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Vincenzo Squadrone; Massimiliano Cocha; Elisabetta Cerutti; et al.

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Continuous Positive Airway Pressure for Treatment of Postoperative Hypoxemia

A Randomized Controlled Trial

Vincenzo Squadrone, MD

Massimiliano Cocha, MD

Elisabetta Cerutti, MD

Maria Maddalena Schellino, MD

Piera Biolino, MD

Paolo Occella, MD

Giuseppe Belloni, MD

Giuseppe Vilianis, MD

Gilberto Fiore, MD

Franco Cavallo, MD

V. Marco Ranieri, MD

for the Piedmont Intensive Care Units
Network (PICUN)

RECOVERY FROM ABDOMINAL surgery is usually fast and uncomplicated, but postoperative hypoxemia complicates between 30% and 50% of cases, even among those undergoing uneventful procedures.¹ Although oxygen administration and incentive spirometry are effective in treating the vast majority of cases of postoperative hypoxemia,² respiratory failure may occur early in the postoperative course,³ requiring endotracheal intubation and mechanical ventilation in 8% to 10% of patients, thus increasing morbidity and mortality and prolonging intensive care unit (ICU) and hospital stay.¹⁻⁴ Loss of functioning alveolar units has been recognized as the underlying mechanism responsible for postoperative hypoxemia.⁵⁻⁷ Pulmonary atelectasis after abdominal surgery is, in fact, common. It may ex-

Context Hypoxemia complicates the recovery of 30% to 50% of patients after abdominal surgery; endotracheal intubation and mechanical ventilation may be required in 8% to 10% of cases, increasing morbidity and mortality and prolonging intensive care unit and hospital stay.

Objective To determine the effectiveness of continuous positive airway pressure compared with standard treatment in preventing the need for intubation and mechanical ventilation in patients who develop acute hypoxemia after elective major abdominal surgery.

Design and Setting Randomized, controlled, unblinded study with concealed allocation conducted between June 2002 and November 2003 at 15 intensive care units of the Piedmont Intensive Care Units Network in Italy.

Patients Consecutive patients who developed severe hypoxemia after major elective abdominal surgery. The trial was stopped for efficacy after 209 patients had been enrolled.

Interventions Patients were randomly assigned to receive oxygen (n=104) or oxygen plus continuous positive airway pressure (n=105).

Main Outcome Measures The primary end point was incidence of endotracheal intubation; secondary end points were intensive care unit and hospital lengths of stay, incidence of pneumonia, infection and sepsis, and hospital mortality.

Results Patients who received oxygen plus continuous positive airway pressure had a lower intubation rate (1% vs 10%; $P=.005$; relative risk [RR], 0.099; 95% confidence interval [CI], 0.01-0.76) and had a lower occurrence rate of pneumonia (2% vs 10%, RR, 0.19; 95% CI, 0.04-0.88; $P=.02$), infection (3% vs 10%, RR, 0.27; 95% CI, 0.07-0.94; $P=.03$), and sepsis (2% vs 9%; RR, 0.22; 95% CI, 0.04-0.99; $P=.03$) than did patients treated with oxygen alone. Patients who received oxygen plus continuous positive airway pressure also spent fewer mean (SD) days in the intensive care unit (1.4 [1.6] vs 2.6 [4.2], $P=.09$) than patients treated with oxygen alone. The treatments did not affect the mean (SD) days that patients spent in the hospital (15 [13] vs 17 [15], respectively; $P=.10$). None of those treated with oxygen plus continuous positive airway pressure died in the hospital while 3 deaths occurred among those treated with oxygen alone ($P=.12$).

Conclusion Continuous positive airway pressure may decrease the incidence of endotracheal intubation and other severe complications in patients who develop hypoxemia after elective major abdominal surgery.

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Author Affiliations and PICUN Members are listed at the end of this article.

Corresponding Author: V. Marco Ranieri, MD, Università di Torino, Dipartimento di Anestesia, Azienda Ospedaliera S. Giovanni Battista-Molinette, Corso Dogliotti 14, 10126 Torino (marco.ranieri@unito.it).

