Intratracheal Pulmonary Ventilation at Low Airway Pressures in a Ventilator-Induced Model of Acute Respiratory Failure Improves Lung Function and Survival*

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Study objective: The pulmonary parenchyma in patients with acute respiratory failure (ARF) is commonly not involved in a homogenous disease process. Conventional mechanical ventilation (MV) at elevated positive end-expiratory pressure (PEEP) and peak inspiratory pressure (PIP) aims at recruiting collapsed or nonventilated lung units. Invariably, those pressures are also transmitted to the healthiest regions, with possible extension of the disease process (barotrauma). During intratracheal pulmonary ventilation (ITPV), a continuous flow of fresh gas is delivered directly at the carina, bypassing the dead space proximal to the catheter tip. In healthy sheep, it allows lowering tidal volume (VT) to as low as 1.0 mL/kg, at respiratory rates (RR) up to 120 breaths/min, while maintaining normocapnia. In a model of ventilator-induced lung injury, we wished to explore whether ITPV, applied at low VT and low PEEP and tailored to ventilate the healthiest regions of the lungs, could provide adequate oxygenation and alveolar ventilation, without any attempt to recruit lungs.

Design: Randomized study in sheep.

Setting: Animal research laboratory.

Participants: We induced ARF in 12 sheep following 1 to 2 days of MV at a PIP of 50 cm H2O, except that 5 to 8% of lungs were kept on apneic oxygenation of 5 cm H2O, sparing those regions from the injury process.

Interventions: Sheep were randomized to volume-controlled MV (control group) (n = 6) with VT of 8 to 12 mL/kg, PEEP of 5 to 10 cm H2O, or to ITPV (n = 6) at PEEP of 3 to 5 cm H2O, VT of 2.5 to 4 mL/kg, PIP of <20 cm H2O, at RR to sustain normocapnia.

Measurements and results: Hemodynamic status in the ITPV group progressively improved, and all six sheep were weaned to room air within 53 ± 54 h. Sheep in the control group had progressively deteriorating conditions and all animals died after a mean of 50 ± 39 h. Barotrauma and postmortem histopathologic changes were more pronounced in the control group.

Conclusion: In this model of ventilator-induced lung injury, low PEEP-low VT ventilation with ITPV sustained normocapnia and prevented further lung injury, allowing weaning to room air ventilation.

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Key words: acute respiratory failure; barotrauma; intratracheal pulmonary ventilation; tracheal gas insufflation

Abbreviations: ARF = acute respiratory failure; CO = cardiac output; CVP = central venous pressure; ETT = endotracheal tube; FiO2 = fraction of inspired oxygen; HFO = high-frequency oscillatory ventilation; ID = inner diameter; I/E = inspiratory/expiratory; ITPV = intratracheal pulmonary ventilation; mPAP = mean pulmonary artery pressure; MV = mechanical ventilation; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PEEP = positive end-expiratory pressure; PEEPc = curvilinear PEEP; PHC = permissive hypercapnia; PIP = peak inspiratory pressure; PVR = pulmonary vascular resistance; RR = respiratory rate; RTC = reverse thrust catheter; SVR = systemic vascular resistance; TCI = tracheal gas insufflation; TSLC = total static lung compliance; VCO2 = carbon dioxide minute production rate; Vd/Vt = physiologic dead space ratio; VT = tidal volume

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Conventional mechanical ventilation (MV) in severe acute respiratory failure (ARF) is frequently applied at relatively large tidal volumes (VT), at high peak inspiratory pressures (PIP), and is often associated with barotrauma. In ARF, the pulmonary disease process is not homogenous, with relatively
healthy regions adjacent to diseased areas of the lungs, and nondependent areas more distorted than the dependent regions, irrespective of the body position.\textsuperscript{1,2} Irrespective of the extent of total involve-

ment of the disease process throughout both lung fields, it may be necessary to ventilate patients with ARF at relatively high \( V_t \) and at high positive end-expiratory pressure (PEEP), to reverse atelectasis and to improve on blood gases.

