Exhaled Breath Condensate Nitrite and Its Relation to Tidal Volume in Acute Lung Injury*

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Study objective: Mechanical ventilation may damage the lung. Low tidal volume (VT) is protective, but VT is scaled to body weight (BW) and may be high in functionally small ARDS lungs. We hypothesized that exhaled breath condensate (EBC) nitrite (NO₂⁻) concentration may increase with lung distension.

Design: Prospective, noncontrolled study.

Setting: University hospital and medical ICU.

Patients: Thirty-five ICU patients requiring mechanical ventilation (severe pneumonia, n = 31; exacerbated COPD, n = 4). Patients were scored according to American and European Consensus Conference on ARDS criteria (AECC) [no lung injury, n = 7; acute lung injury, n = 13; ARDS, n = 15], as well as the Murray lung injury severity score (LISS) [score 0, n = 3; score 0.1 to 2.5, n = 19; score > 2.5, n = 13].

Interventions: EBC was collected and analyzed for NO₂⁻, interleukin (IL)-6, and IL-8. Serum was analyzed for IL-6, IL-8, and procalcitonin.

Results and measurements: EBC NO₂⁻ correlated well with VT (milliliters per kilogram of BW; r = 0.79, p < 0.0001) and expiratory minute volume (r = 0.60, p < 0.0001) but not with other ventilatory parameters or parameters of pulmonary (EBC IL-6, EBC IL-8) or systemic (serum IL-6, IL-8, and procalcitonin) inflammation. The ratio of EBC NO₂⁻ and the size of the VT correlated directly with lung injury (AECC, r = 0.66, p < 0.0001; LISS, r = 0.84, p < 0.0001).

Conclusion: EBC NO₂⁻ increased linearly with VT. The ratio of EBC NO₂⁻ to VT is assumed to reflect NO₂⁻ release at a given VT. An increase in this ratio indicates an inappropriate increase of NO₂⁻ production most likely due to mechanical stress of the remaining open lung units in injured lungs. We conclude that the EBC NO₂⁻/VT ratio may help to identify situations of critical mechanical stress.

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Key words: ARDS; biological markers; exhaled breath condensate; mechanical ventilation; nitric oxide

Abbreviations: AECC = American and European Consensus Conference on ARDS Criteria; ALI = acute lung injury; BALF = BAL fluid; BF = breathing frequency; BW = body weight; EBC = exhaled breath condensate; ELF = epithelial lining fluid; EMV = expiratory minute volume; FIO₂ = fraction of inspired oxygen; IL = interleukin; LISS = Murray lung injury severity score; NO₂⁻ = nitrite; PEEP = positive end-expiratory airway pressure; PIP = peak inspiratory pressure; Pmean = mean airway pressure; VT = tidal volume

It has been recognized for some time that mechanical ventilation may induce lung injury.¹,² High tidal volume (VT) ventilation is detrimental and has been shown to result in increased mortality. Low VT ventilation is regarded as a lung protective strategy.³,⁴ Acute lung injury (ALI) is characterized by decreased pulmonary compliance, alveolar flooding, and inhomogeneous ventilation in the presence of atelectatic lung.⁵,⁶ The size of the remaining open lung is unknown, and a VT adjusted to body weight (BW) may not be appropriate. Consequently, overdistension of ventilated units may still occur although a small VT is administered. A practical parameter of increased mechanical stress of the lung remains to be demonstrated.

Experiments have demonstrated that pulmonary nitric oxide production is stimulated by mechanical
forces. High-frequency oscillatory ventilation for example leads to an increase in exhaled nitric oxide in rabbits. Preliminary data from our laboratory suggest that nitrite (NO₂⁻) concentration in BAL fluid (BALF) of rabbit lungs is influenced strongly by VT. We therefore investigated the applicability of this parameter that is also easy to determine. Increased production of nitric oxide has often been related to inflammatory processes, such as asthma and cystic fibrosis. Mechanical ventilation may also contribute to lung injury and inflammation. Pulmonary nitric oxide release in patients receiving mechanical ventilation may therefore reflect alveolar distension, inflammation, or both. Our study addresses the question whether pulmonary nitric oxide production is related predominately to mechanical factors or to inflammation (pulmonary or systemic).

