

Effects of administration of intravenous naloxone on gas exchange in brain-dead lung donors

Objective—To observe the effect of naloxone on the lung function of potential lung transplant donors with neurogenic pulmonary edema.

Design and Interventions—Donors aged 16 to 55 years without any factors to contraindicate lung donation (pneumonia, pulmonary contusion, etc) were included. Ventilator settings were standardized to a tidal volume of 10 to 12 mL/kg, an FIO_2 of 0.40, and a respiratory rate that kept PCO_2 between 35 and 45 mm Hg. Chest physiotherapy, nebulizer treatments, and frequent suctioning were undertaken. Baseline arterial blood gas analysis and an oxygen challenge were performed. The patients were then given 8 to 10 mg of naloxone. Oxygen challenges and arterial blood gas analyses were repeated every 4 to 6 hours. The data were analyzed by using a paired *t* test, and each patient served as his or her own control.

Setting—These interventions were performed on the 19 LifeQuest donors who met the set criteria from July 2002 to July 2004.

Results—The PaO_2 on the oxygen challenge immediately after administration of naloxone increased from 329 (SD 177) to 363 (SD 191) mm Hg, although the increase from baseline was not significant. The PaO_2 from the second oxygen challenge (median time, 7 hours after administration of naloxone) increased to 413 (SD 177) mm Hg ($P < .01$). (*Progress in Transplantation*. 2009;19:267-271)

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The most significant factor limiting lung transplantation is the availability of suitable donors. Currently, fewer than half of the patients listed for lung transplantation will have a suitable donor available.¹ Most potentially available lung donors are brain-dead patients,² although the recent use of donors that are not brain dead, or donors after cardiac death (DCD),³ has provided a new source of potential organs suitable for transplantation.

In 2007, the Organ Procurement and Transplantation Network reported 22048 solid organs transplanted from 8091 deceased donors.¹ From those donors, only 1465 lung transplants (18%) were performed. The factors precluding the use of lungs for transplantation are many. Deceased donors are exposed to many inflammatory events associated with brain death, including possible aspiration of gastric contents, blood, or upper

airway secretions, the effects of endotracheal intubation and exposure to mechanical ventilation, and the likelihood of ventilator-associated infection, as well as the possibility of neurogenic pulmonary edema.² In addition, brain death induces disruption in homeostatic regulation with secondary disturbances in endocrine function and inflammatory reactions, hypothermia, and coagulopathy.⁴

Complex mechanisms may be involved in deterioration of gas exchange in brain-dead donors. Neurogenic pulmonary edema is common in brain-dead organ donors. Rogers et al⁵ reported that patients who died of head injury consistently had higher lung weights on autopsy and concluded that every patient with a head injury has some degree of neurogenic pulmonary edema.

In a sheep model of increased intracranial pressure, Peterson et al⁶ demonstrated a modest increase in

the postmortem extravascular water volume of the lungs (pulmonary edema) not due to an increase in pulmonary microvascular pressure but to an increase in vascular permeability. Furthermore, they demonstrated that administration of naloxone partially blocked the cardiopulmonary responses of intracranial pressure elevation and prevented development of pulmonary edema.

Naloxone is a semisynthetic opiate-receptor antagonist that is commonly used in clinical practice to antagonize the toxic and clinical effects of opiates (ie, hypotension, excessive sedation), particularly in patients with respiratory depression. Endorphin and enkephalins (endogenous substances with opiate-like activity) exist in higher concentrations in certain respiratory conditions such as chronic obstructive pulmonary disease,⁷ obesity hypoventilation syndrome,⁸ and high-altitude pulmonary edema.

