baseline and 12 hour values.

Timepoint	Baseline	1 hour	4 hours	8 hours	p
Heart Rate (bpm)	59 (\pm 17)	95 (\pm 38)	55 (\pm 18)	47 (\pm 7)**	<0.05
Mean Arterial Pressure (mmHg)	89 (\pm 12)	86 (\pm 8)	88 (\pm 7)	84 (\pm 9)	0.87
PAC Cardiac Output (l min⁻¹)	3.7 (\pm 1.1)	5.5 (\pm 1.1)	5.1 (\pm 3.8)	3.9 (\pm 1.5)	0.61
pH	7.55 (\pm 0.05)	7.38 (\pm 0.06)*	7.48 (\pm 0.08)	7.49 (\pm 0.08)	<0.05
PaO₂ (mmHg)	157 (\pm 2)	122 (\pm 7)	131 (\pm 28)	119 (\pm 48)	0.26
PaO₂:FiO₂ (mmHg)	448 (\pm 7)	347 (\pm 22)	374 (\pm 80)	305 (\pm 187)	0.3
Positive End Expiratory Pressure (cm H₂O)	10 [10-10]	10 [10-10]	10 [10-10]	10 [10-10]	0.55
Peak P_{AW} (cm H₂O)	19 (\pm 2)	19 (\pm 1)	20 (\pm 1)	22(\pm 4)	0.1
Cumulative fluid balance (litres)	1.2 (\pm 0.2)	1.2 (\pm 0.2)	1.2 (\pm 0.2)	7.2 (\pm 1.2)*	<0.0001

Table 4.3 Physiological variables for the aortic balloon occlusion model (n=4)

Data presented as mean (SD) or median [IQR]. PAC, pulmonary artery catheter. * indicates significant changes with respect to baseline values. ** indicates significant changes with respect to 1 hour values.

Timepoint	Baseline	2	3	Final
Li-thermal ITBV (ml kg⁻¹)	21.8 (± 3.7)	22.2 (± 7.8)	20.6 (± 6.0)	22.4 (± 6.3)
ICG-thermal ITBV (ml kg⁻¹)	30.7 (± 8.1)	28.7 (± 3.7)	28.1 (± 3.7)	27.0 (± 4.3)
Single-thermal ITBV (ml kg⁻¹)	27.1 (± 7.4)	23.0 (± 5.0)	22.4 (± 5.9)	26.4 (± 5.3)
Gravimetric EVLW volume (ml kg⁻¹)	-	-	-	9.2 (± 3.0)
Li-thermal EVLW volume (ml kg⁻¹)	5.9 (± 5.1)	7.4 (± 9.0)	6.6 (± 6.2)	7.5 (± 6.5)
ICG-thermal EVLW volume (ml kg⁻¹)	4.7 (± 2.3)	6.7 (± 3.4)	5.5 (± 3.3)	7.7 (± 3.7)
Single thermal EVLW volume (ml kg⁻¹)	13.3 (± 6.3)	12.3 (± 2.1)	11.5 (± 2.5)	15.5 (± 4.7)

Table 4.4 Thoracic fluid volumes (n=10)

Data presented as mean (SD). Li-thermal, lithium-thermal double indicator dilution; ICG-thermal, indocyanine green-thermal double indicator dilution; single-thermal, single-thermal indicator dilution; ITBV, intrathoracic blood volume; EVLW, extravascular lung water volume.

Timepoint	Baseline	12 hours	18 hours	24 hours
Li-thermal ITBV (ml kg⁻¹)	20.0 (± 3.7)	17.7 (± 3.5)	17.0 (± 4.4)	19.8 (± 5.5)
ICG-thermal ITBV (ml kg⁻¹)	32.8 (± 8.4)	30.8 (± 8.6)	28.8 (± 4.4)	28.2 (± 4.1)
Single-thermal ITBV (ml kg⁻¹)	28.5 (± 8.4)	20.3 (± 2.7)	20.8 (± 3.2)	24.6 (± 4.8)
Gravimetric EVLW volume (ml kg⁻¹)	-	-	-	9.8 (± 3.6)
Li-thermal EVLW volume (ml kg⁻¹)	8.8 (± 4.0)	12.0 (± 8.4)	8.5 (± 6.3)	9.1 (± 6.7)
ICG-thermal EVLW volume (ml kg⁻¹)	4.9 (± 2.7)	6.7 (± 3.1)	5.6 (± 3.5)	7.9 (± 4.3)
Single thermal EVLW volume (ml kg⁻¹)	14.0 (± 8.3)	11.3 (± 1.8)	10.0 (± 1.3)	13.5 (± 3.3)

Table 4.5 Thoracic fluid volumes for the sepsis model (n=6)

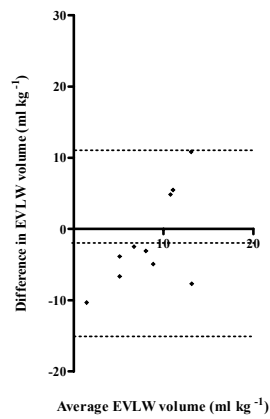
Data presented as mean (SD). Li-thermal, lithium-thermal double indicator dilution; ICG-thermal, indocyanine green-thermal double indicator dilution; single-thermal, single-thermal indicator dilution; ITBV, intrathoracic blood volume; EVLW, extravascular lung water volume.

Timepoint	Baseline	1 hour	4 hours	8 hours
Li-thermal ITBV (ml kg⁻¹)	24.5 (± 3.3)	29.0 (± 7.6)	26.0 (± 3.6)	25.7 (± 6.2)
ICG-thermal ITBV (ml kg⁻¹)	27.5 (± 7.5)	25.5 (± 1.7)	27.0 (± 2.4)	25.5 (± 4.7)
Single-thermal ITBV (ml kg⁻¹)	25.0 (± 6.2)	27.1 (± 5.1)	24.7 (± 8.7)	29.3 (± 5.7)
Gravimetric EVLW volume (ml kg⁻¹)	-	-	-	8.3 (± 3.1)
Li-thermal EVLW volume (ml kg⁻¹)	1.6 (± 3.1)	0.4 (± 4.4)	3.7 (± 5.5)	8.7 (± 3.9)
ICG-thermal EVLW volume (ml kg⁻¹)	4.5 (± 2.0)	6.7 (± 4.5)	5.4 (± 3.5)	7.4 (± 3.5)
Single thermal EVLW volume (ml kg⁻¹)	12.1 (± 1.9)	13.8 (± 1.8)	13.8 (± 2.1)	18.8 (± 5.3)

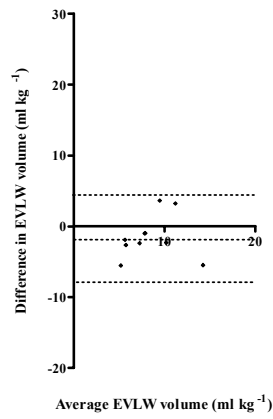
Table 4.6 Thoracic fluid volumes for the aortic balloon occlusion model (n=4)

Data presented as mean (SD). Li-thermal, lithium-thermal double indicator dilution; ICG-thermal, indocyanine green-thermal double indicator dilution; single-thermal, single-thermal indicator dilution; ITBV, intrathoracic blood volume; EVLW, extravascular lung water volume.

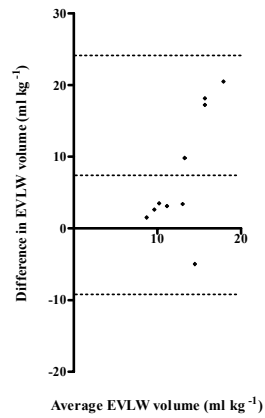
Mean EVLW volume as measured by gravimetry was $9.2 [\pm 3.0] \text{ ml kg}^{-1}$ ($n=10$). Bland-Altman comparisons between Li-thermal, ICG-thermal, single-thermal and gravimetric EVLW volume measurements are presented in figure 4.1. Linear regression analysis against the reference gravimetric measurements identified a poor correlation with each of the three indicator dilution techniques (Li-thermal r^2 0.03, $p=0.65$; ICG-thermal r^2 0.31, $p=0.09$; single-thermal r^2 0.17, $p=0.23$) (figure 4.2). All three techniques showed considerable bias and limits of agreement when compared to the gravimetric technique (table 4.7). Li-thermal and ICG-thermal underestimated EVLW volume (Li-thermal $7.45 [\pm 6.5] \text{ ml kg}^{-1}$, ICG-thermal $7.7 [\pm 3.4] \text{ ml kg}^{-1}$, $p=0.67$) compared to the gravimetric technique, whereas there was overestimation with the single-thermal technique ($17.3 [\pm 6.9] \text{ ml kg}^{-1}$, $p<0.01$).



Li-thermal v gravimetric
 Bias -1.8 ml kg^{-1} (± 6.7), 95% limits
 of agreement $\pm 13.1 \text{ ml kg}^{-1}$



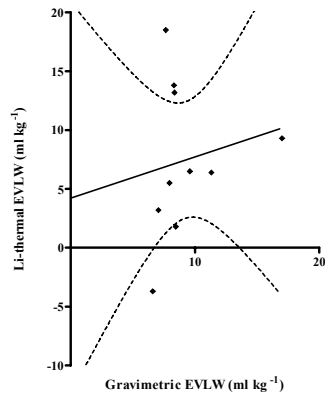
ICG-thermal v gravimetric
 Bias -1.0 ml kg^{-1} (± 3.0), 95% limits
 of agreement $\pm 6.6 \text{ ml kg}^{-1}$



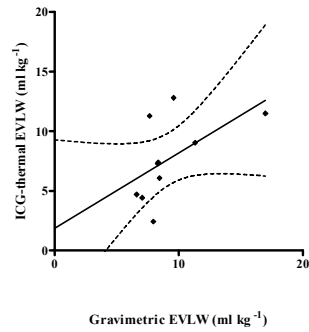
Single-thermal v gravimetric
 Bias $+7.5 \text{ ml kg}^{-1}$ (± 8.5), 95% limits of
 agreement $\pm 16.5 \text{ ml kg}^{-1}$

Figure 4.1 Bland-Altman analysis of Li-thermal, ICG-thermal and single-thermal EVLW vs gravimetric EVLW. Dotted lines indicate bias and limits of agreement.

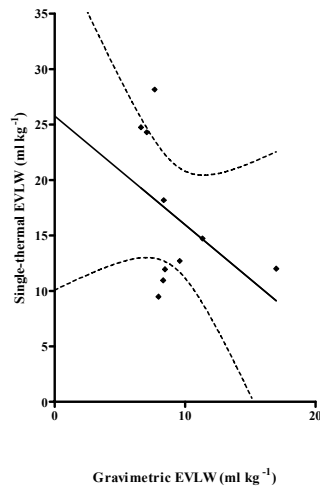
EVLW, extravascular lung water volume; Li-thermal, lithium-thermal double indicator dilution; ICG-thermal, indocyanine green-thermal double indicator dilution; single-thermal, single thermal indicator dilution



Li-thermal v gravimetric



ICG-thermal v gravimetric



Single-thermal v gravimetric

Figure 4.2 Linear regression analysis of Li-thermal, ICG-thermal and single-thermal EVLW vs gravimetric EVLW

Dotted lines indicate 95% confidence intervals for gradient. EVLW, extravascular lung water volume; Li-thermal, lithium-thermal double indicator dilution; ICG-thermal, indocyanine green-thermal double indicator dilution; single-thermal, single thermal indicator dilution

	Li-thermal	ICG-thermal	single-thermal
Bias (ml kg⁻¹)	-1.8	-1	8.5
LOA (ml kg⁻¹)	±13.1	±6.6	±14.5

Table 4.7 Bias and limits of agreement of Li-thermal, ICG-thermal & single-thermal v gravimetric EVLW.

LOA, limits of agreement; Li-thermal, lithium thermal double indicator dilution; ICG-thermal, indocyanine green-thermal double indicator dilution; single-thermal, single thermal indicator dilution; ITBV, intrathoracic blood volume; EVLW, extravascular lung water volume

Comparison of Li-thermal and single-thermal measurements of EVLW volume to the ICG-thermal technique demonstrated considerable variability for both techniques. However there was notable overestimation with the single-thermal technique. Bland-Altman analysis is shown in figure 4.3.

