With permission from David M. Nierman MD (dnierma@smtplink.mssm.edu)

May 9. 1996 No. 0350

Transthoracic Bioimpedance Can Measure Extravascular Lung Water in Acute Lung Injury

DAVID M. NIERNMAN, DEBORAH I. EISEN, EDWARD D. FEIN, EMILY HANNON, JEFFREY I. MECHANICK, AND ERNEST BENJAMIN

Departments of Medicine and Surgery, The Mount Sinai Medical Center, New York, New York 10029-6574

ABSTRACT

We used a porcine endotoxemic model of acute lung injury to compare extravascular lung water (EVLW) measured by right transthoracic bioimpedance to postmortem gravimetric EVLW measurements. Adult pigs were randomized into control (N = 5) or endotoxin groups [150 μg/kg Escherichia coli lipopolysaccharide B for 1 hr followed by 3 hr of resuscitation for a thermodilution cardiac output less than 90% of baseline using either isotonic saline (N = 5) or isooncotic albumin (N = 5)]. Right lung resistance was measured using a novel electrode array and a highly sensitive analyzer and was used to calculate right lung resistivity. At the end of the experiment, animals in the endotoxin-albumin group had higher gravimetric EVLWs than those in the endotoxin-saline or control groups (P < 0.05). Right lung resistivity corrected for body weight significantly correlated with gravimetric EVLW ($r^2 = 0.49$ SEE = 0.96 $P = 0.0038$). Using multiple regression analysis, a predictive equation for EVLW based on right lung resistivity, body weight, and mean pulmonary artery pressure was generated ($r^2 = 0.81$ SEE = 0.60 $P < 0.0001$). These results demonstrate that right lung resistivity measurements can provide a noninvasive estimate of EVLW. In addition, crystalloid may be preferable to colloid for fluid resuscitation in noncardiogenic pulmonary edema. C 1996 Academic Press, Inc.

INTRODUCTION
Measurement of extravascular lung water (EVLW) may help to guide the fluid management of patients with noncardiogenic pulmonary edema [1]. The clinically ideal technique to measure EVLW should be quantitative, noninvasive, nondestructive, accurate, inexpensive, and capable of repeated measurements [2, 3]. No currently available technique fulfills all these requirements. Gravimetric measurements of wet to dry lung weights, which are the gold standard for the determination of lung water, cannot be performed in the clinical setting. Chest radiographs are qualitative and insensitive. The double-indicator technique using heat and isocyanine green dye is invasive and is not commercially available in the United States. Double-indicator techniques using radioisotopes are experimental and are not readily repeatable. Clinicians must therefore rely on less sensitive surrogate tests of lung water such as oxygenation, chest radiographs, and pulmonary artery catheter occlusion pressures to guide fluid therapy when managing patients with noncardiogenic pulmonary edema. A technology that has the potential to quantify EVLW noninvasively is transthoracic bioelectrical impedance analysis (BIA). In BIA, an alternating electric current is passed through biologic tissue and the resistance to that current measured. This resistance is inversely proportional to the amount of water contained by the tissues within the electric field. However, previous attempts to use transthoracic BIA to estimate total lung water and EVLW have been disappointing due to technical and methodological difficulties [4-12]. Although it has been clearly shown that BIA can reflect gross changes in lung water, bioimpedance has never been precise or reproducible enough to be used clinically. Applying recent advances in biomedical engineering, we have developed a new bioimpedance system that includes a modified analyzer and a new tetrapolar electrode array. With this BIA system, we measure right lung resistance and, from this, calculate the resistivity of a cubic centimeter of right lung. In this study we used a porcine endotoxemic model of acute lung injury to compare EVLW measured by this BIA system to the gold standard of postmortem gravimetry. In addition, we used both techniques to compare EVLW following resuscitation with saline to EVLW following resuscitation with albumin.