Bar-Or and associates⁹ reported a well-documented case of severe hypoxia due to high-altitude pulmonary edema in a patient with marked elevation of plasma levels of β -endorphins. The patient had dramatic resolution of hypoxemia after administration of naloxone.⁹

Strategies to optimize the use of a potential lung donor include hemodynamic management directed to achieve euvolemia by using central venous pressure (CVP) as a guide to achieve ideal fluid replacement, which usually will occur with CVP between 6 and 8 mm Hg as well as aggressive pulmonary toilet.¹⁰ Excessive fluid resuscitation in brain-dead donors will cause deterioration in gas exchange.¹¹ If blood pressure remains low after optimal fluid replacement, use of vasopressors such as dopamine or vasopressin helps to optimize the systemic vascular resistance.¹²

Sudden brain death may be associated with a massive release of catecholamines (catecholamine storm), followed by decline in levels of vasopressin, cortisol, thyroxine, and insulin. Hormonal substitution includes administration of a methylprednisolone bolus (15 mg/kg), insulin, and triiodothyronine.² Gas exchange in potential lung donors is further optimized by frequent suctioning, chest physiotherapy, diagnostic and therapeutic bronchoscopies, as well as recruitment maneuvers including transient periods of pressure control ventilation of 25 cm H₂O with increased positive end-expiratory pressure (PEEP) of 15 cm H₂O, to be followed by volume-control ventilation using tidal volumes of 10 to 12 cm H₂O and PEEP of 5 with the lowest FIO₂ that maintains a PaO₂ of 90 to 110 mm Hg. Maneuvers to prevent aspiration such as elevation of the head of the bed and optimal cuff inflation of the endotracheal tube have been described.¹³

Hypothesis

Given the evidence to support a link between the administration of naloxone and the decrease in neurogenic pulmonary edema in sheep, we thought

that the use of naloxone in brain-dead organ donors might decrease the incidence of neurogenic pulmonary edema in potential donors, resulting in an increase in the number of lungs suitable for transplantation. In this report, we detail our clinical observations and changes in ventilation and oxygenation among 19 brain-dead solid organ donors who received intravenous (IV) naloxone during their management.

Materials and Methods

This retrospective observational study involved a sample generated by nonprotocolized data gathering from July 2002 to July 2004. During that period, consented brain-dead organ donors managed by LifeQuest Organ Recovery Services were subjected to the protocol approved by the institutional review board of the University of Florida and described below.

Organ donors included were from 16 to 55 years of age. They did not have any known medical or surgical history that would contraindicate lung recovery and transplantation. History of asthma (not requiring daily inhaled steroids), pulmonary contusion(s), infection, or smoking were not considered absolute contraindications for evaluation and intervention. Synchronized intermittent mandatory ventilation with tidal volumes calculated to 10 to 12 mL/kg was used. Respiratory rate adjustments were made to keep arterial PaCO₂ levels between 35 and 45 mm Hg. PEEP levels were kept constant at 5 cm H₂O. The standard FIO₂ used as baseline was 0.40. After the baseline arterial blood gas levels had been established and PaCO₂ levels were adequate, a baseline "oxygen challenge" was obtained after setting the ventilator to an FIO₂ of 1.0 for a minimum of 15 minutes. Repeat arterial blood gas samples were obtained every 4 to 6 hours as needed and oxygen challenges were performed within 4 and 12 hours after administration of naloxone. All patients had a chest radiograph obtained at baseline that was repeated as needed. Bronchoscopy was performed after consent was obtained, to evaluate airways and to obtain bronchial washings for cultures and gram stains.

Bedside care included chest physical therapy every hour (by manual device or bed module), tilting the donor from side to side every hour to mobilize secretions, and suctioning the endotracheal tube every 1 to 2 hours. All patients had central catheters transduced for monitoring of CVP, and administration of IV fluids or diuretics was gauged to keep CVP between 6 and 8 mm Hg.

Patients received inhaled albuterol every 4 hours. A bolus of methylprednisolone of 30 mg/kg was administered as an IV push within the first hour after consent for donation was obtained. Administration of antibiotics included clindamycin 600 mg intravenously every 8 hours and ceftazidime 1 g intravenously every 12 hours.