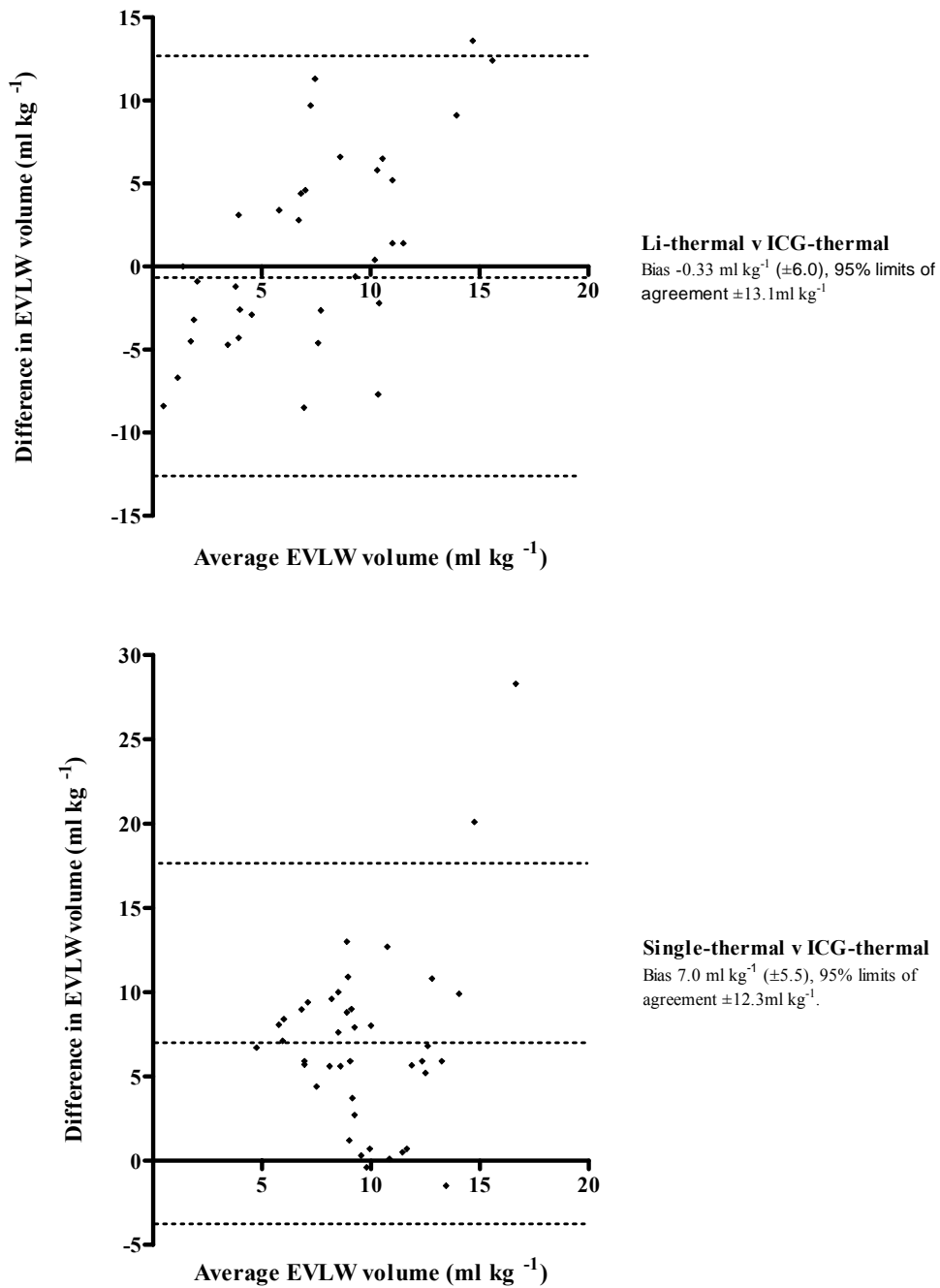


Figure 4.3 Bland-Altman analysis of Li-thermal and single-thermal EVLW vs ICG-thermal EVLW.

Dotted lines indicate bias and limits of agreement.

EVLW, Extravascular lung water volume; Li-thermal, Lithium thermal double indicator dilution; ICG-thermal, Indocyanine Green-thermal double indicator dilution; single-thermal, single thermal indicator dilution.

Both the Li-thermal and single thermal techniques significantly underestimated measurement of ITBV with considerable variability when compared to the ICG-thermal technique, as shown in figure 4.4.

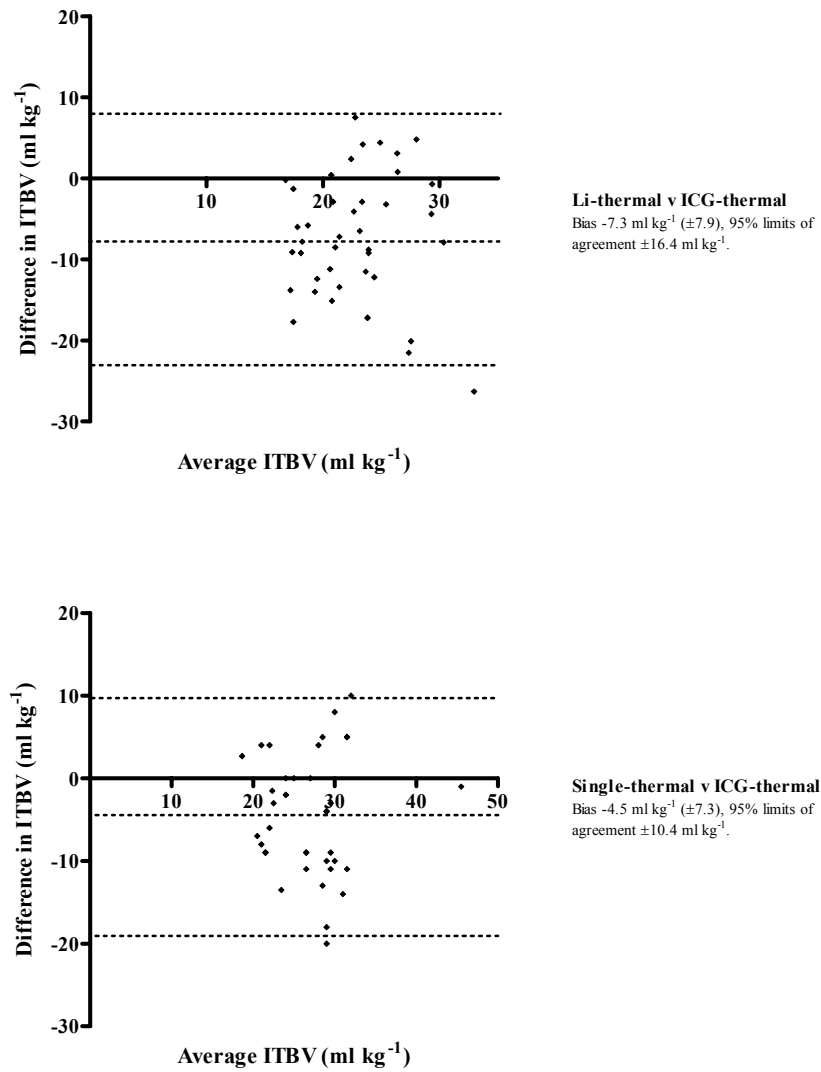


Figure 4.4 Bland-Altman analysis of Li-thermal and single-thermal ITBV vs ICG-thermal ITBV.

Dotted lines indicate bias and limits of agreement.

ITBV, Intrathoracic blood volume; Li-thermal, Lithium thermal double indicator dilution; ICG-thermal, Indocyanine Green-thermal double indicator dilution; single-thermal, single thermal indicator dilution.

Lithium indicator dilution measurements of cardiac output compared well to those taken with the PA catheter whilst both ICG-thermal and single thermal measurements were significantly greater (figure 4.5, n=40). Comparison between lithium and the single-thermal techniques with ICG-thermal double indicator dilution showed considerable inaccuracy and variability (see table 4.8).

	Li-thermal	single-thermal
Bias (l min⁻¹)	-1.5	-1.0
LOA (l min⁻¹)	±2.65	±1.95

Table 4.8 Bias and limits of agreement of Li-thermal & single-thermal v ICG-thermal CO.

LOA, limits of agreement; Li-thermal, lithium thermal double indicator dilution; ICG-thermal, indocyanine green-thermal double indicator dilution; single-thermal, single thermal indicator dilution; CO, cardiac output.

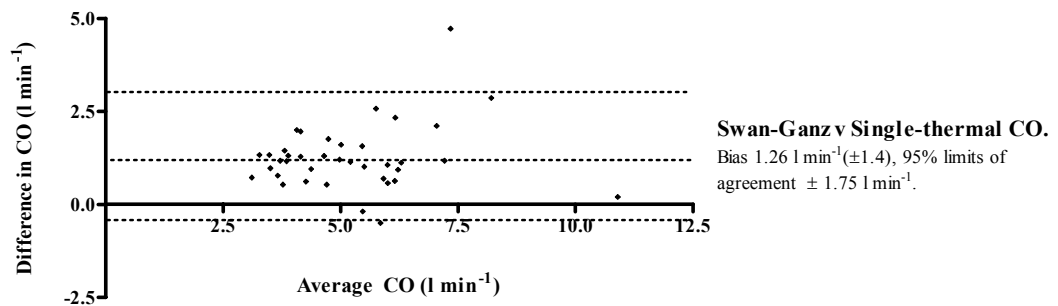
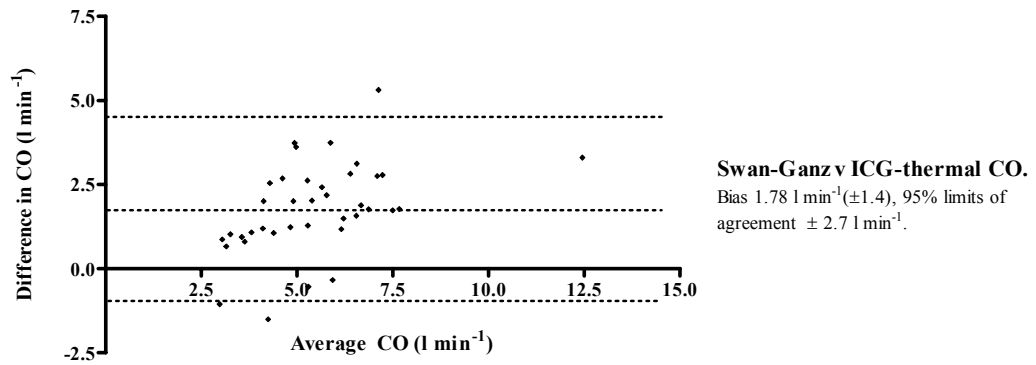
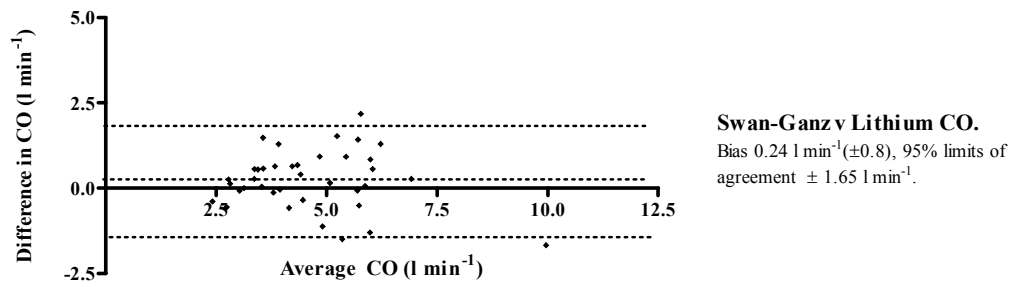


Figure 4.5 Bland-Altman analysis of Li-thermal, ICG-thermal and Single-thermal CO vs PA catheter

CO. Dotted lines indicate bias and limits of agreement.

CO, cardiac output; PA catheter, pulmonary artery catheter; Li-Thermal, lithium thermal double indicator dilution; ICG-thermal, indocyanine green-thermal double indicator dilution; Single-thermal, single thermal indicator dilution

4.4 Discussion

4.4.1 Summary of findings

When compared to the gravimetric method, the Li-thermal and ICG-thermal techniques demonstrated acceptable accuracy, but the wide limits of agreement suggested poor reliability. The single-thermal technique systematically over-estimated EVLW, with unacceptably wide limits of agreement signifying very poor reliability.

4.4.2 Comparison to previous work

The gravimetric technique has been used to measure EVLW volume in a number of laboratory models of acute lung injury (ALI) and sepsis.^{47,48,61,64,114} These studies used either intravenous lipopolysaccharide to induce a septic response or direct instillation of oleic acid to induce ALI. Consistent with these studies, we found that sepsis and ALI were associated with an increased EVLW volume, (9.2 [\pm 3.0] ml kg⁻¹), compared to sham operated animals (6.6 [\pm 0.45] ml kg⁻¹).⁶¹ Reported EVLW as measured with the ICG-thermal technique in control animals (3.9 [\pm 1.2] ml kg⁻¹) is comparable with the pre-intervention measurement in this study (4.8 [\pm 2.1] ml kg⁻¹).⁴⁷ Other studies have used Bland-Altman analysis to compare EVLW volume measurement using ICG-thermal double indicator dilution with gravimetry.^{47,48} These investigators reported a bias of 5.8 (\pm 7.7) ml kg⁻¹⁴⁷ and 5.2 (\pm 1.8) ml kg⁻¹⁴⁸, figures which are comparable with the ICG-thermal data from this study.

EVLW volume determined by the Li-thermal and ICG-thermal techniques (7.45 (± 6.5) and 7.7 (± 3.4) ml kg⁻¹ respectively) were lower than those measured by gravimetry (9.2 [± 3.0] ml kg⁻¹). This is consistent with a report suggesting that the ICG-thermal dilution technique may underestimate EVLW compared to gravimetry.¹¹⁵

4.4.3 Limitations of this study

There are several potential limitations of this study. Whilst manufacturers' instructions were meticulously followed, it is possible that these techniques perform less well in animals than in humans. Moreover, in the visceral ischaemia model, ICG-thermal and single-thermal catheters had to be placed more proximally via the carotid artery, not the femoral artery as would be standard practice. It could be argued however, that this would lead to more accurate measurements of ITBV and hence EVLW, as the catheter tips are sited within the thoracic cavity in the arch of the aorta. Ideally, the indicator sampling point should be at the border of the thoracic cavity to ensure the measured value of MTT is as close as possible to the true physiological value. The indocyanine green-thermal indicator dilution system utilises a thermistor tipped fiberoptic arterial catheter inserted percutaneously via the femoral artery to lie at the level of the diaphragm. The technology used to perform lithium indicator dilution measurement of ITBV however, uses an external sensor attached to a peripheral arterial catheter rather than an internal sensor within a large artery. Consequently, for lithium indicator dilution, the measured value of MTT incorporates the true value and two additional values. The first of these is the time taken for the indicator to travel from the margin of the thoracic cage to the arterial catheter. The second value is the time taken for the indicator to transit from the catheter to the lithium

sensor, a value known to be 13.3 seconds. A bench study demonstrated that the time taken for an indicator bolus to transit the distance from the thoracic cavity border to a peripheral artery should be no more than two seconds.¹¹⁶ This assumed constant delay was incorporated into the calculation of ITBV and hence EVLW.