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ceed 25% of the total lung volume and is seen several days after surgery.⁵⁻⁷

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 viscera 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 oxygen fraction ratio ($\text{PaO}_2/\text{FiO}_2$) of 300 or less (FIGURE 1). Patients were excluded if before surgery they were older than 80 or younger than 18 years; had a New York Heart Association func-

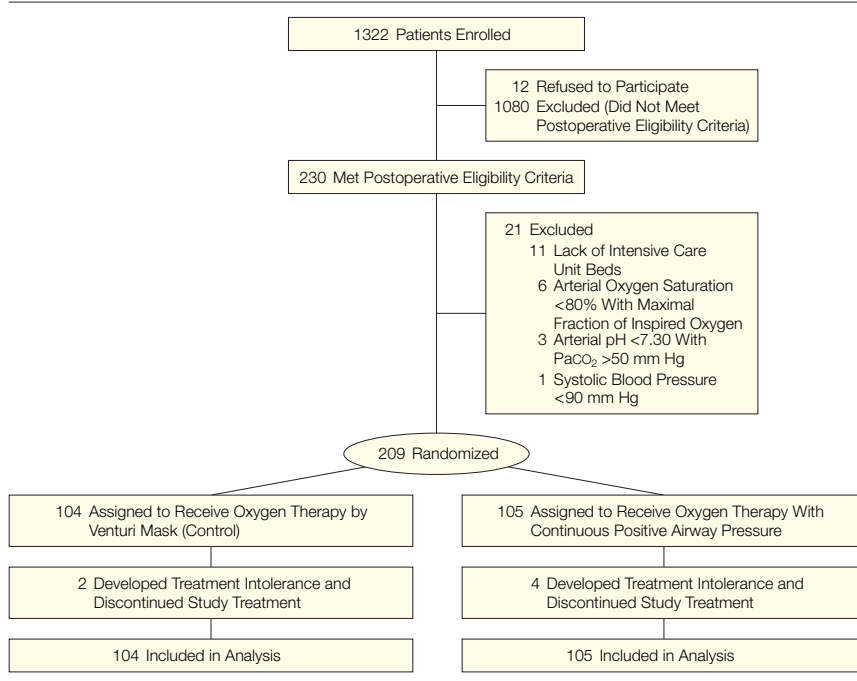
tional class of II, III, or IV; had valvular heart disease, history of dilated cardiomyopathy, implanted cardiac pace maker, unstable angina, or myocardial infarction and cardiac surgery within the previous 3 months; had a history of chronic obstructive pulmonary disease, asthma, or sleep disorders; had preoperative infection, sepsis, or both¹³; 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 syndrome¹⁴; hemoglobin concentration lower than 7 g/dL, serum albumin level lower than 3 g/dL; creatinine level higher than 3.5 mg/dL (309 $\mu\text{mol/L}$); 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 FiO_2 of 0.5 (control patients) or with oxygen at an FiO_2 of 0.5 plus a CPAP of 7.5 cm H_2O .^{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 FiO_2 of 0.3.^{8,15} Patients returned to the assigned treatment if the $\text{PaO}_2/\text{FiO}_2$ ratio was 300 or less; treatment was interrupted if the $\text{PaO}_2/\text{FiO}_2$ ratio was higher

Figure 1. Patient Flow Chart



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, Caradayne, 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).¹⁶ All centers measured the inspiratory oxygen fraction using an oxygen analyzer (Oxichcek, Caradayne, 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 FiO_2 ; (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.¹⁵ The decision to in-

tubate 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, remifentanyl, 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 H_2O , 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 data³ 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 ($P < .016$)¹⁸ 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 χ^2 test, when appropriate. The Kaplan-Meier curve for intubation rate was plotted for the first 7 days after surgery² 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

