Mechanical ventilation affects inflammatory mediators in patients undergoing cardiopulmonary bypass for cardiac surgery: A randomized clinical trial

Enrico Zupancich, MD,^{a,†‡} Domenico Paparella, MD,^{b,*‡} Franco Turani, MD,^{a,c} Christopher Munch, MD,^a Alessandra Rossi, MD,^a Simone Massaccesi, MD,^a and V. Marco Ranieri, MD^b

Objectives: Respiratory support for patients recovering from cardiopulmonary bypass and cardiac surgery uses large tidal volumes and a minimal level of positive end-expiratory pressure. Recent data indicate that these ventilator settings might cause pulmonary and systemic inflammation in patients with acute lung injury. We examined the hypothesis that high tidal volumes and low levels of positive end-expiratory pressure might worsen the inflammatory response associated to cardiopulmonary bypass.

Methods: Forty patients undergoing elective coronary artery bypass were randomized to be ventilated after cardiopulmonary bypass disconnection with high tidal volume/low positive end-expiratory pressure (10-12 mL/kg and 2-3 cm H₂O, respectively) or low tidal volume/high positive end-expiratory pressure (8 mL/kg and 10 cm H₂O, respectively). Interleukin 6 and interleukin 8 levels were measured in the bronchoalveolar lavage fluid and plasma. Samples were taken before sternotomy (time 0), immediately after cardiopulmonary bypass separation (time 1), and after 6 hours of mechanical ventilation (time 2).

Results: Interleukin 6 and interleukin 8 levels in the bronchoalveolar lavage fluid and plasma significantly increased at time 1 in both groups but further increased at time 2 only in patients ventilated with high tidal volume/low positive end-expiratory pressure. Interleukin 6 and interleukin 8 levels in the bronchoalveolar lavage fluid and in the plasma at time 2 were higher with high tidal volume/low positive end-expiratory pressure than with low tidal volume/high positive end-expiratory pressure.

Conclusion: Mechanical ventilation might be a cofactor able to influence the inflammatory response after cardiac surgery.

From Servizio di Anestesia e Rianimazione,^a Azienda Ospedaliera Cardiologico "G.M. Lancisi," Ancona, Italy; Anestesiologia e Rianimazione, Dipartimento di Discipline Medico-Chirurgiche,^b Università di Torino, Ospedale S. Giovanni Battista, Turin, Italy; and Anestesia e Rianimazione,^c Il Università degli Studi di Roma "Tor Vergata," Rome, Italy.

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Address for reprints: V. Marco Ranieri, MD, Università di Torino, Dipartimento di Discipline Medico-Chirurgiche, Sezione di Anestesiologia e Rianimazione, Ospedale S. Giovanni Battista, Corso Dogliotti 14, 10126 Torino, Italy (E-mail: marco.ranieri@unito.it)

*Domenico Paparella is currently affiliated with Sezione di Cardiocirurgia, Dipartimento dell'Emergenza e dei Trapianti d'Organo, Università di Bari, Bari, Italy.

†Deceased in April 2001.

‡Drs Zupancich and Paparella equally contributed and should be therefore both considered as first authors of this study.

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Cardiopulmonary bypass (CPB) is associated with a pulmonary and systemic inflammatory reaction. Although often innocuous, such an inflammatory response might contribute to postoperative complications, including acute lung injury, bleeding disorders, and multiple organ failure.¹

Despite a widespread use of fast-track protocols, patients might still require several hours of ventilatory support to recover from cardiac surgery. Traditional respiratory support uses a large (10-15 mL/kg) tidal volume (V_T) to minimize atelectasis, and the minimal level of positive end-expiratory pressure (PEEP) that improves arterial oxygenation by using low inspiratory oxygen fractions with no hemodynamic consequences.² Recent experimental data indicate that these ventilator settings might worsen pulmonary damage with granulocyte activation, hyaline membrane formation, increased vascular permeability, and pulmonary and systemic release of inflammatory mediators.^{3,4} Three recent randomized controlled clinical trials confirmed these experimental findings, showing that in patients with acute

lung injury, the use of a low V_T decreased the pulmonary and systemic inflammatory response and improved survival.⁵⁻⁷ Whether high PEEP should be associated with low V_T in these patients is still a matter of debate.⁸

We studied the influence of mechanical ventilation on pulmonary and systemic concentration of inflammatory mediators in patients undergoing CPB for cardiac surgery. This study examines the hypothesis that mechanical ventilation with a high V_T and low levels of PEEP might further increase the concentration of inflammatory mediators caused by CPB.

