Noninvasive Ventilation for Treatment of Acute Respiratory Failure in Patients Undergoing Solid Organ Transplantation: A Randomized Trial

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In the past 2 decades, advancements in immunosuppressive strategies and major breakthroughs in surgical and organ preservation techniques have transformed organ transplantation into a therapy for an increasing population of patients with end-stage organ failure. Although preventing rejection remains the principle focus in improving overall survival statistics, pulmonary complications following transplantation are responsible for most morbidity and contribute substantially to the mortality associated with various organ transplantation procedures.1 Approximately 5% of patients undergoing renal, hepatic, cardiac, or pulmonary transplantation develop pneumonia in the period after transplantation, which has an associated crude mortality of 37%.1

Noninvasive positive-pressure ventilation refers to the delivery of assisted mechanical ventilation without the need for an invasive artificial airway.2 In ARF, when noninvasive ventilation (NIV) is effective in avoiding endotracheal intubation, the incidence of bacterial pneumonia is extremely low.3 Small, uncontrolled studies in recipients of lung transplants have reported that NIV permits earlier extu-

Context Noninvasive ventilation (NIV) has been associated with lower rates of endotracheal intubation in populations of patients with acute respiratory failure.

Objective To compare NIV with standard treatment using supplemental oxygen administration to avoid endotracheal intubation in recipients of solid organ transplantation with acute hypoxemic respiratory failure.

Design and Setting Prospective randomized study conducted at a 14-bed, general intensive care unit of a university hospital.

Patients Of 238 patients who underwent solid organ transplantation from December 1995 to October 1997, 51 were treated for acute respiratory failure. Of these, 40 were eligible and 20 were randomized to each group.

Intervention Noninvasive ventilation vs standard treatment with supplemental oxygen administration.

Main Outcome Measures The need for endotracheal intubation and mechanical ventilation at any time during the study, complications not present on admission, duration of ventilatory assistance, length of hospital stay, and intensive care unit mortality.

Results The 2 groups were similar at study entry. Within the first hour of treatment, 14 patients (70%) in the NIV group, and 5 patients (25%) in the standard treatment group improved their ratio of the PaO2 to the fraction of inspired oxygen (FiO2). Over time, a sustained improvement in PaO2 to FiO2 was noted in 12 patients (60%) in the NIV group, and in 5 patients (25%) randomized to standard treatment (P = .03). The use of NIV was associated with a significant reduction in the rate of endotracheal intubation (20% vs 70%; P = .002), rate of fatal complications (20% vs 50%; P = .05), length of stay in the intensive care unit by survivors (mean [SD] days, 5.5 [3] vs 9 [4]; P = .03), and intensive care unit mortality (20% vs 50%; P = .05). Hospital mortality did not differ.

Conclusions These results indicate that transplantation programs should consider NIV in the treatment of selected recipients of transplantation with acute respiratory failure.
bation after transplantation surgery,4 and can prevent need for intubation in those with ARF.13 Randomized studies of NIV in solid organ transplant recipients with hypoxicemic ARF are lacking.

In a previous randomized study we demonstrated the efficacy of NIV to treat immunocompetent patients with ARF of various origins, comparing NIV delivered through a face mask with conventional mechanical ventilation delivered through an endotracheal tube.6

We studied solid organ transplant recipients with hypoxicemic ARF and compared NIV delivered through a face mask with standard treatment using oxygen supplementation to avoid endotracheal intubation and decrease duration of intensive care unit (ICU) stay.

METHODS
Study Design and Patient Selection
We enrolled all consecutive adult recipients of solid organ transplants admitted to the 14-bed general ICU of La Sapienza University Hospital (Rome, Italy) with acute hypoxicemic respiratory failure. Patients enrolled were randomly assigned to receive either standard treatment with oxygen supplementation delivered by Venturi mask or NIV through a face mask. Computer-generated random assignments were concealed in sealed envelopes. A hospital ad hoc ethics committee approved the protocol, and all patients or the next of kin gave written informed consent.