Table 1 Characteristics of the 19 donors

Characteristic	Mean (SD)	Range	Median
Age, y	30 (12)	16-53	25
Height, in	67 (14)	58-72	69
Weight, kg	78 (16)	53-114	74

Once a baseline oxygen challenge was obtained, donors received naloxone, a single IV bolus of 0.1 mg/kg (rounded to the closest single-unit dose, typically 8 mg). Thirty-six patients received IV naloxone during this period. Only 19 of these patients had follow-up arterial blood gas analyses on an F_{iO_2} of 1.0 within 1 to 4 hours and a second sample within the next 8 to 12 hours to have short- and long-term arterial blood gases for evaluation. Those 19 patients are the subject of this report. Each patient therefore served as his or her own control before and after manipulation with IV naloxone. Descriptive statistics were used to analyze the population and the Student 2-tailed *t* test for analysis of paired data was used to compare results before and after administration of naloxone.

Results

The study sample included 19 donors with a mean (SD) age of 30 (12) years, ranging from 16 to 53 (median, 25) years. Their median height was 1.72 m (69 in) and median weight was 74 kg (163 lb; Table 1).

The mean (SD) dose of naloxone administered was 8.1 (1) mg intravenously, with a range from 4 to 10 mg (median, 8 mg). The mean (SD) results of arterial blood gas analysis at baseline before administration of

naloxone were pH 7.39 (0.09), $PaCO_2$ 39 (12) mm Hg, and PaO_2 329 (177) mm Hg (range, 50-571 mm Hg). These arterial blood gases were measured while patients received a tidal volume of 667 (113) mL with an average respiratory rate of 13 (3) breaths/min and a PEEP of 4.8 (1.9) cm H_2O . The first oxygen challenge was repeated at a median time of 3.2 hours after naloxone administration (range, 0.6-6.1 hours). Neither pH nor $PaCO_2$ changed significantly. The mean (SD) PaO_2 increased from a baseline value of 329 (177) mm Hg to 363 (191) mm Hg, but this change was not significant. Thirteen patients showed increased PaO_2 and 6 patients had decreased PaO_2 after administration of naloxone. Nine patients were receiving larger tidal volumes during the repeat oxygen challenge. The mean (SD) tidal volume was 725 (113) mL, which was significantly higher than baseline values ($P = .01$; Table 2).

The second oxygen challenge after administration of naloxone was measured at a median time of 7 hours after naloxone injection (range, 3-24 hours). The mean (SD) PaO_2 increased significantly from the baseline of 329 (177) mm Hg to 413 (177) mm Hg ($P < .01$). Fifteen of these patients showed increased PaO_2 levels, and 4 patients experienced a decline in PaO_2 after therapeutic intervention (see Figure). A substantial segment of this population increased PaO_2 values during oxygen challenge from levels less than 400 mm Hg to levels greater than 400 mm Hg after receiving naloxone (see Figure). The mean tidal volume was higher than the original baseline at 750 (132) mL. Eleven of the 19 patients were receiving a larger tidal volume than they had been receiving at baseline. The respiratory rate was significantly lower than baseline

Table 2 Arterial blood gases at a fraction of inspired oxygen of 1.0 on mechanical ventilation

