Continuous Positive Airway Pressure for Treatment of Postoperative Hypoxemia
A Randomized Controlled Trial

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ECOVERY FROM ABDOMINAL surgery is usually fast and uncomplicated, but postoperative hypoxemia complicates between 30% and 50% of cases, even among those undergoing uneventful procedures. Although oxygen administration and incentive spirometry are effective in treating the vast majority of cases of postoperative hypoxemia, respiratory failure may occur early in the postoperative course, requiring endotracheal intubation and mechanical ventilation in 8% to 10% of patients, thus increasing morbidity and mortality and prolonging intensive care unit and hospital stay. Loss of functioning alveolar units has been recognized as the underlying mechanism responsible for postoperative hypoxemia. Pulmonary atelectasis after abdominal surgery is, in fact, common. It may ex-
ceed 25% of the total lung volume and is seen several days after surgery.²⁷
Continuous positive airway pressure (CPAP) is a breathing mode by which the patient spontaneously breathes through a pressurized circuit against a threshold resistor that maintains a preset positive airway pressure during both inspiration and expiration. Although several studies have demonstrated the efficacy of CPAP to reduce atelectasis and improve oxygenation in patients after abdominal surgery,⁸⁻¹¹ no clinical trials have confirmed that the improvement of gas exchange with CPAP actually results in a reduced need for intubation and mechanical ventilation in patients who develop hypoxemia after abdominal surgery.¹² We conducted a multicenter, prospective, randomized clinical trial to compare the efficacy of CPAP with standard oxygen therapy in the treatment of postoperative hypoxemia. We also set out to examine the hypothesis that early application of CPAP may prevent intubation and mechanical ventilation in patients who develop acute hypoxemia after major abdominal surgery.

**METHODS**

**Patients**

From June 2002 to November 2003, patients were recruited from the centers of the Piedmont Intensive Care Units Network (PICUN; members and institutions are listed in the acknowledgment). Ethics committees approved the protocol and written informed consent was obtained from the patients.

Patients scheduled for elective abdominal surgery and general anesthesia were eligible to participate in the study if they met the following criteria: abdominal surgery requiring laparotomy and time of visceral exposure longer than 90 minutes. At the end of the surgical procedure, patients were extubated and underwent a 1-hour screening test breathing oxygen through a Venturi mask at an inspiratory fraction of 0.3. Patients were included in the study if they developed an arterial oxygen tension to inspiratory fraction of 0.3. Patients were excluded if before surgery they were older than 80 or younger than 18 years; had a New York Heart Association functional class of II, III, or IV; had valvular heart disease, history of dilated cardiomyopathy, implanted cardiac pace maker, unstable angina, or myocardial infarction and cardiac surgery within the previous 3 months; had a history of chronic obstructive pulmonary disease, asthma, or sleep disorders; had preoperative infection, sepsis, or both; had a body mass index higher than 40; had a presence of tracheostomy, facial, neck, or chest wall abnormalities; required an emergency procedure (operation that must be performed as soon as possible and no longer than 12 hours after admission); or had undergone abdominal aortic aneurysm surgery, chemotherapy, or immunosuppressive therapy within the previous 3 months. Patients were also excluded if before randomization they had arterial pH lower than 7.30 with an arterial carbon dioxide tension higher than 50 mm Hg; arterial oxygen saturation lower than 80% with the maximal fraction of inspiratory oxygen; clinical signs of acute myocardial infarction; systolic arterial pressure lower than 90 mm Hg under optimal fluid therapy; presence of criteria for acute respiratory distress syndrome; hemoglobin concentration lower than 7 g/dL; serum albumin level lower than 3 g/dL; creatinine level higher than 3.5 mg/dL (309 μmol/L); or a Glasgow Coma Scale lower than 12.

**Study Design**

Concealed randomization was conducted centrally through a dedicated Web site using a computer-generated block randomization schedule. Patients were randomly assigned to be treated for 6 hours with oxygen through a Venturi mask at an FiO₂ of 0.5 (control patients) or with oxygen at an FiO₂ of 0.5 plus a CPAP of 7.5 cm H₂O.⁸⁻¹⁵ At the end of the 6-hour period, patients underwent a 1-hour screening test breathing oxygen through a Venturi mask at an FiO₂ of 0.3.³⁻¹² Patients returned to the assigned treatment if the PaO₂/FiO₂ ratio was 300 or less; treatment was interrupted if the PaO₂/FiO₂ ratio was higher.
than 300. Nasal oxygen (8-10 L/min) was given if the treatment was not tolerated.