The criteria for eligibility were acute respiratory distress; a respiratory rate greater than 35/min, a ratio of the PaO2 to the fraction of inspired oxygen (FIO2) (PaO2:FIO2) of less than 200 while the patient was breathing oxygen through a Venturi mask; and active contraction of the accessory muscles of respiration or paradoxical abdominal motion.

Exclusion criteria were a requirement for emergent intubation for cardiopulmonary resuscitation, respiratory arrest, severe hemodynamic instability, decreased level of consciousness; respiratory failure caused by neurological disease or status asthmaticus; more than 2 new organ failures (eg, the simultaneous presence of renal and cardiovascular failures); and tracheostomy, facial deformities, or recent oral, esophageal, or gastric surgery. The simplified Acute Physiologic Score was calculated on admission to the study.8

To minimize the risk of bias due to the obvious difficulty of blinding in this study, medical management of the ARF (eg, antibiotic, antiviral, or antifungal agents; bronchodilators; diuretics; frequent respiratory treatments and chest physiotherapy), immunosuppressive therapy (corticosteroids, azathioprine, cyclosporine), time of medical interventions, central venous pressure and cardiac output monitoring, frequency of blood gases, and other aspects of ICU support (head of the bed kept elevated at a 45° angle, nutrition, fluid administration, and correction of electrolyte abnormalities) were similar in the 2 groups. Both groups were treated by the same medical and nursing staff. Patients assigned to the standard treatment group received oxygen supplementation via a Venturi mask starting with an FIO2 equal to or greater than 0.4, and adjusted to achieve a level of arterial oxygen saturation (by oximetry) above 90%. All patients had continuous electrocardiographic and arterial oxygen saturation monitoring (Biox 3700, Ohmeda, Boulder, Colo). We used 2 types of mechanical ventilators: the Puritan Bennett 7200 (Puritan Bennett Co, Overland Park, Kan) and the Servo 900 C Siemens (Siemens Elema, Uppsala, Sweden).

Noninvasive Ventilation
For patients assigned to NIV, the ventilator was connected with conventional tubing to a clear, full face mask with an inflatable soft cushion seal and a disposable foam spacer to reduce dead space (Gibeck, Upplands, Sweden). The mask was secured with head straps. In most patients, a hydrocolloid sheet was applied over the nasal bridge. For patients with a nasogastric tube, a seal connector in the dome of the mask was used to minimize air leakage. After the mask was secured, pressure support was increased to obtain an exhaled tidal volume of 8 to 10 mL/kg, a respiratory rate of fewer than 25/min, the disappearance of accessory muscle activity (as evaluated by palpating the sternocleidomastoid muscle),9 and patient comfort. Positive end-expiratory pressure was increased in increments of 2 to 3 cm H2O repeatedly up to 10 cm H2O until the FIO2 requirement was 0.6 or less. Ventilator settings were adjusted based on continuous oximetry and measurements of arterial blood gases. Patients were not sedated.

Ventilation was standardized according to the protocol of Wysocki et al.10 During the first 24 hours, ventilation was continuously maintained until oxygenation and clinical status improved. Subsequently, each patient was evaluated daily while breathing supplemental oxygen without ventilatory support for 15 minutes. Noninvasive ventilation was reduced progressively in accordance with the degree of clinical improvement and was discontinued if the patient maintained a respiratory rate lower than 30/min and a PaO2 greater than 75 mm Hg with an FIO2 of 0.5 without ventilatory support.

Endotracheal Intubation
Patients who failed standard treatment or NIV underwent endotracheal intubation with cuffed endotracheal tubes (internal diameter of 7.5-8.5 mm) and were mechanically ventilated. Predetermined criteria included failure to maintain a PaO2 above 65 mm Hg with an FIO2 equal to or greater than 0.6; development of conditions necessitating endotracheal intubation to protect the airways (coma or seizure disorders) or to manage copious tracheal secretions, hemodynamic or electrocardiographic instability; inability to correct dyspnea; or inability on the part of the patient randomized to NIV to tolerate the face mask.6