METHODS

Animal preparation and instrumentation. This study was approved by the Animal Care and Use Committee of the Mount Sinai School of Medicine. Adult female Yorkshire pigs (17-33 kg) were sedated with ketamine (7 mg/kg im) and anesthetized with sodium pentobarbital (30 mg/kg initially, followed by a maintenance dose of 17 mg/kg/hr via an iv infusion pump, 6 ml/hr).

Fig. 1. Placement of electrodes for right transthoracic and whole body bioimpedance measurements. Black cables from analyzer attach to source electrodes, white cables attach to chest detector electrodes.

Pigs were positioned supine for the entire experiment. The animals were orotracheally
intubated and mechanically ventilated at an 
\[
\text{F}_1\text{O}_2 = 0.21 \text{ and a rate of 10 breaths/ min, with the tidal volume adjusted to a baseline}
\]
\[
\text{P}_2\text{CO}_2 = 40-45 \text{ Tnm Hg. An EKG was continuously displayed on a cardiac monitor}
\]
and a Foley catheter was inserted into the urinary bladder. After a 20-gauge femoral 
arterial catheter was inserted percutaneously into the left femoral artery to measure 
blood pressure and draw blood samples, a 7.5 French oximetric right ejection fraction 
pulmonary artery (PA) catheter was inserted by cutdown through the right internal 
jugular vein and floated into the pulmonary artery (REF-OX, Edwards Critical Care, 
Irvine, CA). This catheter was used to measure thermodilution cardiac outputs, 
pulmonary artery pressures, pulmonary artery wedge pressures (PCWP), right 
ventricular end systolic (RVESV) and end diastolic volumes (RVEDV), and right 
heart ejection fractions. Arterial blood gases were measured on a Nova Stat5 Analyzer 
(Nova Biomedical, Waltham, MA). Bioimpedance analysis measurements. _BIA 
measurements were made using a tetrapolar spot electrode array and a modified 
Quantum. system analyzer (RJL Systems, Inc., Clinton Twp., MI) interfaced to a 
Zenith Data Systems laptop computer containing BIA interpretation software (RJL 
Systems, Inc.). This analyzer delivers an imperceptible constant 800-IuA alternating 
current at 50 1KHz frequency and was modified by RJL Systems to measure 
resistance (R) to Two decimal places from 0.00 to 250.00 Ohms. Anatomical 
landmarks for whole body and right chest BIA measurements were identified, the sites 
closely shaved, and spot electrodes placed (Fig. 1). Ag/AgCl ECG electrodes 
(Marquette Electronics Jupiter, FL) were used for all measurements. Source electrodes 
to establish the electric field were placed on the right distal joint on the fore foot and 
the hind foot to approximate the human metacarpal and metatarsal locations and were 
used for both whole body and chest measurements (Fig. 1). Two different detector 
electrode pairs were used. For whole body measurements, detector electrodes were 
placed on the large joints proximal to the source electrodes. For right chest 
transthoracic measurements, the detector electrode pair was placed in the right 
middavicular line, with the upper electrode just under the clavicle and the lower 
electrode 10 cm caudal to it (Fig. 1). Source and detector electrodes remained in place 
for the entire study. Baseline measurements. After instrumentation, animals were 
allowed to recover for 30-60 min. Baseline hemodynamic and arterial blood gas 
measurements were done. Whole body and right chest resistance were measured and 3 
ml of blood was drawn into a plastic syringe and allowed to equilibrate for 10 min at 
room temperature. This blood was then injected into a plexiglass physiologic fluid cell 
(cell volume of 0.6787 ml) (RJL Systems, Inc.), and its resistance was measured. 
Measured right chest resistances were then used to calculate right lung resistivities 
(see Appendix). Study protocol. Pigs were randomized into control (N = 5), saline (N 
= 5), and albumin (N = 5) groups. The saline and albumin groups received 150 ug/kg 
of endotoxin in 20 ml saline over an hour (Escherichia coli lipopolysaccharide B, 
Difco, Detroit, MI). The control group received a 20-ml saline infusion over an hour. 
No cardiac output measurements were made during this hour. All measurements were 
repeated at the end of the first hour and again every hour for 3 hr of resuscitation. 
Between 1 and 4 hr, thermodilution cardiac outputs were measured every 15 min using 
three 10-ml boluses of normal saline (120 ml/hr total). In the saline and albumin 
groups, if the cardiac output decreased to less than 90% of baseline at any time (13-
15], a bolus of resuscitation fluid was given (250 ml of saline or 2 ml/kg of 5% albumin). All other fluids were restricted. At 4 hr, pigs were euthanized with an overdose of pentobarbital. The right chest was immediately opened widely, the hilum identified and clamped, and the entire right lung removed for gravimetric determination of extravascular lung water by wet to dry weights [16]. Gravimetric lung water. After removal of the lung, the major bronchi were removed with sharp dissection and the lung parenchyma homogenized in a Waring blender with 100 g of added water. Wet and dry weights were recorded for duplicate 10-ml samples of this homogenate. Detergent (Tween 20, 1.0 ml) was then added to the remaining lung tissue and further homogenized in the blender. Duplicate 5-ml samples of this homogenate were centrifuged at 3000g. The supernatants were aspirated and stored at -70°C until the hemoglobin was determined spectrophotometrically using the cyanmethemoglobin technique (Sigma Diagnostics, St. Louis, MO). This hemoglobin was then used to calculate the red cell mass remaining in the lung. At the end of the experiment, duplicate 3-ml samples of arterial blood were obtained, and the hemoglobin concentration was directly measured. Hemoglobin concentration within the lung was assumed to be the same as that of arterial blood. The lung homogenate, supernatant, and arterial blood samples were weighed wet and then again after drying to constant weight (37°C for 48-72 hr). After drying of the lung homogenate, supernatant, and arterial blood to constant weight, fractional water contents were calculated and used to calculate the total lung water and the intravascular lung water. The difference between TLW and IVLW was the extravascular lung water [16].

