PRELIMINARY COMMUNICATION

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 H_2O, 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 H_2O, 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.

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PATIENTS WITH RELATIVELY NORmal pulmonary function at the time of brain death may have declines in functioning, and only 15% to 20% of these patients' lungs are subsequently suitable for transplantation.[1-3] This may result from the pulmonary damage associated with brain injury[4] or the iatrogenic effects of mechanical ventilation.[5,6]

There is evidence in various settings demonstrating that a lung protective strategy is beneficial. In patients with acute lung injury, ventilation

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with low tidal volumes decreased absolute mortality by 9%.[7] In patients with normal pulmonary function, ventilation with lower tidal volumes was associated with a lower likelihood of developing acute lung injury.[8] In patients with brain injuries, ventilation with higher tidal volumes was an independent factor contributing to development of acute lung injury.[6]

Despite this evidence, there is controversy as to the best ventilatory strategy to use in patients diagnosed as having brain death. A consensus conference[9] 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 H_2O. A subsequent review article[10] and an observational study[11] 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).[12,13]

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.[3,14,15]

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[7] and PEEP of 3 to 5 cm H_2O.[2] An open circuit was used for tracheal suction. Apnea tests were performed by disconnecting the patient from the ventilator while administrating 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 H_2O. A closed circuit was used for tracheal suction.[16] Apnea tests were performed with the ventilator in the continuous positive airway pressure mode.[17] 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)[18] were performed after any disconnection from the ventilator.

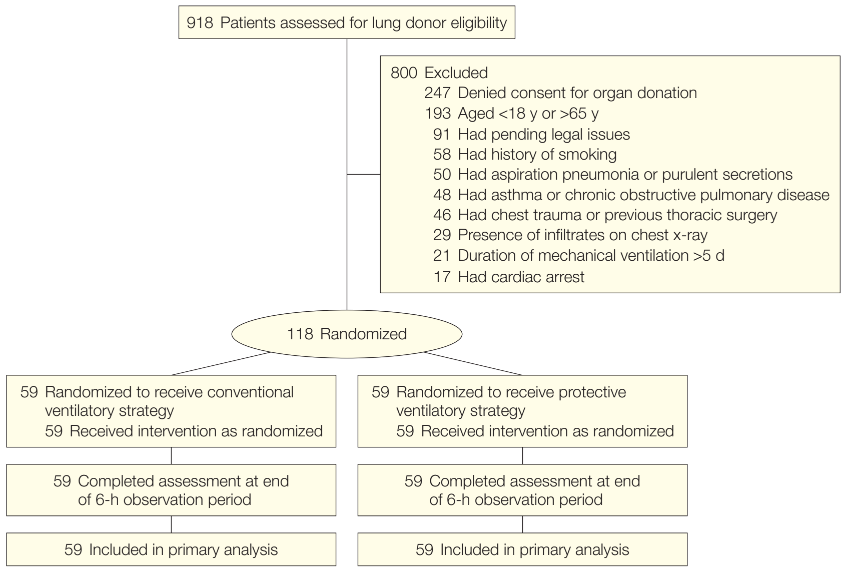
In both strategy groups, respiratory rate was adjusted to obtain Pa_{CO_2} of 40 to 45 mm Hg and fraction of inspired oxygen (F_{IO_2}) was adjusted to obtain Pa_{O_2} of 90 mm Hg or greater. The viability of lungs was assessed at the beginning and at the end of the 6-hour observation period.[3,14] The ratio of Pa_{O_2} to F_{IO_2} and peak airway pressure at the end of the 6-hour observation period were reported to the organ procurement organization.[3,14] 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 Pa_{O_2} to F_{IO_2} was 300 mm Hg or greater, F_{IO_2} was 1.0, and peak airway pressure was less than 30 cm H_2O.[3,14] The officer of the organ procurement organization then reported the potential lung donor to the lung transplant surgeon who, after examining the potential donor, made the final decision on the suitability of the lungs.

The surgeon was blinded to patient allocation and was not otherwise involved in the study. The reasons given by the lung transplant surgeon not to harvest lungs were prospectively classified as (1) lung donor issues (functional lungs that at the moment of harvest no longer met oxygenation and peak airway pressure criteria for eligibility; infectious, clinical, radiological, or laboratory manifestation of pulmonary infection occurring after diagnosis of brain death; or pulmonary contusions observed during inspection of the lungs with the chest open) and (2) lung recipient issues (donor-recipient incompatibility, lack of potential recipients matching size, blood group, or human leukocyte antigen 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



servation period for measurements of IL-1β, IL-1 receptor antagonist, IL-6, IL-8, tumor necrosis factor, and tumor necrosis factor receptors I and II.[5]

In a previous observational study,[2] 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 ($P>.03$).[19]

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 χ^2 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[3] 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 PaO_2 to FIO_2 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 (difference of 27% [95% CI, 10.0% to 44.5%]; $P = .004$).

