Effect of a Lung Protective Strategy for Organ Donors on Eligibility and Availability of Lungs for Transplantation: A Randomized Controlled Trial

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Context Many potential donor lungs deteriorate between the time of brain death and evaluation for transplantation suitability, possibly because of the ventilatory strategy used after brain death.

Objective To test whether a lung protective strategy increases the number of lungs available for transplantation.

Design, Setting, and Patients Multicenter randomized controlled trial of patients with beating hearts who were potential organ donors conducted at 12 European intensive care units from September 2004 to May 2009 in the Protective Ventilatory Strategy in Potential Lung Donors Study.

Interventions Potential donors were randomized to the conventional ventilatory strategy (with tidal volumes of 10-12 mL/kg of predicted body weight, positive end-expiratory pressure [PEEP] of 3-5 cm H₂O, apnea tests performed by disconnecting the ventilator, and open circuit for airway suction) or the protective ventilatory strategy (with tidal volumes of 6-8 mL/kg of predicted body weight, PEEP of 8-10 cm H₂O, apnea tests performed by using continuous positive airway pressure, and closed circuit for airway suction).

Main Outcome Measures The number of organ donors meeting eligibility criteria for harvesting, number of lungs harvested, and 6-month survival of lung transplant recipients.

Results The trial was stopped after enrolling 118 patients (59 in the conventional ventilatory strategy and 59 in the protective ventilatory strategy) because of termination of funding. The number of patients who met lung donor eligibility criteria after the 6-hour observation period was 32 (54%) in the conventional strategy vs 56 (95%) in the protective strategy (difference of 41% [95% confidence interval {CI}, 26.5% to 54.8%]; P < .001). The number of patients in whom lungs were harvested was 16 (27%) in the conventional strategy vs 32 (54%) in the protective strategy (difference of 27% [95% CI, 10.0% to 44.5%]; P = .004). Six-month survival rates did not differ between recipients who received lungs from donors ventilated with the conventional strategy compared with the protective strategy (11/16 [69%] vs 24/32 [75%], respectively; difference of 6% [95% CI, −22% to 32%]).

Conclusion Use of a lung protective strategy in potential organ donors with brain death increased the number of eligible and harvested lungs compared with a conventional strategy.

Trial Registration clinicaltrials.gov Identifier: NCT00260676

There is evidence in various settings demonstrating that a lung protective strategy is beneficial. In patients with acute lung injury, ventilation...
with low tidal volumes decreased absolute mortality by 9%. In patients with normal pulmonary function, ventilation with lower tidal volumes was associated with a lower likelihood of developing acute lung injury. In patients with brain injuries, ventilation with higher tidal volumes was an independent factor contributing to development of acute lung injury.

Despite this evidence, there is controversy as to the best ventilatory strategy to use in patients diagnosed as having brain death. A consensus conference recommended ventilation with low tidal volumes of 10 to 12 mL/kg of measured body weight and positive end-expiratory pressure (PEEP) of 5 cm H2O. A subsequent review article and an observational study suggested that potential donors should receive ventilation with low tidal volumes of 8 to 10 mL/kg of predicted body weight. Guidelines for potential organ donors currently recommend ventilation with higher levels of low tidal volume (10-15 mL/kg of measured body weight).

We hypothesized that a protective lung strategy in patients diagnosed as having brain death would decrease the development of lung dysfunction and increase the number of lungs available for transplantation.

**METHODS**

Potential donors were from 12 intensive care units in Italy and Spain, had normal heart beat patterns, and had been reported to organ procurement organizations between September 2004 and May 2009. The ethics review boards of all of the participating hospitals approved the protocol and relatives of the patients provided consent for organ donation. Exclusion criteria were denied consent for organ donation; legal issues preventing organ donation; history of cardiac arrest; age younger than 18 years or older than 65 years; radiographic pulmonary infiltrates; duration of mechanical ventilation until brain death longer than 5 days; smoking history (>20 pack-years), asthma or chronic obstructive pulmonary disease, chest trauma or previous thoracic surgery; and aspiration pneumonia or purulent secretions diagnosed by bronchoscopy, sputum, or bronchoalveolar lavage positive for Gram stain, fungus, or white blood cells.