Statistics. Measurements are displayed as means ± SD. A P value < 0.05 was considered statistically significant. Differences between measurements and baseline were calculated using paired t tests. Between-group differences were analyzed by ANOVA with post hoc analysis by Scheffe’s test. Correlation coefficients were calculated using Pearson’s correlation coefficient. Stepwise multivariate analysis was used to determine variables predictive of EVLW. All statistics were done on SPSS for Windows, version 6.0 (Chicago, IL).

RESULTS

At baseline, there were no significant differences in hemodynamic, oxygenation, or bioimpedance variables among the three groups. The groups were also e-qualiq matched by weight (control, 24.0 ± 4.3 kg NS, 22.4 ± 4.0 kg alb, 28.4 ± 3.0 kg) and chest circumference (c(control, 60.3 ± 4.3 cm; NS, 59.8 ±; 3.2 cm; alb, 65.5 ±2.9 cm).

Hemodynamic, Hematocrit, and Oxygenation Changes In the 10 pigs that received endotoxin, the hemodynamic changes over the hour of infusion were consistent with that shown by other investigators [13, 15, 171, with a doubling of MPAP and decreases in mean arterial pressure and cardiac output (Table 1). Throughout the 3 hr of resuscitation, fluid resuscitation with albumin maintained the cardiac output and mean arterial pressure better than saline (Table 1). Over the 4 hr of the experiment the $P_{aO_2}$ of the control animals slowly increased, due to hyperventilation. In both endotoxin groups, $P_{aO_2}$ the had already decreased by the end of 1 hr of endotoxin infusion.
## TABLE I. Changes in Oxygenation and Hemodynamic Variables over Time