The underestimation of EVLW volume by indicator dilution may be greater in the presence of ALI, perhaps due to redistribution of pulmonary blood flow away from oedematous areas which is thought to limit indicator diffusion and the consequent detection of oedema.⁴⁷⁻⁵⁰ Another possible explanation is the inability of the indicator to penetrate all lung tissue, particularly congested alveoli, in one trans-pulmonary circulation time. Use of positive end-expiratory pressure (PEEP) during mechanical ventilation has also been shown to affect the accuracy of EVLW volume measurement by indicator dilution.⁵¹ In addition, other studies have suggested that increased cardiac output can result in underestimation of EVLW by ICG-thermal dilution^{52,53}, although there is evidence that resolution of specific technical problems with the equipment can eliminate this error.⁵⁴ More recent work has demonstrated that thermal indicator loss from oedematous lungs does not affect the accuracy of cardiac output measurement by indicator dilution.¹¹⁷

The use of post-mortem gravimetry as the reference method for evaluating EVLW has several limitations.^{34,118} It is predominantly an experimental technique, and being a post-mortem method, only one measurement is possible. The comparison of gravimetric values for EVLW volume with results obtained using other techniques can be influenced by the time elapsed from death to removal of the lungs, and by pathophysiological changes in the lungs after cardiac arrest. Thus, the gravimetric technique can underestimate EVLW

volume because of partial reabsorption of fluid before excision of the lungs. If this were the case, accuracy of the double indicator dilution techniques would worsen whereas accuracy of the single-thermal technique might be enhanced.

4.4.4 Potential sources of error

Estimation of EVLW volume by any indicator dilution technique requires accurate measurement of both MTT and CO. Measurement of CO using lithium indicator dilution has been well validated in both humans and animals in a variety of situations and compares well with PA catheter derived values of CO (Bias +0.24 [± 1.65] l min⁻¹).^{87,91,92,119-121} Comparison of CO measurement by the Li-thermal and ICG-thermal techniques revealed considerable bias and LOA (-1.5 [± 2.7] l min⁻¹) which was also apparent in the comparison of ITBV determined by the same techniques (Bias -7.3 [± 16.4] ml kg⁻¹). It is therefore reasonable to assume that the observed differences values for ITBV and hence EVLW are at least in part due to the differences in CO measurement, given that the ICG-thermal technique compared poorly to the PA catheter (Bias +1.8 [± 1.4] l min⁻¹). However there were also observed differences in the MTT of the two indicators (Bias 0.1 [± 9.9] sec) suggesting indicator transit time to the lithium sensor, most likely from the thoracic border to the arterial catheter, contributed to the observed variability of ITBV and hence EVLW volume measurement.

4.4.5 Conclusions

There were clinically relevant differences between EVLW volume measurements obtained with three in vivo indicator dilution techniques and the gravimetric method. Whilst none of the techniques could be considered ideal, the double indicator methods appear to be more accurate than the single-thermal indicator technique. Further investigation of the prototype Li-thermal technology and comparison with ICG-thermal double indicator dilution in human subjects might improve accuracy and precision.

Chapter 5

Estimation of extra-vascular lung water volume measurement by lithium-thermal indicator dilution in man: Comparison of two clinical techniques

5.1 Introduction

In the proof of concept study, the measurement of intra-thoracic blood volume (ITBV) by trans-pulmonary lithium indicator dilution appeared feasible (chapter 3). The results of this pilot study suggested that this method might allow accurate measurement of ITBV. However, in the porcine model of acute lung injury, both existing indicator dilution methods of EVLW volume measurement and the prototype Li-thermal method compared poorly to the post mortem gravimetric technique (chapter 4). Given the initial promise of the clinical proof of concept study, confirmation of the findings of the laboratory study were required in man. From the data generated by the ICG-thermal technique it is also possible to assess measured versus derived values of ITBV and EVLW and whether the GEDV:ITBV relationship is valid.

The aim of this study was to compare the indocyanine green-thermal (ICG-thermal), lithium-thermal (Li-thermal) and single-thermal indicator dilution techniques of EVLW volume measurement in patients following elective cardiac surgery with cardio-pulmonary

bypass. The GEDV:ITBV relationship used by the commercially available single-thermal device to derive EVLW was also examined (see section 2.2).

5.2 Methods

5.2.1 Patients

This single centre, observational study was prospectively approved by the Local Research Ethics Committee. Patients aged over 50 years undergoing elective cardiac surgery with cardio-pulmonary bypass were eligible for recruitment according to pre-defined criteria. Patients were screened for eligibility prior to surgery, and written informed consent obtained. Exclusion criteria were refusal of consent, concurrent lithium therapy, pregnancy and weight less than 40 kg. Patients with acute arrhythmias, severe peripheral vascular disease, significant cardiac valvular regurgitation and intra-aortic balloon counterpulsation were also excluded as these conditions could affect indicator forward flow.

5.2.2 Clinical Management

Anaesthetic and cardiopulmonary bypass practices were standardised as described for the pilot study, chapter 3, section 3.2.2. An 18G femoral arterial sheath was sited on arrival to the Intensive Care Unit (ICU) through which a COLD-Z catheter (PV 2024 4FG; Pulsion Medical Systems, Munich, Germany) could be positioned at the level of the diaphragm for ICG-thermal indicator dilution measurements (figures 2.4 & 2.8). Patients were managed on the ICU following surgery, where sedation was discontinued and the tracheal tube removed by clinical staff according to local protocols.

5.2.3 ITBV & EVLW measurement using lithium indicator dilution

Paired measurements were taken 1, 2, 4 and 24 hours after surgery using the methods described in chapter 2, section 2.3 and chapter 3, section 3.2.3. EVLW volumes were calculated using the method described in section 4.2.6.

5.2.4 EVLW& ITBV measurement using the ICG-thermal method

ITBV, ITTV and EVLW volume measurements were made using the ICG-thermal indicator dilution technique. (COLD-Z, Pulsion Medical Systems, Munich) detailed in chapter 2, section 2.1.¹¹¹ 20ml of iced 5% dextrose solution containing 25mg ICG was injected via the central venous catheter. Changes in temperature and ICG concentration were detected using a thermistor tipped fiberoptic arterial catheter (Pulsioath PV 2024 4F, Pulsion Medical Systems) attached to the COLD-Z monitor.

5.2.5 Derived single thermal indicator dilution ITBV & EVLW

Measurement of intrathoracic blood volume using single thermal indicator dilution ($ITBV_{\text{thermal}}$) relies on the hypothesis that $ITBV_{\text{thermal}}$ is 25% greater than global end diastolic volume (GEDV).⁵⁸ GEDV is the difference between intrathoracic thermal and pulmonary thermal volumes (ITTV & PTV) as determined by analysis of the thermal curve using the Stewart-Hamilton and Newman equations.^{36,37,43} This allows $EVLW_{\text{thermal}}$ to be derived from ITTV & $ITBV_{\text{thermal}}$ by subtraction. GEDV and ITBV are measured as part of the ICG-thermal technique, therefore allowing comparison of measured and derived values of ITBV and EVLW.

5.2.6 Statistical analysis

ITBV was chosen for sample size calculations as this is the key measurement difference between the Li-thermal and ICG-thermal techniques. Assuming a type I error rate of 5% and a type II error rate of 10%, it was estimated that 20 patients would be required to detect a change in ITBV of 1.5 ml kg^{-1} , standard deviation (SD) 4 ml kg^{-1} . Data are presented as mean (SD) where normally distributed and median (IQR) where not normally distributed. The comparison between ITBV & EVLW measured with lithium indicator dilution, ICG-thermal double indicator dilution and derived data was evaluated using the technique of Bland and Altman. Percentage error was calculated according to the method reported by Critchley, as the limit of agreement ($\pm 2 \text{ SD}$) of the bias divided by the mean CO from the two methods under comparison.¹¹³ Parametric data were compared using the unpaired t-test and non-parametric data were compared with the Mann-Whitney test. Differences in the measurement of EVLW, ITBV and CO made with each technique at each timepoint were compared using repeated measures analysis of variance (ANOVA) with Tukey's correction. Comparison of ITBV and MTT with temperature were analysed by linear regression. Significance was set at $p < 0.05$.

5.3 Results

5.3.1 Patient and equipment data

Seventeen patients were recruited between July and September 2007 after which the supply of specialist COLD-Z arterial catheters was exhausted and further catheters could not be sourced from the UK supplier. There was also failure of the COLD-Z machine caused by worn-out components in the infra-red light emitting hardware. This was irretrievable as repair or replacement parts are not available. The baseline characteristics of these patients are presented in table 5.1 with physiological data shown in table 5.2. After four patients, the final measurement timepoint had to be moved from 24 to 6 hours owing to problems obtaining good quality ICG curves with patient movement on awakening from surgery and the clinical need to remove the femoral arterial catheter for post-operative mobilisation. 16 ICG measurements were excluded because of the poor quality of the ICG indicator dilution curve which did not allow reliable analysis of ITBV or MTT. The COLD-Z machine defaulted to the thermal curve in these situations for the measurement of CO, ITBV and EVLW. This left a total of 52 paired comparisons with good quality data. There were no poor quality lithium curves on post-hoc analysis to affect MTT measurement or CO derivation.

n	17
Age	69 years (± 9)
Gender	15 male
Weight	82 kg (± 19)
Parsonnet score	10 (± 8)
Duration of cardio-pulmonary bypass	74 minutes (± 17)
Coronary artery bypass graft	13
Aortic valve replacement	2
Coronary artery bypass graft and aortic valve replacement as combined procedure	2

Table 5.1 Baseline patient characteristics

Data presented as mean (SD)

Time	1 hours	2 hours	4 hours	6 hours	<i>p</i>
MAP (mm Hg)	71 (±4)	71 (±7)	79 (±9)**	75 (±8)	<0.05
CVP (mm Hg)	12 (±4)	12 (±3)	13 (±4)	11 (±3)	0.52
PaO₂ (kPa)	14.8 [13.1-18.5]	15.3 [13.6-19.9]	15.2 [11.5-17.8]	13.7 [11.5-14.8]	0.22
PaO₂:FiO₂ (kPa)	34 (±10)	37 (±7)	36 (±14)	34 (±9)	0.9
Core Temperature (°C)	36.3 (±0.5)	36.5 (±0.6)	36.9* (±0.5)	37.2*** (±0.5)	<0.0001
Peripheral temperature (°C)	30.6 (±2.0)	31.6 (±2.0)	32.8* (±1.7)	33.1* (±1.6)	<0.05
Temperature difference (°C) (Core-peripheral)	5.4 (±2.2)	4.6 (±2.1)	3.9 (±1.8)	3.5 (±2.0)	0.05
Cumulative fluid balance (ml)	1903 [1740-2631]	2578 [1969-2908]	3015* [2294-3379]	3457* [2621-4506]	<0.001

Table 5.2 Physiological variables (n=14).

Data presented as mean (SD) or median [IQR]. MAP, mean arterial pressure; CVP, central venous pressure. * indicates significant changes with respect to 1 hour values. ** indicates significant changes with respect to 2 hour values.

5.3.2 Thoracic volume and cardiac output data

EVLW data is presented in table 5.3 and figure 5.1. Mean EVLW volume as measured by the ICG-thermal technique was $4.6 (\pm 1.9) \text{ ml kg}^{-1}$ compared to $5.3 (\pm 1.4) \text{ ml kg}^{-1}$ for the single-thermal method. Measurements taken with the Li-thermal method were clearly erroneous ($-7.6 [\pm 7.4] \text{ ml kg}^{-1}$) and compared poorly to simultaneous measurements made using the ICG-thermal method (Bias $+13.2 [\pm 14.4] \text{ ml kg}^{-1}$). For the single-thermal method, there was more acceptable bias, but limits of agreement remained poor (Bias $-0.3 [\pm 2.3] \text{ ml kg}^{-1}$). Agreement between the ICG-thermal and single thermal methods in terms of percentage change in EVLW between time points was also poor (Bias $2.2 \% [72\%]$).

ITBV data is presented in table 5.3 and figure 5.2. Mean ITBV measured by lithium dilution was $1276 (\pm 367) \text{ ml m}^{-2}$ compared to $859 (\pm 149) \text{ ml m}^{-2}$ by the ICG-thermal method. Comparison between the two techniques, lithium versus ICG-thermal, showed significant bias (407 ml m^{-2}) and wide limits of agreement (± 717). The ITBV data obtained using ICG-thermal double indicator dilution was considerably lower during the post-operative period than those obtained with lithium indicator dilution. However the trend in values obtained by ICG-thermal double indicator dilution increased during this period in contrast to decreasing values for lithium (figure 5.3). Measurements from the single-thermal method ($830 [\pm 169] \text{ ml m}^{-2}$) compared better to the ICG-thermal technique ($859 [\pm 149] \text{ ml m}^{-2}$) with minimal bias and LOA ($25.3 [\pm 108] \text{ ml m}^{-2}$).

