An investigation to show the effect of lung fluid on impedance cardiac output in the anaesthetized dog

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Background. Accumulation of lung fluid in the critically ill patient is believed to attenuate impedance cardiac output (COIC) measurements. However, this phenomenon has never been shown experimentally.

Methods. In eight anaesthetized and ventilated dogs (weight 15–22 kg) a high-precision flow probe was placed on the ascending aorta via a left thoracotomy incision and the direct cardiac output (COFP) was measured. Simultaneous COIC measurements were made using a RheoCardioMonitor (ACMA, Singapore). Lung oedema was induced by intravenous oleic acid 0.1 mg kg⁻¹. Lung fluid was assessed by the decrease in basal thoracic impedance (Z_b). Percentage errors between the two methods (COIC–COFP) were calculated and compared as Z_b decreased at 1 V intervals.

Results. During the experiment mean Z_b decreased from 35.9 (SD 5.2) to 27.8 (6.5) Ω (P=0.0037). This occurred over a period of 225 (range 112–338) min and Z_b decreased by 1 Ω every 51 (22–68) min. The presence of excessive lung fluid was confirmed at post-mortem. Before lung oedema was induced, COIC was 1.5 (0.6) litre min⁻¹ and the corresponding value of COFP was 1.5 (0.7) litre min⁻¹ (data from eight dogs). As Z_b decreased, and lung fluid accumulated, the error between COIC and COFP widened (P<0.0001, ANOVA for repeated measures). Eventually, COIC decreased to 0.7 (0.3) litre min⁻¹ and the corresponding value of COFP was 1.2 (0.3) litre min⁻¹ (ΔZ_b=5 Ω, data from six dogs). Mean arterial pressure, central venous pressure and systemic vascular resistance were kept constant.

Conclusion. The presence of lung fluid attenuates COIC measurements with respect to COFP.

Br J Anaesth 2005; 95: 458–64

Keywords: lung, oedema; measurement techniques, cardiac output; model, dog

Accepted for publication: May 31, 2005

Impedance cardiography is a non-invasive method of measuring cardiac output that was developed in the 1970s by Kubicek and modified later by Sramek and Bernstein. It has attracted much interest from researchers and clinicians because of its potential advantages and lack of patient risk compared with other more established, but more invasive, methods of cardiac output measurement such as thermodilution, dye dilution and the Fick method. However, the impedance method was found to lack reliability, as highlighted by a number of papers that showed poor correlations and poor agreement with more accepted methods of cardiac output measurement such as thermodilution. It was found to be particularly unreliable in critically ill patients, who frequently benefit from cardiac output monitoring. Thus impedance cardiography has not been widely accepted by the medical fraternity. A number of explanations for this lack of reliability have been proposed, including excessive lung fluid. Our group has published a number of clinical reports and studies showing that the presence of lung fluid attenuates impedance cardiac output measurements. However, the evidence for this explanation is mainly anecdotal and it has never been rigorously tested in vivo using experimental models of lung oedema.

In the present study we investigated the effects of lung oedema on impedance cardiography measurements. Both impedance and aortic flow probe cardiac output were measured in anaesthetized dogs. Lung oedema was induced by oleic acid. Bias and percentage errors between the two modes of cardiac output measurement were compared as lung oedema developed. Basal transthoracic impedance (Z_b) was used to assess the degree of lung fluid accumulation.
Materials and methods

Anaesthesia and maintenance of homeostasis

Ethical approval for the study was obtained from the Animal Research Ethics Committee, Chinese University of Hong Kong. Male mongrel dogs were provided by the Laboratory Animals Service Centre, Chinese University of Hong Kong. Anaesthesia was induced using intramuscular ketamine (10% (5 mg kg\(^{-1}\)) and xylazine 2% (2 mg kg\(^{-1}\)) and maintained throughout the experiment using inhaled halothane 0.5–1.5% in oxygen, with the level being adjusted to prevent spontaneous movement. The trachea was intubated and the lungs were ventilated with a tidal volume of 10–15 ml kg\(^{-1}\) at a frequency of 12–15 bpm. Intravenous access was secured in the forelimb and used to administer intravenous fluids (warmed saline at 2 ml kg\(^{-1}\) h\(^{-1}\)). The right femoral artery and left internal jugular vein were cannulated to allow monitoring of arterial blood pressure and central venous pressure (CVP). Body temperature was maintained by covering the dog with an insulated blanket.