BALF has been used for monitoring of various pulmonary disorders including ARDS. The procedure is not without complications in the critically ill, and is not suited for multiple repetition. In addition, the dilution factor of epithelial lung fluid (ELF) in BALF varies to some extent, making measurements of solutes and other constituents difficult. Exhaled breath condensate (EBC) is a novel, noninvasive technique of sampling the lining fluid of the lung. EBC has been used for monitoring inflammatory lung diseases such as asthma, COPD, interstitial lung disease, and the ARDS. Hydrogen peroxide, S-isoprostanes, eicosanoids, cytokines, and also nitrite have all been detected in EBC.

Here we report a close correlation between EBC NO₂⁻ and VT (measured during exhalation, standardized to ideal BW [milliliters per kilogram of BW]). No correlation between EBC NO₂⁻ and parameters of pulmonary (interleukin [IL]-6 in EBC and IL-8 in EBC) or systemic inflammation (serum IL-6, serum IL-8, and serum procalcitonin) was found. In addition, the ratio of EBC NO₂⁻ and VT (ie, "VT-normalized NO₂⁻") correlated closely with the extent of lung injury assessed by the American European Consensus Conference on ARDS criteria (AECC) or the Murray lung injury severity score (LISS).

**Materials and Methods**

**Patients**

Inclusion criteria for this study were defined by acute respiratory failure due to pneumonia or COPD exacerbation leading to a minimum of 24 h of mechanical ventilation. After that time, patients had to be hemodynamically (no change in IV catecholamines of > 25% of baseline) and respiratory stable (no alteration in ventilator settings). A time frame of an additional 48 h was allowed to reach these criteria and to collect EBC without interference by necessary ICU procedures. Ventilator settings were also unchanged during the period of EBC collection.

Thirty-five patients (31 patients with severe pneumonia and 4 patients with COPD exacerbation) were included (16 men and 19 women; mean age [SD], 60 ± 14 years) during a period of 6 months. The extent of ALI was noted at the time of EBC collection using criteria of the AECC as well as the LISS. All patients received ventilation by pressure control with the same parameters for at least 4 h before EBC collection. Ventilatory parameters at time of EBC collection shown in Table 1.

**EBC Collection**

EBC was collected by inserting a special conduit (FILT Lung and Chest Diagnostics Ltd; Berlin Germany) into the expiratory limb of the ventilator and Chest Diagnostics Ltd; Berlin Germany) for the breath condensate collecting device (EcoScreen; Jaeger-Toennies; Hoechberg, Germany) into the expiratory limb of the ventilator tubing. Collecting time for EBC was 30 min. All patients received ventilation with identical humidification conditions (external humidifiers with 39°C deionized distilled H₂O).

Condensate from the inspiratory limb of the ventilator was also collected and analyzed for nitrite. NO₂⁻ in all of these samples was below detection levels, so that EBC NO₂⁻ could not have been influenced significantly.

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**Table 1—Ventilatory Parameters of All Patients Classified According to Both AECC and LISS Definitions**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Patients, No.</th>
<th>Pmean, millibar</th>
<th>PEEP, millibar</th>
<th>PIP, millibar</th>
<th>BF breaths/min</th>
<th>Vt, mL/kg BW</th>
<th>EMV, mL/kg BW per min</th>
</tr>
</thead>
<tbody>
<tr>
<td>No lung injury</td>
<td>7</td>
<td>13.7 ± 5.8</td>
<td>8.6 ± 4.8</td>
<td>22.4 ± 8.8</td>
<td>23.4 ± 4.3</td>
<td>6.2 ± 1.9</td>
<td>146.3 ± 57.1</td>
</tr>
<tr>
<td>ALI criteria</td>
<td>13</td>
<td>14.1 ± 3.1</td>
<td>8.7 ± 3.4</td>
<td>20.8 ± 3.5</td>
<td>20.8 ± 4.1</td>
<td>6.5 ± 1.1</td>
<td>134.3 ± 38.9</td>
</tr>
<tr>
<td>ARDS criteria</td>
<td>15</td>
<td>17.3 ± 4.6</td>
<td>11.6 ± 3.6</td>
<td>25.3 ± 8.3</td>
<td>23.6 ± 6.6</td>
<td>6.7 ± 1.6</td>
<td>160.1 ± 62.7</td>
</tr>
<tr>
<td>LISS</td>
<td>No lung injury (score &gt; 0)</td>
<td>3</td>
<td>12.3 ± 6.8</td>
<td>5.0 ± 0.0</td>
<td>20.3 ± 7.0</td>
<td>21.7 ± 4.7</td>
<td>6.0 ± 2.4</td>
</tr>
<tr>
<td>Mild-to-moderate lung injury (score, 0.1–2.5)</td>
<td>19</td>
<td>14.2 ± 3.8</td>
<td>8.6 ± 3.3</td>
<td>20.2 ± 5.7</td>
<td>22.4 ± 4.6</td>
<td>6.6 ± 1.4</td>
<td>148.8 ± 48.2</td>
</tr>
<tr>
<td>Severe lung injury (score &gt; 2.5)</td>
<td>13</td>
<td>17.9 ± 4.3</td>
<td>13.0 ± 3.0</td>
<td>27.9 ± 6.7</td>
<td>22.8 ± 6.8</td>
<td>6.5 ± 1.5</td>
<td>150.5 ± 64.4</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD.*
BAL was performed in study patients if scheduled by the ICU physician for microbiological diagnosis of infiltrates presumed to be caused by bacteria or fungi. In that case, EBC collection was done prior to bronchoscopy. BAL was performed according to guidelines (five 20-mL aliquots) for diagnostic reasons within 1 h of EBC collection. It was filtered through gauze and centrifuged at 300 g for 10 min at 4°C. The cell-free supernatant was used for further analysis. Two milliliters of BALF were used for analysis of nitrite.