The Protective Ventilatory Strategy in Potential Lung Donors Study used a central Web site that created a concealed, computer-generated block randomization schedule that assigned patients to either the conventional or protective lung ventilatory strategy, which was applied during the observation period required for declaration of brain death (6 hours), and maintained until patients arrived in the operating department for organ extraction.

In the conventional strategy, patients received ventilation with low tidal volumes of 10 to 12 mL/kg of predicted body weight and PEEP of 3 to 5 cm H2O. An open circuit was used for tracheal suction. Apnea tests were performed by disconnecting the patient from the ventilator while administering high-flow oxygen.

In the protective strategy, patients received ventilation with low tidal volumes of 6 to 8 mL/kg of predicted body weight and PEEP of 8 to 10 cm H2O. A closed circuit was used for tracheal suction. Apnea tests were performed with the ventilator in the continuous positive airway pressure mode. Continuous positive airway pressure was set equal to the previous PEEP used during mechanical ventilation. Recruitment maneuvers (doubling ventilation with low tidal volumes for 10 breaths) were performed after any disconnection from the ventilator.

In both strategy groups, respiratory rate was adjusted to obtain PACO2 of 40 to 45 mm Hg and fraction of inspired oxygen (FiO2) was adjusted to obtain PaO2 of 90 mm Hg or greater. The viability of lungs was assessed at the beginning and at the end of the 6-hour observation period. The ratio of PaO2 to FiO2 and peak airway pressure at the end of the 6-hour observation period were reported to the organ procurement organization. The officer of the organ procurement organization was not aware of patient allocation and was not involved in the study. The officer of the organ procurement organization declared the potential donor as eligible for harvesting of the lungs when the ratio of PaO2 to FiO2 was 300 mm Hg or greater, FiO2 was 1.0, and peak airway pressure was less than 30 cm H2O.

The number of lungs harvested and the number of potential donors were the number of potential recipients matching size, organ compatibility; or logistical [inability of the surgical team to proceed in time for harvest, collection, and transplantation]). The number of harvested hearts, livers, and kidneys in both groups was recorded.

The primary outcome of the study was the number of potential donors meeting eligibility criteria for lung harvest at the end of the 6-hour observation period. Other clinical outcomes were the number of lungs harvested and the number of patients who received lung transplants who were alive at 6 months.

Six-month survival also was recorded for patients who received other organs harvested from the donors. Duration of intensive care unit stay was recorded in lung transplant recipients. Blood samples were collected at the beginning and at the end of the 6-hour ob-
Figure. Assessment of Eligibility and Inclusion in the Protective Ventilatory Strategy in Potential Lung Donors Study

918 Patients assessed for lung donor eligibility
800 Excluded
247 Denied consent for organ donation
190 Aged <18 y or ≥65 y
91 Had pending legal issues
58 Had history of smoking
50 Had aspiration pneumonia or purulent secretions
48 Had asthma or chronic obstructive pulmonary disease
46 Had chest trauma or previous thoracic surgery
29 Presence of infiltrates on chest x-ray
21 Duration of mechanical ventilation ≥5 d
17 Had cardiac arrest

118 Randomized
59 Randomized to receive conventional ventilatory strategy
59 Received intervention as randomized
59 Completed assessment at end of 6-h observation period
59 Included in primary analysis
59 Randomized to receive protective ventilatory strategy
59 Received intervention as randomized
59 Completed assessment at end of 6-h observation period
59 Included in primary analysis

A LUNG PROTECTIVE STRATEGY FOR ORGAN DONORS

In a previous observational study, we found that 54% of potential lung donors met eligibility criteria for lung donation. Based on this, the study was powered for 200 patients to demonstrate a 25% absolute increase in eligible lungs (from 50% to 75%), with a 5% risk of type I error, and a power level of 90%. An interim analysis was planned after data were obtained on the first 100 patients. The stopping boundaries of the study were based on the primary end point and were designed to allow termination of the study if the protective strategy was better than the conventional (control) strategy (P<.003) or for futility (P>.03).10