<table>
<thead>
<tr>
<th></th>
<th>Hour</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>pO2 (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>100 ± 13</td>
<td>105 ± 15</td>
<td>106 ± 13*</td>
<td>112 ± 20</td>
<td>120 ± 27</td>
</tr>
<tr>
<td>NS</td>
<td>100 ± 15</td>
<td>82 ± 21</td>
<td>80 ± 32</td>
<td>76 ± 29</td>
<td>72 ± 22*</td>
</tr>
<tr>
<td>ALB</td>
<td>89 ± 17</td>
<td>60 ± 19*</td>
<td>54 ± 19*</td>
<td>52 ± 16*</td>
<td>46 ± 19*</td>
</tr>
<tr>
<td><strong>Heart Rate (beats/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>114 ± 34</td>
<td>106 ± 32</td>
<td>95 ± 20</td>
<td>89 ± 25</td>
<td>86 ± 23</td>
</tr>
<tr>
<td>NS</td>
<td>112 ± 6</td>
<td>107 ± 13</td>
<td>95 ± 18</td>
<td>98 ± 22</td>
<td>93 ± 23</td>
</tr>
<tr>
<td>ALB</td>
<td>105 ± 15</td>
<td>115 ± 20</td>
<td>125 ± 20</td>
<td>124 ± 25</td>
<td>120 ± 29</td>
</tr>
<tr>
<td><strong>Mean Arterial Pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>100 ± 10</td>
<td>102 ± 14</td>
<td>101 ± 13</td>
<td>98 ± 18</td>
<td>98 ± 16</td>
</tr>
<tr>
<td>NS</td>
<td>102 ± 11</td>
<td>91 ± 9*</td>
<td>57 ± 13*</td>
<td>58 ± 11*</td>
<td>62 ± 19*</td>
</tr>
<tr>
<td>ALB</td>
<td>109 ± 7</td>
<td>103 ± 21*</td>
<td>67 ± 10*</td>
<td>67 ± 9*</td>
<td>80 ± 10*</td>
</tr>
<tr>
<td><strong>Mean Pulmonary Artery Pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>21 ± 6</td>
<td>20 ± 6</td>
<td>20 ± 6</td>
<td>19 ± 8</td>
<td>18 ± 7</td>
</tr>
<tr>
<td>NS</td>
<td>17 ± 4</td>
<td>33 ± 7*</td>
<td>26 ± 4*</td>
<td>30 ± 3*</td>
<td>30 ± 5*</td>
</tr>
<tr>
<td>ALB</td>
<td>20 ± 6</td>
<td>37 ± 7*</td>
<td>30 ± 4*</td>
<td>31 ± 9*</td>
<td>34 ± 8*</td>
</tr>
<tr>
<td><strong>Cardiac Output (liters/min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>3.45 ±</td>
<td>3.14 ±</td>
<td>2.97 ±</td>
<td>2.43 ±</td>
<td>2.40 ±</td>
</tr>
</tbody>
</table>
With resuscitation, the $P_{aO_2}$ continued to decrease steadily. The pigs who received albumin had consistently worse oxygenation throughout the study than did those who received saline (Table 2).

* $P < .05$ compared to baseline.
Bioimpedance Changes: Whole body resistance did not change in the control pigs, but decreased equally in the endotoxin pigs after resuscitation with either saline or albumin (Table 2).