In all centers, CPAP was generated using a flow generator with an adjustable inspiratory oxygen fraction set to deliver a flow of up to 140 L/min (Whisperflow, Caradyne, Ireland) and a spring-loaded expiratory pressure valve (Vital Signs Inc, Totoma, NJ) and applied using a latex-free polyvinyl chloride transparent helmet (CaStar, Starmed, Italy). All centers measured the inspiratory oxygen fraction using an oxygen analyzer (Oxicheck, Caradyne, Ireland) through the Venturi mask or the helmet.

If intolerance (defined as patient inability to tolerate the helmet or the Venturi mask because of discomfort, claustrophobia, or pain) was observed, both treatments were interrupted and 8 to 10 L of oxygen was administered through nasal probe.

Outcome Variables
The primary outcome variable was endotracheal intubation within the first 7 days after surgery since intubation for respiratory failure is commonly seen during this period.2,17 Intubation was performed when patients presented with 1 of the following: (1) severe hypoxemia, defined as arterial oxygen saturation lower than 80% despite the use of the maximal FiO2; (2) respiratory acidosis, defined as arterial pH level lower than 7.30 with a carbon dioxide tension higher than 50 mm Hg; (3) signs of patient distress with accessory muscle recruitment and paradoxical abdominal or thoracic motion; (4) hemodynamic instability defined as an 80- to 90-mm Hg increase or a 30- to 40-mm Hg decrease in systolic blood pressure relative to the baseline value or need for inotropic drugs for at least 2 hours to maintain systolic blood pressure higher than 85 mm Hg or electrocardiogram evidence of ischemia or significant ventricular arrhythmias; (5) need for sedation for major agitation; (6) decreased alertness defined as a Glasgow Coma Score lower than 9; or (7) cardiac arrest.19 The decision to intubate a patient was made by the attending clinician, who recorded the reasons for intubation from the list of possible reasons.

Secondary outcome variables were ICU and hospital length of stay; incidence of pneumonia, infection, and sepsis within the first month after surgery;2,16; and hospital mortality. Pneumonia, infection, and sepsis were identified using standard definitions.13 To attenuate effects on outcome variables, anesthesia, postoperative pain control, and respiratory physiotherapy were constrained by protocols. Anesthesia was induced and maintained with propofol, atracurium, remifentanil, and sevoflurane. Lactated Ringer solution was given throughout surgery (8 mL/kg per hour) and to compensate for blood loss (3 mL for every milliliter of blood loss); allogenic red blood cells were given for blood losses exceeding 20% of circulating blood volume. Tidal volume, minute ventilation, positive end-expiratory pressure, and inspiratory oxygen fraction were 8 to 10 mL/kg, 100 mL/kg, 4 to 5 cm of H2O, and no more than 0.5, respectively; patients were extubated when awake and with an oxygen saturation higher than 90% at air temperature. Postoperative analgesia was managed with intramuscular opioids given to obtain values lower than 30 mm on a visual analog scale (from 0 mm corresponding to “no pain” to 100 mm corresponding to “the worst pain ever felt”). Chest physiotherapy (diaphragmatic breathing, pursed-lip breathing, and forced expiration) was given once preoperatively, once on the day of operation, and twice daily for 3 days after the operation.

Power and Statistical Analysis
Based on previous data and on a retrospective evaluation of medical charts, the predicted intubation rate of patients fulfilling study criteria was approximately 10% to 15%. The trial was designed to enroll 600 patients to demonstrate at least a 50% reduction in the intubation rate with a 5% risk of type I error and a power of 80%. Interim analyses were conducted by an independent data and safety monitoring board after enrollment of each successive group of approximately 200 patients. The interim analysis was based on the comparison of intubation rate in the 2 treatment groups with the use of a normal approximation for a 2-sided α level of .05. Stopping boundaries were designed to allow termination of the study if the use of CPAP was found to be either efficacious (P < .016) or ineffective (P > .022).19

All analyses were conducted on an intention-to-treat basis. Because values were normally distributed, results are reported as mean (SD). Continuous variables were compared with the use of the unpaired t test. Categorical variables were compared with the use of Fisher exact test or the χ² test, when appropriate. The Kaplan-Meier curve for intubation rate was plotted for the first 7 days after surgery and was compared by the log-rank test. A probability of .05 on 2-sided testing was regarded as being significant. Analyses were performed using SAS statistical software version 8.2 (SAS Institute, Cary, NC).