Multivariate and regression logistic analyses showed that eligibility at the end of the 6-hour observation period was associated with the protective strategy (OR, 25.4 [95% CI, 5.6-114.6]; $P = .001$) and with use of vasoactive drugs at randomization (OR, 4.3 [95% CI, 1.2-16.0]; $P = .02$). The number needed to treat to benefit was 3.0 (95% CI, 1.8-3.7). Sixteen patients (50%) in the conventional strategy compared with 24 patients (43%) in the protective strategy (difference of 7% [95% CI, 0%-29.3%]; $P = .52$) met lung donor eligibility criteria at the end of the 6-hour observation period but their lungs were rejected by the surgeon for subsequent transplantation (Table 3). We did not find any individual hospital effect when cumulative OR was used as a measure of effect size in a robust logistical regression model.

The number of patients classified as not meeting eligibility criteria by the blinded officer of the organ procurement organization was 27 in the conventional strategy and 3 in the protective strategy at the end of the eligibility test, which lasted a median of 38 minutes (IQR, 25 to 40 minutes). Patients had a ratio of PaO_2 to FIO_2 of 208 (83) in the conventional strategy and 224 (47) in the protective strategy (difference of proportion, 16; 95% CI, −86 to 116) and a peak airway pressure of 31 (5) cm H_2O in the conventional strategy and 34 (6) cm H_2O in the protective strategy (difference of proportion, 3; 95% CI, −2.9 to 9.1).

The number of patients classified as meeting eligibility criteria by the blinded officer of the organ procurement organization was 32 in the conventional strategy and 56 in the protective strategy at the end of the eligibility test, which lasted a median of 33 minutes (IQR, 20 to 43 minutes). Patients had a ratio of PaO_2 to FIO_2 of 454 (76) in the conventional strategy and 491 (115) in the protective strategy (difference of proportion, 37; 95% CI, −8 to 82) and a peak airway pressure of 26 (4) cm H_2O in the conventional group and 25 (4) cm H_2O in the protective group (difference of proportion, 1; 95% CI, −0.5 to 3.2). None of these differences was statistically significant.

The median length of mechanical ventilation from the end of the 6-hour observation period to the moment of organ harvest was 6 hours (IQR, 3-16 hours) in the conventional strategy and 4 hours (IQR, 3-18 hours) in the protective strategy. During this period, the ventilator settings selected at randomization were maintained for all patients.

The median intensive care unit length of stay for patients who received lungs from donors in the conventional strategy was 12 days (IQR, 1 to 100 days) compared with 8 days (IQR, 2 to 100 days) for patients who received lungs from donors in the protective strategy. The 6-month survival rate was 69% (11/16) for patients who received lungs from donors in the conventional strategy compared with 75% (24/32) for patients who received lungs from donors in the protective strategy (difference of 6%; 95% CI, −22% to 32%). The number of other organs harvested did not differ between the con-

Table 1. Patient Characteristics at Enrollment

	Ventilatory Strategy	
	Conventional (n = 59)	Protective (n = 59)
Age, mean (SD), y	45 (13)	42 (13)
Female sex, No. (%)	27 (46)	34 (58)
Primary diagnosis, No. (%)		
Traumatic brain injury	17 (29)	12 (20)
Cerebrovascular hemorrhagic accident	37 (63)	45 (76)
Other[a]	5 (8)	2 (3)
Duration of mechanical ventilation prior to randomization, median (IQR), h	38 (6-120)	34 (2-120)
Ventilatory pattern, mean (SD)		
FIO_2	45 (12)	44 (11)
Tidal volume, mL/kg of predicted body weight	9.3 (1.5)	9.0 (1.6)
Respiratory rate, breaths/min	13 (3)	13 (2)
PEEP, cm H_2O	4.3 (2.9)	5.0 (2.8)
Peak inspiratory pressure, cm H_2O	21 (5)	22 (4)
Plateau pressure, cm H_2O	16 (3)	16 (4)
Minute ventilation, L/min	7.2 (1.9)	7.0 (1.7)
Ratio of PaO_2 to FIO_2	393 (144)	400 (124)
Arterial blood gases, mean (SD)		
PaO_2, mm Hg	171 (112)	173 (74)
SaO_2, %	98 (2)	99 (1)
$PaCO_2$, mm Hg	36 (5)	36 (6)
Arterial pH	7.44 (0.07)	7.43 (0.07)
Hemodynamic variables, mean (SD)		
Mean arterial pressure, mm Hg	84 (16)	83 (16)
Central venous pressure, mm Hg	6.4 (2.9)	7.5 (2.8)
Vasoactive drug use	47 (80)	47 (80)
Concomitant treatment[b]		
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)

Abbreviations: FIO_2, fraction of inspired oxygen; IQR, interquartile range; PEEP, positive end-expiratory pressure; SaO_2, arterial oxygen saturation.
[a] Such as for ischemic stroke.
[b] Eighteen patients in each group received dopamine and norepinephrine in combination.