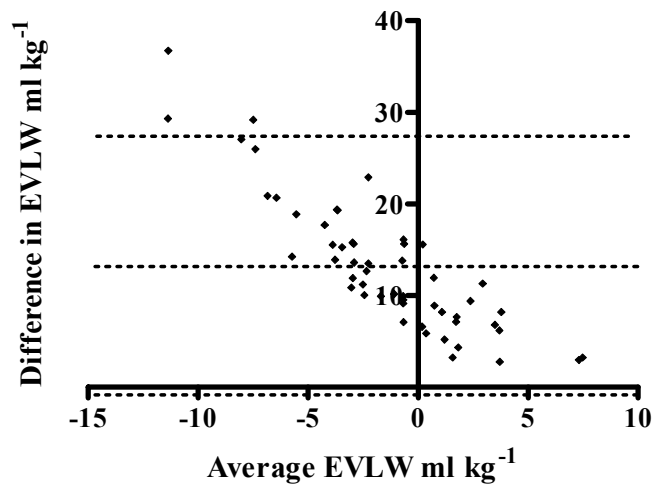
Errors in the Li-thermal data resulted from a considerable over-estimate of ITBV, due in turn to an over-estimate of MTT (see table 5.4). Analysis of mean transit time (MTT)

measurement demonstrated considerable inconsistencies (Bias 12.8 [\pm 13] sec) (figure 5.4). Cardiac index, the other component variable of ITBV was similar between the two techniques (Bias 0.39 [\pm 0.9] l min⁻¹ m⁻², p<0.0001, figure 5.5). Analysis of individual time points suggested the ITBV and MTT difference decreased over time (477 to 289ml m⁻², p=0.16 and 16.0 to 10.6sec respectively, p<0.05, figures 5.6 & 5.7). Core and peripheral temperatures significantly increased over the same time period, p<0.001 & p<0.05 respectively (figures 5.8 & 5.9). There was no correlation between core:peripheral temperature difference and the measured ITBV ($r^2=0.004$) or MTT difference ($r^2=0.05$).

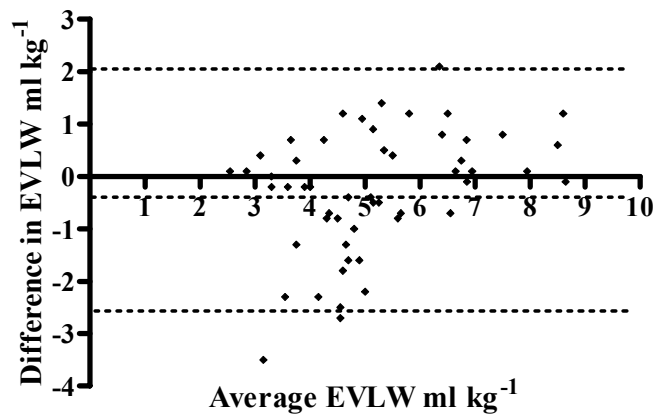
Time	1 hour	2 hours	4 hours	6 hours
ICG-thermal EVLW (ml kg⁻¹)	5.6 (±2.1)	4.6 (±1.9)	5.4 (±2.0)	4.8 (±1.4)
Li-thermal EVLW (ml kg⁻¹)	-7.8 (±5.6)	-9.9 (±5.6)	-7.9 (±10.5)	-6.6 (±7.0)
Single-thermal EVLW (ml kg⁻¹)	5.5 (±1.7)	4.9 (±1.4)	5.6 (±1.4)	5.3 (±1.0)
ICG-thermal ITBV (ml m⁻²)	794 (±165)	856 (±156)	880 (±140)	915 (±146)
Li-thermal ITBV (ml m⁻²)	1271 (±336)	1318 (±350)	1309 (±407)	1203 (±311)
Single-thermal ITBV (ml m⁻²)	777 (±180)	827 (±129)	880 (±175)	880 (±170)
ITBV difference (ml m⁻²) (Li-ICG)	477 (±288)	462 (±298)	429 (±401)	289 (±318)

Table 5.3 Measurements of EVLW and ITBV at individual time points using three different methods of indicator dilution (n=14).

Data presented as mean (SD). Li-thermal: lithium-thermal indicator dilution; ICG-thermal: indocyanine green-thermal indicator dilution; Single-thermal, single-thermal indicator dilution; ITBV, intrathoracic blood volume; EVLW, extravascular lung water volume.



Li-thermal v ICG-thermal
 Bias 13.2ml kg⁻¹, 95% limits of agreement ±14.4ml kg⁻¹.

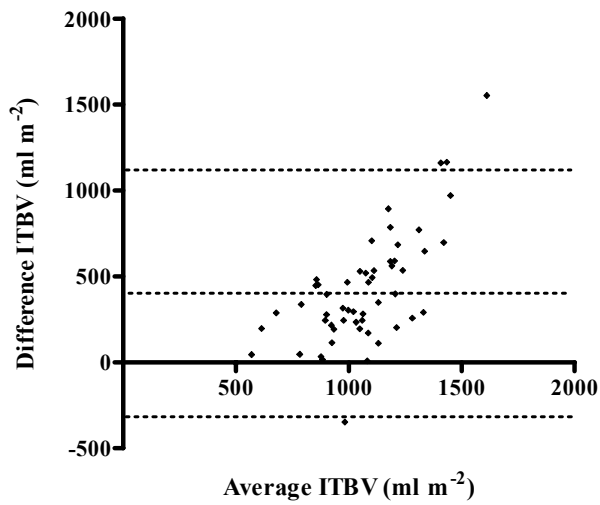


Single-thermal v ICG-thermal
 Bias -0.3ml kg⁻¹, 95% limits of agreement ±2.3ml kg⁻¹.

Figure 5.1 Bland-Altman analysis of Li-thermal and single-thermal EVLW vs ICG-thermal EVLW.

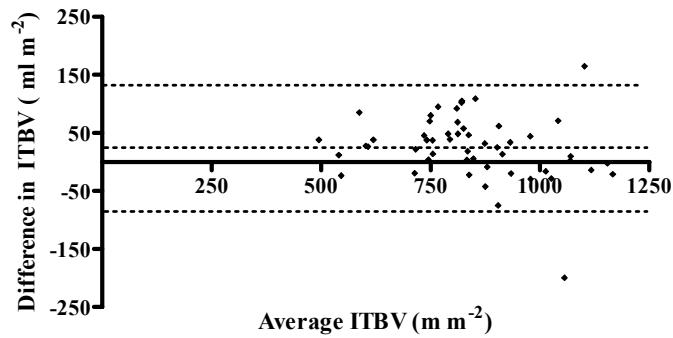
Dotted lines indicate bias and limits of agreement.

EVLW, Extravascular lung water volume; Li-thermal, Lithium thermal double indicator dilution; ICG-thermal, Indocyanine Green-thermal double indicator dilution; single-thermal, single thermal indicator dilution.



Li-thermal v ICG-thermal

Bias 407 ml m⁻², 95% limits of agreement ±717ml m⁻².



Single-thermal v ICG-thermal

Bias 25 ml m⁻², 95% limits of agreement ±108 ml m⁻².

Figure 5.2 Bland-Altman analysis of Li-thermal and single-thermal ITBV vs ICG-thermal ITBV.

Dotted lines indicate bias and limits of agreement.

ITBV, Intrathoracic blood volume; Li-thermal, Lithium thermal double indicator dilution; ICG-thermal, Indocyanine Green-thermal double indicator dilution; single-thermal, single thermal indicator dilution

Time	1 hour	2 hours	4 hours	6 hours
Li-thermal MTT (seconds)	35.1 (±8.1)	33.2 (±4.6)	29.4 (±7.2)	28.7 (±5.5)
ICG-thermal MTT (seconds)	19.0 (±3.4)	18.5 (±3.6)	17.8 (±3.3)	18.1 (±3.4)
MTT difference (seconds) (Li-ICG)	16.1 (±8.5)	14.5 (±4.4)	11.5 (±6.8)	10.6 (±5.8)
Li-thermal cardiac index (l min⁻¹ m⁻²)	2.3 (±0.5)	2.4 (±0.6)	2.6 (±0.7)	2.6 (±0.7)
ICG-thermal cardiac index (l min⁻¹ m⁻²)	2.5 (±0.7)	2.8 (±0.6)	3.0 (±0.6)	3.1 (±0.6)

Table 5.4 Measurements of mean indicator transit time (MTT), cardiac index and temperature at individual time points.

Data presented as mean (SD). Li-thermal: lithium-thermal indicator dilution; ICG-thermal: indocyanine green-thermal indicator dilution.

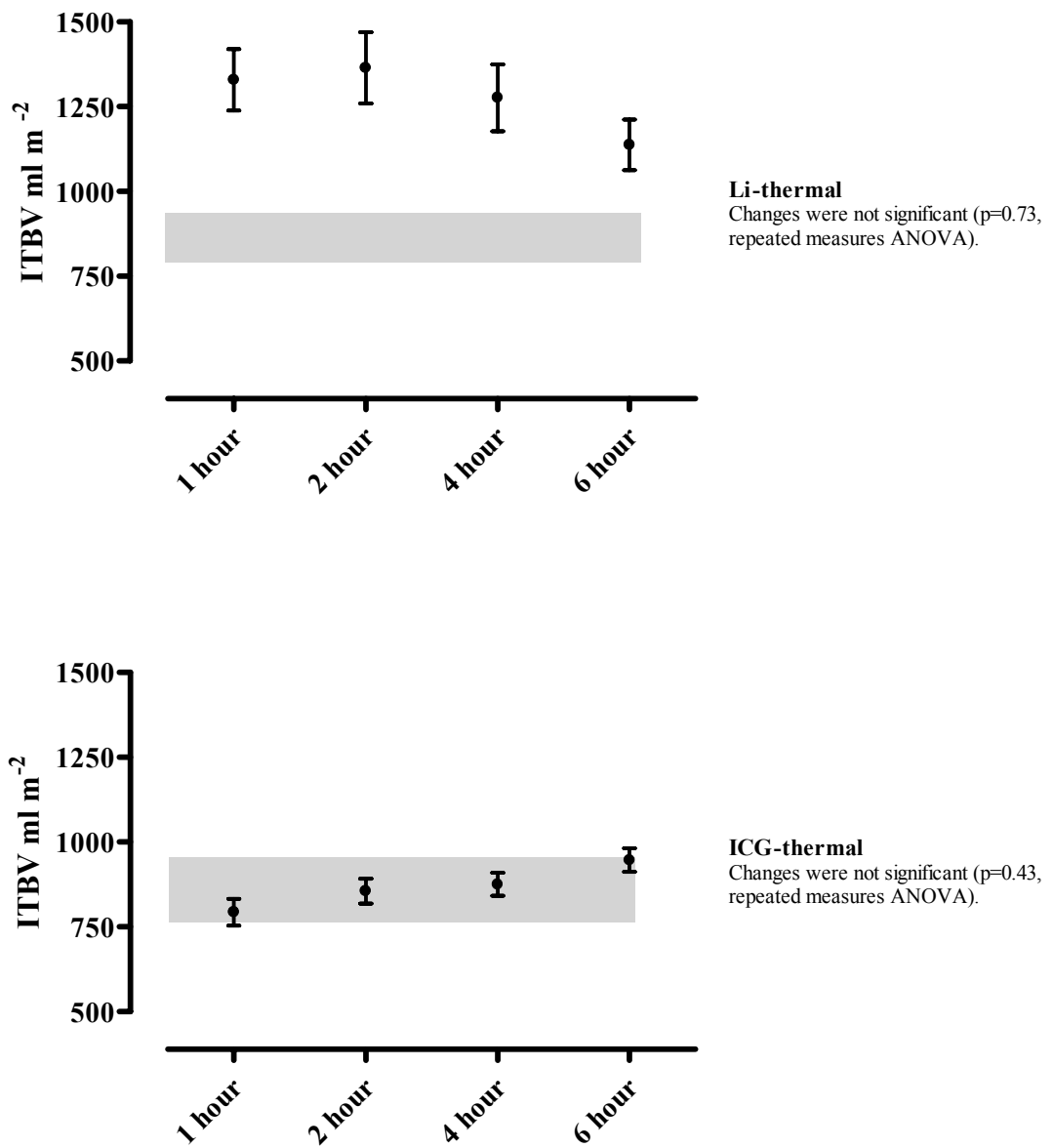


Figure 5.3 ITBV measured by Li-thermal and ICG-thermal at different timepoints. Data presented as mean (SD).

Shaded area indicates normal value of ITBV.

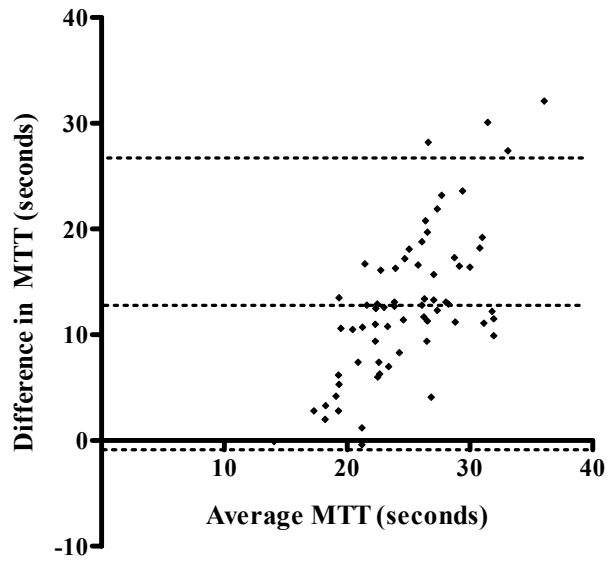


Figure 5.4 Bland-Altman analysis of lithium MTT versus ICG MTT. Bias 12.8 seconds, 95% limits of agreement ± 13 seconds.