RESULTS
The independent data and safety monitoring board stopped the trial at the first interim analysis because the observed intubation rate in the group of patients treated with oxygen plus CPAP was lower than in the group of patients treated with oxygen alone (P = .005).

Study Population
Of the 1332 patients enrolled, 11 patients refused to participate, 230 patients matched the study criteria (17%) and 209 underwent randomization. The remaining 21 patients were not randomized for the following reasons: no bed available in the ICU (n = 11); arterial oxygen saturation lower than 80% with the maximal fraction of inspiratory oxygen (n = 6); arterial pH lower than 7.30 with an arterial carbon dioxide tension higher than 50 mm Hg (n = 3); systolic arterial pressure lower
than 90 mm Hg under optimal fluid therapy (n = 1; Figure 1). Extubation and the screening test were performed in the recovery room immediately after surgery in 86% of patients while in the remaining 14% of patients they were performed in the ICU in a mean (SD) of 9 (4) hours after surgery.

Baseline characteristics, site, and duration of surgery did not differ between groups (Table 1). The visual analog scale values for postoperative analgesia were a mean (SD) of 20 (5) mm in the control group and 22 (4) mm in the CPAP group.

The mean (SD) PaO2/FiO2 ratio at the end of treatment was higher in patients treated with CPAP plus oxygen than in patients treated with oxygen alone (432 [45] and 341 [32], respectively, \( P < .001 \)). The mean (SD) time of treatment required to obtain the oxygenation goal was 19 (22) hours in the CPAP group and 28 (27) hours in the control group (\( P = .006 \)). Two of the 104 (2%) patients in the control group and 4 of the 105 (4%) patients in the CPAP group developed intolerance. All intolerances were observed during the first 6 hours of treatment. None of the patients who developed intolerance to treatment required intubation.

**Primary End Points**

Figure 2 shows the Kaplan-Meier estimates of intubation rate by treatment group. The cumulative probability of remaining unintubated was higher in patients treated with CPAP (\( P = .005; \) log-rank test): 10 patients (10%) in the control group and 1 patient (1%) in the CPAP group required intubation (\( P = .005 \)). The reasons for intubation were severe hypoxemia (8 patients), hemodynamic instability (1 patient), and cardiac arrest (1 patient) in control patients and severe hypoxemia in the CPAP patient. Relative risk (RR) for intubation was 0.099 (95% confidence interval [CI], 0.01-0.76).

**Secondary End Points**

The mean (SD) ICU length of stay was shorter in the oxygen plus CPAP group than in the oxygen alone group (2.6

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**Table 1. Baseline Characteristics of the Patients at Study Inclusion Before Randomization**

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 104)</th>
<th>CPAP (n = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>64 (62)</td>
<td>71 (68)</td>
</tr>
<tr>
<td>Women</td>
<td>40 (38)</td>
<td>34 (32)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>65 (10)</td>
<td>66 (9)</td>
</tr>
<tr>
<td>Body mass index, mean (SD)*</td>
<td>26.3 (4.5)</td>
<td>26.5 (4.7)</td>
</tr>
<tr>
<td>Current smoker, No. (%)†</td>
<td>21 (20)</td>
<td>19 (18)</td>
</tr>
<tr>
<td>SAPS II, mean (SD)‡</td>
<td>28 (8)</td>
<td>27 (7)</td>
</tr>
<tr>
<td>Type of surgery, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colectomy</td>
<td>38 (36)</td>
<td>39 (36)</td>
</tr>
<tr>
<td>Gastroctomy</td>
<td>7 (6)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Pancreatico-duodenectomy</td>
<td>18 (17)</td>
<td>19 (18)</td>
</tr>
<tr>
<td>Retropertitoneal mass</td>
<td>4 (3)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Liver resection</td>
<td>24 (22)</td>
<td>22 (21)</td>
</tr>
<tr>
<td>Liver transplant</td>
<td>13 (12)</td>
<td>16 (15)</td>
</tr>
<tr>
<td>Pathology, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>64 (62)</td>
<td>67 (64)</td>
</tr>
<tr>
<td>Noncancer</td>
<td>40 (38)</td>
<td>38 (36)</td>
</tr>
<tr>
<td>Comorbidities, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (11)</td>
<td>16 (15)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42 (40)</td>
<td>37 (35)</td>
</tr>
<tr>
<td>Postoperative gases, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2/FiO2</td>
<td>255 (31)</td>
<td>247 (33)</td>
</tr>
<tr>
<td>Arterial, pH</td>
<td>7.39 (0.05)</td>
<td>7.38 (0.04)</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>39 (5)</td>
<td>39 (7)</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mean (SD), mm Hg</td>
<td>86 (10)</td>
<td>85 (11)</td>
</tr>
<tr>
<td>Time of surgical procedure, mean (SD), h§</td>
<td>226 (95)</td>
<td>227 (91)</td>
</tr>
</tbody>
</table>