**EBC NO₂⁻**

EBC NO₂⁻ and BALF NO₂⁻ were photometrically determined using the Griess reaction; 400 μL of Griess reagent were added to 300 μL of EBC. Absorption was read at 550 nm.

**Markers of Inflammation**

EBC samples were examined for amylase activity (α-Amylase ES1491300 kit; Boehringer Mannheim; Mannheim, Germany) in order to exclude a relevant contamination by saliva. Five-milliliter aliquots of EBC were lyophilized, reconstituted in 500 μL, and used in IL-6 and IL-8 enzyme-linked immunosorbent assays (Quantikine HS human IL-6; Quantiglo human IL-8; R&D Systems; Minneapolis, MN). In addition, IL-6, IL-8 (Immulite; DPC Biemann; Bad Nauheim, Germany), and procalcitonin (LUMItest PCT; BRAHMS Diagnostica; Henningsdorf/Berlin, Germany) were measured from serum concomitantly.

**Statistical Analysis**

Statistical analysis was performed with the SPSS software package (SPSS; Chicago, IL). Linear regression analysis was performed to correlate EBC NO₂⁻ with ventilatory parameters and lung injury scores. Comparisons of groups were performed by analysis of variance testing and post hoc analysis. Statistical significance was accepted at the 5% level; results are mean ± SD.

**Results**

**EBC NO₂⁻ and Clinical Scores**

EBC NO₂⁻ was significantly different in the three patient groups: EBC NO₂⁻ was increased in patients with ARDS compared to patients with ALI criteria or patients without signs of lung injury according to both AECC (ARDS, 6.28 ± 1.94 μmol/L; ALI, 4.56 ± 1.32 μmol/L; no lung injury, 3.58 ± 1.52 μmol/L) as well as LISS criteria (ARDS, 6.26 ± 1.71 μmol/L; ALI, 4.61 ± 1.70 μmol/L; no lung injury, 3.23 ± 2.07 μmol/L) [Fig 1].

**EBC NO₂⁻ and Ventilatory Parameters**

Table 2 summarizes the correlations between EBC NO₂⁻ and ventilatory parameters. EBC NO₂⁻ was closely correlated both to VT and expiratory minute volume (EMV) [in each case normalized to ideal BW] but not to positive end-expiratory pressure (PEEP), peak inspiratory pressure (PIP), or breathing frequency (BF). There was a weak correlation of EBC NO₂⁻ and mean inspiratory airway pressure (Pmean; correlation coefficient < 0.5).

