

Monitoring lung fluid content in CHF patients under intravenous diuretics treatment using bio-impedance measurements

D Freimark¹, M Arad¹, R Sokolover², S Zlochiver² and S Abboud²

¹ Department of Cardiology, Sheba Medical Center, Ramat-Gan, Israel

² Department of Biomedical Engineering, Faculty of Engineering, Tel-Aviv University, Israel

E-mail: abboud@eng.tau.ac.il

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Abstract

A pulmonary edema monitoring system (PulmoTraceTM, CardioInspect, Tel-Aviv University, Israel) was evaluated for tracking lung resistivity during diuretics treatment in congestive heart failure (CHF) patients. The system incorporates a bio-impedance measurement algorithm and enables, by employing an eight-electrode thoracic belt, the assessment of both the left- and right-lung resistivity values. A clinical study was conducted on a group of 13 CHF patients under intravenous diuretics treatment. The group was measured twice—before the beginning of treatment and following a period of a couple of hours. An increase of 8% of the mean lung resistivity (median value) was found between the two measuring sessions, which indicates a dehydration of the lungs, and a significant correlation ($R = 0.73$, $p = 0.004$) was found between the lung resistivity change and the urine output. In conjunction with previously reported results, which demonstrated the system's reproducibility and long-term monitoring capabilities, this study further supports the diagnostics value of the system.

Keywords: Diuretics treatment, bio-impedance, pulmonary edema

Introduction

Cardiogenic pulmonary edema (CPE) is a major cause of morbidity and mortality in congestive heart failure (CHF) patients. The heart's inability to pump blood in proportion to the tissues' metabolism results in a compensatory increase in pulmonary venous pressure. Once the hydrostatic pressure in pulmonary capillaries exceeds the plasma oncotic pressure, fluid and colloid start leaking through the alveolo-capillary membrane. Pulmonary congestion occurs when lymphatic outflow does not suffice to remove the fluid accumulating in the interstitium.

As the intravascular pressure increases along with the amount of extravascular liquid, the lungs become less compliant and less permeable to oxygen, leading to respiratory discomfort (dyspnea), hypoxemia and tachypnea. Once the capacity of the interstitial space is exceeded, the fluid floods the alveoli and airways resulting in full-blown CPE, an acute respiratory distress and a major medical emergency in heart failure patients (Guyton 1991).

Timely treatment of pulmonary congestion is of great importance, as CPE can rapidly deteriorate to respiratory insufficiency, further impair cardiac function and prove fatal. This is usually achieved by introducing diuretic agents, which remove excessive body fluids through the passing of urine. However, diuresis over-treatment can result in hypovolemia, thus reducing cardiac output, interfering with renal function and producing weakness and lethargy. Diuretics might also cause hypokalemia due to a concentration decrease of important ions in the blood circulation. Therefore, for optimizing medicinal treatment with diuretics, i.e., to allow accurate lung fluid management, one should be able to monitor temporal changes in the lungs' fluid content on a frequent basis (Schuller *et al* 1991).

Currently practiced monitoring methods, both invasive and non-invasive, are unsatisfactory, being either inconvenient or inaccurate. The single or double thermal dye dilution methods and the measuring of the pulmonary capillary wedge pressure are intrusive procedures, which might cause complications. Moreover, they cannot be utilized regularly in pre-clinical conditions, and although regarded as a gold standard, they provide inconsistent results and low accuracy of about 20% (Brown *et al* 1996, Miniati *et al* 1987). Thoracic x-ray radiography is widely practiced, yet it cannot detect CPE at its early stages and involves ionizing radiation, thus cannot be regularly employed. Imaging modalities, e.g. MRI or x-ray CT, though indicative of CPE severity level, are quite expensive for a routine monitoring or incorporate ionizing radiation.