Methods

After approval of the institutional review board and after informed consent was obtained, patients were enrolled in the study protocol at the Lancisi hospital (Ancona, Italy). Inclusion criteria were age of 18 years or older and elective coronary artery bypass surgery. Exclusion criteria were the presence of cardiogenic pulmonary edema, emergency or urgent cases, preexisting chronic obstructive pulmonary disease, smoking history, major chest wall abnormalities, and enrollment in other studies.

All patients received diazepam (0.15 mg/kg), morphine (0.1 mg/kg), and scopolamine (0.3 mg/kg). Radial and pulmonary catheters were introduced. After tracheal intubation, lungs were ventilated with intermittent positive pressure ventilation. V_T , respiratory frequency, and fraction of inspired oxygen (F_{IO_2}) were adjusted to maintain an arterial P_{CO_2} of between 35 and 40 mm Hg and an arterial oxygen saturation of greater than 95%. Sternotomy and internal thoracic artery harvesting were performed in all patients. Heparin was administered at a dose of 3 mg/kg to achieve a target activated clotting time of 420 seconds or more. CPB was established and conducted at moderate hypothermia (30°C). Mechanical ventilation was stopped after cardioplegic arrest by disconnecting the patient from the ventilator.

After weaning from CPB, mechanical ventilation was restored after 1 to 2 minutes of manual ventilation (F_{IO_2} , 0.5); patients were randomly assigned to a high- V_T /low-PEEP (10-12 mL/kg measured body weight and 2-3 cm H_2O , respectively) or low- V_T /high-PEEP (8 mL/kg measured body weight and 10 cm H_2O , respectively) group. In both ventilatory strategies, F_{IO_2} was 0.5, inspiratory/expiratory ratio was 1:2, and respiratory rate was 12 to 15 breaths/min. After chest closure, patients were transferred to the intensive care unit and ventilated, with the ventilatory pattern selected randomly. Sedation and muscle relaxation was maintained, and patients were kept in the supine position throughout the study period.

Protocol withdrawal occurred with any of the following a priori conditions: need for levels of dobutamine or dopamine of greater than 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, hemodynamically unstable condition with PEEP, or major cardiac arrhythmia. Patients were extubated when hemodynamically stable, fully rewarmed, awake, without surgical bleeding, and with optimal blood gases.

BAL fluid and blood samples were taken before sternotomy (time 0), immediately after protamine administration and CPB separation (time 1), and 6 hours after mechanical ventilation was restored (time 2).

TABLE 1. Prerandomization patient characteristics

	Low V_T /high PEEP	High V_T /low PEEP
Male/female sex, n	12/8	15/5
Age, y	66.5 $\pm$ 9.8	68.7 $\pm$ 7.4
Body surface area, m	1.95 $\pm$ 0.21	1.88 $\pm$ 0.13
Left ventricular ejection fraction, %	68 $\pm$ 25	55 $\pm$ 15
Diabetes	6 (30%)	5 (25%)
Hypertension	16 (80%)	15 (75%)
Hyperlipidemia	12 (60%)	14 (70%)
Peripheral vascular disease	4 (20%)	5 (25%)
CPB time, min	91 $\pm$ 19	83 $\pm$ 25
CPB temperature, °C	30 $\pm$ 2	30 $\pm$ 2
Crossclamp time, min	60 $\pm$ 17	50 $\pm$ 20

Data are presented as means $\pm$ standard deviation. V_T , Tidal volume; PEEP, positive end-expiratory pressure.