Conventional Ventilation
Intravenous benzodiazepines (diazepam, 0.2 mg/kg bolus) or propofol (2 mg/kg) were used for sedation at the moment of intubation, and none of the patients received paralyzing agents. The
initial ventilator setting was an assisted-controlled ventilation mode with a delivered tidal volume of 10 mL/kg and a respiratory rate of 14 to 18/min, a positive end-expiratory pressure of 5 cm H2O, and an FiO2 of 0.8. Positive end-expiratory pressure was increased in increments of 2 to 3 cm H2O up to 10 cm H2O until the FiO2 requirements were less than or equal to 0.6. The head of the bed was kept elevated at 45° to minimize the risk of aspiration. When spontaneous breathing reappeared, the ventilator settings were changed to intermittent mandatory ventilation (rate, 4-7/min) with pressure support (14 to 20 cm H2O) titrated to achieve a spontaneous tidal volume of 8 to 10 mL/kg, a respiratory rate less than 25/min, and disappearance of accessory muscle activity. All patients were weaned from the ventilator by reducing the level of pressure support by 4 cm H2O twice and then decreasing the ventilatory rate by 2/min at 2-hour intervals as tolerated. If the patient tolerated an intermittent mandatory ventilation rate of 0.5/min, with a pressure support level of 8 cm H2O and an FiO2 of less than or equal to 0.5, a 2-hour T-piece trial was initiated. Patients were extubated if they maintained a respiratory rate less than 30/min and a PaO2 greater than 75 mm Hg.

End Points and Definitions

The primary outcome variable was the need for endotracheal intubation and mechanical ventilation at any time during the study. Secondary end points included complications not present on admission, duration of ventilatory assistance, length of the hospital stay, and ICU mortality.

Arterial blood gas levels were determined at baseline, at 1 hour, and at 4-hour intervals. Improvement in gas exchange was defined as ability to maintain the defined improvement in PaO2:FiO2 until mechanical ventilation was discontinued, as confirmed by serial blood gas measurements.

Patients were monitored for the development of infections or other complications. Sepsis, severe sepsis, and septic shock were defined according to consensus guidelines. Infection was diagnosed using strict criteria. Patients in whom clinical manifestation of pneumonia developed underwent bronchoscopy with bronchoalveolar lavage. The methods and laboratory procedures followed consensus guidelines. Bacterial pneumonia was diagnosed when more than 104 colony-forming units of bacteria per milliliter were measured in bronchoalveolar lavage fluid. Diagnostic criteria for opportunistic pneumonia were previously described. Because infections in patients receiving mechanical ventilation are frequently associated with an invasive device, an index of invasiveness was established by counting the number of devices (central venous, arterial, pulmonary artery and urinary catheters, drainage tubes, endotracheal, and nasogastric tubes) per patient at study entry. The duration of use of the invasive devices was calculated as the number of days during which all the invasive devices counted on admission were maintained per patient. Criteria for adult respiratory distress syndrome (ARDS) followed consensus guidelines. Multiple organ failure was defined as previously described.

Statistical Analysis

Results are given as mean (SD). Demographic and physiologic characteristics for the 2 groups were compared using the t test for continuous data and with the Mantel-Haenszel extended $\chi^2$ test for categorical data. The 2-tailed Fisher exact test was used when the expected number of cases per cell was less than 5.

In the 2 years preceding this study, 70% of recipients of solid organ transplants with ARF required endotracheal intubation. In the same period, 30% of patients without organ transplantation and with acute hypoxemic respiratory failure supported with NIV required endotracheal intubation. A sample size of 40 patients was chosen to detect, with a 95% probability, a difference between the postulated 70% rate of intubation in the standard treatment group and a 30% rate in the NIV group, with a power of 80%. The odds ratios (ORs), relative risks, and 95% confidence intervals (CIs) are given with the $\chi^2$ values and P values.