All analyses were conducted on an intention-to-treat basis. Data are presented as mean (SD) or median (interquartile range [IQR]). Comparisons between groups and within groups were made using the t test, the Wilcoxon rank sum test, the χ² test, the Fisher exact test, and the McNemar test. All tests were 2-tailed. The primary outcome also was evaluated using multivariate logistic regression analyses. To examine the temporal effect across groups during the 6-hour observation period, relevant clinical variables were analyzed using a mixed-linear regression model for repeated measures in which each parameter was the dependent variable, while time and group were the independent variables. The number needed to treat to benefit also was estimated (ie, the number of patients with brain death who had to be treated with the protective strategy to obtain an extra lung donor who met acceptability criteria). Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). To account for individual hospital effects, the cumulative OR was used as a measure of effect size in a robust logistical regression model. The level of statistical significance was set at .05. Statistical analysis was conducted using SAS software version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

The steering committee stopped the Protective Ventilatory Strategy in Potential Lung Donors Study before the planned interim analysis was performed because of termination of funding. The steering committee did not have knowledge of the clinical outcomes at the time this decision was made.

Of the 918 potential organ donors reported to the organ procurement organization, 118 patients were randomized and included in the final analysis. Denied consent, legal issues, and cardiac arrest were the reasons for excluding 355 patients (39%). The remaining 445 patients (42%) were excluded based on the standard criteria used to identify nonoptimal lungs (FIGURE). There were no missing data and no patients were lost to follow-up.

Baseline characteristics were similar in both groups (TABLE 1). After randomization, ventilation with low tidal volume was lower and respiratory rate, PEEP, and central venous pressure were higher in the protective strategy compared with the conventional strategy. The ratio of PaO₂ to FiO₂ was higher in the protective strategy compared with the conventional strategy at the third and sixth hour of the observation period (TABLE 2).

At study enrollment, the number of patients who met eligibility criteria did not differ between the conventional strategy and the protective strategy. At the end of the 6-hour period, the number of patients meeting lung donor eligibility criteria decreased in the conventional strategy from 49 (83%) to 32 patients (54%) (difference of 29% [95% CI, 12% to 46%]; P=.001). The number of patients meeting lung donor eligibility criteria at the end of the 6-hour period increased slightly in the protective strategy from 51 (86%) to 56 patients (95%) (difference of 9% [95% CI, −2.1% to 19.1%], P=.13). The number of patients in the conventional strategy who met lung donor eligibility criteria at the end of the 6-hour observation period was 32 (54%) compared with 56 (95%) in the protective strategy (difference of 41% [95% CI, 26.5% to 54.8%]; P<.001) (TABLE 3). The number of patients in whom lungs were harvested was 16 (27%) in the conventional strategy compared with 32 (54%) in the protective strategy.
had a ratio of PaO2 to FIO2 of 208 (83) utes (IQR, 25 to 40 minutes). Patients


test, which lasted a median of 38 minutes. Patients


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tive strategy at the end of the eligibility


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ventilation from the end of the 6-hour observation period


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tive strategy was 12 days (IQR, 1 to 100 days) compared with 8 days