Abbreviations: CPAP, continuous positive airway pressure; PaO2/FiO2, arterial oxygen to inspiratory oxygen fraction ratio; PaCO2, arterial carbon dioxide.

*Body mass index is the weight in kilograms divided by the square of the height in meters.
†Patients who had smoked within 8 weeks of surgery were defined as current smokers.
‡Simplified Acute Physiology Score (SAPS II) (range, 0-63) is an index of the severity of illness; higher values indicate greater severity.
§Time of surgical procedure is the time encompassed between the skin incision and the first suture placed to close skin incision.

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Estimates of intubation rates are according to whether or not patients received oxygen alone (control) or oxygen plus continuous positive airway pressure (CPAP). The cumulative probability of remaining without intubation was higher in patients treated with CPAP (\( P = .005; \) log-rank test).
CPAP FOR POSTOPERATIVE HYPOXEMIA

Table 2. Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 104)</th>
<th>CPAP (n = 105)</th>
<th>Difference of Means (95% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU length of stay, mean, d</td>
<td>2.6</td>
<td>1.4</td>
<td>−1.2 (−2.0 to −0.3)</td>
<td>.09</td>
</tr>
<tr>
<td></td>
<td>(1-11)</td>
<td>(1-14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital length of stay, mean (SD), d</td>
<td>17 (15)</td>
<td>15 (13)</td>
<td>−2 (−6 to 2)</td>
<td>.10</td>
</tr>
<tr>
<td></td>
<td>(7-47)</td>
<td>(6-35)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relative Risk (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 104)</th>
<th>CPAP (n = 105)</th>
<th>Difference of Means (95% CI)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia, No. (%)†</td>
<td>10 (10)</td>
<td>2 (2)</td>
<td>0.19 (0.04 to 0.88)</td>
<td>.02</td>
</tr>
<tr>
<td>Infection, No. (%)‡</td>
<td>11 (10)</td>
<td>3 (3)</td>
<td>0.27 (0.07 to 0.94)</td>
<td>.03</td>
</tr>
<tr>
<td>Sepsis, No. (%)§</td>
<td>9 (9)</td>
<td>2 (2)</td>
<td>0.22 (0.04 to 0.99)</td>
<td>.03</td>
</tr>
<tr>
<td>Anastomotic leakage, No.</td>
<td>6</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia, No.</td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths, No. (%)</td>
<td>3</td>
<td>0</td>
<td></td>
<td>.12</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CPAP, continuous positive end-expiratory pressure; ICU, intensive care unit.

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nally designed to deliver oxygen during hyperbaric treatments has been proposed recently as an alternative interface to deliver CPAP. The helmet contains the head and the neck of the patient and is secured by 2 armpit braces at an anterior and a posterior hook on a plastic ring joining the helmet to a soft collar that adheres to the neck and ensures a sealed connection once the helmet is inflated. The flow generator and the spring-loaded expiratory pressure valve are connected to the inlet and outlet of the helmet; a 2-way security valve allows the patient to breathe from outside should the helmet deflate due to loss in circuit pressure or disconnection. Recent studies demonstrated that although improvement in oxygenation and functional residual capacity was similar, intolerance to ventilatory treatment, incidence of skin necrosis, gastric distension, and eye irritation were less common with the helmet than with the face mask. The use of the helmet to deliver CPAP could therefore explain the reduced incidence of intolerance seen in our study (4%) compared with a previous trial (14%) that administered CPAP through a full face mask. However, the helmet used to deliver CPAP in our study is presently available in only a few European countries; further studies are therefore required to evaluate whether use of more widely available interfaces for CPAP administration, such as full face or nasal masks, would provide results similar to those that we describe herein.