<table>
<thead>
<tr>
<th>TABLE 2 - Changes in Bioimpedance Variables and Hematocrit Over Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Chest resistance (Ohms)</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>NS</td>
</tr>
<tr>
<td>ALB</td>
</tr>
<tr>
<td>Right lung resistivity (Ohms-cm)</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>NS</td>
</tr>
<tr>
<td>ALB</td>
</tr>
<tr>
<td>Lung resistivity/body weight (Ohms-cm/kg)</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>NS</td>
</tr>
<tr>
<td>ALB</td>
</tr>
<tr>
<td>Whole-body resistance (Ohms)</td>
</tr>
<tr>
<td>C</td>
</tr>
</tbody>
</table>
In vivo blood resistance showed a biphasic response in the 10 animals that received endotoxin. During the hour of endotoxin infusion, blood resistance significantly increased, reflecting hemoconcentration. In both endotoxin groups, blood resistance gradually decreased with fluid resuscitation. These changes mirrored the parallel changes in hematocrit. For all time points (N = 65), hematocrit and blood resistance were highly correlated (r^2 = 0.81; P < 0.001). In all three groups of animals, right chest resistances, calculated right lung resistivities, and right lung resistivities corrected for baseline body weight decreased over the first hour (Table 2). However, in the five control animals, following an initial decrease of 4.2% (P < 0.05), lung resistivities remained unchanged for the remainder of the experiment (Fig. 2). Following endotoxin, although chest resistivities for each endotoxin resuscitation group decreased, this was not statistically significant. However, for all 10 pigs that received endotoxin, chest resistances and resistivities decreased by 15.7% over the initial hour (P < 0.05) and continued to decrease during the 3 hr of fluid resuscitation. At the end of the experiment, lung resistivities of the animals who received saline were 25% lower, and lung resistivities of those who received albumin were 30% lower than baseline (Fig. 2). At postmortem, the lungs of the animals who received endotoxin were heavy and congested. Total lung water was greater in the NS (5.98 ± .64) and albumin groups (7.26 ± .66 mUkg; P < 0.05 compared to control) than the control group (4.45 ± 1.31 ml/kg). There was no difference among the three groups in intravascular lung water (control, 91 ± .61 ml/kg; NS, .93 ± .21 ml/kg; alb, 1.03 ± .32 ml/kg). Therefore, the increase in TLW was entirely due to an increase in the extravascular water. EVLW by gravimetry averaged

<table>
<thead>
<tr>
<th></th>
<th>NS</th>
<th>79 ± 3</th>
<th>77 ± 4</th>
<th>7*</th>
<th>7*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALB</td>
<td>67 ± 10</td>
<td>63 ± 9</td>
<td>62 ± 9</td>
<td>59 ± 10*</td>
<td>57 ± 10*</td>
</tr>
</tbody>
</table>

### Blood resistance (Ohms)

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>200 ± 15</th>
<th>203 ± 10</th>
<th>199 ± 9</th>
<th>205 ± 7</th>
<th>203 ± 9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NS</td>
<td>207 ± 14</td>
<td>240 ± 9*</td>
<td>227 ± 20</td>
<td>215 ± 13</td>
<td>204 ± 16</td>
</tr>
<tr>
<td></td>
<td>ALB</td>
<td>214 ± 10</td>
<td>273 ± 25*</td>
<td>242 ± 17*</td>
<td>220 ± 12</td>
<td>235 ± 23</td>
</tr>
</tbody>
</table>

### Hematocrit (%)

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>26 ± 3</th>
<th>26 ± 2</th>
<th>26 ± 2</th>
<th>27 ± 1</th>
<th>27 ± 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS</td>
<td>28 ± 3</td>
<td>34 ± 1*</td>
<td>31 ± 4*</td>
<td>29 ± 2</td>
<td>28 ± 3</td>
<td></td>
</tr>
<tr>
<td>ALB</td>
<td>28 ± 3</td>
<td>35 ± 3*</td>
<td>32 ± 3*</td>
<td>31 ± 2*</td>
<td>32 ± 4*</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05 compared to control.
3.54 ± 0.78 ml/kg (83 ± 13 ml total volume) in the control group, 5.05 ± 0.65 ml/kg (113 ± 23 ml) in the saline group (P < 0.5 compared to controls), and 6.23 ± 0.51 ml/kg (177 ± 27 ml) in the albumin group (P < 0.05 compared to both control and saline groups) (Fig. 3).

**FIG. 2.** Right lung resistivity/body weight over time for control (N = 5), endotoxin + saline (N = 5), and endotoxin + albumin (N = 5) groups. *P < 0.05 compared to control.