Table 1. Patient Characteristics at Enrollment

<table>
<thead>
<tr>
<th>Ventilatory Strategy</th>
<th>Conventional (n = 59)</th>
<th>Protective (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD), y</strong></td>
<td>45 (13)</td>
<td>42 (13)</td>
</tr>
<tr>
<td><strong>Female sex, No. (%)</strong></td>
<td>27 (46)</td>
<td>34 (58)</td>
</tr>
<tr>
<td><strong>Primary diagnosis, No. (%)</strong></td>
<td>37 (63)</td>
<td>45 (76)</td>
</tr>
<tr>
<td><strong>Cerebrovascular hemorrhagic accident</strong></td>
<td>17 (20)</td>
<td>12 (20)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>5 (8)</td>
<td>2 (3)</td>
</tr>
<tr>
<td><strong>Duration of mechanical ventilation prior to randomization, median (IQR), h</strong></td>
<td>38 (6-120)</td>
<td>34 (2-120)</td>
</tr>
<tr>
<td><strong>Ventilatory pattern, mean (SD)</strong></td>
<td>45 (12)</td>
<td>44 (11)</td>
</tr>
<tr>
<td><strong>Tidal volume, mL/kg of predicted body weight</strong></td>
<td>9.3 (1.5)</td>
<td>9.0 (1.6)</td>
</tr>
<tr>
<td><strong>Respiratory rate, breaths/min</strong></td>
<td>13 (3)</td>
<td>13 (2)</td>
</tr>
<tr>
<td><strong>PEEP, cm H2O</strong></td>
<td>4.3 (2.9)</td>
<td>5.0 (2.8)</td>
</tr>
<tr>
<td><strong>Peak inspiratory pressure, cm H2O</strong></td>
<td>21 (5)</td>
<td>22 (4)</td>
</tr>
<tr>
<td><strong>Plateau pressure, cm H2O</strong></td>
<td>16 (3)</td>
<td>16 (4)</td>
</tr>
<tr>
<td><strong>Minute ventilation, L/min</strong></td>
<td>7.2 (1.9)</td>
<td>7.0 (1.7)</td>
</tr>
<tr>
<td><strong>Ratio of PaO2 to FIO2</strong></td>
<td>393 (144)</td>
<td>400 (124)</td>
</tr>
<tr>
<td><strong>Arterial blood gases, mean (SD)</strong></td>
<td>171 (112)</td>
<td>173 (74)</td>
</tr>
<tr>
<td><strong>PaO2, mm Hg</strong></td>
<td>98 (2)</td>
<td>99 (1)</td>
</tr>
<tr>
<td><strong>PaCO2, mm Hg</strong></td>
<td>36 (5)</td>
<td>36 (6)</td>
</tr>
<tr>
<td><strong>Arterial pH</strong></td>
<td>7.44 (0.07)</td>
<td>7.43 (0.07)</td>
</tr>
<tr>
<td><strong>Hemodynamic variables, mean (SD)</strong></td>
<td>84 (16)</td>
<td>83 (16)</td>
</tr>
<tr>
<td><strong>Mean arterial pressure, mm Hg</strong></td>
<td>6.4 (2.9)</td>
<td>7.5 (2.8)</td>
</tr>
<tr>
<td><strong>Central venous pressure, mm Hg</strong></td>
<td>47 (80)</td>
<td>47 (80)</td>
</tr>
</tbody>
</table>

Abbreviations: FIO2, fraction of inspired oxygen; IQR, interquartile range; PEEP, positive end-expiratory pressure; SaO2, arterial oxygen saturation.

Concomitant treatment:

- **Dopamine, median (IQR), µg/kg/min** | 7.5 (1-15) | 6.5 (0.9-17) |
- **Norepinephrine, median (IQR), µg/kg/min** | 0.13 (0.02-0.25) | 0.16 (0.02-0.30) |
- **Prednisolone, No. (%)** | 10 (17) | 12 (20) |
- **Triiodothyronine or thyroxine, No. (%)** | 9 (15) | 8 (14) |
- **Vasopressin, No. (%)** | 2 (3) | 1 (2) |

**A LUNG PROTECTIVE STRATEGY FOR ORGAN DONORS**

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ventional strategy and the protective strategy (hearts: 25 [42%] vs 28 [47%], respectively, difference of 5% [95% CI, −13% to 23%]; livers: 48 [81%] vs 52 [88%], difference of 7% [95% CI, −6.4% to 19.9%]; kidneys: 83 [70%] vs 94 [80%], difference of 10% [95% CI, −1.8% to 20.4%]). Six-month survival did not differ between patients who received other organs from donors in the conventional strategy and the protective strategy (hearts: 70% vs 80%, respectively, difference of 10% [95% CI, −15% to 36%]; liver: 94% vs 94% difference of 0% [95% CI, −0.01% to 0.08%]; kidneys: 95% vs 94%, difference of 1% [95% CI, −0.06% to 0.07%]).