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

	Control (n = 104)	CPAP (n = 105)
Sex, No. (%)		
Men	64 (62)	71 (68)
Women	40 (38)	34 (32)
Age, mean (SD), y	65 (10)	66 (9)
Body mass index, mean (SD)*	26.3 (4.5)	26.5 (4.7)
Current smoker, No. (%)†	21 (20)	19 (18)
SAPS II, mean (SD)‡	28 (8)	27 (7)
Type of surgery, No. (%)		
Colectomy	38 (36)	39 (36)
Gastrectomy	7 (6)	6 (6)
Pancreatico-duodenectomy	18 (17)	19 (18)
Retroperitoneal mass	4 (3)	3 (4)
Liver resection	24 (22)	22 (21)
Liver transplant	13 (12)	16 (15)
Pathology, No. (%)		
Cancer	64 (62)	67 (64)
Noncancer	40 (38)	38 (36)
Comorbidities, No. (%)		
Diabetes	11 (11)	16 (15)
Hypertension	42 (40)	37 (35)
Postoperative gases, mean (SD)		
PaO ₂ /FiO ₂	255 (31)	247 (33)
Arterial, pH	7.39 (0.05)	7.38 (0.04)
PaCO ₂ , mm Hg	39 (5)	39 (7)
Mean arterial blood pressure, mean (SD), mm Hg	86 (10)	85 (11)
Time of surgical procedure, mean (SD), h§	226 (95)	227 (91)

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

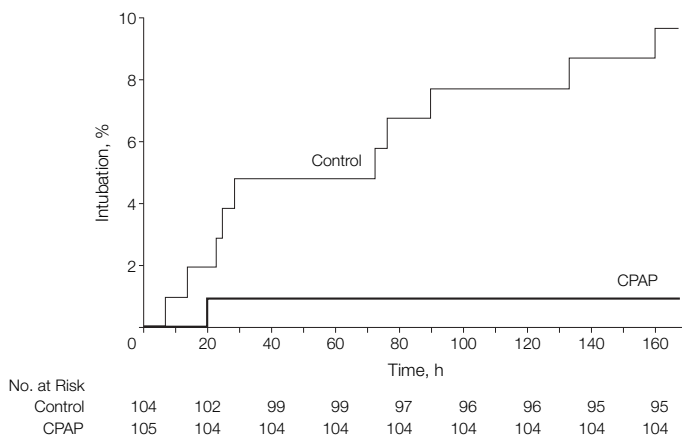
*Body mass index is the weight in kilograms divided by the square of the height in meters.

†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.

Figure 2. Kaplan-Meier Estimates of Intubation Rate



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).

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

[4.2] days vs 1.4 [1.6] days, $P = .09$). Four patients in the oxygen plus CPAP group remained in the ICU for at least 4 days after surgery vs 13 patients in the oxygen alone group (RR, 0.30; 95% CI, 0.10 - 0.90; $P = .02$). All cases of pneumonia were observed within the first week after surgery. Two percent of patients treated with oxygen plus CPAP had pneumonia within the first week of surgery vs 10 in the oxygen alone group (RR, 0.19; 95% CI, 0.04-0.88; $P = .02$). Cases of infection (3% vs 10%; RR, 0.27; 95% CI, 0.07-0.94; $P = .03$) and sepsis (2% vs 9%; RR, 0.22; 95% CI, 0.04-0.99; $P = .03$) were less frequent in patients treated with oxygen plus CPAP than in patients treated with oxygen alone, respectively; all occurred after the first week after surgery. All cases of infection were related to infection of the surgical wound. Sixty-seven percent of the sepsis were related to anastomotic leakage while the remaining 33% were related to pneumonia. The mean (SD) hospital length of stay did not differ between groups (15 [13] days in patients treated with CPAP vs 17 [15] days in patients treated with oxygen, $P = .10$). All patients treated with CPAP left the hospital alive while 3 patients died in the group treated with oxygen alone ($P = .12$; TABLE 2).

COMMENT

Our study demonstrates that early treatment with CPAP reduces the need for intubation, the ICU length of stay and the incidence of pneumonia, infection, and sepsis in patients who develop acute hypoxemia after elective major abdominal surgery.