Placement of flow probe

A thoracotomy was performed at the left fourth intercostal space. The pericardium was incised longitudinally to expose the aortic root. The ascending aorta was separated from the pulmonary artery for 2–3 cm by blunt dissection using the finger. Free fat surrounding the aorta was carefully removed. A snug-fitting flow probe, either 16 or 20 mm A-series ultrasonic probe (Transonic Systems Inc., Ithaca, NY, USA), was placed around the ascending aorta and ultrasonic gel was applied. The probe size was chosen such that it neither compressed the vessel wall nor was loose enough to allow kinking. The probe cable was brought out of the thorax posteriorly. The pericardium was closed with sutures, a chest drain to an underwater seal was inserted, the collapsed lung was re-expanded and the chest wall was closed with sutures.

Blood flow and pressure measurements

Aortic blood flow was measured by the flow probe which used a high-precision four-crystal array. It was connected to a T106 single-channel flowmeter (Transonic Systems Inc., Ithaca, NY, USA) that also processed the transduced arterial blood pressure wave. CVP was measured intermittently using the same transducer. The arterial pressure system was kept patent with a 10 ml h\(^{-1}\) saline infusion. The data were collected on a laptop computer and displayed using the software WinDaq (DataQ Instruments, OH, USA).

Impedance measurements

The impedance method of cardiac output measurement involves detecting the transthoracic impedance to a high-frequency (50–100 MHz) low-amperage (1–5 mA) electric current passed between the neck and lower thorax. The impedance waveform of aortic blood flow during each cardiac cycle is thus detected and impedance variables are measured from the waveform, notably the initial upslope (dZ/dt\(_{\text{max}}\)) which coincides with aortic blood flow and the left ventricular ejection time (LVET). Stroke volume and cardiac output are derived from these variables using the Kubicek equation.\(^{1}\)

In the present study, cardiac output (CO\(_{\text{IC}}\)) and Z\(_{\theta}\) were measured using a RheoCardioMonitor (RheoCardio-Technologies, Singapore). This impedance system consists of six leads which are connected to the subject, a cardiograph module, a visual display unit and a dedicated computer that analyses the signal and stores data. An alternating current (100 kHz, 2 mA) was applied to the thorax of the dogs by two electrodes placed on the head and lower limb. The impedance to this current was detected by two pairs of opposing electrodes placed laterally on the mid-neck and the lower thorax at the level of the diaphragm. Normally surface electrodes are used, but we used subcutaneous needle electrodes to improve skin contact.

Stroke volume (SV) was calculated by the RheoCardioMonitor using a modified Kubicek equation:\(^{16}\)

\[
SV = kp \left( \frac{L}{Z_\theta} \right) \left( \frac{\text{LVET} dZ}{dt_{\text{max}}} \right) + Z_{\theta-q}
\]

where L is the distance between the two current detecting electrodes \(\rho\) is the resistivity of the thorax, \(dZ/dt_{\text{max}}\) is the impedance index of flow and \(Z_{\theta-q}\) compensates for the asynchronicity between the right and left ventricles. These variables are obtained from the impedance waveform.\(^{16}\) The factor K in the calculation represents a complex formula based on the subject’s body habitus.\(^{16}\) The RheoCardioMonitor was calibrated before use by inputting the thoracic length L and the circumferences of the neck and lower thorax into the computer. Cardiac output was derived by multiplying SV by heart rate.

Preparation of oleic acid

Oleic acid (Sigma, St Louis, MO, USA) was stored as frozen oil at \(-20^\circ\text{C}\). The frozen oil was weighed and dissolved by vortexing (gentle shaking) for 20 s in 100% ethanol to produce a 10 mg ml\(^{-1}\) solution.

Induction of pulmonary oedema

After baseline measurements, oleic acid 0.1 mg kg\(^{-1}\) was slowly injected (over 3 min) into the right atrium via the central line to induce pulmonary oedema. Lung oedema developed over 1–2 h, although the rate was variable.