Given such an inhomogenous pattern of lesions in ARF, the bulk of conventional MV and the adverse effects therefrom may be directed to the healthiest, more compliant regions of the lungs, causing overt-ivestigation of lung units. Avoiding high peak cycling alveolar pressures and limiting plateau pressures by lowering \( V_t \) according to \( P-V \) curve have been advocated by some clinical investigators to decrease the risk of ventilator-related lung injury.\textsuperscript{3,4}

A recent study by Muscedere and coworkers\textsuperscript{5} on excised lavaged lungs has identified end-expiratory lung volume as a potential critical variable in venti-
lator-related lung injury, without high alveolar pres-
ures and large \( V_t \). The authors concluded that ongoing low lung volume may contribute to lung injury, although the exact mechanism remains un-
certain. It is also suggested that repeated alveolar opening and closure could deplete surfactant and further increase mechanical stress.\textsuperscript{6}

McCulloch and colleagues\textsuperscript{7} have studied the effects of high-frequency oscillatory ventilation (HFO) applied in a surfactant-deficient lung model at high and low lung volumes above functional residual capacity. Ac-
cording to their histopathologic and lung mechanic data, they concluded that during HFO, lung injury was minimized when atelectasis was reversed and the mean airway pressure was left sufficiently high to maintain adequate residual alveolar volume.

In a more recent study, the same authors compared the short-term effects of HFO and conventional MV at high and low expiratory lung volumes on adult saline solution-lavaged lungs in rabbits, after surfactant replacement therapy.\textsuperscript{8} In that study, end-expiratory lung volume was adjusted by titrating \( P\text{EEP} \) or mean airway pressure according to \( \text{PaO}_2/\text{fraction of inspired oxygen (FiO}_2) \). Although the mean airway pressure and cycling volumes in the high- and low-volume HFO groups were not different, the group with alveolar reexpansion plus maintenance of the recruited lung volume showed better lung mechanics, gas exchange, and pathologic condition.

A recent study on saline solution-lavaged adult rabbit lungs by Imai and coworkers\textsuperscript{9} found the inflammatory response to be lower using an atelec-
tasis reversal ventilatory strategy with HFO compared with conventional MV at the same mean airway pressure and, although not indicated, at much greater cycling volumes, suggesting an important role of atelectasis reversal.

In the setting of ARF, the choice of \( V_t \) and PEEP depends, in part, on the type and stage of the underlying pulmonary disease process. Despite experimental evidence that a lung protective ventilatory strategy avoids atelectasis and repeated opening and closing of terminal lung units, timing and degree of atelectasis reversal may differ at different stages of ARF. While limiting peak cycling alveolar pressure is now commonly agreed upon, there is less agreement on level of PEEP.\textsuperscript{10}

We have shown previously that normal alveolar ventilation can be sustained in sheep at normal PIP and at high respiratory rates (RR) with but 12.5\% of lungs remaining, provided fresh gas was directly delivered to the level of the carina, with \( V_t \) proportionally reduced.\textsuperscript{11} A variant of continuous tracheal gas insufflation (TGI),\textsuperscript{12} we called our method intratracheal pulmo-
nary ventilation (ITPV).\textsuperscript{13} A continuous flow of fresh gas was delivered directly to the level of the carina, so that the bulk of major upper airways dead space was effectively bypassed. In the current study, ITPV was applied in a model of ARF in sedated and paralyzed sheep, where all but a small fraction of the lungs (5 to 8\%) was acutely injured from effects of MV at high cycling airway pressures and volumes.\textsuperscript{14} We hypothe-
sized that low PEEP-low \( V_t \) ventilation would prefer-
entially direct pulmonary blood flow (and ventilation) to regions of the lungs still “healthy” and with low vascular resistance, improving on ventilation/perfusion mismatch. To test our hypothesis, we elected by design not to recruit diseased regions of the lungs. We hence applied ITPV at low \( V_t \) and low PEEP, to keep \( P\text{IP} \) always within the normal range, while still maintaining normocapnia (ITPV group). A group with similarly induced ARF was managed with MV in the volume controlled mode using a ventilatory strategy with min-
imal PEEP, guided by \( \text{Fio}_2 \) and hemodynamics, with conventional \( V_t \) (control group).