The bio-impedance technique was suggested already in 1969 as a non-invasive method to assess the amount of lung fluids (Pomerantz *et al* 1969). In that study, the transthoracic impedance of a canine was assessed by injecting electrical current and measuring the developing voltage using two electrodes placed on the two thoracic extremities. A correlation between the measured impedance and the amount of lung-injected saline was found. The physical rationale for this finding was the distinct electrical properties of air-filled and fluid-filled lungs. As watery lungs are good conductors of electrical current—thus associated with a low impedance value, air-filled lungs are more insulating—thus associated with a high impedance value. Being the organs largest in volume inside the thoracic cavity, this change in the lungs' conducting attributes reflects well in the measured whole thoracic impedance. The four-electrode configuration has been adopted by many later clinical studies for diagnosing pulmonary edema (Kubicek *et al* 1970, Fein *et al* 1979, Saunders 1988, Zellner *et al* 1990, Charach *et al* 2001), and provided good immunity to changes of tidal volume and chest movement errors.

All of the aforementioned studies suffer from an inherent limitation: that is, providing only a global measure of the whole thoracic impedance, a weighted average of the impedance values of all its constituent organs. In that sense, the transthoracic method cannot provide localized impedivity information, being unable to discriminate between lungs' impedivity changes and that of other thoracic organs. In this manner, the right and left lungs' impedivity values cannot be specified and asymmetric lung pathologies cannot be correctly diagnosed or monitored.

Electrical impedance tomography (EIT) overcomes that problem by providing a cross-sectional resistivity distribution of the thoracic cavity. The technique involves the attachment of an array of electrodes on the thoracic circumference, through which a small-magnitude alternating current is injected, each time using a different electrode pair (Barber and Brown

1984). For each injection, the developing voltages are simultaneously measured by the remaining electrodes. The collected data are analyzed for computing the cross-sectional resistivity distribution that gave rise to the observed voltages, thus providing local, anatomical information. The technique is safe, inexpensive and works in real time.

The EIT technique, while enabling the reconstruction of specific, local impedance values, suffers from a low resolution and limited reproducible imaging, mainly due to the inherent high sensitivity of its mathematical formulation to measurement noise, which may arise either due to patient movement or due to electronic or thermal noise. These inherent limitations make EIT not accurate enough for monitoring patients under diuretics treatment. In addition, the numerous electrodes that need to be attached make such systems impractical for daily clinical use.

In this study, a novel bio-impedance system ('CardioInspect' Tel-Aviv University, Israel), which combines the principles of both bio-impedance measurements and EIT algorithms, was employed for monitoring CHF patients under diuretics treatment. By using only eight electrodes and parametric reconstruction, rather than a full resistivity distribution reconstruction, the system employed should be less sensitive to measurement noise than a conventional EIT system, yet capable of measuring the resistivity of the right and left lungs as whole organs. The system reproducibility and ability to separate healthy from edemic subjects were previously demonstrated (Zlochiver *et al* 2007).

Methods

A clinical study was conducted at the department of cardiology in Sheba Medical Center, Israel, and was approved by a local ethics committee. A study group consisted of 13 regularly monitored CHF patients (all males, aged 64 ± 9 years), all of whom signed an informed consent and were not carrying a cardiac pacemaker or other implantable device. Two bio-impedance measurements of the left- and right-lung resistivity were taken for each subject during diuretics treatment—one measurement before an intravenous injection of Fusid and one following a resting period of approximately 4 h. The medication dose was typically 80 (range 40–120) mg furosemide by intravenous drip. The main factors determining the diuretic dose in these adult CHF patients were the extent of volume overload, renal function and prior responsiveness to diuretics. The diuretic dose was adjusted by integrating the patient weight (as an indirect measure of fluid gain) with the self-reported degree of dyspnea, physical findings and capillary oxygen saturation. As needed, an additional diuretic (metolazone) was added to potentiate the effect.