Dotted lines indicate bias and limits of agreement. MTT, mean transit time

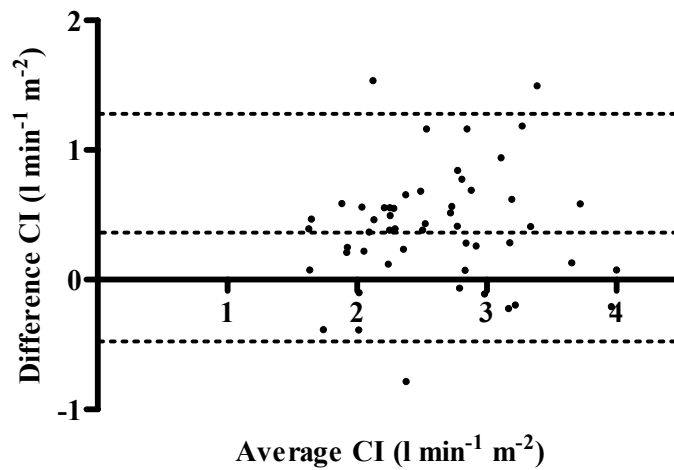


Figure 5.5. Bland-Altman analysis of lithium cardiac index versus ICG cardiac index. Bias $0.39 \text{ l min}^{-1} \text{ m}^{-2}$, 95% limits of agreement $\pm 0.9 \text{ l min}^{-1} \text{ m}^{-2}$.

Dotted lines indicate bias and limits of agreement.

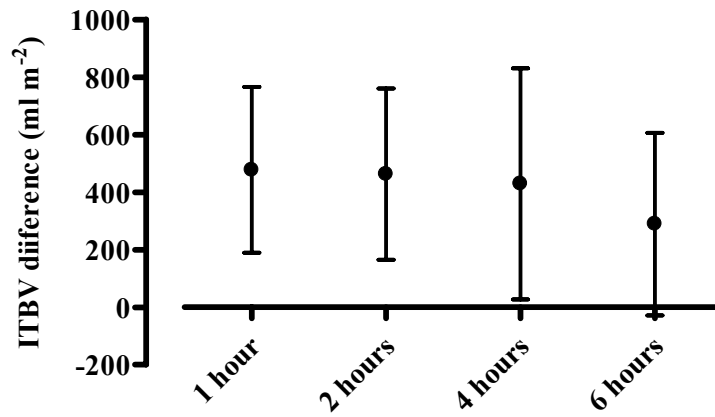


Figure 5.6 Difference in ITBV at different time-points. Data presented as mean (SD).

Changes in ITBV difference were not significant ($p=0.46$, repeated measures ANOVA)

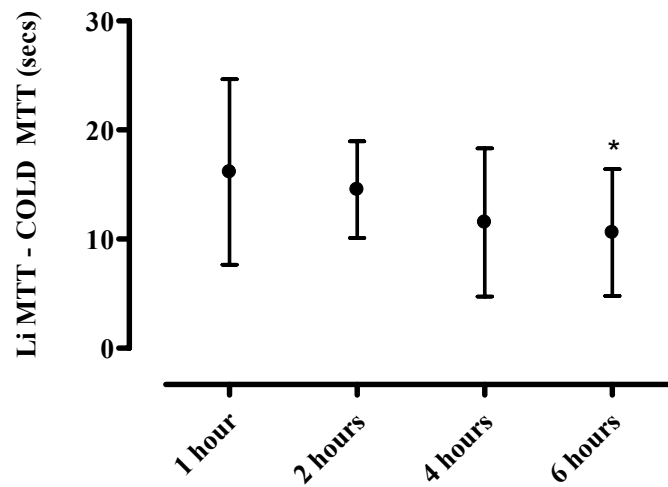


Figure 5.7 Difference in MTT at different time-points. Data presented as mean (SD).

Changes in MTT difference were significant ($p<0.05$, repeated measures ANOVA). * indicates significant changes with respect to 1 hour values.

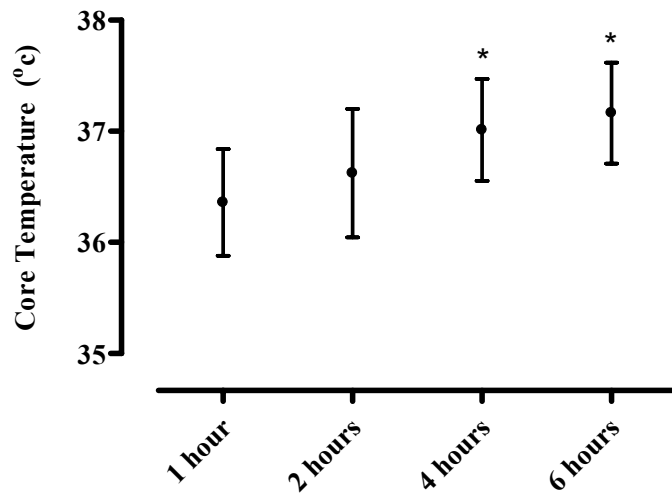


Figure 5.8 Core temperature change at different time-points. Data presented as mean (SD).

Changes in core temperature were highly significant ($p < 0.001$, repeated measures ANOVA). * indicates significant changes with respect to 1 hour values.

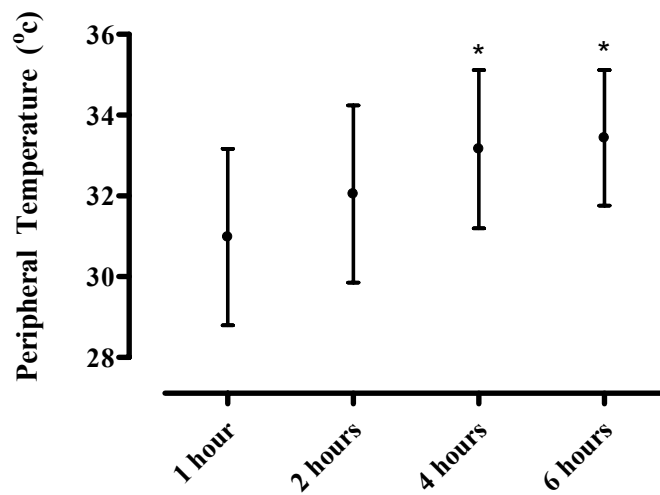


Figure 5.9 Peripheral temperature change at different time-points. Data presented as mean (SD).

Changes in peripheral temperature were significant ($p < 0.05$, repeated measures ANOVA). * indicates significant changes with respect to 1 hour values.

5.4 Discussion

5.4.1 Summary of findings

This study describes a comparison between measurements of EVLW obtained with the prototype lithium-thermal indicator dilution and derived single thermal techniques and the accepted clinical reference standard of ICG-thermal double indicator dilution. The principle finding of this study was that neither the prototype Li-thermal nor the single thermal methods provided acceptable measurements of EVLW volume when compared to the ICG-thermal technique. Whilst there was minimal bias associated with the single-thermal method, limits of agreement were approximately 45% of the normal value of EVLW volume. The Li-thermal method performed very poorly due to the over-estimation of mean indicator transit time using an external lithium ion electrode. These data suggest that neither the Li-thermal nor the single thermal method provide measurements of EVLW volume that are sufficiently accurate to guide clinical interventions in individual patients.

5.4.2 Sources of error

Comparison of the Li-thermal and ICG-thermal techniques to the gravimetric measurement of EVLW volume in a porcine model of acute lung injury revealed much closer agreement between the two methods. However, in this investigation, the external lithium ion electrode was attached to a centrally placed femoral or carotid arterial catheter. These data suggest that, for accurate EVLW volume measurement by indicator dilution, blood must be sampled via an arterial catheter sited within the aorta at the level of the diaphragm. ITBV is a product of CO and MTT, therefore the recorded error must be due to difficulties and

potential differences in measuring these two variables. Whilst measurements of cardiac output were similar for the two techniques, there were considerable differences in MTT. As discussed in the methods, for lithium indicator dilution, the measured value of MTT incorporates the true value and two additional values. Flow through the external tubing to the sensor is regulated by the peristaltic pump and can thus be regarded as constant. Data from a previous study suggested that the additional time from the thoracic cage to the radial artery would be approximately two seconds, and this was incorporated into the calculations.¹¹⁶ However, this assumption was clearly incorrect, the delay not only being longer but also variable. This prevented accurate adjustment of the calculation of MTT and hence ITBV.

The variable and inconsistent transit time of the lithium indicator bolus in the peripheral circulation was clearly unexpected. Interestingly however, there appeared to be a reduction in the ITBV difference measured by the two techniques as the study progressed. This coincided with increasing trends in CI ($2.4 - 2.8 \text{ l min}^{-1} \text{ m}^{-2}$, $p=0.2$), core temperature ($36.3 - 37.2^{\circ}\text{C}$, $p<0.0001$) and peripheral temperature ($30.6 - 33.1^{\circ}\text{C}$, $p<0.05$). Unfortunately there was no correlation between ITBV or MTT difference and the core/peripheral temperature difference, indicating that no allowance or adjustment could be made to the algorithm to improve accuracy or reliability.

Consequently it appears that ITBV measurements using lithium indicator dilution detected by an external sensor at the radial artery are unreliable in this patient population due to variable and unpredictable indicator transit time in the peripheral circulation.

5.4.3 Derived ITBV and EVLW volumes

Single thermal indicator dilution measurement of ITBV (as derived from the assumption that $ITBV=(GEDV*1.25)-28.4$) appears to correlate well with ICG-thermal double indicator dilution (Bias 25.3ml m⁻²), in addition to showing minimal variability (LOA±108). However, EVLW calculation using the derived value of ITBV, showed considerable variability (bias -0.27ml kg⁻¹ LOA±2.31), although agreement between the two methods was reasonable. Findings of a previous study comparing the ICG-thermal and single-thermal methods of EVLW volume measurement were inconsistent.⁵⁹ Similarly, in this investigation, there were wide limits of agreement between the single-thermal and ICG-thermal methods. In some cases, adjustment of the single-thermal algorithm is required to account for the individual circumstances of the experiment (as discussed in section 1.4.3).⁶⁰⁻⁶² The credibility of using this technique to make important clinical decisions regarding ventilation and fluid therapy in critically ill patients is therefore questionable.

5.4.4 Conclusions

Both the prototype Li-thermal and the single thermal measurements of EVLW volume showed poor agreement with those obtained using the ICG-thermal method. Poor agreement between the ICG-thermal and Li-thermal techniques appears to be due to inaccurate measurement of lithium mean transit time using an external sensor attached to a peripheral radial arterial catheter. Derived single-thermal EVLW volumes, whilst demonstrating reasonable agreement, showed considerable variability. These findings

suggest that trans-pulmonary indicator dilution measurements of ITBV and EVLW volume are not sufficiently accurate to safely guide clinical interventions in individual patients.

Chapter 6

Dye curve analysis – a comparison of automated versus manual systems

6.1 Introduction

Throughout this series of studies, all comparisons of thoracic volumes measured by indicator dilution, namely ITBV and EVLW, have used data generated by computer analysis of the dilution curve constructed by the three techniques; lithium, ICG-thermal and single thermal. Comparison of the lithium and ICG-thermal techniques in man post-cardiac surgery showed unacceptable bias and LOA, leading to the conclusion that the measurement of ITBV and EVLW using the lithium indicator dilution technology in its existing form is invalid.

The ICG-thermal technique uses computer hardware and software analysis that is almost 20 years old. It was the data generated from this dye curve analysis that was compared to the lithium indicator dilution system which is subjected to a continuing programme of computer hardware and software development. It is possible that the error observed in the clinical study was due in part to inaccurate indicator dilution curve analysis, potentially for both techniques. The aim of this study was to compare cardiac output and thoracic fluid volume data derived manually, with that obtained automatically, to assess any potential

sources of error. I would like to thank Dr Chris Wolff for the considerable input and support he provided with the analysis and methodology described in this chapter.

6.2 Background

Measurement of ITBV and EVLW volume using indicator dilution has its origins in the derivation of cardiac output, a necessary part of the calculations in ascertaining these volumes. Measurement of cardiac output by indicator dilution requires knowledge of the indicator dose given and the area under the concentration curve generated after passage in the blood to a recording device.

$$CO = \frac{D}{A}$$

Equation 6.1 Derivation of cardiac output using indicator dilution

CO, cardiac output; D, indicator dose; A, area under the indicator dilution curve

Deriving the area under a dilution curve is complicated by re-circulating dye that causes distortion of the end of the curve. However this problem can be overcome by evaluating the early part of the downslope which is truly exponential (figure 6.1, upper curve).

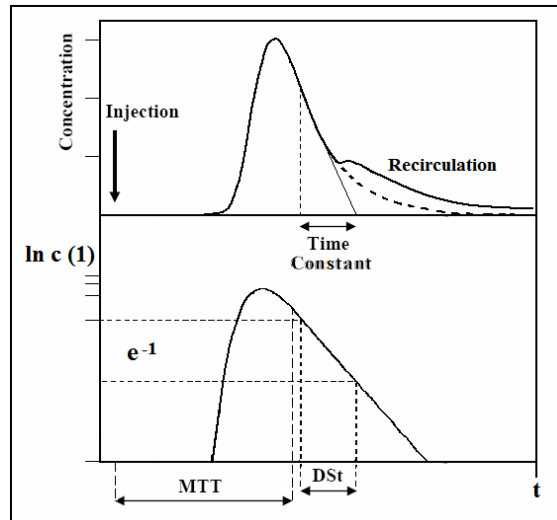


Figure 6.1 Illustration of an indicator dilution curve with re-circulation.

Dotted line highlights exponential part of the curve

The area under such an exponential from a given time point, is the product of the concentration and the time constant, which is gained from the natural logarithm of the curve at this exponential point. The total area under the curve is thus (equation 6.2):

$$A = \int_0^{td} C d\tau$$

Equation 6.2 Evaluation of the area under an indicator dilution curve

A, area under the indicator dilution curve; Td, timepoint up to exponential part of the curve; Cd, indicator concentration; τ, time constant

Clearly manual integration and calculation of the area under the curve is laborious and would be impractical for routine clinical use. Computer software can quickly generate cardiac output data, as proven by the numerous devices available commercially for this purpose. However, for the derivation of thoracic fluid volumes, automated systems have also to measure MTT. In the case of pulmonary blood volume derivation, the software also

has to calculate the downslope time by taking the natural logarithm of the curve and extrapolating a straight line to the x-axis (figure 6.1, bottom curve). It is important that automated dye curve analysis derives accurate and repeatable data as any measurement error, however small, will be multiplied throughout the process of calculating these volumes and could result in significant inaccuracy of the final figures.