Our results show that in sheep ventilated with ITPV at low PEEP, while limiting \( V_t \) and peak cycling pressures, gas exchange progressively improved over 2 to 3 days, with weaning to room air. In the control group, MV at moderately high cycling pressures and volumes resulted in death from pro-
gressive cardiorespiratory failure.

Materials and Methods

\textbf{Animal Preparation}

This study was conducted in 12 healthy female sheep of mixed breed, with an average body weight of 24 ± 5 kg (range, 16 to 32
Induction with tip provided to pentobarbital used as a continuous infusion at a rate of 0.5 mg/kg/h and 0.08 mg/kg/h, respectively. Throughout the course of the study, the animals received a 1:1 mixture of 0.9% NaCl and 5% D/W IV at a rate of 6 mL/kg/h. The left external jugular vein was percutaneously cannulated with two angiocatheters (16 gauge) for IV fluid administration. A 12F catheter was introduced into the bladder for hourly urine collection. Following surgical exposure of the vessels, a 7F Swan-Ganz thermodilution catheter was introduced through the right external jugular vein into the pulmonary artery. The right common carotid artery was cannulated for continuous BP monitoring and arterial blood sampling.

Each sheep underwent a tracheotomy approximately 5 cm above the sternum. A standard cuffed 11.0-mm inner diameter (ID) endotracheal tube (ETT) [Rusch, AG; Wablingen, Germany] was inserted through the tracheotomy while the orotracheal ETT was discarded. This size ETT was required for the passage of a 10-mm silicone rubber “mushroom” plug mounted onto a 1.6-mm Teflon catheter (see below).

Blood electrolytes and arterial blood gases were measured hourly (Anova Statplus 8; Nova Biomedical Analyzer; Walton, MA). If metabolic acidosis ensued, 0.9 M sodium bicarbonate (7.5%) was administered as needed to maintain base excess between +3.0 and −3.0 mmol/L. KCl and CaCl2 were administered as needed. Ceftriaxone sodium was administered at 0.5 g IV every 12 h. Systemic BP, pulmonary artery pressure (PAP), central venous pressure (CVP), and pulmonary artery wedge pressure (PAWP) were measured with calibrated pressure transducers (Bentley Laboratories; Irvine, CA) zeroed at the midaxillary line and continuously recorded on an ink recorder (Gould 200; Cleveland, OH). Cardiac output (CO) was measured using the thermodilution method (Cardiac Output Computer 9520 A; American Edwards Laboratories). Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were computed using standard equations. Total static lung compliance (TSLC) was computed from pressure-volume tracings after injecting stepwise 100 mL of inspired gas mixture every 5 s, up to an airway pressure of 25 to 30 cm H2O. The volume necessary to yield approximately 20 cm H2O airway pressure was used to compute TSLC divided by the body weight. Before each measurement, the airways were suctioned, followed by 10 manual inflations of approximately 0.5 L.

Following surgery, sheep were placed in the prone position and mechanically ventilated in the volume-controlled mode with an inspiratory/expiratory (I/E) ratio of 1:2, RR of 10 to 18 breaths/min, VT of 8 to 12 mL/kg, an FIO2 of 0.40, and PEEP of 2 to 5 cm H2O. The ventilator circuit was made of low-compliance silicone rubber tubing. We took baseline chest radiographs and arterial blood gases to ascertain good pulmonary function. The esophageal and blood temperature were continuously monitored. The blood temperature was kept at 38 to 38.5°C throughout the experiment by means of a thermal water blanket (Blanketrol; Cincinnati Sub Zero Product; Cincinnati, OH). Animals were fed twice a day through a gastric tube.

Induction of Lung Injury

It was our goal to induce acute lung injury involving the entire lungs, except for a discrete 5 to 8% of the parenchyma that was to be spared. To protect this small part of the lungs, a 1.6-mm Teflon catheter with a pliable 10-mm silicone mushroom shaped tip provided with a radiopaque maker was advanced through the ETT and wedged in position, commonly in a branch of the right lower lobe bronchus. Once firmly in position, no effort was made to reposition the mushroom plug. Following this, lung function was again evaluated by repeating baseline measurements. The isolated segmental lobe of the lung was visualized on chest radiographs following injection of 5 mL of 41% iopamidol (Iovue 200; Squibb Diagnostics; Princeton, NJ). During the experimental injury process, the protected lung segment was maintained on anemic oxygenation at a PEEP of 5 cm H2O (Figs 1, 2).