The bio-impedance measurements were taken using the CardioInspect's PulmoTrace™ portable clinical system, which is comprehensively described in our previous publication (Zlochiver *et al* 2007). Briefly, the system consists of eight electrodes attached to a modular thoracic-belt, an analogue amplifying unit and a control/analysis unit (figure 1a). The system employs the bio-impedance measuring technique and the EIT principles in order to assess the right- and left-lung resistivity values which correlate to the fluid retention in the lungs. The system injects a low-magnitude, low-frequency current to the body (3 mA, 20 kHz), each time through a different pair of source–sink electrodes using a switch matrix in the opposite configuration. The developing surface potentials are measured differentially by the remaining electrodes, amplified and filtered using a band-pass of 1 kHz around the carrier frequency. The measurements are synchronized to an ECG signal, which is recorded prior to the impedance measurements using two of the eight electrodes. This synchronization ensures that all measurements are taken at the same phase during the cardiac cycle, so that blood perfusion into the lungs remains similar. The entire measurement procedure

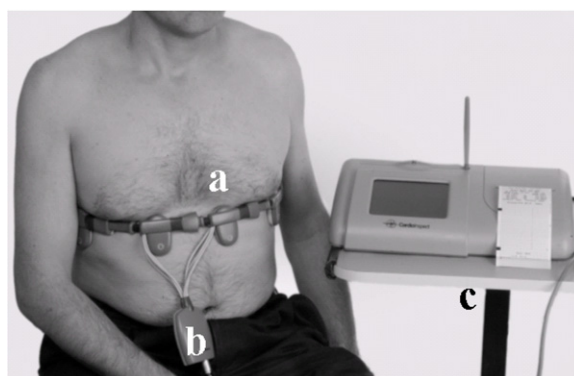


Figure 1a. A typical measurement session. An eight-electrode thoracic belt (a) is attached to a sitting patient, and connected through an analogue driving and amplification unit (b) to a control/display unit (c). The belt length can be manually fitted to the patient's thoracic perimeter.

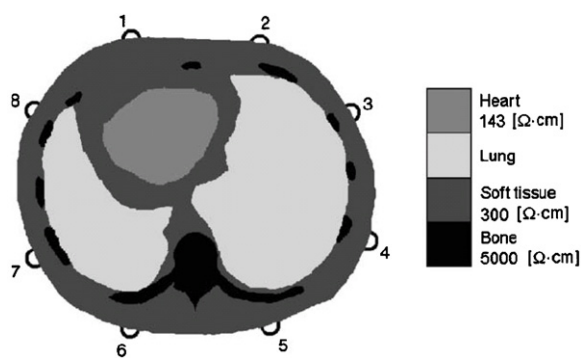


Figure 1b. Two-dimensional volume conductor model of the thoracic cavity. The positions of the eight electrodes are marked. The tissue resistivity values were kept constant except for those of the left and right lung, which were set as the reconstruction algorithm parameters.

lasts less than 1 min. A parametric Newton–Raphson optimization algorithm is utilized for associating the measured data with the resistivity values of both lungs, using a fixed volume conductor model of the thorax and a finite volume numerical solver (figure 1b). In our previous publication (Zlochiver *et al* 2007), we have demonstrated that in a group of $n = 33$ healthy subjects, no significant correlation between the reconstructed lung resistivity values and various anthropometric parameters (e.g. height, weight or body mass index) was found. On the other hand, we have already demonstrated that the system is capable of discriminating control from heart failure patients, and to assess patients' condition in a long-term monitoring (Zlochiver *et al* 2005, 2007). Hence, the usage of a fixed geometry model was found adequate. The lung resistivity values are given in absolute values of (Ω cm). It should be noted though that these values are scaled by a normalization factor so that the average reconstructed resistivity values for healthy subjects were similar to the normal lung resistivity in tidal respiration (Woo *et al* 1992).

For ensuring minimal alterations of the measured subjects' posture and associated volume conductor geometry, all measurements were taken while in a sitting position, during tidal respiration. The electrode belt was attached to the patients' thorax on the plane of the fifth intercostal space in the midclavicular line using conventional ECG Ag/AgCl disposable