Result of arterial blood gas analysis	Before naloxone	After naloxone 1 (N1) Median, 3.2 hours (range, 0.6-6.1 hours)	After naloxone 2 (N2) Median, 7.3 hours (range, 3.5-24.4 hours)	<i>P</i>
pH, mean (SD), range, median	7.39 (0.09), 7.14-7.56, 7.42	7.42 (0.06), 7.25-7.51, 7.43	7.40 (0.05), (7.28-7.50) 7.41	N1: .16 N2: .71
$PaCO_2$, mean (SD), range, median	39 (12), 29-73, 35	35 (6), 27-53, 35	37 (4), 32-44, 36	N1: .18 N2: .39
PaO_2 , mean (SD), range, median	329 (177), 50-571, 368	363 (191), 60-624, 399 (12 increased, 7 decreased)	413 (177), ^a 69-639, 434 (14 increased, 5 decreased)	N1: .21 N2: .005
Tidal volume, mean (SD), range, median	667 (113), 450-900, 700	725 (131), ^a 450-950, 700 (9 higher)	750 (132), ^a 450-1050, 750 (11 higher)	N1: .007 N2: .003
Respiratory rate, mean (SD), range, median	13.2 (3), 10-18, 12	13 (4), 8-22, 12	11 (3), ^a 8-17, 10	N1: .27 N2: .005
Positive end-expiratory pressure, mean (SD), range, median	4.8 (1.9), 0-8, 5	5.8 (1.6), 5-10, 5 (4 higher)	5.9 (2), 5-12, 5 (4 higher)	N1: .09 N1: .16

^a Denotes statistically significant changes in values from baseline.

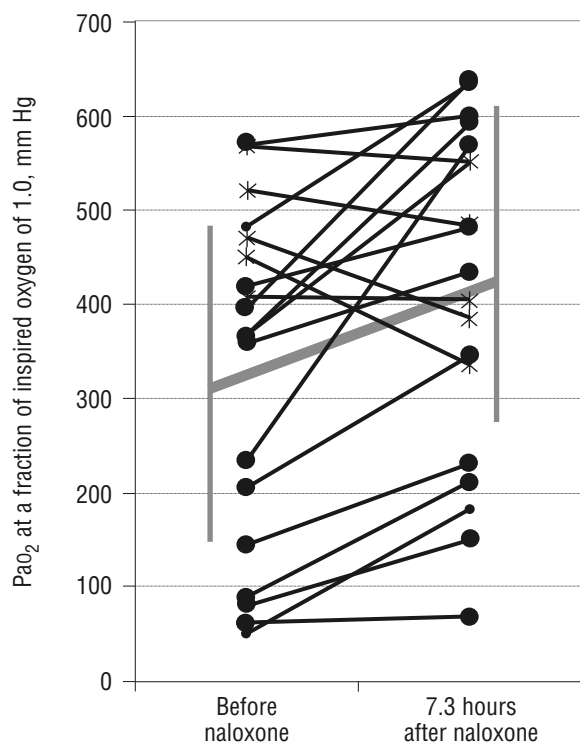


Figure 3 Graph shows the changes in PaO_2 during oxygen challenge for each individual case. Five patients with a PaO_2 less than 400 mm Hg at baseline had their PaO_2 improve to greater than 400 mm Hg after the administration of naloxone, and in 1 patient PaO_2 increased from less than 300 mm Hg to more than 300 mm Hg. Therefore, 6 of 19 patients improved oxygenation over thresholds acceptable to most transplant centers. Improvements in patients with a baseline PaO_2 less than 200 mm Hg were present but still remained less than 300 mm Hg in 5 patients.

values (11 [3] breaths/min). The pH, PaCO_2 , and PEEP were unchanged, reflecting effective ventilation achieved by using a lower respiratory rate and larger tidal volumes but still resulting in the same minute ventilation (Table 2).

The patients in this sample had 21 lungs transplanted into 14 recipients, for a utilization rate of 55.3%. A comparable group of donors that did not receive naloxone had 16 lungs transplanted into 10 recipients for a 42.1% utilization rate.