To induce lung injury, the ventilator was set at a PEEP of 0 cm H2O, FIO2 of 0.40, in the synchronized intermittent mandatory ventilation mode, pressure limited to 50 cm H2O. The inspiratory and expiratory times were 1.3 s and 14 s, respectively. The resulting VT ranged between 50 and 60 mL/kg. The airway pressure tracing recorded at the mouth showed a square inspiratory waveform. To maintain eucapnia, we introduced supplemental CO2 gas into the inspiratory gas mixture to increase fraction of inspired carbon dioxide (FICO2) to 0.03 to 0.04. The supplemental CO2 was adjusted as needed to maintain Paco2 within baseline range. Arterial blood gases and chest radiographs were taken every 2 h or when otherwise indicated. TSLC was measured every 4 h. Any significant pneumothorax was promptly drained through the insertion of a chest tube (Trocar catheter 20F; Deknatel; Falls River, MA), and kept under continuous suction.

The injury process was continued until all the following end point criteria for ARF were met: (1) Pao2/FIO2 <200 mm Hg; (2) TSLC decreased by approximately 20% compared with baseline values (invariably, there was an early rise in TSLC within a few hours upon starting high-pressure MV, before final decline); (3) Paco2 within the baseline range, with all supplemental CO2 discontinued; and (4) extensive diffuse bilateral infiltrates seen on chest radiographs.

ITPV System

During ITPV, the entire inspiratory VT was delivered at the level of the carina through a reverse thrust catheter (RTC). A continuous flow of air/oxygen was supplied through a 1.8-mm Teflon RTC,7 introduced through an adapter and advanced to reach the distal end of the ETT (Fig 1). The correct position of the RTC was checked radiographically. All gas flow was supplied to the ventilator and to the ITPV system through the same gas blender. The ITPV gas flow passed through an in-series three-stage humidifier system (Conchatherm; Hudson Respiratory Care Inc; Temecula, CA). All gas tubing was insulated with a plastic wrap to prevent heat loss. The gas mixture entered the RTC and emerged through a narrow annular gap (0.250 mm) at its distal (occluded) tip outward, in a direction away from the carina (Fig 3). Carinal PEEP was adjusted through changes of the external PEEP at the ventilator.13 The ventilator (Servo), calibrated with a water spirometer, was set in the pressure-controlled mode with the inspiratory pressure above the PEEP level at 0 cm H2O (ie, no flow was delivered by the ventilator). The I/E cycle was controlled by the expiratory valve of the ventilator, which alone controlled RR and the I/E ratio set on the front panel. In essence, the expiratory valve acted as a shutter: when it was closed, all the gas from the RTC entered the lungs; when the expiratory valve opened, all gas returning from the lungs, plus the continuous flow from the RTC, were exhaled through the ETT. Exhalation of the gas was facilitated by the outward thrust of the RTC flow.

Proximal airway pressure, minute volume, and expiratory VT were monitored by the ventilator (Servo).13 The ITPV system could also operate in the hybrid-ITPV mode, when the continuous intratra¬cheal flow was combined with pressure-controlled ventilation. The catheter flow contributed to inspired VT and allowed washout of the anatomic dead space proximal to the catheter tip.

Carinal airway pressure was measured through a 1-mm ID Teflon catheter provided with distal side holes, inserted through

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an adapter to the ETT, and positioned approximately 2 cm below the inlet of the RTC. This catheter was connected to a pressure transducer (Bentley Laboratories; Irvine, CA); carinal PIP, mean carinal airway pressure, and carinal PEEP (PEEPc) were recorded continuously.