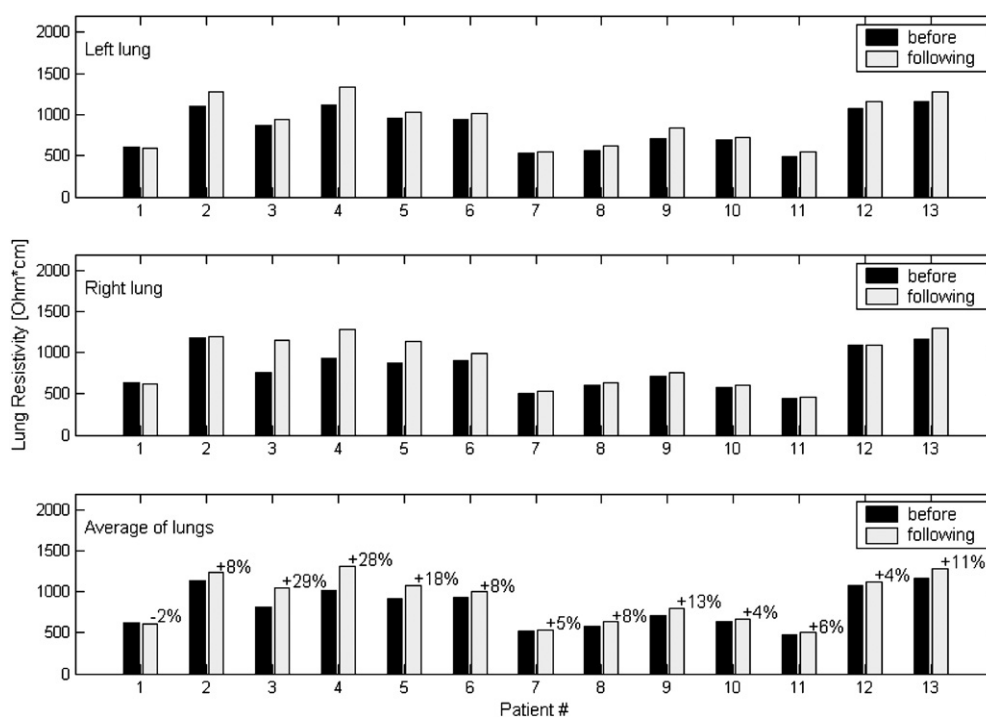


Figure 2. Left (up), right (middle) and average (bottom) lung resistivity measurements before (dark bars) and following (light bars) diuretics treatment. The change in the average lung resistivity as a percentage is noted.

electrodes. Eight specially designed elongation mechanisms on the electrode belt were used for adapting the electrode belt length to the thoracic perimeter of the subject, ensuring a fixed angular distance between the electrodes (figure 1a). The electrode belt was removed between measurements. The urine output of the patients in the time interval between the two measurements was also measured for comparison.

Results

The bio-impedance measurements before the intravenous diuretics treatment and following the resting period are shown in figure 2 for all 13 patients. The upper, middle and lower graphs in figure 2 relate to the left-, right- and average-lung resistivity values. It can be seen that in all cases but one the post-treatment measurement indicates an increase in the resistivity value of both lungs (resistivity increase median value—8%, 25 percentile—4.75%, 75 percentile—14.25%), which corresponds to a dehydration of the lungs, as expected from the diuretics treatment. These changes cannot be attributed to measurement inconsistency, as we have previously shown that the system reproducibility, both within and between test, is better than 2%, in a 5 month monitoring period (Zlochiver *et al* 2007). A correlation graph between the absolute change in lung resistivity and the urine output is given in figure 3, demonstrating a significant linear relationship with a correlation ratio of $R = 0.73$ ($p = 0.004$). A regression plot of the relative lung resistivity change (as a percentage) as a function of the urine output also demonstrated a significant linear relationship with a correlation ratio of $R = 0.64$ ($p < 0.02$).

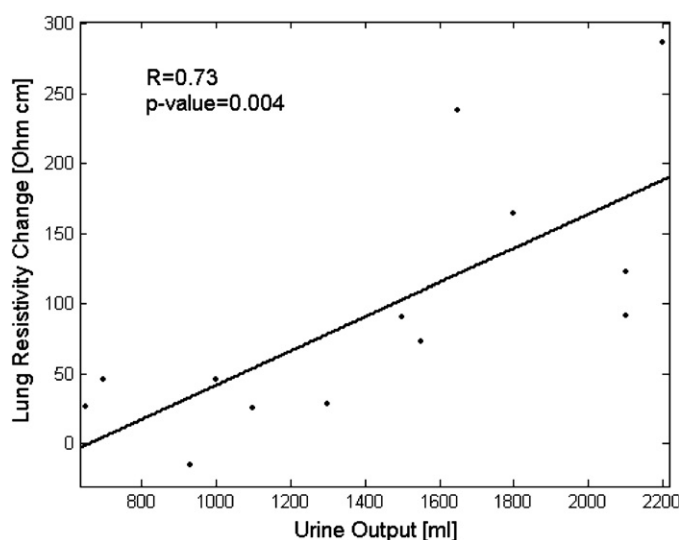


Figure 3. Correlation plot between average lung resistivity change and urine output.