**FIG. 3.** Extravascular lung water measured by gravimetry compared to that calculated from transthoracic bioimpedance, body weight, and mean pulmonary artery pressure (see text). $r^2 = 0.81$; SEE = 0.90; $P < 0.0001$. 
Right lung resistivity at the final measuring point (N = 15) correlated with gravimetric EVLW (P 0.0 14) and TLW (P= 0.031) but not with IVLW (P 0.237). Linear regression analysis with EVLW as the dependent variable and resistivity as the independent variable showed a significant relationship, with an r’ of 0.38 [P = 0.014, standard error of the estimate (SEE) = 1.05]. This improved to an r 2 of 0.49 (P = 0.0038, SEE = 0.96) when resistivity was divided by baseline weight as a partial correction for body size. EVLW could be calculated from resistivity/weight as EVLW = 7.95 - .272*(Resistivity/Weight). Stepwise multiple regression analysis was done using EVLW as the dependent variable and all hemodynamic, gas exchange, and bioimpedance measurements at the final measuring point as independent variables. Mean pulmonary artery pressure and right lung resistivity corrected for weight were the two variables that led to the best EVLW regression equation (r 2 .81; SEE = 0.60; P < 0.0001): EVLW = 4.45 167 * Resistivity + (0. 85 * MPAP),Weight ) Using 6.1 cc/kg as the cutoff between normal and abnormal porcine EVLW [17], this equation has a sensitivity of 100% and a specificity of 80% to detect increased EVLW (Fig. 3).

DISCUSSION

We used a porcine acute lung injury model of endotoxin infusion followed by fluid resuscitation to test our new bioimpedance system against the gold standard of postmortem gravimetric EVLW. The primary study aim was to determine if this system could noninvasively quantify EVLW. Right lung resistivity corrected for body weight significantly correlated with gravimetric EVLW and can be used in a simple regression equation to estimate EVLW. The addition of mean pulmonary artery pressure measured invasively by a pulmonary artery catheter significantly improved this relationship. The secondary study aim was to compare EVLW following resuscitation with isotonic crystalloid to that following resuscitation with isooncotic colloid.

EVLW measured by both techniques was consistently higher in animals resuscitated with colloid. Both variables of MPAP and chest resistivity selected by regression analysis as predictors of EVLW are consistent with underlying physiologic principles. Hydrostatic pressure is the most important factor responsible for pulmonary transmicrovascular fluid exchange [18-19]. Mean pulmonary artery pressure is a major component of the hydrostatic driving pressure pushing fluid out of the pulmonary circulation into the interstitium. In both hydrostatic and increased permeability pulmonary edema it is expected that as the MPAP increases, EVLW will increase.

Resistance and resistivity are inversely proportional to the amount of water contained by tissues within an electric field. Previous animal and human studies of changes in impedance of the entire thorax and total lung water have confirmed this predictable inverse relationship between lung water and resistance to current flow through the
These studies, however, have been limited by technical and methodologic problems with the bioimpedance systems used. This has led to unreliable, inaccurate results. In the last clinical study, a tetrapolar electrode array (pairs at the neck and lower rib cage) was used to determine the thoracic impedance of normal subjects and of fluid-overloaded patients [12]. The authors concluded that transthoracic impedance was an insensitive measure of total lung water when compared to chest radiographs. Following that study, transthoracic BIA was essentially abandoned as a clinical tool for patient care.