Auto-PEEP was measured by interrupting, through manual occlusion at end expiration, all ITPV and ventilator flow, and recording changes in PEEPc. The I/E ratio set on the ventilator was checked by recording the pressure tracing of the respiratory cycles during conventional MV, both while on ITPV or in the hybrid-ITPV mode.

Mixed expired gas was sampled continuously from a 5-L gas mixing chamber attached to the expiratory port of the ventilator. We measured expired mean CO2 concentration with an infrared CO2 analyzer (LB-2; Beckman Instruments; Fullerton, CA). Carbon dioxide production/elimination rate (VCO2) was monitored constantly as the product of mixed expired CO2 concentration and total expired minute volume (including ITPV flow and the inspiratory flow from the ventilator when in the hybrid-ITPV mode). Physiologic dead space ratio (Vd/Vt) was calculated from the Enghoff modification of the Bohr equation.

**Experimental Protocol**

After end points of ARF were met, MV at high PIP was discontinued, and the mushroom plug was removed. The 11-mm ETT, used to introduce the larger silicone mushroom plug, was then replaced with a standard length 8.0-mm ID ETT (Rusch AG; Bad-Liebenzel, Germany), a more appropriate size for the weight of the animal. The ETT was advanced through the tracheotomy to 1 to 2 cm above the carina, and was tightly fixed in place with ligatures. The correct position of the ETT was verified radiographically.

After returning to baseline (preinjury) ventilator settings, we measured arterial blood gases and evaluated lung function. The conditions of the sheep were then stabilized for 30 to 60 min. Following this, sheep were randomly assigned to one of two groups: control group (n = 6), mechanically ventilated in the volume controlled mode; and ITPV group (n = 6), managed with ITPV or hybrid-ITPV.

**ITPV Group**

MV was changed from volume controlled to ITPV. By protocol, PEEPc was set between 3 and 5 cm H2O. RR was increased and Vt was lowered to limit peak inflating pressures <20 cm H2O, and to maintain normocapnia. The I/E ratio was set at 1:1. The hybrid-ITPV mode was adapted when the total catheter flow rate required to sustain normocapnia was >9 L/min, at RR of approximately 100 breaths/min. PaO2 was kept >60 to 80 mm Hg by adjusting FIO2.

**Control Group**

Sheep were mechanically ventilated in the volume controlled mode using a constant flow square inspiratory waveform, with a

![Figure 1: Model of lung injury. A small catheter provided with a mushroom-shaped tip was wedged into a segmental bronchus. This isolated fraction of lung was maintained on apneic oxygenation, while the rest of the lungs were exposed to the effects from high-pressure MV.](image)
VT ranging from 8.0 to 12.0 mL/kg, I/E ratio 1:1. As in the ITPV group, minute volume was adjusted to keep PaCO₂ within the physiologic range. In random order we measured arterial blood gas response to PEEP of 0, 5, and 10 cm H₂O. We selected the minimal PEEP that sustained arterial O₂ saturation >90% at an FIO₂<0.60, while maintaining an adequate CO.15,16

As needed, in both groups we suctioned the trachea, followed by manual inflation of approximately 0.5 L.

Fluid Management

We infused crystalloids to sustain adequate preload and CO. To correct hypotension (mean BP <60 mm Hg) we infused stepwise 50 mL of crystalloids, up to a total of 500 mL. A rise in filling pressures >40 to 50% and/or lack of response in BP was followed by the administration of inotropic agents, titrated to maintain mean systemic BP >80 mm Hg. We administered furosemide IV to correct oliguria/anuria.

Treatment was continued until death or weaning to room air (ie, PaO₂ >60 mm Hg at FIO₂ of 0.21). Sheep that could be weaned to room air were killed with an IV dose of sodium pentobarbital and KCl.