Experimental protocol

Haemodynamic data, including cardiac output measurements comparing the impedance cardiography with the flow probe, were recorded as lung oedema developed. The dogs were kept anaesthetized throughout the experiment. The haemodynamic status was kept as constant as practical throughout the experiment by maintaining a constant CVP of 8–10 mmHg with i.v. boluses of normal saline (100 ml).
The use of drugs that maintain blood pressure and cardiac output were avoided. After several hours the degree of lung oedema became so severe that the dogs could no longer tolerate the circulatory effects and died, which concluded the experiment.

**Data collection and statistical analysis**

Fluid intake and output were recorded. The volume of saline given over the course of the experiment was divided by the duration to give the hourly fluid intake. The dog’s bladder was catheterized and urine collected in a beaker. The urine collected over the course of the experiment was measured and divided by the duration to yield the hourly fluid output.

The following impedance and haemodynamic variables were recorded at 1 min intervals: CO$_{IC}$, Z$_b$, flow probe cardiac output (CO$_{FP}$), mean arterial pressure (MAP) and CVP. The systemic vascular resistance (SVR) was calculated from the equation

$$SVR = \left(\frac{MAP - CVP}{CO_{FP}}\right) \times 80 \text{ dyn s cm}^{-5}.$$  

The decrease in Z$_b$ as lung oedema accumulated was used as an index of lung fluid content. The decrease in CO$_{IC}$ compared with CO$_{FP}$ measurements as lung oedema developed was assessed using bias (CO$_{IC}$–CO$_{FP}$) and percentage error (see below). Bias, CO$_{FP}$ and Z$_b$ were plotted against time for all eight dogs to show how these parameters varied with the development of lung oedema (Fig. 1).

The Z$_b$ data before and after the development of lung oedema were compared using a paired $t$-test. The cardiac output data were grouped into 1 min epochs for statistical purposes. The value of the baseline impedance Z$_{b(i)}$ at the beginning of the experiment was taken as zero. Thus the epochs were 0 to $-1$, $-1$ to $-2$ etc. The value of each CO$_{IC}$ reading was rescaled so that it was in keeping with the magnitude of the baseline CO$_{FP(i)}$ value. This was done by multiplying each CO$_{IC}$ reading by a scaling factor (CO$_{FP(i)}/$ CO$_{IC(i)}$) based on the initial baseline cardiac output values. The percentage error between each set of cardiac output measurements was then estimated using the equation

$$\text{Percentage error} = \left(\frac{\text{CO}_{IC} - \text{CO}_{FP}}{\text{CO}_{FP}}\right) \times 100\%.$$  

(CO$_{FP}$ was used in preference to mean CO as it was deemed to be closer to the true value.) Thus the initial percentage error was reset to zero and gradually became more negative as lung oedema developed. This transformation of the CO$_{IC}$ data facilitated statistical analysis when comparing experiments. As the error data from the eight dogs were not normally distributed, they were presented as box plots with median and quartile values with 5th and 95th percentile whiskers. However, the medians from each Z$_b$ epoch were normally distributed and therefore were analysed using analysis of variance (ANOVA) for repeated measures with Bonferroni post hoc tests. A $P$-value $<0.05$ was considered statistically significant. Results are presented as mean (SD) or mean (range).

**Results**

Data from eight adult male anaesthetized dogs (weight 15–22 kg) are presented. All dogs developed lung oedema after the injection of the oleic acid. This was confirmed at post-mortem, where the macroscopic appearance showed both lungs and pleural cavities filled with fluid. The average fluid intake over the duration of the experiment was 1.2 (range 0.6–1.9 ml) litre or 301 (270–320) ml h$^{-1}$, and urine output was 0.5 (0.3–0.9) litre or 135 (120–150) ml h$^{-1}$

The average duration of data collection after injection of oleic acid and the development of lung oedema was 225 (112–338) min. Z$_b$ decreased by 3–6 Ω during the experiment, i.e. a decrease of 1 Ω every 51 (22–68) min. The absolute value of Z$_b$ decreased from 35.9 (5.2) to 27.8 (6.5) Ω, i.e. a decrease of 22% ($P=0.0037$).