RESULTS

Between December 1995 and October 1997, 238 adults received a solid organ transplant (liver, lung, or kidney). Fifty-one patients were treated in our ICU for hypoxic ARF occurring at different time intervals after transplantation (TABLE 1). Three patients had an exclusion criterion (1 tracheostomy and 2 cases of impaired consciousness) and 8 refused to participate, thus 40 were enrolled. Twenty patients were assigned to each group and all completed the study and follow-up. The baseline characteristics of the 2 groups were similar (Table 1). Reasons for transplantation for the NIV group and standard treatment group were as follows, respectively, liver transplantation: posthepatic cirrhosis, 6 and 7; hepatic cancer, 2 and 2; cystic fibrosis, 1 and 0; amanita phalloides intoxication, 1 and 0; and alcoholic cirrhosis, 0 and 3; and lung transplantation: cystic fibrosis, 2 and 2; α-1 antitrypsin deficiency, 1 and 0; and severe bronchiectasis, 1 and 0. One patient in the NIV group received a single lung transplant. The other 3 in the NIV group and those in the standard treatment group had bilateral lung transplantation. Reasons for renal transplantation were as follows: membranous glomerulonephritis, 2 and 3; Berger disease, 2 and 1; chronic pyelonephritis, 1 and 2; and polycystic kidney disease, 1 and 0. All renal transplantation recipients had end-stage renal failure on hemodialysis.

At study entry, 11 patients had a recent diagnosis of pneumonia made by bronchoscopic bronchoalveolar la-
NONINVASIVE VENTILATION IN PATIENTS WITH SOLID ORGAN TRANSPLANTS

Table 1. Baseline Characteristics of the Patients and Causes of Acute Respiratory Failure

<table>
<thead>
<tr>
<th></th>
<th>Noninvasive Ventilation Group (n = 20)</th>
<th>Standard Treatment Group (n = 20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>45 (19)</td>
<td>44 (10)</td>
<td>.89</td>
</tr>
<tr>
<td>No. (%) of men</td>
<td>13 (65)</td>
<td>12 (60)</td>
<td>.50</td>
</tr>
<tr>
<td>Simplified Acute Physiologic Score</td>
<td>13 (4)</td>
<td>13 (3)</td>
<td>.93</td>
</tr>
<tr>
<td>No. of invasive devices per patient</td>
<td>5 (1)</td>
<td>5 (1)</td>
<td>.90</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>96 (20)</td>
<td>101 (14)</td>
<td>.38</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>38 (3)</td>
<td>37 (1)</td>
<td>.32</td>
</tr>
<tr>
<td>Body temperature, °C</td>
<td>37.2 (0.9)</td>
<td>37 (0.7)</td>
<td>.35</td>
</tr>
<tr>
<td>White blood cells, ×10^9/L</td>
<td>0.005 (0.002)</td>
<td>0.007 (0.005)</td>
<td>.12</td>
</tr>
<tr>
<td>No. (%) of infections prior to entry</td>
<td>8 (40)</td>
<td>9 (45)</td>
<td>.19</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>135 (23)</td>
<td>140 (24)</td>
<td>.53</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.46 (0.05)</td>
<td>7.43 (0.04)</td>
<td>.13</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>42 (10)</td>
<td>38 (9)</td>
<td>.14</td>
</tr>
<tr>
<td>No. (%) of patients with PaCO₂ &gt;45 mm Hg</td>
<td>7 (35)</td>
<td>3 (15)</td>
<td>.13</td>
</tr>
<tr>
<td>Ratio of PaCO₂ to fraction of inspired oxygen</td>
<td>129 (30)</td>
<td>129 (30)</td>
<td>.96</td>
</tr>
<tr>
<td>No. (%) of patients who received an organ transplant</td>
<td>10 (50)</td>
<td>12 (60)</td>
<td>.37</td>
</tr>
<tr>
<td>Liver</td>
<td>5 (20)</td>
<td>2 (10)</td>
<td>.33</td>
</tr>
<tr>
<td>Kidney</td>
<td>6 (30)</td>
<td>6 (30)</td>
<td>.63</td>
</tr>
<tr>
<td>Time from transplantation, d†</td>
<td>23 (14)</td>
<td>22 (15)</td>
<td>.88</td>
</tr>
<tr>
<td>Causes of acute respiratory failure‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (10)</td>
<td>2 (10)</td>
<td>.69</td>
</tr>
<tr>
<td>Cardiogenic pulmonary edema</td>
<td>4 (20)</td>
<td>5 (25)</td>
<td>.50</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome§</td>
<td>8 (40)</td>
<td>7 (35)</td>
<td>.50</td>
</tr>
<tr>
<td>Mucous plugging or atelectasis</td>
<td>5 (25)</td>
<td>5 (25)</td>
<td>.64</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>.75</td>
</tr>
</tbody>
</table>