At necropsy, the chest was opened and the appearance of the lungs were noted. Gross anatomic findings were graded as previously described.14 The lungs were then removed en bloc and weighed. The total lung weight and body weight ratio was determined in each animal and compared with a sample of healthy sheep.11 Tissue samples of about 12×12×6 mm were taken from each lobe except the right upper lobe, to include the visceral pleura, without attempt at lung inflation, fixed in 10% formalin and stained with hematoxylin-eosin for light microscopic studies. The right upper lobe was not included in the histologic evaluation as it is commonly atelectatic in sheep (ie, the ostia of the bronchus was frequently obstructed by the ETT). Observation of histopathologic changes was performed on two sections obtained from each lung sample, and focused on the following: (1) emphysematous changes; (2) alveolar hemorrhage; (3) alveolar neutrophil infiltration; (4) alveolar macrophage proliferation; (5) type II cell proliferation; (6) hyaline membrane formation; (7) organization of alveolar exudate; (8) interstitial congestion; (9) lymphocyte infiltration; (10) interstitial thickening; (11) interstitial fibrosis; and (12) intra-alveolar exudate. Each histologic specimen was graded for abnormalities by a pathologist blind to the groups on a scale of zero = 0, slight = 1, mild = 2, moderate = 3, severe = 4, as previously described by Tsuno et al.17

Statistical Analysis

All data are expressed as mean ± SD. A Wilcoxon Rank Sum Test was used for statistical analysis of the histologic data.15 As duration of treatment in the two groups was different, we performed for all variables a repeated-measures regression analysis over the same time period of follow-up (first 15 h). Changes in Ventilation in the two groups were tested with repeated-measures analysis of variance. Student’s t test for paired and unpaired data was used for the remaining data analysis. p<0.05 was accepted as level of significance.

Results

The physiologic measurements at baseline MV and after the insertion of the mushroom catheter into the right lower lobe bronchus are shown in Tables 1 and 2 (left columns). Lung mechanics and gas exchange were not affected by the insertion of the mushroom plug. In an ex vivo estimation on a series of five sheep, the isolated lung segment consistently amounted to 5 to 8% of the total lung parenchyma.

Effects of Lung Injury

All sheep in both groups met end point entry criteria. The time to reach end point of lung injury was 38 ± 20 h and 39 ± 19 h in ITPV group and control group, respectively. During the induction of lung injury, two sheep in the ITPV group developed a pneumothorax as did one sheep in the control group. Postinjury lung function variables after sheep were returned to baseline ventilation are shown in Table 1 (right columns). TSLC did not differ significantly between the two groups. TSLC decreased between 20% and 30% when compared with the respective baseline values (Table 1, p<0.05). PaO₂/FIO₂ ratio just prior to discontinuing the lung injury process was not statistically different (193 ± 47 mm Hg and 189 ± 49 mm Hg in ITPV and control groups, respectively).

Figure 2. Chest radiograph obtained after the injection of radioopaque dye through the mushroom-shaped plug, wedged in a segmental bronchus.
Hemodynamics

Baseline hemodynamic variables for the two groups before and after the induction of lung injury are shown in Table 2. At the preinjury stage, BP, SVR, and PAWP were greater in volume controlled group. At the end of injury, mean pulmonary artery pressure (mPAP) and PVR were significantly higher in the control group compared with the ITPV group, while filling pressures did not differ. A slight but statistically significant difference in CO was observed between the two groups at the postinjury stage (Table 2, right columns).

Hemodynamic parameters throughout treatment for the two groups are shown in Table 3. Invariabily, CVP, PAWP, and mPAP were greater in the control group than in the ITPV group; CO was lower in the control group.

In the ITPV group, two of six sheep required temporary inotropic support for hemodynamic instability; both sheep were later weaned off catecholamines. Urinary output averaged 7.0 ± 1.2 mL/kg/h during the course of treatment in the ITPV group and 2.2 ± 0.9 mL/kg/h in the control group (p < 0.05). No diuretics were administered at any time.

All hemodynamic data for control group were obtained under continuous infusion of catecholamines (norepinephrine, 0.5 to 20 μg/min). Sheep in the control group invariably required loading volumes of crystalloids and catecholamines because of hemodynamic instability. Over the entire study period, there was a positive fluid balance of 1.1 ± 2.5 and 2.5 ± 1.7 L in the ITPV and the control group, respectively (p < 0.05).