Recently, however, a group of investigators has reevaluated the use of transthoracic bioimpedance as a noninvasive way to estimate EVLW in two animal models of acute lung injury and compared it to EVLW measured by the thermal green dye double-dilution technique [20, 21]. In both studies, total chest impedance (using an electric field that encompassed both hemithoraces and the mediastinum) was measured using a monofrequency analyzer and two pairs of needle electrodes on the upper and lower thorax. For the initial study acute lung injury was induced by the infusion of oleic into the right atrium of dogs and lung was measured for the next 60 min [20]. Although changes in thoracic impedance correlated with increases in EVLW over time, the baseline agreement between the two methods was poor. In a subsequent study designed to improve the measurements, acute lung injury was induced by infusing live Pseudomonas aeruginosa into pigs. Changes in hematocrit and right ventricular volumes measured with a volumetric pulmonary artery catheter were added to the thoracic impedance measurements [21]. Although this improved the correlation coefficient between the two techniques to $r = 0.85$, there remained concern about the agreement between the baseline measurements. In our experiment, the use of right heart volumes measured by volumetric pulmonary artery catheter did not improve our regression equations. This may have been because of the very different bioimpedance system that we used.

We developed our bioimpedance system with the technical and theoretical problems that have previously limited the sensitivity and accuracy of transthoracic measurements in mind. One problem has been the difficulty in avoiding the heart and major intrathoracic blood vessels so as to only measure the lung. Our detector electrodes were placed to isolate the right lung as much as possible, and we used an analyzer that measures resistance, not impedance. Impedance ($Z$) is the sum of the resistance ($R$), which is the pure opposition to flow of electric current and the reactance ($Xc$), which is the opposition to flow caused by tissue interfaces and trilaminar cell membranes, where $Z^2 = R^2 + Xc^2$ [22]. In all previous transthoracic BIA studies, thoracic impedance ($Z$) was measured. By measuring the resistance component of impedance, we can solve for lung resistivity. Lung resistivity reflects the characteristics of a standardized measurement of a theoretically definable geometric volume of lung, i.e., a cubic centimeter (see Appendix). Standardizing the BIA measurement to a resistivity of lung parenchyma removes some of the measurement variability related to differences in chest size and shape.

Our chest modeling assumptions are based on the path that electric current follows when it is injected through a cylindrical beaker containing electrolyte solution. This
model suggests that our external chest lead placement measures lung resistance at a point in the thorax midway between the detector electrodes at a depth equal to the distance between them, i.e., 10 cm deep within the right thorax. Admittedly this point remains inexact. Although we believe we are measuring lung parenchyma, this assumption cannot be confirmed in vivo. We recognize that a limitation inherent in all transthoracic BIA measurements is that the path that electric current running between the right leg and the right arm takes through the right hemithorax is unknown.

Previous segmental BIA studies suggest that electric current travels in an anisotropic path (along 010 direction A& the muscle fiber through muscle tissue SLICCh ZIS tile arm and the leg. However, since RILISCIC fibers in the trunk travel in several different directions, the current must traverse many different tissue Interfaces. It is therefore impossible to know the exact path that current takes through the chest. Another problem with transthoracic BIA has been correcting for the cyclical changes in gas volume inside the lung. Lung impedance is directly proportional to the volume of air in the lung, i.e., as air increases, impedance increases. The relationship between impedance change (DeltaZ) and volume of air moved (DeltaV) is nearly linear under most circumstances and depends on electrode location and subject size [23]. We kept our source electrodes on the distal extremities as in standard whole body BIA measurements and only moved the detector electrodes up to the chest. This electrode array has been shown to minimize the cyclical changes and to give stable values throughout the respiratory cycle [23]. In all previous transthoracic studies, the source and detector electrode pairs were moved together up to the chest. With the source electrodes on the distal limbs and the detector electrodes on the anterior right chest, changes in lung volume lead to very small changes in impedance about 0.3-0.4 Miter [23]. This implies that even with a vital capacity of 3.5 liters, there would be a difference in impedance of only 1.051A 9 over the entire voluntary respiratory range. At tidal volumes of 350 ml, the changes in impedance would only be 0. 11 to 0. 14 Q, with even smaller changes in resistance. Theoretically, using this BIA system, an estimated 0. 1-9. increase in resistance upon inspiration would lead to only a 0.7% change in right lung resistivity.