*Values are expressed as mean (SD) unless otherwise indicated.
†Median time from transplantation to study entry was 18 days (range, 5-60 days). All transplant recipients were treated in our intensive care unit (ICU) both for their immediate postoperative care and for complications. All patients were already hospitalized at the time of ICU admission. Five patients (25%) in the noninvasive group and 4 (20%) in the standard treatment group were discharged from the hospital after transplantation and readmitted.‡Conditions for acute respiratory distress syndrome are reported for the noninvasive ventilation group and standard treatment group, respectively: complicated pneumonia, 5 and 2; extrapulmonary sepsis, 2 and 4; massive blood transfusion, 1 and 0; and acute pancreatitis, 0 and 1.

Changes in PaO₂/FIO₂ and PaCO₂ are shown in Figure 1. Within the first hour of treatment, 14 patients (70%) in the NIV group and 5 patients (25%) in the standard treatment group had an improvement in PaO₂/FIO₂ by study criteria (OR, 7; 95% CI, 1.4-37; P = .005). A sustained improvement in PaO₂/FIO₂ over time (Table 2) was observed in 12 patients randomized to NIV (mean [SD], 142 [29] at baseline vs 271 [98] at the end of treatment; P < .001) and in 5 patients randomized to standard treatment (149 [22] at baseline vs 270 [18] at the end of treatment; P < .001). All patients with sustained improvement in PaO₂/FIO₂ over time avoided endotracheal intubation (Table 2). Four patients in the NIV group did not have sustained improvement in PaO₂/FIO₂, did not meet the preselected criteria for intubation, avoided intubation, and survived.

Figure 1. Changes in the Ratio of PaO₂ to Fraction of Inspired Oxygen (FIO₂) and PaCO₂ Over Time

Data are presented as mean (SD). Asterisk indicates P<.001; dagger, P<.005 vs baseline. A paired t test was used for the statistical comparison. Termination of treatment refers to the last arterial blood gas value obtained prior to intubation or prior to removal of oxygen supplementation.
Overall, 18 patients underwent intubation (10 orotracheal and 8 nasotracheal) at a mean (SD) of 43 (45) hours into the study (Table 2). 4 patients (20%) in the NIV group and 14 patients (70%) in the standard treatment group (P = .002). None required emergent intubation. The reasons for intubation by NIV group and standard treatment group, respectively, included failure to maintain PaO₂ level above 65 mm Hg (3 and 5), hemodynamic instability (1 and 3), management of secretions (0 and 3), and severe persistent dyspnea (0 and 3).

Thirteen patients required intubation within 24 hours of study entry, 10 in the standard treatment group and 3 in the NIV group (P = .02; Figure 2). In a subgroup analysis shown in Table 2, patients with ARDS due to either pulmonary or nonpulmonary causes randomized to NIV had an intubation rate of 38% vs 86% in the standard treatment group (P = .08). Irrespective of randomization, patients with pneumonia (opportunistic or nosocomial) had a similar intubation rate. Among patients with pulmonary edema or pulmonary embolism, all those randomized to NIV avoided intubation, while 5 (83%) of the 6 patients randomized to standard treatment required intubation (P = .01).

Positive end-expiratory pressure applied to the patients in the NIV group was lower than that used for the 14 patients who failed standard treatment and required intubation (mean [SD], 6 [1] vs 8 [2] cm H₂O; P = .02). The mean duration of NIV was 50 hours (range, 16-94) for the 16 patients whose treatments were successful and 43 hours (range, 10-120) for the 4 patients whose treatments failed. As shown in Table 2, the invasive devices present at study entry were used for a shorter period of time in the group randomized to NIV than in the group randomized to standard treatment (mean [SD] days, 5 [5] vs 9 [6]; P = .05).

Length of stay in the ICU was not different in the 2 groups, but the 16 survivors in the NIV group stayed in the ICU shorter than 10 survivors in the standard treatment group (mean [SD] days, 5.5 [3] vs 9 [4]; P = .03).