The haemodynamic status of each dog was kept reasonably constant by giving i.v. boluses of fluids during the experiment. There was little change in CO$_{FP}$, MAP, CVP and SVR until the dog’s condition started to deteriorate and Z$_b$ had decreased by 4–6 Ω (Table 1 and Fig. 1). However, CO$_{IC}$ decreased with respect to CO$_{FP}$ as Z$_b$ decreased ($P<0.0001$). The effects on bias are shown for each dog experiment in Figure 1, where Z$_b$ and bias are seen to decrease. The wide variation in the value of bias between sequential bias measurements, indicating a lack of reproducibility, should be noted. The effect of changes in CO$_{FP}$ (upper plots) on bias measurements, particularly in dog 4, should also be noted. The increasing negative percentage error between the two cardiac output measurements as Z$_b$ decreases is summarized for all eight experiments in the box plot in Figure 2.

**Discussion**

The present study showed that CO$_{IC}$ decreased with respect to CO$_{FP}$ with decreasing Z$_b$. As the decrease in Z$_b$ is related to lung fluid content, this finding provides confirmation that the accumulation of fluid within the thorax attenuates impedance-cardiac output measurements. This electrophysiological response of impedance cardiography has not previously been shown experimentally.

A number of explanations have been proposed for the repeatedly poor results found in critically ill patients. Over 30 years ago, Van de Water and colleagues suggested that excessive lung fluid has a detrimental effect on dZ/dt$_{max}$ (the flow factor in the Kubicek equation). Bernstein was the first to report that the BoMed, a predecessor of the current generation of impedance cardiographs, underestimated impedance in patients with sepsis, which he attributed to impedance currents traversing the luxuriantly perfused skin and thoracic musculature which, being highly conductive, diverted them away from the aorta. Later, Shoemaker and colleagues suggested that the excessive lung fluid, or pulmonary oedema, affected impedance measurements and recommended a lower limit of 20 Ω for Z$_b$, below which the use of impedance cardiography is contraindicated.
Fig 1 Plots showing the individual data points from all eight experiments. Each experimental set of plots shows changes in flow probe cardiac output (CO) (upper plot), bias between impedance and flow probe cardiac output readings (middle plot) and baseline impedance ($Z_b$) (lower plot) as lung oedema developed. The flow probe CO readings were fairly consistent. However, there was a wide dispersion between consecutive bias measurements which arose mainly from the variability in impedance CO measurements. The measurement of bias was also influenced by changes in CO. As CO increased, the magnitude of the bias increased (negative deflection) proportionally (e.g. plot for dog 4, 180–240 min). The thoracic impedance $Z_b$ also decreases with time and the development of lung oedema.
Increasing lung oedema

Table 1 Measured haemodynamic variables (mean [SD]) as basal thoracic impedance decreased. \( \Delta Z_b \) is the decrease in basal thoracic impedance \( Z_b \) from the baseline value

<table>
<thead>
<tr>
<th>( \Delta Z_b ) (( \Omega ))</th>
<th>Dog no.</th>
<th>CO(_{TF}) (litre min(^{-1}))</th>
<th>CO(_{FP}) (litre min(^{-1}))</th>
<th>MAP (mm Hg)</th>
<th>CVP (mm Hg)</th>
<th>SVR (dyn s cm(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8</td>
<td>1.5 (0.6)</td>
<td>1.5 (0.7)</td>
<td>75 (24)</td>
<td>8.7 (1.6)</td>
<td>3996 (1662)</td>
</tr>
<tr>
<td>-1</td>
<td>8</td>
<td>1.4 (0.4)</td>
<td>1.5 (0.6)</td>
<td>80 (18)</td>
<td>8.7 (1.5)</td>
<td>4079 (1103)</td>
</tr>
<tr>
<td>-2</td>
<td>8</td>
<td>1.3 (0.4)</td>
<td>1.7 (0.6)</td>
<td>79 (24)</td>
<td>8.8 (1.3)</td>
<td>3522 (1097)</td>
</tr>
<tr>
<td>-4</td>
<td>8</td>
<td>1.1 (0.3)</td>
<td>1.6 (0.7)</td>
<td>80 (24)</td>
<td>8.7 (1.5)</td>
<td>3868 (1364)</td>
</tr>
<tr>
<td>-5</td>
<td>7</td>
<td>0.9 (0.2)</td>
<td>1.2 (0.5)</td>
<td>74 (26)</td>
<td>9.2 (1.5)</td>
<td>4464 (1043)</td>
</tr>
<tr>
<td>-6</td>
<td>6</td>
<td>0.7 (0.3)</td>
<td>1.2 (0.3)</td>
<td>78 (29)</td>
<td>9.4 (1.3)</td>
<td>4484 (889)</td>
</tr>
<tr>
<td>-7</td>
<td>3</td>
<td>0.7 (0.1)</td>
<td>0.9 (0.1)</td>
<td>61 (11)</td>
<td>8.6 (1.1)</td>
<td>4586 (852)</td>
</tr>
</tbody>
</table>