Discussion

In this study, the feasibility of a novel portable system (PulmoTrace™, CardioInspect, Tel-Aviv University, Israel) for monitoring lung resistivity in CHF patients undergoing diuretics treatment was demonstrated. The system provides a non-invasive and safe means for assessing lung fluids retention in pulmonary edema conditions utilizing the principles of bio-impedance measurements and a parametric EIT technique. Unlike the whole-thoracic bio-impedance measurement, which is based on the four-electrode model of Kubicek *et al* (1970), the present system provides information regarding the *specific* resistivity values of the right and the left lungs rather than a general, global index of the thoracic fluid content. In that sense, pathologies such as unilateral pulmonary edema, enlarged cardiac volume or unilateral pleural effusion can be better monitored with the present system.

A standard EIT technique, where the resistivity spatial distribution over a thoracic slice is reconstructed, has been employed in other studies. Campbell *et al* (1994b) have monitored transient changes in intrathoracic fluid content in healthy subjects under intravenous fluid infusion of saline. They have employed the Sheffield mark I EIT system that injects a 5 mA, 50 kHz current through an array of 16 electrodes, and uses a back-projection algorithm for reconstruction. Due to the low frequency that was utilized, only extracellular water could be measured, thus supplying resistivity, rather than impedivity, information. At total lung capacity, a gradual resistivity decrease for both lungs was found, being more significant in the right lung (19%, compared to 15% for the left lung). Measurements were also compared with tidal breathing and residual volume conditions, showing similar conclusions. In another study from the same group, similar measurements were performed on patients during sequential aspiration of unilateral pleural effusions (Campbell *et al* 1994a). By applying a region-of-interest calculation for the left and right lungs on the EIT images, it was possible to detect small changes in the resistivity during fluid aspiration (up to about 7%), most prominently on the side of the effusion. These two studies employed single-frequency EIT measurements, which cannot produce absolute fluid volumes, but rather relative values, compared to a reference

image. Furthermore, large inter-patient variability was found due to uncertainty of exact electrode locations and body movements.

Brown *et al* (1996) have measured right-lung resistivity changes in goats under oleic acid injection using EIT spectroscopy, in which current is applied in several discrete frequencies, and measurements are used to fit a Cole model for the tissue. A resistivity decrease of about 22% at 9.6 kHz was measured for an intravenous infusion of 0.07 ml kg⁻¹ oleic acid. The results correlated well with double-indicator lung water measurements ($R \sim 0.8$). Higher decrease values were found at higher current frequencies, as intracellular electrical properties contribute to the total resistivity.

A similar study to the present work was performed, where lung impedance changes of healthy volunteers under diuretic challenge were monitored (Noble *et al* 2000). The Sheffield mark 3A was employed and measurements were taken during tidal respiration in intervals of 15 min. The large sensitivity to noise due to patient and electrode movement made it difficult to trace the diuresis process monotonically in the impedance measurements.

Other studies have demonstrated the feasibility of detecting specific temporal lung water changes in pulmonary edema condition during either fluid intravenous infusion or diuresis in both animal models (Woo *et al* 1992, Newell *et al* 1996, Frerichs *et al* 1998) and human patients (Kunst *et al* 1999, Noble *et al* 1999).

The standard EIT technique, as utilized by these and other former studies, is aimed at fully reconstructing the spatial distribution of resistivity, and as such is usually under-determined and suffers from low spatial resolution. Consequently, the sensitivity to either noise, electronic noise on the measuring leads or geometrical noise, due to incorrect knowledge of the thoracic boundary shape and electrode positions is extremely large and imaging artifacts are prone to arise (Morucci and Marsili 1996, Somersalo *et al* 1992).