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, −0.11% 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 group ($P<.01$), but not in 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

	Duration of Treatment and Ventilatory Strategy					
	First Hour		Third Hour		Sixth Hour	
	Conventional (n = 59)	Protective (n = 59)	Conventional (n = 59)	Protective (n = 59)	Conventional (n = 59)	Protective (n = 59)
Ventilatory variables, mean (SD)						
FIO_2	47 (17)	42 (7)	48 (18)	44 (12)	50 (19)	44 (11)
Tidal volume, mL/kg of predicted body weight	10.1 (1.6)	7.9 (1.1)[a]	10.1 (1.6)	7.8 (1.0)	10.1 (1.7)	7.8 (1.0)
Respiratory rate, breaths/min	11 (2)	13 (3)[a]	11 (2)	14 (3)	11 (2)	14 (3)
PEEP, cm H_2O	4.2 (1.6)	8.7 (1.4)[a]	4.4 (1.5)	9.0 (1.4)	4.3 (1.6)	9.2 (1.8)
Peak inspiratory pressure, cm H_2O	22 (5)	23 (5)	23 (5)	23 (4)	22 (5)	23 (5)
Plateau pressure, cm H_2O	16 (4)	17 (4)	17 (4)	17 (3)	17 (4)	18 (4)
Minute ventilation, L/min	6.9 (1.5)	6.5 (1.7)	6.8 (1.8)	6.6 (1.8)	6.8 (1.7)	6.7 (1.9)
Ratio of PaO_2 to FIO_2	360 (120)	402 (118)	342 (126)	402 (129)[b]	332 (170)	396 (107)[b]
Blood gas analysis, mean (SD)						
PaO_2, mm Hg	164 (72)	166 (54)	165 (92)	176 (72)	156 (84)	169 (49)
SaO_2, %	99 (1)	99 (1)	98 (3)	99 (1)	98 (2)	99 (1)
$PaCO_2$, mm Hg	39 (7)	39 (6)	41 (8)	42 (5)	42 (10)	41 (5)
Arterial pH	7.42 (0.06)	7.41 (0.07)	7.41 (0.07)	7.39 (0.07)	7.40 (0.07)	7.39 (0.09)
Hemodynamic variables						
Mean arterial pressure, mean (SD), mm Hg	83 (14)	84 (15)	84 (15)	83 (14)	82 (16)	86 (17)
Central venous pressure, mean (SD), mm Hg	7.0 (2.7)	8.3 (2.9)[b]	6.5 (2.8)	8.2 (3.2)	7.0 (2.8)	8.5 (2.8)
Vasoactive drug use, No. (%)	49 (83)	47 (80)	49 (83)	46 (78)	50 (85)	44 (75)

Abbreviations: FIO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; SaO_2, arterial oxygen saturation.
[a] $P<.001$ for comparison with conventional ventilatory strategy.
[b] $P<.05$ for comparison with conventional ventilatory strategy using mixed-model linear regression for repeated measures.

the interpretation of our trial because the decision to stop early was made prior to the unblinding of outcomes by study group and before transmitting the data to the data and safety monitoring board.

In any randomized controlled trial, it is important to ensure that the control group represents a standard of care. We ensured this by basing the control strategy on a consensus conference recommendation that potential lung donors be ventilated with low tidal volumes of 10 to 12 mL/kg of measured body weight using a PEEP of 5 cm H_2O.[9] In addition, prior to the current trial, we performed an observational study[2] that confirmed that the ventilatory strategy used after declaration of brain death was similar to these published recommendations. Despite a review article[10] and an observational study[11] suggesting that potential lung donors should be ventilated with low tidal volumes of 8 to 10 mL/kg of predicted body weight, guidelines for the management of potential organ donors still recommend ventilation with low tidal volumes of 10 to 15 mL/kg of measured body weight and PEEP of 5 cm H_2O.[12,13] These discrepancies persist because there has been no high-grade evidence demonstrating the superiority of any specific strategy for potential lung donors.[10,21]

By their nature, the study interventions could not be blinded. To minimize potential bias, we assessed lung viability using well-accepted cutoffs for ratio of PaO_2 to FIO_2 and peak airway pressure obtained during fixed ventilator settings.[3,14] These values were communicated to the organ procurement organizations, who then informed the transplant surgeon. The final decision to proceed to lung harvest was made by the transplant surgeon after examining the potential donor. Members of the organ procurement organization and surgeons were blinded to study group and not otherwise involved in the study.