6.2 Dye curve analysis

6.2.1 Introduction

Measurements made in the present study were designed to examine CO and derived thoracic fluid volumes postoperatively in patients having cardiac operations for a variety of conditions. Both the LiDCO and COLD-Z machines can store data generated by each measurement, allowing comparison of the results reported by the machine algorithm and analyses of the dye curves made by hand from the stored recordings. This also allowed for examination of the relationship between ITBV and GEDV in a set of patients with different pathology from those studied in the paper by Sakka et al, which led to the development of the single-thermal indicator dilution technique.⁵⁸

6.2.1 ICG-Thermal indicator curve analysis

The seventeen patients (fifteen male, two female) recruited for the clinical study had all the indicator dilution curves that were digitally stored, downloaded onto storage media for processing. The dye curve files were uploaded from the storage media into a laptop computer and imported into Cambridge Electronic display software files (CED, Cambridge, Spike 2, version 6.1.0) for display, and to allow conversion into text files for analysis in

Microsoft Excel spreadsheets. Text files for each time point were imported to Microsoft Excel. There were values from five channels, only three of which contained recorded data; input temperature and output temperature allowing for generation of a thermal dye curve, and indo-cyanine green concentration for generation of the dye curve. Three time intervals are required to allow manual derivation of thoracic fluid volumes:

- 1) Beginning of each dye curve (referred to as the toe of the curve). The thermal and ICG curve onset times were virtually identical.
- 2) Mean transit times, MTT_{thermal} and MTT_{ICG} .
- 3) The time constant values for both thermal and ICG curves, which were independent of the timing of the input curve.

6.2.1.1 Elimination of curve baseline drift

The two raw dye curves (thermal and ICG) were plotted on separate spread sheets. In order to generate the thoracic fluid volume data, it was necessary to eliminate any baseline drift as this could have altered the shape of the curve, and hence the area under the curve and the true MTT. The baseline trend was fitted by copying the section of the baseline that looked most representative, fitting a linear regression line, and then generating a baseline around zero by subtraction (figure 6.2).

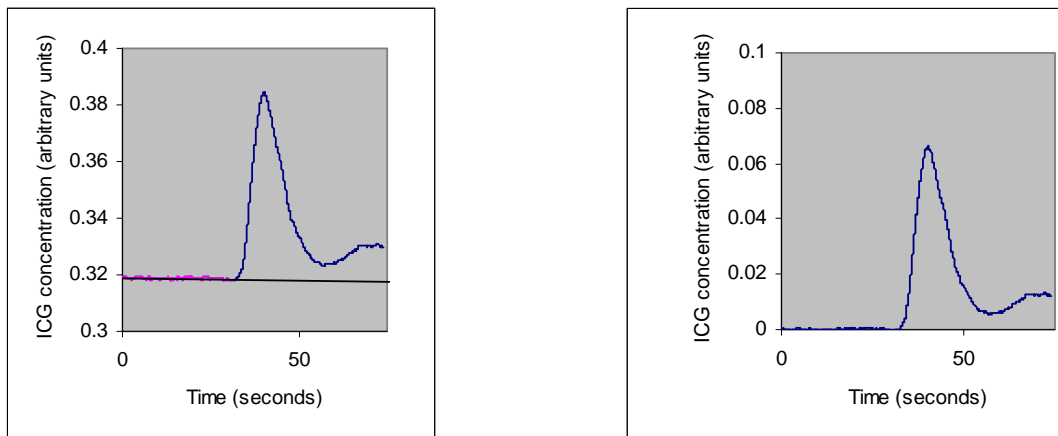


Figure 6.2 ICG dye curve after removal of baseline drift

ICG, Indocyanine green. Left hand figure illustrates curve generated, using study patient data, having been downloaded from the COLD-Z machine and imported into excel using Spike2 software with the baseline drift apparent (pink line). Right hand figure illustrates curve after adjustment to x-axis and removal of baseline drift.

The adjusted plot then acted as the true curve for identification of:

- 1) The onset of mixing; referred to as the toe (beginning) of the dye curve
- 2) The area under the curve up to a point beyond the peak (A1)
- 3) A logarithmic version of the curve to identify the exponential section of the downslope (linear part of the logarithmic curve)
- 4) The area under the remaining part of the curve, not including recirculation (A2)
- 5) Mean transit time – the timing of arrival of the integral at half the total area

6.2.1.2 Deriving the area under the indicator dilution curve

The procedure adopted to obtain the total area under the curve was relatively straightforward. The curve was essentially divided into two, A1 and A2. Area A1 is calculated by integrating from the toe, up to the time point 0.1s prior to timepoint v , which in this example would be 45.5 seconds. A2 is the part of the curve that includes recirculation of dye which needs to be excluded (See figure 6.3).

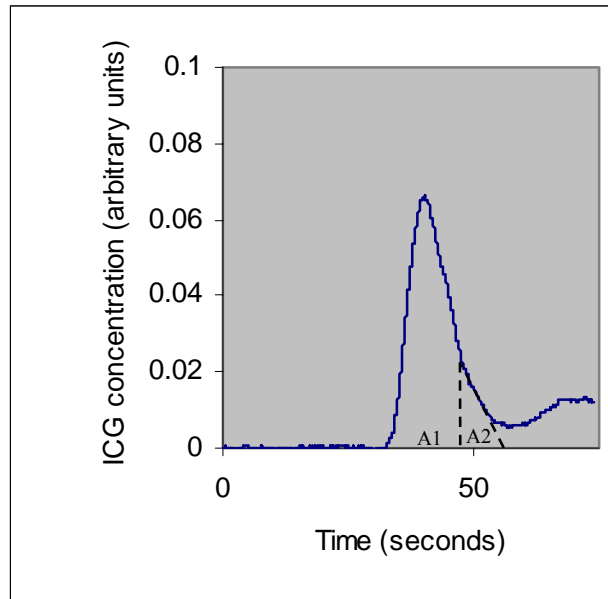


Figure 6.3 Illustration of areas A1 & A2. Total AUC = A1+A2.

AUC, Area under the curve; ICG, Indocyanine Green

This is achieved by adopting a logarithmic version of the curve, inspecting the down-sloping section for a linear section, then fitting a linear regression line (figure 6.4 – pink line).

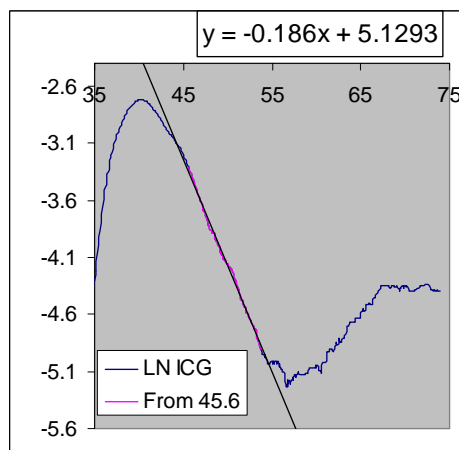


Figure 6.4 Logarithmic ICG dye curve allowing generation of τ and required time points for curve area calculation

ICG, Indocyanine Green; τ , time constant. In this case, τ is 45.6 seconds.

The slope of this line is the rate constant, and its reciprocal the time constant (τ). Taking the value at the time point immediately following A1 (v) then:

$$A2 = v.\tau$$

Equation 6.3 Calculation of A2

A2, area under curve from truly exponential point; v , time point at the start of exponential curve decay; τ , time constant.

Therefore the total area under the curve (AUC) is the sum of A1 and A2.

$$AUC = \int_{v-0.1}^0 + (v.\tau)$$

Equation 6.4 Derivation of total area under the indicator dilution curve

AUC, area under the curve; v , time point at the start of exponential curve decay; τ , time constant.

6.2.1.3 Derivation of MTT and CO

The calculation of the AUC allows derivation of MTT_{icg} and $MTT_{thermal}$ as this is the time at half the total curve area. The thermal curve was used to derive cardiac output with $AUC_{thermal}$ and $MTT_{thermal}$ calculated in identical fashion to that of ICG. The value used as the dose consisted of the input (injectate) volume multiplied by the difference between the input and output temperature. Once the thermal dose had been divided by the total area under the thermal curve, the values from 12 time points on three patients were compared with those given by the machine (algorithm). This gave a scaling factor K (0.0002) which was then used for all calculations of cardiac output and hence, calculation of all thoracic fluid volumes.

$$CO = \frac{VI.(TB - TI).60.K}{AUC}$$

Equation 6.5 Calculation of cardiac output using the thermal dilution curve

CO, cardiac output; VI, volume of injectate; TB, blood temperature; TI, injectate temperature; AUC, area under the curve; K, scaling factor

6.2.2 Lithium indicator curve analysis

The principles applied to ICG-thermal curve analysis also apply to the analysis of lithium curves but with some additional factors that needed to be considered. Initially, the raw lithium curves had a near zero baseline trend fitted by copying the section of the baseline that looked most representative, fitting a linear regression line, and then generating a baseline around zero by subtraction in similar fashion to the ICG analysis (figure 6.5).

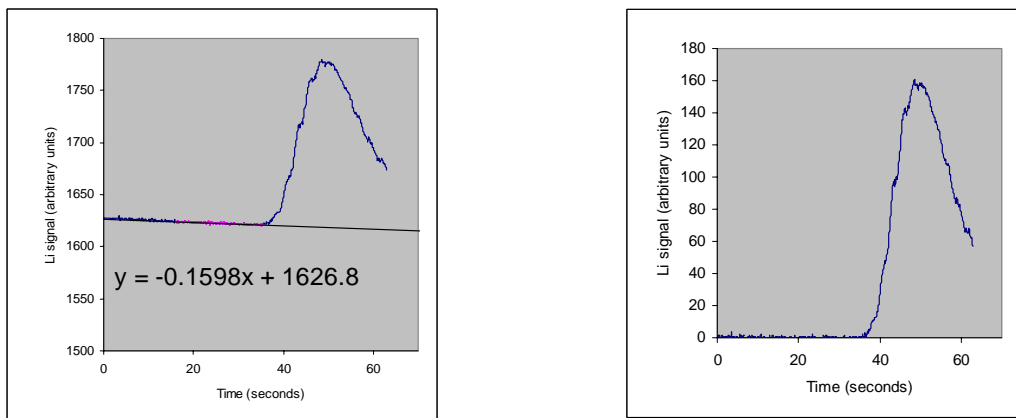


Figure 6.5 Lithium indicator curve after removal of baseline drift

Left hand figure illustrates curve generated, using study patient data, once downloaded from the LiDCO machine and imported into excel with baseline drift apparent (pink line). Right hand figure illustrates curve after adjustment to x-axis and baseline drift removal.

Subsequent conversion of Li units into mV via a machine generated calibration factor (figure 6.6) allows derivation of Li concentration in mM (Li_{mM}) and curve generation.

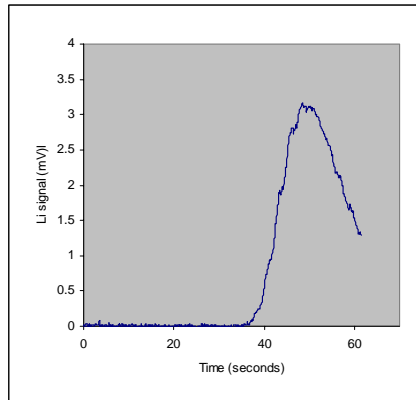


Figure 6.6 Lithium indicator curve demonstrating excess mV

Li, Lithium; mV, millivolts. The excess mV generated by the lithium indicator bolus are incorporated into the following equation that incorporates the presence of Na^+ in the plasma: $\text{Li}_{\text{mM}} = (10^{\wedge} (\text{Excess mV}/61) * \text{Li} \equiv \text{Na}) - \text{Li} \equiv \text{Na} \cdot [\text{Li} \equiv \text{Na} = 140 * (\text{Na}^+_{\text{plasma}}/140)]$.

The calculation of the AUC is then similar to that for the ICG-thermal curves (see sections 6.2.1.1 and 6.2.1.2) and so allows derivation of MTT ,CO (see equation 2.1) and hence ITBV.

6.3 Results

Comparison of automated and manual dye curve analysis was possible for a total of 52 paired lithium, ICG and thermal curves. The key parameters examined were cardiac output (CO), mean transit time (MTT) and intrathoracic blood volume (ITBV). Automated and manual dye curve analysis of extravascular lung water (EVLW) as measured by the ICG-thermal double indicator dilution system was also performed.

Whilst there was minimal bias in the cardiac output data, it was interesting to observe a degree of variability for both techniques (machine v manual); Li bias -0.121 min^{-1} , 95% LOA ± 1.08 , ICG-thermal bias -0.091 min^{-1} , 95% LOA ± 1.6 (figures 6.7 & 6.8).