We hypothesized that the presence of lung fluid resulted in a short circuit of the heart and major blood vessels, including the aorta which is the origin of the impedance signal.\(^{13–14} \) These blood-filled organs are highly conductive compared with normal lung tissue which consists of mainly air-filled alveoli. Hence, during impedance cardiography, most of the impedance-detecting current normally flows through the blood-filled structures. However, the presence of lung fluid causes the mediastinum to be partly bypassed and consequently the impedance signal is attenuated, resulting in cardiac output measurements which are lower than expected.\(^{14} \) However, the evidence for this explanation is mainly anecdotal and it had never been rigorously tested in vivo using experimental models of lung oedema. Thus the present study provides in vivo evidence of the wet-lung effect.

Although animal models do not fully replicate the clinical situation, they allow data to be collected and pathological conditions to be produced that could not be achieved ethically in human studies. Thus, by creating a dog model of pulmonary oedema and directly measuring aortic blood flow we were able to show the effects of increasing lung fluid on impedance cardiography. When extrapolated to the clinical setting our data provide a further explanation of why impedance cardiography has been found to be unreliable in critically ill patients in whom pulmonary oedema and lung pathology are very common. Thus lung fluid can be added to the list of factors, such as changes in peripheral resistance due to sepsis and vasopressor therapy\(^{17} \) and cardiac arrhythmias, anomalies and valve defects,\(^{7} \) that have been reported to have an adverse effect on impedance cardiography measurements in critically ill patients.

Oleic acid is the most common agent used experimentally to induce pulmonary oedema; hence it was used in the present study.\(^{18–19} \) The alternative method of overloading the circulation with fluids was found to be unreliable and produced large changes in haemodynamic parameters, which would have complicated our data analysis. However, liberal volumes of i.v. saline were still given throughout the study to maintain CVP and encourage the accumulation of lung fluid. This is reflected in the high urine outputs of 120–150 ml h\(^{-1} \) observed in this study. A number of techniques are available for assessing lung fluid content, such as double-indicator dilution (the gold standard method), chest radiography and thoracic impedance.\(^{18–22} \) Only the latter was available in the present study. We also confirmed at post-mortem that lung fluid had indeed accumulated.

Throughout the experiment we aimed to maintain the dog’s circulation in a steady state. This was of particular importance as other haemodynamic factors, such as changes in peripheral resistance, have also been shown to affect impedance measurements.\(^{17} \) Unwanted haemodynamic effects may still have influenced some of our plots in Figure 1. There was also occasional loss of impedance data because the RheoCardioMonitor failed to function at times as lung oedema developed (Fig. 1). Drugs that support blood pressure and cardiac output were also omitted, and the circulating blood volume, measured by CVP, was maintained at a constant level by giving aliquots of i.v. saline. Changes in CO\(_{FP}\) and SVR were seen only when \( Z_b \) decreased by \( >4 \) \( \Omega \) or CO\(_{FP}\) changed (Table 1 and Fig. 1; dogs 3, 5, 7 and 8).