BAL was performed by wedging the tip of a fiberoptic bronchoscope in a segmental airway of the right lower lobe and injecting 2 aliquots of 40 to 50 mL of sterile isotonic saline. Lavage with a third aliquot was performed if there was less than 30 to 40 mL of recovered fluid from the first 100 mL. The first aliquot was discarded, and the remaining BAL fluid was rapidly filtered through sterile gauze and then spun at 4°C and 400g for 15 minutes. The supernatant was centrifuged at 80,000g for 30 minutes at 4°C to remove the surfactant-rich fraction and then concentrated 10-fold on a 5000-d molecular weight cutoff filter (Amicon, Beverly) under nitrogen. The concentrated supernatant was then frozen at $-80^\circ C$. Blood samples (20 mL) obtained from a central venous line were placed in a specimen tube containing heparin and centrifuged at 1500g for 10 minutes, and then the plasma was aspirated and stored at $-80^\circ C$. All cytokine determinations on the BAL fluid and plasma were carried out in duplicate in Turin, with the technician blinded to ventilation strategy using a solid-phase enzyme-linked immunoabsorbent assay method (Immunotech).⁵

The values for the cytokine concentrations were not normally distributed. Therefore $\log_{10}$ transformations were performed to normalize the data to permit the application of parametric statistics.

On the basis of previous data,⁵ the trial was designed to enroll 40 patients to demonstrate a 50% reduction in inflammatory mediators after CPB between high V_T /low PEEP and low V_T /high PEEP ($\alpha = .05$, power = 0.8). Repeated-measures analysis of variance with the Bonferroni method was used to evaluate differences over time of cytokine values within each group. The Fisher exact test for categorical variables, the t test with unequal variance for continuous variables, and the Mann-Whitney rank sum test for ordinal variables were used to evaluate differences between the 2 groups. All tests of significance were 2-tailed.

Results

Baseline anthropometric characteristics and clinical parameters were similar in the 2 groups (Table 1). There were neither deaths nor major complications in either group, and no patient had to undergo reoperation or be readmitted after

TABLE 2. Physiologic parameters measured 6 hours after mechanical ventilation was restored

	Low V_T /high PEEP	High V_T /low PEEP
V_T , mL/kg	6.8 ± 1.2	$10.9 \pm 1.5^*$
PEEP, cm H ₂ O	9.1 ± 3.5	$2.1 \pm 2.2^*$
End-inspiratory plateau pressure, cm H ₂ O	18.4 ± 3.5	$25.6 \pm 4.1^*$
Minute ventilation, L/min	8.1 ± 1.2	$12.2 \pm 1.7^*$
P_{aO_2} , mm Hg	162 ± 60	172 ± 47
P_{aCO_2} , mm Hg	42 ± 9	$33 \pm 5^*$
Arterial pH	7.36 ± 0.08	$7.45 \pm 0.06^*$
Pulmonary arterial wedge pressure	11.7 ± 6	10.3 ± 4
Right atrial pressure, mm Hg	9.4 ± 3.50	7.7 ± 3.6
Mean arterial pressure, mm Hg	84.1 ± 12.0	$72.7 \pm 3.3^*$

Data are presented as means $\pm$ standard deviation. V_T , Tidal volume; PEEP, positive end-expiratory pressure; P_{aO_2} , partial pressure of oxygen, arterial; P_{aCO_2} , partial pressure of carbon dioxide, arterial. * $P < .001$.

intensive care unit discharge. Postoperatively, all patients were in hemodynamically stable condition, no patients had postoperative low cardiac output requiring dobutamine or dopamine of greater than $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ or intra-aortic balloon pump counterpulsation, and all patients tolerated postoperative PEEP; therefore no patients had to be excluded from the study.

Values of ventilator settings and arterial blood gases 6 hours after re-establishing mechanical ventilation are shown in Table 2. Arterial P_{O_2} did not differ between groups, but patients in the low- V_T /high-PEEP group showed values of arterial pressure of carbon dioxide higher and arterial pH lower ($P < .001$) than those observed in patients in the high- V_T /low-PEEP group.