Controversy continues regarding the type of resuscitation fluid to use in cases of increased permeability pulmonary edema [18]. Our indication for giving discrete fluid boluses was a cardiac output less than 90% of baseline [13-15]. In previous studies of respiratory impairment that have compared crystalloid to colloid resuscitation, pulmonary capillary wedge pressure was used as the primary end point [24]. In our three groups, pulmonary capillary wedge pressures remained unchanged throughout the study. Despite this, although resuscitation with isoconcotic albumin was more effective than isotonic saline at maintaining the cardiac output and the blood pressure, it also resulted in consistently wetter lungs. Although almost five times more saline than albumin was needed, gravimetric EVLW was consistently lower in the saline group. Theoretically, this implies that exogenous albumin remains in the interstitiurn and draws in additional water [18]. In a management approach to acute lung injury that emphasizes restricting the EVLW while maintaining systemic oxygen delivery, crystalloid may be a better resuscitation fluid to use. We would caution, however, that chest resistivity corrected for body weight in the albumin group was consistently lower than in the other two groups at baseline and throughout the study. Although this
was not statistically different at baseline, it is possible that this groups of animals began with wetter lungs. Other extremely complicated electrical impedance imaging systems intended for lung water measurement are currently in eat-Iv development. In a recent study of oleic acid-induced pulmonary edema in dogs, a circumferential 32-copper-electrode array placed in the third intercostal space was used, with 32 alternating currents at 28.8 kHz coming from them. High-speed reconstruction algorithms were then used to create computer-generated "admittivity- (the inverse of resistivity) images of defined lung regions {25}. With the induction of pulmonary edema, lung admittivity increased. Interestingly, these investigators found that admittivity increased (consistent with our decrease in resistivity) in their control animals during the first 40 to 80 min of data recording followed by stability. We also found that chest resistivities in the control group decreased over the first hour and then stabilized. Possible explanations for this include changes in skin temperature and rehydration of the hydrogel in the electrodes used [25]. Our much simpler BIA system allows an objective noninvasive, bedside measurement of EVLW that is commercially available and can run continuously. With the addition of a pulmonary artery catheter, excellent agreement with EVLW measured gravimetrically can be obtained. Under conditions of increased permeability pulmonary edema, BIA- measured resistivity may allow titration of therapy to quantitative end point with a sensitive bedside measurement of fluid movement into and out of the lungs. Combined with other standard ICU monitoring, transthoracic BIA may provide a useful tool to help manage patients with acute lung injury.

**ACKNOWLEDGMENTS**

We thank Rudy Liedtke of RJL Systems, Inc. for valuable advice and-technical support, Yongzhi La for technical assistance with gravimetry, and John Doucette for statistical assistance.

**APPENDIX**

*Right Lung Resistivity Calculation* The ability of any biological tissue to resist a constant electric current depends on the relative proportions of water and electrolytes it contains and is called resistivity (in 9-cm) (23). Resistivity is inversely proportional to the number of free electrolytic ions per unit volume in the tissue. To calculate in vivo right lung resistivity, we assumed the thorax to be a roughly cylindrical electrical conductor and used the equation \( \rho = \frac{\text{Resistance} \times \text{circumference}^2}{4 \times \pi \times \text{length}} \) where \( \rho \) (rho) is resistivity(Ohms-cm), circumference is chest circumference, resistance is midelavicular parallel resistance, and length is the distance between the detector electrode pair ( cm). Theoretically, this yields the resistivity of a cubic centimeter of lung 10 cm deep in the right thorax at right angles to the midpoint between the two detector electrodes. Examples of known resistivities of biologic specimens from mammals includes 50 ohms-cm for plasma, 150 ohms-cm for human blood, 820-ohms-cm for dog liver, 1500 ohms -cm for lung and 2500 ohms-cm for fat[23].

**REFERENCES**


tissue edema after crystalloid or colloid resuscitation in porcine endotoxic shock: Comparison of ringer's lactate and 6% hetastarch. Circ. Shock, 30. 385. 1990.