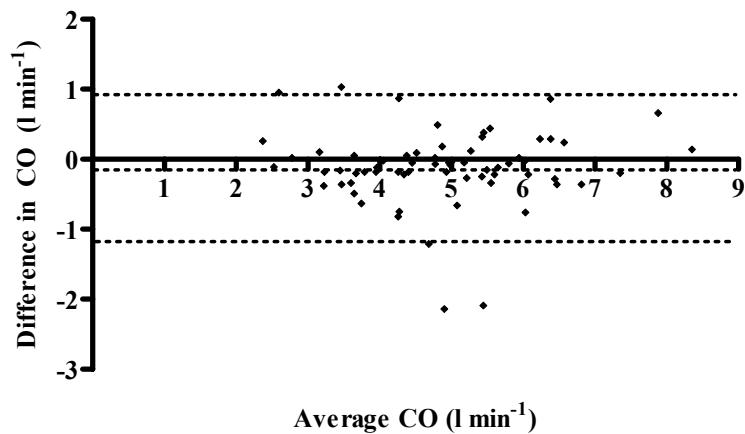


Figure 6.7 Bland-Altman analysis of CO_{machine} versus CO_{manual} derived from lithium indicator dilution curves. Bias -0.11 min^{-1} , 95% limits of agreement $\pm 1.041 \text{ min}^{-1}$.

Dotted lines indicate bias and limits of agreement. CO_{machine} , Cardiac output derived from automated machine analysis. CO_{manual} , Cardiac output derived manually.

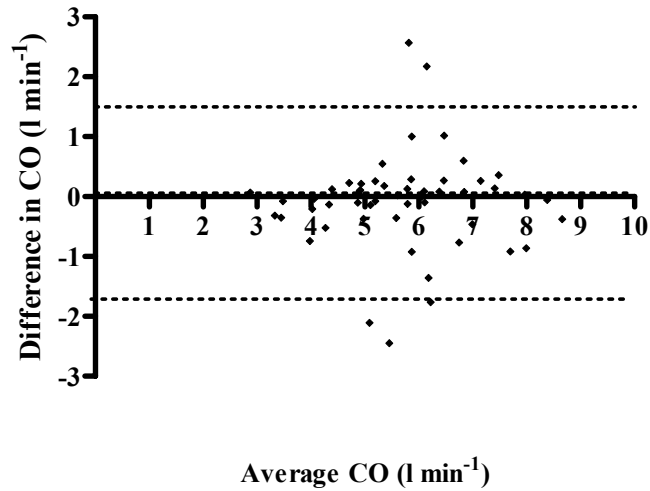


Figure 6.8 Bland-Altman analysis of CO_{machine} versus CO_{manual} derived from indocyanine green-thermal double indicator dilution curves. Bias -0.11 min^{-1} , 95% limits of agreement $\pm 1.61 \text{ min}^{-1}$.

Dotted lines indicate bias and limits of agreement. CO_{machine} , Cardiac output derived from automated machine analysis. CO_{manual} , Cardiac output derived manually.

Manual lithium indicator dilution curve analysis also demonstrated considerable bias and LOA in the measurement of the MTT (Bias -2.8sec , 95% LOA ± 5.2), however the automated ICG-thermal MTT data was much more accurate and less variable for both the ICG and thermal curves (ICG bias 1.7sec , 95% LOA $\pm 1.1\text{sec}$; Thermal bias 2.3sec , 95% limits of agreement ± 2.4) - figures 6.9 - 6.11.

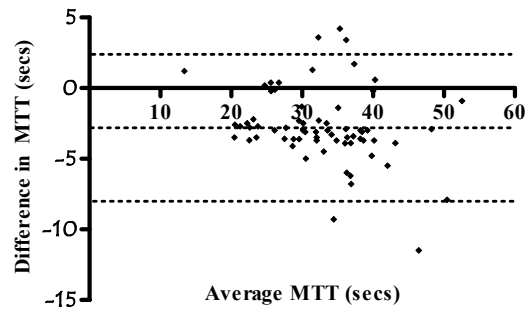


Figure 6.9 Bland-Altman analysis of $MTT_{machine}$ versus MTT_{manual} derived from lithium indicator dilution curves. Bias -2.8sec, 95% limits of agreement ± 5.2 sec.

Dotted lines indicate bias and limits of agreement. $MTT_{machine}$, Mean Transit Time derived from automated machine analysis. MTT_{hand} , Mean Transit Time derived manually.

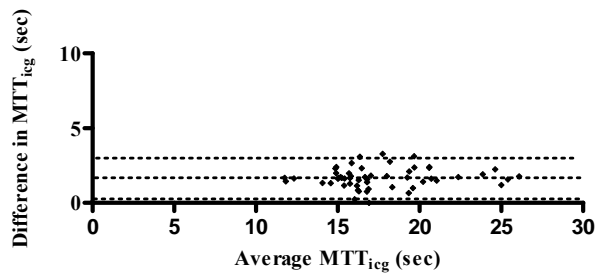


Figure 6.10 Bland-Altman analysis of $MTT_{machine}$ versus MTT_{manual} derived from indocyanine green indicator dilution curves. Bias 1.7sec, 95% limits of agreement ± 1.6 sec.

Dotted lines indicate bias and limits of agreement. $MTT_{machine}$, Mean Transit Time derived from automated machine analysis. MTT_{hand} , Mean Transit Time derived manually.

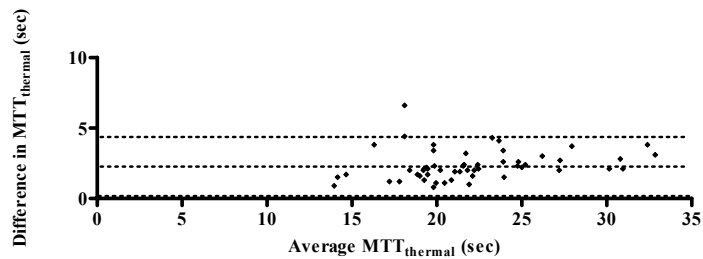


Figure 6.11 Bland-Altman analysis of $MTT_{machine}$ versus MTT_{manual} derived from thermal indicator dilution curves. Bias 2.3sec, 95% limits of agreement ± 2.4 sec.

Dotted lines indicate bias and limits of agreement. $MTT_{machine}$, Mean Transit Time derived from automated machine analysis. MTT_{hand} , Mean Transit Time derived manually.

In keeping with the greater accuracy of the automated analysis compared to manual analysis of CO and MTT for the ICG-thermal technique, ITBV derivation was also more accurate than lithium indicator dilution (ICG-thermal bias 69ml m^{-2} , 95% LOA ± 145 ; Li bias -132ml m^{-2} , 95% LOA $\pm 396\text{ml}$)- figures 6.12 & 6.13). ITTV analysis however revealed considerably less accuracy and more variability (bias 155ml m^{-2} , 95% limits of agreement $\pm 258\text{ml m}^{-2}$) – figure 6.14.

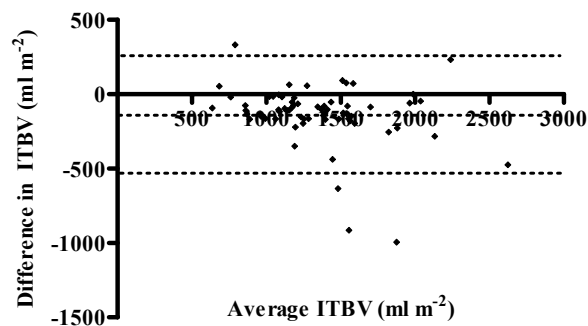


Figure 6.12 Bland-Altman analysis of $\text{ITBV}_{\text{machine}}$ versus $\text{ITBV}_{\text{manual}}$ derived from lithium indicator dilution curves. Bias -132ml m^{-2} , 95% limits of agreement $\pm 396\text{ml m}^{-2}$. Dotted lines indicate bias and limits of agreement. $\text{ITBV}_{\text{machine}}$, Intrathoracic blood volume derived from automated machine analysis. $\text{ITBV}_{\text{hand}}$, Intrathoracic blood volume derived manually.

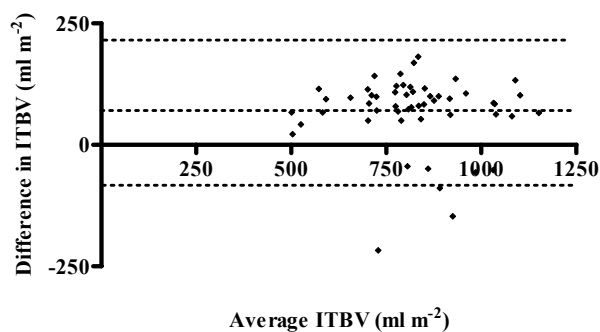


Figure 6.13 Bland-Altman analysis of $\text{ITBV}_{\text{machine}}$ versus $\text{ITBV}_{\text{manual}}$ derived from indocyanine green indicator dilution curves. Bias 69ml m^{-2} , 95% limits of agreement $\pm 145\text{ml m}^{-2}$. Dotted lines indicate bias and limits of agreement. $\text{ITBV}_{\text{machine}}$, Intrathoracic blood volume derived from automated machine analysis. $\text{ITBV}_{\text{hand}}$, Intrathoracic blood volume derived manually.

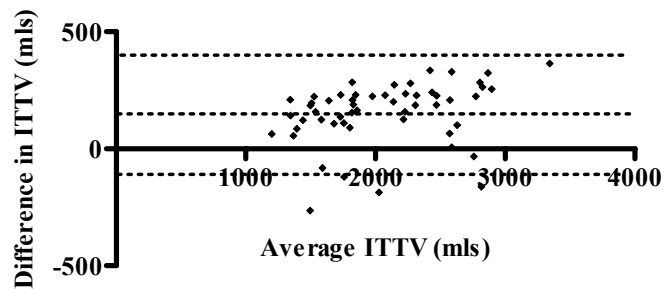


Figure 6.14 Bland-Altman analysis of $ITTV_{\text{machine}}$ versus $ITTV_{\text{manual}}$ derived from thermal indicator dilution curves. Bias 155ml m^{-2} , 95% limits of agreement $\pm 258\text{ml m}^{-2}$.

Dotted lines indicate bias and limits of agreement. $ITTV_{\text{machine}}$, Intrathoracic thermal volume derived from automated machine analysis. $ITTV_{\text{hand}}$, Intrathoracic thermal volume derived manually.

Despite the automated ICG-thermal curve analysis functioning adequately for CO, MTT and ITBV calculation, the observed variability in the derivation of ITTV appears to impact on the derivation of EVLW considerably. The observed bias of automated versus manual analysis was 0.5ml kg^{-1} , with 95% LOA ± 1.3 (figure 6.15).

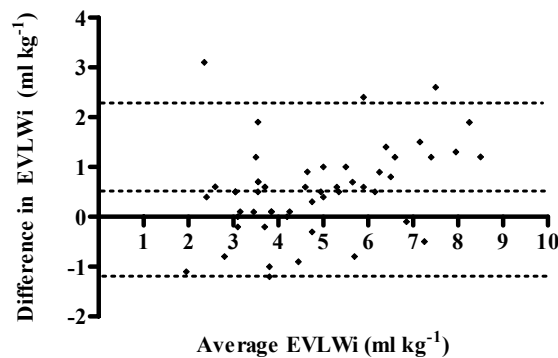


Figure 6.15 Bland-Altman analysis of $EVLW_{\text{machine}}$ versus $EVLW_{\text{manual}}$ derived from the mean transit times of indocyanine green-thermal indicator dilution curves. Bias 0.5ml kg^{-1} , 95% limits of agreement $\pm 1.3\text{ml kg}^{-1}$.

Dotted lines indicate bias and limits of agreement. $EVLW_{\text{machine}}$, Extravascular lung water volume derived from automated machine analysis. $EVLW_{\text{hand}}$, Extravascular lung water volume derived manually.

The equation for EVLW calculation can be rearranged such that it is the difference in the MTT of the thoracic fluid volumes, as measured by the ICG and thermal indicators, multiplied by the CO, rather than the difference in the fluid volumes themselves. This principle can be extended further when considering fluid volumes derived from analysis of the downslope time of the curves. The volumes, PBV and PTV, which can be calculated from ICG and thermal curve analysis respectively, also allow EVLW volume derivation by the same principle. Hence the difference in Dst should yield similar EVLW volumes as the difference in MTT, with the time difference also being comparable. Linear regression analysis of the difference in MTT versus difference in Dst yielded reasonable correlation ($R^2=0.71$, $p<0.0001$). However comparison of EVLW volume derived using MTT or Dst, whilst the bias was minimal (0.1ml kg^{-1}), demonstrated considerable variability (95% LOA ± 2.4), figures 6.16 & 6.17.

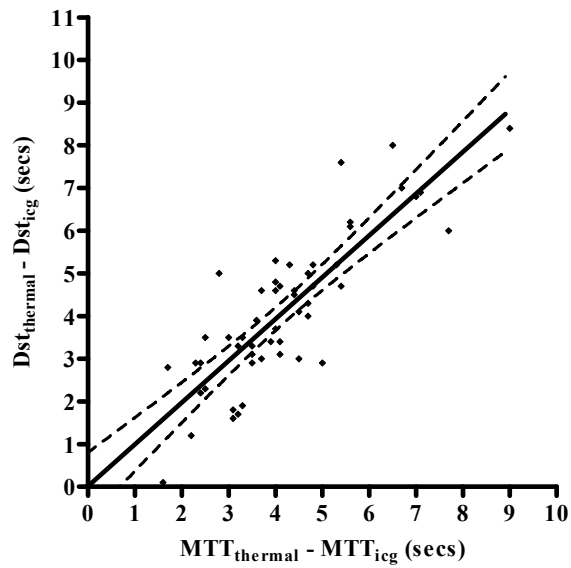


Figure 6.16 Linear regression analysis of the difference in mean transit times versus the difference in downslope times derived from indocyanine green-thermal indicator dilution curves. $r^2=0.71$, $p<0.0001$.

Dotted lines indicate 95% confidence intervals. MTT_{ig} , Indocyanine green mean transit time. $MTT_{thermal}$, Thermal indicator mean transit time. Dst_{ig} , Indocyanine green downslope time. $Dst_{thermal}$, Thermal indicator downslope time.