All 918 consecutive patients diagnosed as having brain death were assessed for inclusion in the study. However, 39% were excluded for denied consent, legal issues, and cardiac arrest and 42% were excluded based on published criteria that identified nonideal lungs (Figure).[3] Similarly to other clinical multiorgan donor programs,[1,3] our randomized cohort represented 13% of eligible patients. It should be noted that transplant programs participating in the present study did not allow marginal donors (ie, patients whose lungs had relative contraindications such as age, smoking history, contusion, prolonged mechanical ventilation, etc).[22]

Recent findings suggest that deterioration of lung function may be due to mechanisms directly related to brain death.[23,24] We hypothesized that ventilation with low tidal volumes and higher PEEP levels would prevent the deterioration of lung function associated with brain death.[25] A number of lines of evidence support this hypothesis and the hypothesis that a lung protective strategy will decrease lung injury. First, animal data demonstrate that massive brain injury predisposes the

Table 3. End Points by Conventional and Protective Ventilatory Strategies

	Ventilatory Strategy, No. (%)		
	Conventional (n = 59)	Protective (n = 59)	Difference of Percentage (95% CI)
Met lung donor eligibility criteria			
At study inclusion	49 (83)	51 (86)	3 (−4.0 to 24.4)
6 h after randomization	32 (54)[a]	56 (95)[b]	41 (26.5 to 54.8)
Lungs harvested			
Yes	16 (27)	32 (54)[c]	27 (10.0 to 44.5)
No	16/32 (50)[d]	24/56 (43)[d]	7 (0 to 29.3)
Reasons lungs not harvested			
Functional	4 (25)	7 (29)	
Infectious	3 (19)	4 (17)	
Inspection	3 (19)	5 (21)	
Donor-recepient incompatibility	4 (25)	5 (21)	
Logistical	2 (12)	3 (12)	

Abbreviation: CI, confidence interval.
[a] $P<.001$ using the McNemar test at study inclusion compared with 6 hours after randomization.
[b] $P=.001$ for comparison with conventional ventilatory strategy using the Fisher exact test.
[c] $P=.004$ for comparison with conventional ventilatory strategy using the χ^2 test.
[d] Values expressed as number/total (percentage).

Table 4. Cytokines in the Conventional and Protective Ventilatory Strategies

	Conventional Ventilatory Strategy		Protective Ventilatory Strategy	
	At Baseline (n = 20)	At Sixth Hour (n = 20)	At Baseline (n = 17)	At Sixth Hour (n = 17)
Plasma concentration, median (interquartile range), pg/mL				
IL-1β	0.24 (0.01-1.28)	0.52 (0.01-2.18)	0.35 (0.01-0.84)	0.28 (0.01-0.73)
IL-1 receptor antagonist	129 (97-686)	158 (84-562)	133 (71-672)	48 (7-539)
IL-8	17 (0.49-72)	18 (8-117)	16 (0.01-77)	14 (0.01-56)
IL-6	407 (31-3138)	1025 (282-4716)[a]	158 (13-3622)	259 (21-2620)
Tumor necrosis factor (TNF)	1.40 (0.10-22.0)	1.0 (0.10-15.0)	1.0 (0.01-15)	1.0 (0.01-14)
TNF receptor I	2571 (1083-5426)	4105 (3001-63 351)[a]	2381 (923-4266)	2625 (1368-5185)
TNF receptor II	5245 (2011-10 632)	8889 (6064-19 323)[a]	4359 (2480-9673)	5187 (2392-9612)

[a] $P<.05$ for comparison with baseline using paired *t* test on log_{10}-transformed values.

lung to ventilator-induced lung injury.[26] Second, application of a protective ventilatory strategy in an experimental model improved lung function after lung transplantation.[27] 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.[6] Fourth, protective lung strategies in patients with relatively normal lungs decreased subsequent development of lung injury.[8] 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,[7] and decreased the development of acute lung injury.[8] To prevent atelectasis, we used higher levels of PEEP, performed apnea tests using continuous positive airway pressure,[17] used a closed system for tracheal suctioning,[16] and used recruitment maneuvers after any disconnection from the ventilator.[18]

Which of these factors specifically improved respiratory functions 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.[7] However, peak pressure and end-inspiratory plateau pressure ranged between 12 and 20 cm H_2O in both groups, values that are substantially lower than the recommended upper limit of 30 cm H_2O.[28] 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.[5,29]

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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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)