The linear type of relationship of EBC NO₂⁻ to VT (y = 1.06x − 1.80, r = 0.79, n = 35, p < 0.0001) is depicted in Figure 2. The strong relationship of the two parameters seems to confirm our hypothesis that EBC NO₂⁻ is related to pulmonary distension. When patients were analyzed with regard to the extent of lung injury (AECC definition), regression lines were shifted up and somewhat steeper in the presence of ARDS, or shifted down and less steep in the absence of lung injury (ARDS, y = 1.12x − 1.21, r = 0.90, p < 0.0001; ALI, y = 0.90x − 1.24,

![Figure 1. EBC NO₂⁻ for patients grouped according to AECC and LISS scores (Table 1). Left panel (AECC scoring): white column, no lung injury; gray column, ALI; black column, ARDS. Right panel (LISS scoring): white column, no lung injury; gray column, mild-to-moderate lung injury; black column, severe lung injury (data are presented as mean ± SD); p values for the comparison among the groups are given.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21998/)
Correlation coefficients and p values for the relation of EBC NO\textsubscript{2\textsuperscript{-}} with V\textsubscript{t} were determined (Table 2). In contrast, no correlation of V\textsubscript{t} alone with either LISS or Pao\textsubscript{2}/FiO\textsubscript{2} was observed (LISS, r = 0.05, p = 0.77; Pao\textsubscript{2}/FiO\textsubscript{2}, r = 0.17, p = 0.32). Figure 3 indeed demonstrates significant correlations of the continuous-parameter LISS with EBC NO\textsubscript{2\textsuperscript{-}}/VT ratio (Fig 3, right; r = 0.84, p < 0.0001) as well as of the Pao\textsubscript{2}/fraction of inspired oxygen (FiO\textsubscript{2}) ratio (the continuous parameter of the AECC classification) with EBC NO\textsubscript{2\textsuperscript{-}}/VT (Fig 3, left; r = 0.66, p < 0.0001). In contrast, no correlation of V\textsubscript{t} alone with either LISS or Pao\textsubscript{2}/FiO\textsubscript{2} was observed (LISS, r = 0.05, p = 0.77; Pao\textsubscript{2}/FiO\textsubscript{2}, r = 0.17, p = 0.32).

**Correlation of EBC NO\textsubscript{2\textsuperscript{-}} and BAL NO\textsubscript{2\textsuperscript{-}}**

In 10 patients in whom a BAL was indicated for microbiologic diagnosis, BAL NO\textsubscript{2\textsuperscript{-}} was determined and compared to EBC NO\textsubscript{2\textsuperscript{-}}. A significant correlation between both values was found (r = 0.79, p = 0.012).

**Discussion**

Nitrite, generated by nitric oxide in aqueous media, has often been regarded to be a marker of inflammation.\textsuperscript{11,26} It may therefore not have come to anyone’s surprise that NO\textsubscript{2\textsuperscript{-}} was observed in EBC of ventilated patients with lung injury due to pneumonia or exacerbation of COPD. At first sight, a relation of inflammation and EBC NO\textsubscript{2\textsuperscript{-}} is further suggested by a (weak) correlation of lung injury scores and EBC NO\textsubscript{2\textsuperscript{-}}. However, further analysis of factors influencing EBC NO\textsubscript{2\textsuperscript{-}} has led us to suggest a different interpretation of this initial relation.

The major finding in this study was a strong correlation of EBC NO\textsubscript{2\textsuperscript{-}} with V\textsubscript{t} (milliliters per kilogram of BW) [r = 0.79, p < 0.0001]. While EBC NO\textsubscript{2\textsuperscript{-}} was to some extent influenced by the extent of lung injury, V\textsubscript{t} was not. The ratio of EBC NO\textsubscript{2\textsuperscript{-}} and V\textsubscript{t}, however, exhibited a strong correlation with the extent of lung injury, much stronger than that of EBC NO\textsubscript{2\textsuperscript{-}} with lung injury. Similarly regression lines for the correlation of EBC NO\textsubscript{2\textsuperscript{-}} with V\textsubscript{t} (Fig 2) were shifted up and somewhat steeper in the presence of ARDS, while they were shifted down and less steep in the absence of lung injury. In