Concentrations of inflammatory mediators in the BAL fluid and plasma at time 0 were low and significantly increased at time 1 in both groups. Concentrations of interleukin (IL) 6 and IL-8 in the BAL fluid and plasma further increased after 6 hours of mechanical ventilation with high V_T /low PEEP, although it did not change after 6 hours of mechanical ventilation with low V_T /high PEEP. Concentrations of IL-6 and IL-8 in the BAL fluid and in the plasma after 6 hours of mechanical ventilation were higher in patients ventilated with high V_T /low PEEP than in patients ventilated with low V_T /high PEEP; BAL and plasma concentrations of IL-6 and IL-8 at time 0 and time 1 did not differ between groups (Figures 1 and 2).

Discussion

Patients undergoing cardiac surgery are exposed to numerous possible triggers of a systemic inflammatory response. Interventions aimed to attenuate the CPB-induced inflammatory response result in improvement of physiologic parameters and clinical outcome.¹ The present study indicates

Figure 1. Effect of different ventilatory strategies on IL-6 and IL-8 concentrations in BAL fluid before sternotomy (time 0), after CPB (time 1), and 6 hours after re-establishment of mechanical ventilation (time 2). Graphics are clustered box plots summarizing the median and quartiles. * $P < .01$ versus time 0; # $P < .01$ versus time 1; † $P < .01$, high V_T /low PEEP versus low V_T /high PEEP.

Figure 2. Effect of different ventilatory strategies on IL-6 and IL-8 concentrations in the plasma before sternotomy (time 0), after CPB (time 1), and 6 hours after re-establishment of mechanical ventilation (time 2). Graphics are clustered box plots summarizing the median and quartiles. * $P < .01$ versus time 0; # $P < .01$ versus time 1; † $P < .01$, high V_T /low PEEP versus low V_T /high PEEP.

that although conventional mechanical ventilation further increases the pulmonary and systemic concentration of inflammatory mediators consequent to CPB, use of lower V_T and higher PEEP might attenuate the pulmonary and systemic inflammatory response. These data first demonstrate that mechanical ventilation could be a cofactor able to influence the inflammatory response after cardiac surgery.

Mechanical ventilation is essential to maintain adequate ventilation and systemic oxygenation in patients recovering from cardiac surgery and CPB. Recent experimental studies have demonstrated that mechanical ventilation can induce morphologic and functional alteration of the lungs caused by stress failure generated by overinflation of some alveolar regions and by shear stress generated by continuous alveolar opening and closing.^{4,5} Explanation of these results relies on the observation that, in a nonuniformly injured lung, mechanical ventilation might generate stress failure and shear forces that amplify pressure in some alveolar regions as high as 140 cm H_2O , even though pressure applied at the airway opening amounts only to 30 cm H_2O .⁹ These forces might initiate, worsen, or both a pulmonary and systemic inflammatory response^{4,5} and contribute to the development of multiple organ failure.^{10,11} A recent multicenter trial including patients with acute respiratory distress syndrome (ARDS) compared traditional ventilation with a V_T of 12 mL/kg with ventilation with a V_T of 6 mL/kg; mortality was significantly lower in patients treated with the lower V_T .⁷

The incidence of ARDS after elective cardiac surgery is as low as 1% to 3%, whereas impairment of lung function and oxygenation are found in 20% to 90% of patients who have undergone CPB and have been recognized as an important cause of postoperative morbidity.¹² At time 1, the Pao_2/Fio_2 ratio was 290 ± 116 and 264 ± 120 and the pulmonary arterial wedge pressure was 10.3 ± 4 and 11.7 ± 6 in the high- V_T /low-PEEP and low- V_T /high-PEEP groups, respectively; none of the patients had bilateral infiltrates on standard chest radiography. Under these circumstances, none of the patients included in the present study had ARDS.¹³

Similar to patients after abdominal surgery, the lungs of patients after CPB are asymmetric along the vertical axis, with relatively normal regions located in the nondependent zones, areas of partially collapsed lung and/or alveolar filling located in the middle zones, and area of pulmonary consolidation located in the most dependent regions.^{14,15} Under these circumstances, mechanical ventilation might stress the lungs because of recruitment-derecruitment of atelectatic alveoli and hyperinflation of normal alveoli when inappropriate levels of PEEP are used, when the large part of the inflating volume is distributed to the normal lung regions, or both.¹⁶ However, Wrigge and coworkers^{17,18} found that in patients after major noncardiac surgery, mechanical ventilation with a V_T of 0.8 to 1.2 L and zero PEEP induces no relevant increase in inflammatory mediators. We found that pulmonary and plasmatic concentrations of in-