Four patients (20%) in the NIV group and 10 patients (50%) in the standard treatment group (all of whom required intubation) died in the ICU (OR, 4; 95% CI, 0.8-20; P = .05). A subgroup death rate is reported in Table 2. Four patients (2 patients with myocardial infarction and 1 with a new pulmonary embolism in the NIV group and 1 with septic shock in the standard treatment group) died in the hospital after ICU discharge.

The complications and events leading to death are shown in Table 3. Fatal complications were less frequent in the NIV group than in the standard treatment group (4 vs 10; P = .05). As shown in Table 3, severe sepsis (with or without septic shock) developed as frequently in the NIV group than in the standard treatment group (4 vs 10; P = .05). Four patients randomized to NIV developed criteria for severe sepsis or septic shock after study entry. The sources of sepsis included 2 cases of pneumonia present at study entry that worsened, and 2 ventilator-associated pneumonia cases that developed after endotracheal intubation. Ten patients in the standard treatment group developed criteria for severe sepsis (6) or septic shock (4) after study entry and developed multiple organ failure including renal failure. The sources of sepsis included 2 cases of pneumonia and 1 pancreatic abscess present at

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**Table 2. Outcome Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Noninvasive Ventilation Group (n = 20)</th>
<th>Standard Treatment Group (n = 20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial improvement in ratio of PaO₂ to fraction of inspired oxygen</td>
<td>14 (70)</td>
<td>2 (25)</td>
<td>.005</td>
</tr>
<tr>
<td>Sustained improvement in ratio of PaO₂ to fraction of inspired oxygen, without intubation</td>
<td>12 (60)</td>
<td>5 (25)</td>
<td>.03</td>
</tr>
<tr>
<td>Patients intubated within 24 h of study entry</td>
<td>3 (15)</td>
<td>10 (50)</td>
<td>.02</td>
</tr>
<tr>
<td>Patients requiring intubation</td>
<td>4 (20)</td>
<td>14 (70)</td>
<td>.002</td>
</tr>
<tr>
<td>Failures per subgroup of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute respiratory distress syndrome (pulmonary etiology)†</td>
<td>2/5 (40)</td>
<td>2/2 (100)</td>
<td>.28</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome (extrapulmonary etiology)†</td>
<td>1/3 (33)</td>
<td>4/5 (80)</td>
<td>.28</td>
</tr>
<tr>
<td>Pneumonia†</td>
<td>1/2 (50)</td>
<td>1/2 (50)</td>
<td>.83</td>
</tr>
<tr>
<td>Cardiogenic pulmonary edema†</td>
<td>0/1 (0)</td>
<td>5/5 (100)</td>
<td>.007</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0/1 (0)</td>
<td>0/1 (0)</td>
<td>.99</td>
</tr>
<tr>
<td>Mucous plugging or atelectasis†</td>
<td>0/5 (0)</td>
<td>2/5 (40)</td>
<td>.22</td>
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<tr>
<td>Duration of mechanical ventilation, d‡</td>
<td>4 (5)</td>
<td>5 (6)</td>
<td>.58</td>
</tr>
<tr>
<td>Duration of mechanical ventilation in survivors, d‡</td>
<td>2 (0.7)</td>
<td>1.6 (2)</td>
<td>.50</td>
</tr>
<tr>
<td>Duration of use for all invasive devices present at study entry, d‡</td>
<td>5 (5)</td>
<td>9 (6)</td>
<td>.06</td>
</tr>
<tr>
<td>Length of intensive care unit stay, d‡</td>
<td>7 (5)</td>
<td>10 (6)</td>
<td>.18</td>
</tr>
<tr>
<td>Length of intensive care unit stay in survivors, d‡</td>
<td>5.5 (3)</td>
<td>9 (4)</td>
<td>.03</td>
</tr>
<tr>
<td>Intensive care unit deaths</td>
<td>4 (20)</td>
<td>10 (50)</td>
<td>.05</td>
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<tr>
<td>Intensive care unit deaths per subgroup of patients†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>3/8 (37)</td>
<td>4/7 (57)</td>
<td>.40</td>
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<td>Pneumonia</td>
<td>1/2 (50)</td>
<td>1/2 (50)</td>
<td>.80</td>
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<td>Cardiogenic pulmonary edema</td>
<td>0/4 (0)</td>
<td>4/5 (80)</td>
<td>.04</td>
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<td>Pulmonary embolism</td>
<td>0/1 (0)</td>
<td>0.1 (0)</td>
<td>.99</td>
</tr>
<tr>
<td>Mucous plugging or atelectasis</td>
<td>0/5 (0)</td>
<td>1/5 (20)</td>
<td>.50</td>
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<tr>
<td>Hospital deaths¶</td>
<td>7 (35)</td>
<td>11 (55)</td>
<td>.17</td>
</tr>
</tbody>
</table>