In the present system, a parametric approach was adopted, where only a limited number of parameters are reconstructed, which are the right- and left-lung resistivity values for monitoring lung edema. The parametric approach significantly stabilizes the reconstruction algorithm and reduces the noise sensitivity.

The clinical study that was conducted on CHF patients revealed a lung resistivity increase with a median value of 8% following intravenous diuretics treatment, indicating an improvement in their condition (normal and CHF lung resistivity values that are measured with the present system are about 1200 and 900 Ω cm, respectively (Zlochiver *et al* 2005)). In addition, a significant correlation between lung resistivity changes and urine output of $R = 0.73$ ($p = 0.004$) was demonstrated. These results are in accordance with those found for a group of healthy volunteers (Noble *et al* 2000). In that study, an increase of 7.8% in right-lung impedance was found following fluid depletion and a correlation between lung impedance and urine output was demonstrated.

Pulmonary edema in healthy subjects, created under experimental conditions or clinical situations (e.g. Tachyarrhythmia, extreme volume overload), produces a brisk diuretic response mediated by neurohumoral mechanisms: release of natriuretic peptide and decreased excretion of antidiuretic hormone. In heart failure patients these regulatory mechanisms are attenuated and even suppressed by other stimuli evoked by abnormal hemodynamics: low cardiac output, decreased renal perfusion, activated sympathetic and renin–angiotensin system and multiple medications affecting the renal and neurohumoral function. In heart failure excess fluid accumulates in blood vessels (i.e. venous congestion) tissue interstitium (i.e. edema involving the lungs, extremities, intestine, etc) and third spaces (pleural effusion or ascitis). The distribution of volume overload is highly variable and depends on type and chronicity of heart failure as well as nutritional status, liver and kidney function and local factors. During diuretic therapy fluid is mobilized first from the intravascular compartment, then from the interstitium

and finally from body cavities. The water content of the lungs is only one factor related to urine output under diuretic therapy. However, since there is a gross correlation between the degree of lung congestion and general fluid overload in CHF, there should be a positive correlation between fluid loss and decrease in lung water content. A correlation of 0.73 (explaining more than 50% of experimental variance) is rather remarkable given the complex distribution of excess water in advanced heart failure.

In one of our measurements, a negative resistivity change was recorded (see figure 2, patient 1) for a patient with a urine output of ~900 ml. Such a negative change was most probably a result of a misconducted measurement which may have occurred due to abrupt patient movement.

The current results clearly demonstrate the feasibility of the 'PulmoTraceTM' portable system for long-term monitoring of CHF patients and its diagnostic value. In our previous studies, the capability of the system to separate between normal and CHF conditions was demonstrated, and its reproducibility was found to be better than 2% (Zlochiver *et al* 2005, 2007). Therefore, the resistivity changes that were measured in the study of up to 300 Ω cm, which are up to 25% of the reference lung resistivity values, are significant. The large inter-patient variability that was observed in the impedance changes was thus directly correlated to the urine output. Excess fluid, salt and caffeine and in particular hydration status could influence the urine output. However, because the patients were under a steady and restricted drinking and diet regimen, which included a hospital meal on the study day, we do not consider these factors to be a major source of variability in this study.

It should be noted, though, that in the present study, the absolute air volume of the lungs at the time of each measurement was not assessed, which may result in measurement perturbations. Still, all of our measurements were taken during shallow breathing in tidal respiration, thus such perturbations were kept minimal. In addition, for some patients, the resistivity change of the right lung was significantly different from that of the left lung. We surmise that such variance is of physiological origin, since this variance was such that it mostly compensated an initial imbalance between the two lungs, probably due to a different fluid retention.

The current and former results suggest that by employing the bio-impedance and parametric EIT principles, a convenient, non-invasive, reproducible and safe monitoring of lung edema is feasible, which goes some way toward achieving the 'ideal' CHF monitoring device envisaged by Staub (1986). A system following individual chest impedance provides important additional information about lung water excess which is relatively free of confounders complicating the currently used clinical measures.

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