**Table 2—Correlations of Ventilatory Parameters With EBC NO\textsubscript{2\textsuperscript{-}}**

<table>
<thead>
<tr>
<th>Parameters of Ventilation</th>
<th>Correlation with EBC NO\textsubscript{2\textsuperscript{-}}</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF, breaths/min</td>
<td>0.12</td>
<td>0.48</td>
</tr>
<tr>
<td>PEEP, millibar</td>
<td>0.34</td>
<td>0.05</td>
</tr>
<tr>
<td>PIP, millibar</td>
<td>0.23</td>
<td>0.18</td>
</tr>
<tr>
<td>Pmean, millibar</td>
<td>0.42</td>
<td>0.012</td>
</tr>
<tr>
<td>EMV, mL/kg of BW per min</td>
<td>0.60</td>
<td>0.0001</td>
</tr>
<tr>
<td>V\textsubscript{t}, mL/kg of BW</td>
<td>0.79</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**Table 3—Correlations of Inflammatory Markers With EBC NO\textsubscript{2\textsuperscript{-}}**

<table>
<thead>
<tr>
<th>Markers of Inflammation</th>
<th>Correlation with EBC NO\textsubscript{2\textsuperscript{-}}</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6, pg/mL</td>
<td>0.12</td>
<td>0.48</td>
</tr>
<tr>
<td>EBC IL-6, pg/mL</td>
<td>0.33</td>
<td>0.06</td>
</tr>
<tr>
<td>IL-8, pg/mL</td>
<td>0.30</td>
<td>0.08</td>
</tr>
<tr>
<td>EBC IL-8</td>
<td>0.15</td>
<td>0.39</td>
</tr>
<tr>
<td>Procalcitonin</td>
<td>0.01</td>
<td>0.95</td>
</tr>
</tbody>
</table>

\[
EBC NO\textsubscript{2\textsuperscript{-}} = 0.74, p < 0.004; \text{ no lung injury, } y = 0.78x - 1.27, r = 0.96, p < 0.0008).\]

**EBC NO\textsubscript{2\textsuperscript{-}} and Inflammation**

Correlation coefficients and p values for the relations between EBC NO\textsubscript{2\textsuperscript{-}} and pulmonary or systemic markers of inflammation are depicted in Table 3. No significant correlation between the chosen markers of inflammation and EBC NO\textsubscript{2\textsuperscript{-}} were observed. A correlation of EBC NO\textsubscript{2\textsuperscript{-}} with pulmonary or systemic inflammation is therefore not supported by our results.

**EBC NO\textsubscript{2\textsuperscript{-}} Normalized to V\textsubscript{t}**

If EBC NO\textsubscript{2\textsuperscript{-}} truly reflects pulmonary distension, and if distension is greater in more severe lung injury due to derecruitment, the relation of EBC NO\textsubscript{2\textsuperscript{-}} and V\textsubscript{t} (ie, EBC NO\textsubscript{2\textsuperscript{-}}/VT milliliters per kilogram of BW) ratio should be directly correlated to the extent of lung injury. In support of this assumption,
patients with more severe lung injury, higher EBC NO$_2^−$ values were thus detected at a given VT (high EBC NO$_2^−$/VT ratio) compared to patients without lung injury (low EBC NO$_2^−$/VT ratio). The strong relationship of EBC NO$_2^−$ and VT mentioned before suggests that this may result from a greater extent of pulmonary distension (at similar VT) due to a reduction of functional lung volume in ALI/ARDS known as the “baby lung” effect.

This interpretation assumes a mechanism coupling nitric oxide production and lung distension. Preliminary data from our laboratory support this assumption.$^9$ Alternatively the increased EBC NO$_2^−$ may be caused independently by pulmonary/airway inflammation as has been demonstrated in acute asthma.$^{11,26,27}$ and cystic fibrosis.$^{10}$ Pulmonary or systemic inflammation, however, does not seem to be the primary determinant of EBC NO$_2^−$ in our study for several reasons: (1) EBC NO$_2^−$ does not significantly correlate with proinflammatory cytokines IL-6 and IL-8 (measured in EBC and serum) or with procalcitonin; (2) the strong relation of EBC NO$_2^−$ and VT observed in all patient subgroups independent of severity of disease may not be explained by a direct relation between inflammation and EBC NO$_2^−$; and (3) mechanical distension may influence the extent of inflammation and indirectly stimulate nitric oxide production. However, inflammation is influenced by a variety of factors, and a simple strong correlation of EBC NO$_2^−$ with VT such as the one observed here would hardly be expected.