Third, previous studies showed that application of CPAP several hours after the end of surgery did not result in any clinical benefit. In our study, hypoxemia was identified and treated immediately after surgery and CPAP was applied for a mean (SD) of 19 (22) hours and interrupted only when the oxygenation target for stopping treatment was reached.

Postoperative complications occur with a distinct temporal pattern: respiratory failure and pneumonia are seen within the first week while sepsis and surgical reintervention predominantly occur a week after surgery. In our study, all cases of pneumonia occurred within the first week from surgery while all cases of infection and sepsis occurred after the first week; all were more frequent in patients treated with oxygen than in patients treated with CPAP. These findings may be explained by recent data showing that atelectasis promotes bacterial growth in the lung and increases lung permeability; reducing atelectasis by positive end-expiratory pressure decreases bacterial growth in the lung, mitigates bacterial translocation from the lung into the bloodstream, and normalizes the permeability of the epithelial-endothelial barrier.

In a recent study, Plant et al showed that use of noninvasive ventilation on general wards was feasible and clinically effective at reducing the need for intubation and the mortality associated with acute exacerbations of chronic obstructive pulmonary disease. A recent consensus conference recommends that treatment of severe hypoxemia with noninvasive ventilation should be performed in an ICU or within a system of care capable of providing high levels of monitoring, with immediate access to staff skilled in invasive airway management. Antonelli et al recently observed that the frequency of failure of noninvasive ventilation requiring immediate intubation was higher in patients with severe hypoxemia associated with atelectasis or postsurgical sepsis than in patients with severe hypoxemia associated with cardiogenic pulmonary edema. Application of noninvasive CPAP in patients who develop severe hypoxemia after major abdominal surgery, therefore, should be limited to ICUs or high-dependency units where immediate intubation for worsening of hypoxemia can be rapidly accomplished.

Allocation to treatment with oxygen or oxygen plus CPAP was not blinded. To minimize potential bias in the assessment of some of the study end points, we used measures such as objective criteria for endotracheal intubation and standardization of all interventions that could have influenced outcome variables such as anesthesia, postoperative pain control, and respiratory physiotherapy. Moreover, lack of blindness unlikely influenced the reduced ICU length of stay observed in patients treated with CPAP since shortage of ICU beds is such that ICU attending physicians (not involved in the study) always tried to discharge the patients as soon as was safely possible.

We originally intended to enroll 600 patients and conduct interim analyses after enrollment of each successive group of approximately 200 patients. Although commonly used in randomized clinical trials, repeated interim analyses may lead to the experimental treatment being incorrectly declared as different from control. We used classic methods developed by Gordon and DeMets and Pocock for performing interim analyses, using “stopping rules” that were less stringent with respect to ineffectiveness than with respect to efficacy with a $P$ value required to stop the study for efficacy at the first interim analysis ($P < .016$) more stringent than the conventional $P < .05$. An independent data and safety monitoring board, composed of 3 biostatisticians, a bioethicist, and a clinician who was knowledgeable about the study question, stopped the trial after the first interim analysis because CPAP was found to be efficacious for the primary outcome variable ($P = .005$). Despite this being, to the best of our knowledge, the largest multicenter trial demonstrating a clinically important outcome benefit of CPAP in this cohort of patients, its early termination resulted in a relatively small number of end points being reached and analyzed in each group. Nevertheless, the results show that compared with standard treatment, early use of CPAP decreased the incidence of endotracheal intubation and other complications in patients with postoperative hypoxemia after major abdominal surgery. Because of the low costs and the reduced risks associated with this approach, early use of CPAP appears to be a practical method for treating postoperative hypoxemia in patients recovering from elective major abdominal surgery.
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Administrative, technical, or material support: Squadron, Coha, Cerutti, Schellino, Biolino, Occella, Belloni, Vilianis, Fiore. Supervision: Ranieri.

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