*Values are expressed as number (percentage) unless otherwise indicated.
†Values are expressed as No./total (percentage).
‡Values are expressed as mean (SD).
§Duration of mechanical ventilation in patients randomized to standard treatment group refers to those patients who failed standard treatment and were intubated.
¶All deaths were due to complications that occurred after intubation.
¶In the 2 years preceding this study, our overall institutional mortality for solid organ transplant recipients was 24%, and for those developing acute hypoxic respiratory failure, 83%.

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Two patients in the NIV group and 4 in the standard treatment group developed ventilator-associated pneumonia (2 cases of \textit{P. aeruginosa}, 1 case of \textit{Acinetobacter}, 2 cases of methicillin-resistant \textit{S. aureus}, and 1 case of \textit{Serratia marcescens}) diagnosed 5.6 (1) days after intubation, and all died due to multiple organ failure. None developed clinical or radiographic manifestations of pneumonia during NIV. One patient in the NIV group had facial skin necrosis that resolved within 8 days.

**COMMENT**

In this randomized trial that was powered to address intubation differences and not mortality, early application of NIV in a group of solid organ recipients with hypoxemic ARF was well tolerated and associated with a rapid and sustained improvement in gas exchange. Compared with standard treatment with supplemental oxygen, patients randomized to NIV had significantly lower rates of endotracheal intubation, septic complications, fatal complications, and ICU mortality.

Half of the patients in the standard treatment group necessitated endotracheal intubation within 24 hours of study entry. Physiological studies have shown that NIV can improve the pathophysiology of hypoxemic respiratory failure caused by pneumonia, cardiogenic pulmonary edema, atelectasis, and postoperative changes in pulmonary function. Similar to our prior report in immunocompetent patients with hypoxemic respiratory failure, the ventilator protocol for NIV achieved a rapid and sustained improvement in gas-exchange abnormalities. We expanded on prior uncontrolled reports of 4 patients with lung and heart-lung transplants supported with NIV after developing severe respiratory infections leading to ARF.

Few studies have reported on the application of NIV in ARDS. In a recent randomized study of patients with hypoxemic ARF requiring mechanical ventilation, we reported that 7 (22%) of 32 patients randomized to NIV had ARDS of varied etiology. Four (58%) of the 7 patients with ARDS avoided intubation and survived, while 3 patients (42%) required intubation and died. Rocker et al \textsuperscript{10} recently reported the use of NIV during 12 episodes of hypoxemic ARF occurring in hemodynamically stable patients with acute lung injury or ARDS. Intubation was required in 34% of the episodes, and ICU mortality was 30%. In our study, the 8 ARDS patients randomized to NIV had an intubation rate of 37.5% and a mortality rate of 37%. These findings are limited to a small selected patient population and are insufficient for evaluating the role of NIV in ARDS. The studies published to date should not be interpreted to support the use of NIV in ARDS, but should provide the rationale for a prospective randomized study.