Of the 1332 patients enrolled, 209 developed hypoxemia an hour after extubation and underwent randomization (16%); the incidence of severe hypoxemia in our study is consistent with previous reports: Moller and coworkers²⁰ found that hypoxemia occurred in 13% of 200 patients who had undergone elective surgery. The intubation rate within the first week after surgery in the control group in our study was 10%. Previous reports indicate that the

Table 2. Secondary Outcomes

	Control (n = 104)	CPAP (n = 105)	Difference of Means (95% CI)	P Value*
ICU length of stay, mean, d	2.6	1.4	-1.2 (-2.0 to -0.3)	.09
Median (95% CI), d	1 (1-11)	1 (1-4)		
Hospital length of stay, mean (SD), d	17 (15)	15 (13)	-2 (-6 to 2)	.10
Median (95% CI)	12 (7-47)	11 (6-35)		
			Relative Risk (95% CI)	
Pneumonia, No. (%)†	10 (10)	2 (2)	0.19 (0.04 to 0.88)	.02
Infection, No. (%)‡	11 (10)	3 (3)	0.27 (0.07 to 0.94)	.03
Sepsis, No. (%)§	9 (9)	2 (2)	0.22 (0.04 to 0.99)	.03
Anastomotic leakage, No.	6	1		
Pneumonia, No.	3	1		
Deaths, No. (%)	3 (3)	0 (0)		.12

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

*All P values are 2-tailed. Comparisons between control and CPAP by Fisher exact test for categorical variables and 2-tailed t test for continuous variables.

†Pneumonia was defined as the presence of an infiltrate on chest radiograph, plus at least 1 of the following: purulent endotracheal aspirate; known pathogens on a Gram stain, or cultured from sputum or blood; temperature higher than 38.5°C or lower than 36°C, white blood cell count higher than $12 \times 10^3/\mu\text{L}$ or less than $3.5 \times 10^3/\mu\text{L}$, or 20% immature forms.

‡Infection was defined as the presence of a pathogenic microorganism, clinical infection, or both, necessitating antibiotic administration.

§Sepsis was defined as infection plus at least 3 of the following: core temperature higher than 38°C or lower than 36°C, heart rate higher than 90/min, a respiratory rate higher than 20/min, or an arterial carbon dioxide lower than 32 mm Hg or the use of mechanical ventilation; white cell count higher than $12 \times 10^3/\mu\text{L}$ or lower than $4 \times 10^3/\mu\text{L}$, or a differential count showing more than 10% immature neutrophils.

intubation rate in surgical patients can vary between 5% and 15% based on previous physical status and the complexity of the surgical procedure.^{3,21,22}

The most evoked mechanism of hypoxemia after abdominal surgery is the impairment of the pulmonary ventilation-perfusion ratio due to atelectasis caused by recumbent position, high oxygen concentration, temporary diaphragmatic dysfunction, impairment of pulmonary secretion clearance, and pain.⁵⁻⁷ Several studies have shown that, in patients with postoperative hypoxic respiratory failure, CPAP improves gas exchange, minimizes atelectasis formation, and increases functional residual capacity.⁸⁻¹¹ However, although randomized clinical trials involving patients with cardiogenic pulmonary edema²³ and with congestive heart failure and sleep-related breathing problems²⁴ showed that improvement of physiological parameters with CPAP corresponded to a better clinical outcome, 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 de-

velop hypoxemia after abdominal surgery.^{12,25,26} A recent study of 123 patients showed that, despite early physiological benefits, treatment with CPAP did not reduce the need for intubation in patients with acute hypoxic respiratory failure.¹⁵ Several factors could explain the results of our trial.