flammatory mediators increased after 6 hours of mechanical ventilation only in patients ventilated with high V_T /low PEEP, whereas these values did not change in patients ventilated with low V_T /high PEEP. These results might be explained by the ischemia of the lung caused by the cessation of pulmonary arterial flow after aortic crossclamping. This might lead to pulmonary endothelial dysfunction,¹⁹ platelet-neutrophil accumulation,²⁰ increase in myeloperoxidase activity,²¹ and activation of adhesion molecules.²² Data of the present investigation therefore support the concept that stress caused by mechanical ventilation represents a relevant inflammatory stimulus only in the presence of a previous inflammatory stimulus represented in our patients by CPB. Preliminary data from Wrigge and coworkers²³ indicate that after cardiac surgery, ventilation with a lower V_T decreases pulmonary inflammatory mediators, particularly in patients in whom CPB induced a more relevant increase in the pulmonary concentration of inflammatory mediators. Recently, Koner and colleagues²⁴ found no difference in systemic cytokine release in patients after cardiac surgery ventilated with a V_T of 6 mL/kg and PEEP of 5 cm H₂O compared with those ventilated with a V_T of 10 mL/kg with and without PEEP at 5 cm H₂O. Unfortunately, in their protocol the last blood sample for IL-6 and TNF- α measurements was taken only 2 hours after the end of CPB, while the inflammatory reaction was still increasing. A protective effect of low V_T /high PEEP in our study was observed 6 hours after the end of CPB, which is the mechanical ventilation time usually necessary for patients who have undergone uncomplicated cardiac surgery.

Several studies have found that post-CPB inflammatory reactions influence lungs function. Kotami and associates²⁵ found that the pulmonary concentration of IL-8 after disconnection from CPB was significantly correlated to values of arterial oxygenation and intrapulmonary shunt at the end of surgical intervention. Holmes and coworkers²⁶ correlated postoperative clinical outcome with inflammatory mediators release and found that the length of mechanical ventilation after surgical intervention was longer in patients with a larger magnitude of inflammation after CPB. Consistently, Rothenburger and colleagues²⁷ observed that the postoperative concentration of IL-8 was higher in patients ventilated for more than 24 hours than in patients ventilated for less than 24 hours.

Adoption of a smaller V_T to protect the lung from lung stretch might potentially lead to an increase of arterial P_{CO_2} and respiratory acidosis.⁵⁻⁷ In our study patients ventilated for 6 hours with low V_T /high PEEP had values of arterial P_{CO_2} of 42 ± 9 mm Hg and an arterial pH of 7.36 ± 0.08 . Recent data suggest that hypercapnic acidosis is highly protective in experimental models of pulmonary²⁸ and myocardial²⁹ ischemia-reperfusion injury.

Our study was not designed to produce significant clinical outcome data. The effect of this observation is limited by the unblinded data collection procedure and needs to be confirmed in appropriately designed future trials.

Several factors are able to influence inflammatory response measured after CPB. These factors can be synthesized preoperatively (patient characteristics and preoperative inflammatory state), intraoperatively (surgical trauma, time on CPB, aortic crossclamp time, type of CPB equipment, anesthesia management, and use of anti-inflammatory drugs), and postoperatively (use of anti-inflammatory drugs, postoperative low cardiac output syndrome, and postoperative infections).¹ Table 1 shows that there are no significant preoperative difference between the groups; surgical intervention was performed in all patients through a sternotomy with similar CPB equipment and anesthesia management. No patient received antifibrinolytic drugs at any time, had low cardiac output syndrome, had to undergo reoperation for bleeding, or showed signs of infection during the study period. Nevertheless, our trial was a proof-of-concept study to determine whether ventilatory strategy could affect BAL and serum cytokine levels in patients undergoing cardiac surgery and CPB; future clinical trials with larger sample sizes and protocols designed to standardized clinical interventions are required to confirm our observation and evaluate the effects of ventilatory strategies on clinical endpoints.

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