Discussion

The mechanisms involved in gas exchange among potential lung donors are multiple and complex. Metabolic, hormonal, and inflammatory changes associated with brain death are complex and in many cases may result in acute lung injury and pulmonary edema. The underlying medical, traumatic, or surgical events leading to brain death are inherently associated with likelihood of aspiration of upper airway or gastric contents into lower airways. The required intubation and mechanical ventilation procedures bypass the

Table 3 Selection criteria for lung transplant donors

Age <55 years ABO blood group compatibility
Normal findings on chest radiograph
$\text{PaO}_2 >300$ mm Hg at mechanical ventilator settings of 1.0 FiO_2 and +5 PEEP
Tobacco history <20 packs/year
Absence of chest trauma
No evidence of aspiration or pneumonia
No prior cardiopulmonary surgery
No purulent secretions noted during bronchoscopy
Abbreviations: FiO_2 , fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

natural mechanisms of defense and favor development of nosocomial or ventilator-associated pneumonia. Associated lung contusion and aggressive fluid resuscitative efforts before brain death also add to the likelihood of pulmonary edema and thus abnormal gas exchange. Elevated plasma endorphin levels may play a role in the presence of pulmonary edema associated with brain death.

Meticulous management of an organ donor may reverse or prevent development of lung injury. Lungs are considered suitable for donation when they meet certain criteria with respect to gas exchange, bronchoscopic findings, and chest radiographic findings, in addition to meeting criteria related to the donor's medical history (Table 3).

Time-honored maneuvers such as chest physiotherapy, endotracheal suctioning, use of inhaled bronchodilators, adequate mechanical ventilation, alveolar recruitment maneuvers, optimal fluid management, and diuresis when indicated conform to the standard practices to optimize the care of potential lung donors. Despite these maneuvers, lung retrieval remains the lowest among solid organs (mean, 18%).

It is therefore important to explore any conceivable maneuver that could optimize and enhance the pulmonary management of donors, and with such expectation, this experimental protocol was planned. We observed increases in PaO_2 in 15 of 19 patients after IV administration of naloxone. After a median time of 7.3 hours, mean PaO_2 had increased significantly compared with baseline (see Figure). This raises the possibility that some brain-dead donors with impaired gas exchange related to endogenous or exogenous pulmonary edema could improve oxygenation with the administration of naloxone. In fact, 6 of these donors improved from a PaO_2 that would not be considered suitable for transplant to a value that most transplant centers would deem acceptable (see Figure).

The main limitations in these observations are related to the difficulty in maintaining all clinical

variables constant owing to the hardships associated with the intense management of a multiorgan donor. The need to adjust the mechanical ventilatory parameters resulted in the same minute ventilation before and 7 hours after naloxone, but this minute ventilation was achieved by larger tidal volumes and lower respiratory rates. Therefore it could be argued that some of the gas exchange improvement could be related to less microatelectasis related to larger tidal volumes. Another limitation with this observational study is the lack of a randomized control group.

These preliminary observations should not be ignored, however, particularly because the observations on certain individual cases were rather dramatic. At least 6 donors showed increases in excess of 100 mm Hg in PaO₂ within a few hours after administration of naloxone.

Further research with control groups is needed to validate these observations. These preliminary observations should serve as the basis in planning and conducting a prospective, randomized, placebo-controlled trial in which variables could be controlled. Ideally, a clinical study should be conducted with a design that would involve obtaining baseline hemodynamic and gas exchange variables after all ventilatory maneuvers have been conducted to achieve optimal gas exchange. Brain-dead donors showing PaO₂/FIO₂ values of less than 300 mm Hg should be selected. Baseline values of plasma β-endorphins could be obtained and then in a clinically randomized fashion administration of naloxone could be compared with administration of a placebo, to be followed by repeated hemodynamic and gas exchange variables at defined periods (1 and 4 hours after administration). Such randomized study could demonstrate unequivocally if naloxone indeed has a role in the management of brain-dead organ donors.

In summary, this preliminary observational study suggests that some brain-dead organ donors may have significant improvement in oxygenation after administration of naloxone. The utilization rate from this sample was 11% higher than the use rate in a similar cohort

that did not receive naloxone. Further large, randomized, placebo-controlled studies will be necessary to define the role that naloxone may play in the management of brain-dead solid-organ donors.

Financial Disclosures

None reported.

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