If EBC NO$_2^−$ is related to pulmonary distension, and if the available lung volume is reduced in more severe lung injury, the increase in the EBC NO$_2^−$/VT ratio may reflect the increased alveolar distension in the remaining open units of the injured lung. Indeed, we observed a strong correlation of EBC NO$_2^−$/VT ratio with scores of lung injury (LISS and AECC; Fig 3). This correlation is best in injured lungs (PaO$_2$/FiO$_2$ < 300, LISS > 1). Additional mechanisms may contribute to EBC NO$_2^−$ baseline concentration in lungs with normal PaO$_2$/FiO$_2$ and thus influence the EBC NO$_2^−$/VT ratio to a greater extent in uninjured lungs.

Our results are supported by previous studies$^5,6$ that report a relation between pulmonary nitric oxide release and mechanical stimuli resulting from, eg, pulmonary artery or venous pressure elevation or from high-frequency oscillatory ventilation. The biological function of distension-induced nitric oxide, which will result in generation of NO$_2^−$ is unclear; however, it has been reported that nitric oxide protects alveolar type II epithelial cells from apoptosis following mechanical overdistension.$^{30}$ In addition, nitric oxide may induce a selective pulmonary vasodilation with improved perfusion of well-ventilated alveoli, reduced intrapulmonary shunt volume, and improved oxygenation.$^{31,32}$ Endogenous-released nitric oxide has also been shown to aggravate lung damage via peroxynitrite formation.$^{34,35}$ This has been referred to as “nitrosative stress.” Increased NO$_2^−$ in BALF detected as NO$_2^−$ and nitrate has been found in patients at risk for ARDS and with ARDS, and has been related to increased mortality.$^{36}$ The question whether nitric oxide released in response to increased mechanical distension is beneficial or a mechanism of further injury of the lung cannot be resolved on the basis of our data.

Does EBC in part reflect ELF? EBC NO$_2^−$ was compared to BALF NO$_2^−$ in a subset of 10 of the 35 patients in whom BAL was scheduled for diagnostic reasons, and a strong correlation of BALF NO$_2^−$ and EBC NO$_2^−$ was observed. Considering the variation in ELF dilution that is inherent to BALF, this finding supports that EBC NO$_2^−$ results are repre-
sentative of ELF. In fact EBC NO$_2^-$ has been shown to represent nitric oxide production better than exhaled nitric oxide in patients with cystic fibrosis.\textsuperscript{37}

EBC is obtained by exhaling into a cold trap. Commercial devices are available, and the method can be adapted to mechanical ventilation by inserting an appropriate conduit into the expiratory limb of the ventilator tubing. Although mostly water vapor, EBC contains other constituents, such as small molecules, proteins, and even DNA.\textsuperscript{12,38} The mechanisms that contribute to the presence of nonvolatile molecules in EBC have not yet been elucidated, but the formation of an aerosol during opening of alveoli or at the branching of small airways is a likely mechanism. We have previously reported that the amount of breath condensate collected depends almost exclusively on the expired volume.\textsuperscript{39} We therefore suggest a mechanism linking alveolar dispersion to the production of nitric oxide and subsequently to the generation of nitrite in the ELF. This is likely a mechanism located in the periphery of the lung, since EBC is thought to be generated in the lower respiratory tract and the alveoli.\textsuperscript{40}

The results of our investigation suggest a close relation of EBC NO$_2^-$ and pulmonary distension but no correlation with parameters of pulmonary or systemic inflammation. EBC NO$_2^-$ normalized to VT can indicate inappropriate distension (ie, NO$_2^-$ release) at a given VT, and exhibited close correlation with clinical scores of lung injury in this study. This inappropriate distension may be the consequence of increasing derecruitment with increasing lung injury. Further evaluation of this marker may reveal its clinical usefulness as a practical marker to monitor patients receiving mechanical ventilation for increased mechanical stress.

**REFERENCES**

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NOTICE OF ANNUAL MEETINGS

The Annual Meeting of the current Board of Regents of the American College of Chest Physicians (the “College”) will convene at 1:00 p.m. Friday, October 24, 2003, at the Gaylord Palms Resort & Convention Center, 6000 West Osceola Parkway, Kissimmee, Florida, to transact such business as shall properly come before the meeting.

The Annual Meeting of the College Fellows will convene at 1:30 p.m. Saturday, October 25, 2003, at the Gaylord Palms Resort & Convention Center, 6000 West Osceola Parkway, Kissimmee, Florida, to receive the report of the Nominations Committee, to elect Officers, Regents and Governors to hold office for the following year, and to transact such other business as shall properly come before the meeting.