First, we excluded patients who, before randomization, presented with hypercapnia and respiratory acidosis, severe hypoxemia, presence of criteria for acute respiratory distress syndrome, clinical signs of acute myocardial infarction, hypotension, and consciousness impairment since controversies exist on the use of CPAP under these conditions^{12,26} and included patients who likely developed hypoxemia only because of postoperative atelectasis.⁵⁻⁷

Second, among factors that may limit the application of noninvasive CPAP, the use of a face or nasal mask appears to be particularly relevant. Inability to fit the mask, leaks, and patient discomfort may limit continuous and long-term application of noninvasive CPAP and account for a large proportion of the failures.^{15,27} A transparent latex-free polyvinyl chloride helmet origi-

nally designed to deliver oxygen during hyperbaric treatments has been proposed recently as an alternative interface to deliver CPAP.^{16,28-30} 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.^{16,28-30} Recent studies demonstrated that although improvement in oxygenation and functional residual capacity was similar,²⁹ intolerance to ventilatory treatment, incidence of skin necrosis, gastric distension, and eye irritation were less common with the helmet than with the face mask.¹⁶ 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.¹⁵ 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 surgery³¹ or for a short period³² 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.^{2,17} 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.^{33,34}

In a recent study, Plant et al³⁵ 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.¹² Antonelli et al³⁶ 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 cointerventions 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,^{37,38} repeated interim analyses may lead to the experimental treatment being incorrectly declared as different from control.^{37,38} We used classic methods developed by Gordon and DeMets¹⁸ and Pocock¹⁹ 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.

Author Affiliations: Dipartimento di Anestesia, Azienda Ospedaliera S. Giovanni Battista-Molinette, Università di Torino (Drs Squadrone, Cocha, Cerutti, Schellino, Occeola, and Ranieri), Servizio di Anestesia e Rianimazione, Ospedale Civile di Chivasso (Dr Biolino), Servizio di Anestesia e Rianimazione, Ospedale Civile di Ivrea (Dr Belloni), Servizio di Anestesia e Rianimazione, Ospedale Civile di Pinerolo (Dr Vilianis), Servizio di Anestesia e Rianimazione, Ospedale S. Croce di Moncalieri (Dr Fiore), and Dipartimento di Sanità Pubblica e Microbiologia, Università di Torino (Dr Cavallo), Italy.

Author Contributions: Dr Ranieri had full access to all of the data and takes complete responsibility for the integrity of the data, and the accuracy of data analysis. *Study conception and design:* Squadrone, Cavallo, Ranieri.

Acquisition of data: Squadrone, Cocha, Cerutti, Schellino, Biolino, Occeola, Belloni, Vilianis, Fiore, Ranieri.

Analysis and interpretation of data: Squadrone, Cavallo, Ranieri.

Drafting the manuscript: Squadrone, Cavallo, Ranieri. *Critical revision of the manuscript for important intellectual content:* Cocha, Cerutti, Schellino, Biolino, Occeola, Belloni, Vilianis, Fiore.

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Participating Members of the Piedmont Intensive Care Unit Network (PICUN): Ospedale S. Giovanni Battista-

Molinette, Anestesia e Rianimazione 1-3, Torino: A.G. Viale; Ospedale Civile, Chivasso: E. Castenetto; Ospedale Civile Ivrea: M. R. Salsuni; Ospedale E. Agnelli, Pinerolo: L. Del Piano; Ospedale Civile S. Croce, Moncalieri: P. Buffa; Ospedale Civile, Asti: S. Cardellino, S. Perno; Ospedale Civile, Ciriè: P. Giugiaro; Osp. S. Annunziata, Savigliano: G. Vai, M. Testa; Ospedale degli Infermi, Rivoli: B. Barberis, B. Babuin; Ospedale S. Giovanni Antica Sede, Torino: L. Musso; Ospedale Martini, Torino: A. Parigi, M. Torta; Ospedale Maggiore della Carità, Novara: F. Della Corte, A. Gratarola; Ospedale S. Giovanni Battista-Molinette, Anestesia e Rianimazione 6, Torino: P. Donadio, M. Vaj; IRCC Candiolo, Torino: F. De Bernardi, E. Moselli; Ospedale Giovanni Bosco, Torino: E. Guglielmotti. Clinical coordinating center: Ospedale S. Giovanni Battista Molinette, Università di Torino: G. Rosboch, A. Rossi, S. Vendramin. Data safety and monitoring board: C. Filippini, M. Pizzio, M. Eandi, G. Costa, and A. Pesenti. Protocol Review Committee: C. Gregoretto, A. Tempia, G. Carbone.

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