The necessity of using immunosuppressive therapy to prevent rejection in recipients of solid organ transplants increases morbidity and mortality associated with pulmonary infections. Nosocomial pneumonia is a frequent complication of mechanical ventilator...


\begin{table}
\centering
\caption{Serious Complications and Fatal Events in the 2 Groups} \label{tab:serious_complications}
\begin{tabular}{lccc}
\hline
 & Noninvasive Ventilation Group (n = 20) & Standard Treatment Group (n = 20) & \textit{P} Value \\
\hline
No. (%) of patients with complications & 8 (40) & 12 (60) & .17 \\
No. of complications occurring after intubation and causing death in intensive care unit & 4 & 10 & .05 \\
No. of complications per patient & 1.12 & 1.4 & .60 \\
Total No. of complications/No. causing death in intensive care unit & & & \\
Cardiogenic shock & 1/0 (5) & 2/2 (10) & .50 \\
Organ rejection & 4/0 (20) & 3/0 (15) & .25 \\
Primary liver malfunction & 1/0 (5) & 1/0 (5) & .75 \\
Worsening of infections present at study entry* & 2/2 (10) & 3/3 (15) & .50 \\
Ventilator-associated pneumonia & 2/2 (10) & 4/4 (20) & .33 \\
Severe sepsis and septic shock with multiple organ failure after study entry & 4/4 (20) & 10/8 (50) & .05 \\
Gastrointestinal bleeding & 1/0 (5) & 0/0 (0) & .99 \\
\hline
\end{tabular}
\end{table}

*At study entry, 5 patients had an identified infection without meeting clinical criteria for severe sepsis; 4 had pneumonia; and 1 had pancreatic abscess. These infections worsened; at 3 (2) days, expressed as mean (SD), after study entry the patients met criteria for severe sepsis (2 pneumonia, 1 in each group), or septic shock (2 pneumonia and 1 pancreatic abscess). The other 9 septic complications occurred 12 (5) days after study entry. Note that the number of septic complications occurring after the study entry included those infections present at study entry that worsened and pneumonia leading to severe sepsis and septic shock.
tion and is an important factor in determining outcome of respiratory failure. In the present study, ventilator-associated pneumonia developed after intubation in one third of patients and was associated with 100% mortality. As previously observed in immunocompetent patients with hypoxic or hypercapnic ARF, 6,12 patients randomized to NIV had fewer fatal septic complications than patients randomized to standard treatment, with a lower mortality in the ICU. These findings are in agreement with the observations of a recent prospective epidemiological study of patients with ARF requiring mechanical ventilation. Nourdine et al 27 reported that patients supported noninvasively vs those that received intubation had a lower incidence of nosocomial infections (pulmonary and extrapulmonary; \( P < .01 \)), a shorter duration of ICU stay (\( P < .01 \)), and a lower mortality (\( P < .01 \)). In our study, we found that a longer use of invasive devices was associated with a higher incidence of septic complications. Transplant recipients randomized to NIV had a shorter use of invasive devices and a lower rate of nosocomial infections. Avoiding intubation with early implementation of NIV should be an important objective in the management of respiratory failure after solid organ transplantation, and NIV may help achieve that goal.

In this study, 3 of the 4 patients with cystic fibrosis and who received lung transplantation required endotracheal intubation, and 2 died of pneumonia (1 patient from each group). In patients with cystic fibrosis who are heavily colonized with \( P \) aeruginosa, endotracheal intubation with conventional ventilation is frequently associated with dissemination of the pulmonary infection and development of septic shock. 28 Several reports have described the successful implementation of NIV as a bridge to transplantation in patients with cystic fibrosis. 29,30 In one study, duration of intubation and ICU stay after transplantation were much shorter in cystic fibrosis patients supported operatively with NIV. 30 In the present study, 1 of the 4 lung recipients who had cystic fibrosis received NIV as a bridge for transplantation. He was randomized to the NIV group after ARF in the posttransplantation period, avoided intubation, and was successfully discharged from the hospital. In this study, hospital mortality was similar in the 2 groups. Individual factors and evolution of the surgical complications might be important determinants of the final outcome. Studies specifically powered to address mortality are needed before drawing conclusions on this issue.

In conclusion, in a group of organ transplant recipients with ARF of various origins, early administration of NIV was well tolerated and associated with a significant reduction in the rate of endotracheal intubation, fatal complications, and ICU mortality. Active transplantation programs should consider NIV in the treatment of eligible patients with ARF who have no contraindications and who can be monitored safely in the appropriate environment.

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