Blood samples were obtained in 20 patients in the conventional strategy and in 17 patients in the protective strategy. Cytokine concentrations at baseline were similar in both groups (Table 4). A significant increase over time in IL-6 and tumor necrosis factor receptors was observed in the conventional strategy and the protective group; all other measured cytokines did not change over time.

**COMMENT**

This study demonstrates that a lung protective strategy in potential organ donors resulted in a higher number of eligible donors and harvested lungs compared with a conventional strategy. Of importance, the number of harvested hearts, livers, and kidneys did not differ between the conventional and protective strategies.

An interim analysis, performed by an independent data and safety monitoring board was planned after data were obtained on the first 100 patients. The steering committee, however, stopped the trial prior to the planned interim analysis because accrual had been slow, and all of the funding for the trial had been spent.

Patient No. 100 was randomized on September 30, 2008. The steering committee met to decide whether to ask the data and safety monitoring board to perform the interim analysis as planned by the statistical analysis plan or stop accrual and analyze all included patients as the final data set. Because supplementary funds had been requested, the steering committee was unsure whether the study would proceed. It was decided to maintain the planned interim analysis to avoid the potential loss of α level and continue recruitment until responses from grant agencies were released (expected by spring 2009). On May 30, 2009, the steering committee was informed that sufficient extra funds to complete the study would not be provided. The steering committee decided (1) to halt the study and stop randomization, (2) to lock the database with patient No. 118 as the last patient (randomized on May 26, 2009), and (3) to analyze the data using the criteria that were prespecified for the final analysis. Of note, if the formal interim analysis had been performed, the data and safety monitoring board members may have stopped the trial at that point because the results crossed the predefined threshold for stopping for efficacy.

Early stopping for efficacy of randomized controlled trials may inflate the estimated treatment effect.20 We believe this issue may not be relevant in

### Table 2. Ventilatory and Hemodynamic Variables During the 6 Hours of Treatment

<table>
<thead>
<tr>
<th></th>
<th>First Hour</th>
<th>Third Hour</th>
<th>Sixth Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of Treatment and Ventilatory Strategy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ventilatory variables, mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIO2</td>
<td>47 (17) n = 59</td>
<td>42 (7) n = 59</td>
<td>48 (18) n = 59</td>
</tr>
<tr>
<td>Tidal volume, mL/kg of predicted body weight</td>
<td>10.1 (1.6) n = 59</td>
<td>7.9 (1.1) a n = 59</td>
<td>10.1 (1.6) n = 59</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>11 (2) n = 59</td>
<td>13 (3) b n = 59</td>
<td>11 (2) n = 59</td>
</tr>
<tr>
<td>PEEP, cm H2O</td>
<td>4.2 (1.6) n = 59</td>
<td>8.7 (1.4) a n = 59</td>
<td>4.4 (1.5) n = 59</td>
</tr>
<tr>
<td>Peak inspiratory pressure, cm H2O</td>
<td>22 (5) n = 59</td>
<td>23 (5) n = 59</td>
<td>23 (5) n = 59</td>
</tr>
<tr>
<td>Plateau pressure, cm H2O</td>
<td>16 (4) n = 59</td>
<td>17 (4) n = 59</td>
<td>17 (4) n = 59</td>
</tr>
<tr>
<td>Minute ventilation, L/min</td>
<td>6.9 (1.5) n = 59</td>
<td>6.5 (1.7) n = 59</td>
<td>6.8 (1.8) n = 59</td>
</tr>
<tr>
<td>Ratio of PaO2 to FIO2</td>
<td>360 (120) n = 59</td>
<td>402 (118) n = 59</td>
<td>342 (126) n = 59</td>
</tr>
</tbody>
</table>