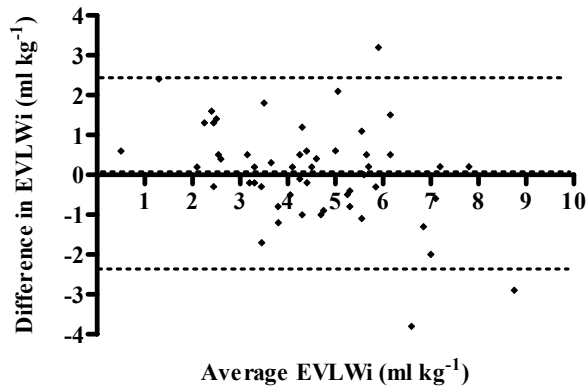


Figure 6.17 Bland-Altman analysis of $EVLW_{MTT}$ versus $EVLW_{Dst}$ derived from indocyanine green-thermal indicator dilution curves. Bias 0.1ml kg^{-1} , 95% limits of agreement $\pm 2.4\text{ml kg}^{-1}$.

Dotted lines indicate bias and limits of agreement. $EVLW_{MTT}$, Extravascular lung water volume derived from mean transit time analysis. $EVLW_{Dst}$, Extravascular lung water volume derived from downslope time analysis

6.4 Discussion

6.4.1 Summary of findings

This study demonstrates that automated dye curve analysis is subject to error. The ICG-thermal curve analysis is sufficiently accurate for the measurement of CO, MTT and ITBV. However, this accuracy is not maintained for all volumes, particularly when the thermal curve contributes to these calculations. The lithium indicator dilution curve software analysis is accurate for measurement of CO but unacceptably inaccurate when deriving MTT and ITBV.

6.4.2 Observed errors

The observed variability of CO measurement seen with both techniques having analysed the curves by hand was unexpected, however the observed errors seen appear unlikely to impact on clinical practice. The bias and wide limits of agreement observed in the measurement of MTT by the lithium indicator (Bias -2.8sec, 95% LOA ± 5.2 sec) highlights the problems with this technique using the current equipment configuration and software analysis. This error appears to be integral to the measurement of ITBV with the bias and LOA (-132 ml m^{-2} [$\pm 396 \text{ ml m}^{-2}$]) also being considerable. It is worth considering that comparison of ITBV, using lithium and the ICG-thermal indicators in the clinical study, generated a bias of 407 ml m^{-2} and $\text{LOA} \pm 717 \text{ ml m}^{-2}$, and whether or not more reliable automated curve analysis could have impacted on this analysis to the point of enhancing the reliability of the technique.

The automated ICG-thermal curve analysis appeared to function adequately for CO, MTT and ITBV calculation with acceptable bias and limits of agreement in the clinical setting. On the other hand there was considerable observed variability for the measurement of ITTV. Consequently there was greater than expected inconsistency in the EVLW volume derivation, with potentially clinically significant errors (Bias 0.5ml kg⁻¹, LOA ±1.3ml kg⁻¹). It is possible to derive EVLW volume from analysis of the difference between either the MTT or Dst of the ICG and thermal curves. Theoretically this time difference should be identical if the dye curve analysis is precise. However, it was possible to demonstrate that, despite good correlation on linear regression analysis ($R^2=0.71$, $p<0.0001$), comparison of the subsequently derived EVLW volumes resulted in considerable variability (Bias 0.1ml kg⁻¹, 95% limits of agreement ±2.4ml kg⁻¹). It is likely that the observed error is a result of problems analysing the downslope of the dye curve, as there was considerable bias and limits of agreement comparing PBV and GEDV (PBV bias -65ml, 95% LOA±186ml, GEDV bias 162ml, LOA ±266ml).

6.4.3 Conclusions

Manual lithium indicator dilution curve analysis highlighted that the poor accuracy of MTT and consequently ITBV seen in the clinical study may in part be due to the software used to analyse the curves. There was also unexpected variability of CO measurement that too may be a result of software problems. ICG-thermal dye curve analysis suggested that thoracic blood volumes derived from measurement of ICG MTT are reliable, but volumes involving analysis of the thermal MTT and downslope times may be inaccurate.

Chapter 7

Conclusions

7.1 Summary of findings

The results of the pilot study were promising and indicated that measuring ITBV by lithium indicator dilution should be feasible. Both peri-operative trends and absolute measurements of ITBV were consistent with previously published data acquired using indocyanine green indicator dilution during and after cardiac surgery with cardio-pulmonary bypass.

The results of the porcine acute lung injury models revealed clinically significant differences between EVLW measurements obtained with three in vivo indicator dilution techniques and the post-mortem gravimetric method. The Li-thermal and ICG-thermal techniques demonstrated acceptable accuracy, but the wide limits of agreement suggested poor reliability. The single-thermal technique systematically over-estimated EVLW, with unacceptably wide limits of agreement signifying poor reliability.

In post-operative cardiac surgery patients there was poor agreement between measurements obtained with both the prototype Li-thermal and the single thermal measurements of EVLW volume, and those obtained using the ICG-thermal. Poor agreement between the ICG-thermal and Li-thermal techniques appeared to be due to inaccurate measurement of lithium mean transit time using an external sensor attached to a peripheral radial arterial catheter. Derived single-thermal EVLW volumes, whilst demonstrating reasonable

agreement, showed considerable variability. These findings suggest that trans-pulmonary indicator dilution measurements of ITBV and EVLW volume are not sufficiently accurate to safely guide clinical interventions in individual critically ill patients regardless of the method used.

7.2 Strengths and weaknesses of this work

Lithium indicator dilution is a proven technology for CO measurement and was compared to the standard reference and clinical techniques used for the measurement of EVLW and ITBV. All indicator dilution measurements made throughout this research programme were performed by the same individual. The cardiac surgical population has been well studied in this area with all patients receiving standardised peri-operative care. The study involving animal models of acute lung injury were performed in a laboratory with over 20 years of experience ensuring the reliability of data collection and the experimental protocol.

Unfortunately, there was a loss of two animals during the gravimetric study. However, given the findings, the effect on study power may not have influenced our conclusion. The gravimetric technique is not commonly used and the derived data is susceptible to operator error despite best efforts. The comparative clinical study suffered irretrievable equipment malfunction with the consequential failure to recruit three further patients. Again, given our findings the results would appear to still be valid.

7.3 Comparison to previous work

7.3.1 Indicator dilution

There were two clinical studies in this research programme during which ITBV and EVLW volumes were determined. In both studies, measurements of ITBV using lithium indicator dilution were consistent with those taken during previous investigations in the cardiac surgical population.^{104,106-108} Direct comparison between studies is not straightforward because previous reports present data indexed either according to body mass or surface area, or as absolute values.^{104,106-108} The peri-operative trends and absolute measurements of ITBV in the present studies were consistent with those taken using indocyanine green indicator dilution during and after cardiac surgery with cardio-pulmonary bypass.¹⁰⁴ However the comparative ICG-thermal measurements made in the second clinical study did not trend as in previous work, nor were the absolute numbers equivalent. This may be due to two factors; operator error in obtaining the data, or differences in the fluid management of post-op cardiac surgical patients. This may not have been measured appropriately by the lithium indicator technique due to the intrinsic problems of MTT measurement and the trend in the proof of concept study may have been coincidental.

7.3.2 Gravimetry

Although considered by some to be the ‘gold standard’, the gravimetric method of EVLW volume measurement has some limitations.^{34,118} Only one post-mortem measurement is possible and fluid re-absorption during the interval between death and lung removal may affect the accuracy of this method. However, the values obtained were similar to those of

previous studies that used the gravimetric technique in models of acute lung injury and sepsis^{48,61} and greater than those in sham operated animals.⁶¹ Similarly, the pre-intervention ICG-thermal measurements of EVLW volume were consistent with those in control animals from a previous study.⁴⁷ Also in keeping with the current study, this previous work suggested that the ICG-thermal dilution technique underestimates EVLW volume when compared to gravimetry.⁴⁷ Such underestimates may be more frequent during acute lung injury or the application of positive end-expiratory pressure.^{48,51} It is not clear why none of the indicator dilution methods proved particularly reliable in comparison to gravimetry. In every case, measurements were carefully performed by experienced investigators according to the manufacturer's instructions. Whilst previous comparisons of the ICG-thermal and single-thermal methods suggest good agreement with gravimetric measurements,^{45,63} other studies have demonstrated a need for adjustment of the algorithm, particularly in laboratory based animal experiments.^{61,64,122}

7.4 General concerns using indicator dilution

An ideal indicator should meet certain criteria that allow it to be used to determine cardiac output and thoracic fluid volumes. These would include uniform distribution throughout the physiological compartment under investigation, no loss from the system during passage from the point of injection to the site of detection, and being stable, non-toxic and easily measured. The indicator should then dissipate rapidly to avoid errors resulting from recirculation. Perhaps not surprisingly, the perfect indicator does not exist. The most common practical disadvantages include poor stability and difficulties with measurement, recirculation or accumulation. Accumulation of the indicator, and concerns regarding

potential toxic effects from elevated plasma levels, usually limit the maximum number of reliable, safe measurements, although as explained earlier, accumulation and recirculation can be potentially overcome by extrapolation of the dilution curve. Hypoxic pulmonary vasoconstriction can result in re-distribution of pulmonary blood flow to relatively spared regions of the lung, whilst areas of lung with high water content may be under-represented, resulting in an underestimate of total EVLW volume.

Of particular concern with the single thermal indicator dilution technique is the loss of the thermal signal as the indicator bolus transits the pulmonary compartment. This causes a small amplitude dilution curve in comparison to the intravascular indicators, such as ICG or lithium, which may compromise the validity of subsequent curve analysis.

Cardiac output measurement error may also result in inaccurate determination of EVLW volume by ICG-thermal dilution,⁵³ perhaps explaining the wide limits of agreement seen in this programme of research. However the findings of a recent investigation suggest thermal indicator loss from oedematous lungs does not affect the accuracy of cardiac output measurement by indicator dilution.¹¹⁷

In one report it has been suggested that the ICG-thermal dilution technique may underestimate EVLW in comparison with gravimetry.¹¹⁵ This underestimation, which may be enhanced during ALI, has been explained by redistribution of pulmonary blood flow away from oedematous areas which is thought to prevent indicator diffusion and the consequent detection of oedema.⁴⁷⁻⁵⁰ Positive end-expiratory pressure (PEEP) during

mechanical ventilation has also been shown to cause underestimation of EVLW volume measurement.⁵¹

At present, trans-pulmonary thermal (single) indicator dilution is the only commercially available method of EVLW volume measurement at the bedside. This technique involves the estimation of ITBV through the assumption of a constant relationship with GEDV.⁵⁸ Whilst this assumption allows a simplified method of EVLW volume measurement using a single indicator, there is considerable concern regarding the validity of this approach.⁶⁶ This programme of research also questions the assumptions made by this technique in deriving EVLW.

7.5 Suggestions for future work

The outcomes of this thesis have highlighted the need for further work to establish whether the proposed technique of lithium-thermal double indicator dilution for the measurement of EVLW volume is feasible. As it is not possible to measure a thermal signal using an external sensor due to the indicator dilution curve being undetectable, it would appear logical to develop a technique using an intravascular catheter sited in a central artery. This would then negate the problems observed during this programme of research of measuring ITBV using lithium indicator dilution with an external sensor. The simultaneous introduction of a thermistor would enable measurement of EVLW volume. Validation with gravimetry in animal subjects, then comparative studies in human subjects with ICG-thermal double indicator dilution, could verify the accuracy of this proposed technique. It ought then to be possible to instigate clinical studies of goal directed therapy, with ITBV and EVLW

volume as the targets examining a variety of different clinical outcomes in critically ill patients.

7.6 Conclusion

The proposed lithium-thermal double indicator dilution technique for measuring ITBV and EVLW is not accurate in its current configuration. Investigation of existing alternative technologies compared to gravimetry, the reference technique for EVLW volume measurement, suggests double indicator dilution methods are more accurate than the single thermal indicator dilution technique. Indeed, this programme of research suggests that single thermal indicator dilution is not sufficiently reliable to guide clinical decisions for individual patients based on the EVLW volume data acquired with this technique. Theoretically lithium indicator dilution will measure ITBV but it appears measurement is necessary at a more central artery. Combination with a thermal indicator should allow derivation of EVLW volume. As a thermal signal can not be measured using the existing external sensor arrangement, an intravascular catheter would need to be developed which would generate further research opportunities.

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List of abbreviations

ANOVA	analysis of variance
CO	cardiac output
EVLW	extravascular lung water
GEDV	global end diastolic volume
ICG	indocyanine green
ICU	intensive care unit
ITBV	intrathoracic blood volume
ITTV	intrathoracic thermal volume
IQR	interquartile range
LOA	limits of agreement
MTT	mean transit time
PTV	pulmonary thermal volume
SD	standard deviation

Appendix

Original Research

Maddison B, Best T, Wolff C, Jones P, Hinds C, Pearse R. Transpulmonary lithium indicator dilution: a new method of intrathoracic blood volume measurement. *Critical Care* 2007; **11** (Suppl 2): 295

Maddison B, Giudici R, Calzia E, Wolff C, Hinds C, Radermacher P, Pearse RM. Extravascular lung water volume measurement by a novel lithium-thermal indicator dilution method: comparison of three techniques to post-mortem gravimetry. *Intensive Care Med* 2008; **34** (11): 2106-2111

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Review Articles

Maddison BJ, Best T, Pearse RM. Measurement of extravascular lung water. *Yearbook of Intensive Care and Emergency Medicine* 2007 (Springer-Verlag)