Thoracic impedance has been used for many years to assess extravascular lung fluid.\(^{11,20,21} \) Spinale and colleagues\(^{20} \) showed in a pig model, where lung oedema was also induced by oleic acid, that decreases in \( Z_b \) were related to increases in extravascular lung fluid.\(^{20} \) These
Lung fluid and impedance cardiography

authors used the gold standard method of double-indicator dilution to assess lung fluid. Zb is not a very consistent measurement of lung fluid and varies greatly between individuals. The normal value for Zb in humans is quoted to range between 20 and 35 Ω owing to differences in chest size and morphology.11,23 Later, Spinale and colleagues24 improved their agreement between Zb and lung fluid measurements in pigs by adjusting for factors such as thoracic shape, haematocrit and right ventricular end-diastolic volume. Roos and colleagues25 tried to overcome this problem of varying body habitus in critically ill patients by indexing Zb to thoracic length. This variability in the baseline value makes it difficult to use Zb as a bedside measure of lung fluid and it is the relative change that is more important. This point was evident in the present study where baseline Zb ranged from 29 to 43 Ω, but the change in Zb with the development of pulmonary oedema was only 3–6 Ω. It is also noteworthy that the values of Zb in the present dog study (29–43 Ω) were higher than that in human subjects (20–35 Ω), reflecting differences in the size and shape of the thorax between the two species. Despite these topographical differences between canine and human morphology, the underlying electrophysiological principles are the same. Thus it would be reasonable to apply our findings in animals to the clinical setting. Zb values <20 Ω in humans are generally regarded as indicative of lung oedema,12,14 and most impedance cardiograph manufacturers warn that their systems become unreliable and should not be used below the 20 Ω threshold.

Our data also demonstrated a wide variation from the mean (or SD) of individual impedance cardiac output readings as measurements were repeated (Fig. 1). Assuming that the flow probe provided relatively consistent readings, and the quoted error is 1–2%,26,27 most of the variability in the error arises from the impedance measurements. For patient safety reasons, the RheoCardioMonitor uses a relatively small transthoracic current (2 mA) to detect the thoracic impedance. This results in a high signal-to-noise ratio with other bioelectric signals, such as respiratory movement and electrical activity of the heart and muscle movement, as well as electrical artifacts arising from the electrode system and device circuitry. The RheoCardioMonitor incorporates a number of signal-processing and filter technologies aimed at reducing these artifacts.10,28 However, the system still provides an impedance signal that contains a significant element of noise, making the measurement of impedance variables such as dZ/dΩmax and LVET unreliable. Whether this problem exists in other impedance cardiography devices is not known. Therefore impedance measurements should be averaged over a number of readings to provide reliable measurements of impedance cardiac output. This problem potentially detracts from the use of the method as a real-time monitor of acute changes in cardiac output. To overcome the problem in the experimental setting and permit statistical analysis, we grouped the data at 1 Ω intervals and used median values (Fig. 2).

In conclusion, we have demonstrated an association between lung oedema induced by oleic acid and changes in impedance cardiac output estimates. There appears to be an attenuation of the COIC value as lung fluid accumulates. This finding helps to explain why the impedance method fails to provide reliable data in critically ill patients.

Acknowledgements

We would like to thank Mr A. E. James, Director of the Laboratory Animals Services Centre, Chinese University of Hong Kong, and his staff for their support and for making this study possible. We would also like to thank Mr D. Burrows and his staff at the Agriculture, Fisheries and Conservation Department of the Hong Kong Government for providing the animals used in this study.

References

1 Kubicek WG, Karnegis JN, Patterson RP, Witsoe DA, Mattson RH. Development and evaluation of an impedance cardiac output system. Aerosp med 1966; 37: 1208–12
6 Young JD, McQuillan P. Related comparison of thoracic electrical bioimpedance and thermodilution for the measurement of cardiac index in patients with severe sepsis. Br J Anaesth 1993; 70: 58–62
10 Tremper KK. Continuous noninvasive cardiac output: are we getting there? Crit Care Med 1987; 15: 278–9
17 Critchley LA, Peng ZY, Fok BS, James AE. The effect of peripheral resistance on impedance cardiography measurements in the anaesthetized dog. Anesth Analg 2005; 100: 1708–12