### Table 2. Ventilatory and Hemodynamic Variables During the 6 Hours of Treatment

<table>
<thead>
<tr>
<th></th>
<th>First Hour</th>
<th>Third Hour</th>
<th>Sixth Hour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood gas analysis, mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>164 (72) n = 59</td>
<td>166 (54) n = 59</td>
<td>165 (92) n = 59</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>99 (1) n = 59</td>
<td>99 (1) n = 59</td>
<td>98 (3) n = 59</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>39 (7) n = 59</td>
<td>39 (6) n = 59</td>
<td>41 (8) n = 59</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.42 (0.06) n = 59</td>
<td>7.41 (0.07) n = 59</td>
<td>7.41 (0.07) n = 59</td>
</tr>
</tbody>
</table>

### Hemodynamic variables

- Mean arterial pressure, mm Hg: 83 (14) n = 59 vs 84 (15) n = 59, difference of 1% [95% CI, −1.0% to 2.0%]; 84 (15) n = 59 vs 83 (14) n = 59, difference of 1% [95% CI, −1.0% to 2.0%]; 83 (14) n = 59 vs 82 (16) n = 59, difference of 1% [95% CI, −1.0% to 2.0%]; 82 (16) n = 59 vs 86 (17) n = 59, difference of 5% [95% CI, −2.0% to 12%].
- Central venous pressure, mm Hg: 7.0 (2.7) n = 59 vs 8.3 (2.9) a n = 59, difference of 1% [95% CI, −1.0% to 2.0%]; 8.3 (2.9) a n = 59 vs 8.2 (3.2) n = 59, difference of 1% [95% CI, −1.0% to 2.0%]; 8.2 (3.2) n = 59 vs 7.0 (2.8) n = 59, difference of 1% [95% CI, −1.0% to 2.0%]; 7.0 (2.8) n = 59 vs 8.5 (2.8) n = 59, difference of 5% [95% CI, −2.0% to 12%].
- Vasoactive drug use, No. (%): 49 (83) n = 59 vs 47 (80) n = 59, difference of 1% [95% CI, −1.0% to 2.0%]; 47 (80) n = 59 vs 48 (83) n = 59, difference of 1% [95% CI, −1.0% to 2.0%]; 48 (83) n = 59 vs 46 (78) n = 59, difference of 1% [95% CI, −1.0% to 2.0%]; 46 (78) n = 59 vs 50 (85) n = 59, difference of 5% [95% CI, −2.0% to 12%].

Abbreviations: FIO2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; SaO2, arterial oxygen saturation.

aP<.001 for comparison with conventional ventilatory strategy.
bP<.05 for comparison with conventional ventilatory strategy using mixed-model linear regression for repeated measures.

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By their nature, the study interventions could not be blinded. To minimize potential bias, we assessed lung volumes using well-accepted criteria for the management of potential organ donors still recommending guidelines for the management of potential organ donors be ventilated with low tidal volumes of 6 to 8 mL/kg of predicted body weight.2,14 These values were similar to those published recommendations. Despite this, we performed an observational study to determine if patients whose lungs had relative contraindications were excluded based on functional criteria (Figure), compared with conventional ventilatory strategy (Table 4).

### Table 4. Cytokines in the Conventional and Protective Ventilatory Strategies

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Conventional Ventilatory Strategy</th>
<th>Protective Ventilatory Strategy</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β (pg/mL)</td>
<td>36 (31-41)</td>
<td>30 (26-34)</td>
<td>6 (2-10)</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>32 (28-36)</td>
<td>28 (24-32)</td>
<td>4 (1-7)</td>
</tr>
<tr>
<td>IL-8 (pg/mL)</td>
<td>22 (18-26)</td>
<td>18 (14-22)</td>
<td>4 (1-7)</td>
</tr>
<tr>
<td>IL-1 receptor antagonist (pg/mL)</td>
<td>129 (97-161)</td>
<td>158 (124-192)</td>
<td>29 (15-43)</td>
</tr>
<tr>
<td>TNF (pg/mL)</td>
<td>1.2 (0.05-2.5)</td>
<td>1.0 (0.01-2.0)</td>
<td>0.2 (0.01-0.4)</td>
</tr>
<tr>
<td>IL-1 receptor antagonist (pg/mL)</td>
<td>129 (97-686)</td>
<td>158 (84-562)</td>
<td>29 (15-43)</td>
</tr>
</tbody>
</table>

### Table 3. End Points by Conventional and Protective Ventilatory Strategies

<table>
<thead>
<tr>
<th>End Points</th>
<th>Conventional Ventilatory Strategy</th>
<th>Protective Ventilatory Strategy</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung function</td>
<td>1.0 (0.01-2.0)</td>
<td>1.0 (0.01-2.0)</td>
<td>0.0 (0.01-0.0)</td>
</tr>
<tr>
<td>Functional criteria</td>
<td>1.0 (0.01-2.0)</td>
<td>1.0 (0.01-2.0)</td>
<td>0.0 (0.01-0.0)</td>
</tr>
<tr>
<td>Logistic criteria</td>
<td>1.0 (0.01-2.0)</td>
<td>1.0 (0.01-2.0)</td>
<td>0.0 (0.01-0.0)</td>
</tr>
<tr>
<td>Donor-receptor incompatibility</td>
<td>1.0 (0.01-2.0)</td>
<td>1.0 (0.01-2.0)</td>
<td>0.0 (0.01-0.0)</td>
</tr>
<tr>
<td>Infection</td>
<td>1.0 (0.01-2.0)</td>
<td>1.0 (0.01-2.0)</td>
<td>0.0 (0.01-0.0)</td>
</tr>
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</table>

In any randomized controlled trial, it is important to ensure that the control group represents a standard of care. Members of the organ procurement organization and surgeons were blinded as having brain death was assessed in the study. Lung harvest was not allowed for marginal donors (ie, patients whose lungs were unable to be ventilated with low tidal volumes and acceptable peak airway pressure obtained during fixed ventilatory settings).
lung to ventilator-induced lung injury. Second, application of a protective ventilatory strategy in an experimental model improved lung function after lung transplantation. Third, observational studies demonstrated that ventilation with higher tidal volumes was an independent contributing factor for subsequent development of acute lung injury in patients with acute brain injury. Fourth, protective lung strategies in patients with relatively normal lungs decreased subsequent development of lung injury. Our results are in accord with these lines of evidence.

Prior to randomization, the number of patients who matched eligibility criteria did not differ between the conventional and protective strategies. At the end of the 6-hour period, the number of patients meeting lung eligibility criteria significantly decreased in the conventional strategy while they increased slightly in the protective strategy.

Our multifaceted lung protective intervention addressed 4 factors we hypothesized might affect lung preservation. We used ventilation with low tidal volumes, which improved outcomes in patients with acute lung injury, and decreased the development of acute lung injury. To prevent atelectasis, we used higher levels of PEEP, performed awake tests using continuous positive airway pressure, used a closed system for tracheal suctioning, and used recruitment maneuvers after any disconnection from the ventilator.

Which of these factors specifically improved respiratory function is not certain. Ventilation with low tidal volumes of 10 to 12 mL/kg of predicted body weight may overstretch normal lungs in the presence of markedly decreased pulmonary compliance, which occurs in patients with severe acute lung injury. However, peak pressure and end-inspiratory plateau pressure ranged between 12 and 20 cm H₂O in both groups, values that are substantially lower than the recommended upper limit of 30 cm H₂O. Under these circumstances, prevention of alveolar overstretch likely does not explain the improvement of lung function observed in the protective strategy. On the other hand, recruitment of collapsed alveoli (obtained by application of recruitment maneuvers), prevention of end-expiratory collapse (obtained by the use of continuous positive airway pressure during the apnea test and of closed suctioning circuit), and maintenance of recruited alveoli (using higher levels of PEEP) may have prevented the pulmonary damage caused by ventilation at low tidal volumes.

In conclusion, our results suggest that the use of a lung protective strategy prevents the decline of pulmonary function consequent to brain death and roughly doubled the number of lungs available for transplantation.

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REFERENCES


He only has known the full joy of living who somewhere and at some time has struck a decisive blow for the freedom of the human spirit.

—Walter Lippmann (1889-1974)