Ventilation

In ITPV group, VT ranged between 2.5 and 6.0 mL/kg, and RR ranged from 30 to 80 breaths/min. PIP was kept <20 cm H₂O (Fig 4). PEEP was kept constant at ±5 cm H₂O throughout the study. There was no measurable auto-PEEP at the carina. Three of six sheep were managed with hybrid-ITPV ventilation when then total gas flow through the RTC,

Table 1—Gas Exchange and Lung Mechanics*

<table>
<thead>
<tr>
<th></th>
<th>Preinjury</th>
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<th>Postinjury</th>
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<tbody>
<tr>
<td></td>
<td>ITPV Group (n = 6)</td>
<td>Control Group (n = 6)</td>
<td>ITPV Group (n = 6)</td>
<td>Control Group (n = 6)</td>
</tr>
<tr>
<td>VT, mL/kg</td>
<td>9.0 ± 1.0</td>
<td>9.5 ± 0.5</td>
<td>9.0 ± 2.0</td>
<td>11.0 ± 0.8</td>
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<tr>
<td>RR, breaths/min</td>
<td>17.5 ± 3.0</td>
<td>11.5 ± 0.6</td>
<td>17.3 ± 3.0</td>
<td>14.6 ± 4.0</td>
</tr>
<tr>
<td>PIP, cm H₂O</td>
<td>15.2 ± 0.1</td>
<td>17.0 ± 1.0</td>
<td>26.2 ± 4.0</td>
<td>29.2 ± 5.0f</td>
</tr>
<tr>
<td>PaO₂/FiO₂, mm Hg</td>
<td>390 ± 87</td>
<td>400 ± 95</td>
<td>139 ± 58f</td>
<td>145 ± 80f</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>33.0 ± 2.5</td>
<td>35.6 ± 2.1</td>
<td>37.2 ± 7.0f</td>
<td>36.8 ± 2.4</td>
</tr>
<tr>
<td>pH</td>
<td>7.465 ± 0.03</td>
<td>7.416 ± 0.03</td>
<td>7.420 ± 0.07</td>
<td>7.387 ± 0.03</td>
</tr>
<tr>
<td>Vt/Vt</td>
<td>0.34 ± 0.10</td>
<td>0.36 ± 0.09</td>
<td>0.49 ± 0.11f</td>
<td>0.63 ± 0.10f</td>
</tr>
<tr>
<td>TSLC, mL (cm H₂O)/kg</td>
<td>1.0 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>0.79 ± 0.2f</td>
<td>0.76 ± 0.0f</td>
</tr>
<tr>
<td>VCO₂, mL/kg/min</td>
<td>4.0 ± 0.6</td>
<td>3.9 ± 0.4</td>
<td>4.2 ± 0.7</td>
<td>4.0 ± 0.4</td>
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</tbody>
</table>

*Ventilatory variables during control ventilation at zero end-expiratory pressure at baseline, and after discontinuation of injury (ITPV group and control group). Baseline readings were recorded following insertion of the mushroom plug. Postinjury data were obtained while on baseline control ventilation, after removal of the mushroom plug. Data are expressed as mean ± SD.

†p < 0.05 comparisons for ITPV group and control group, postinjury vs baseline data.

‡p < 0.05 ITPV group vs control group at baseline and at postinjury.
required to maintain eucapnia, exceeded approximately 9 L/min. The ventilator-delivered \( V_t \) accounted for approximately 40% of the inspired \( V_t \). Those sheep were ventilated with hybrid-ITPV for approximately the first 24 h; thereafter, as they improved, they were switched to pure ITPV. The condensate in the water trap of the ventilator expiratory gas circuit consisted of copious amounts of turbid, viscous liquid.

In the control group, \( V_t \) averaged 12.0 ± 1.0 mL/kg, and RR ranged from 15 to 28 breaths/min (Fig 5). PEEP was 7.5 ± 2.0 cm H\(_2\)O (range, 5 to 10 cm H\(_2\)O). PIP slowly increased from a mean of 32 cm H\(_2\)O and reached a mean value of 43.5 ± 5.0 cm H\(_2\)O just before death. With the repeated-measures analysis, RR, \( V_t \), and PIP differed significantly from the ITPV group within the first 15 h of treatment (p<0.05). The condensate in the water trap of the expiratory gas circuit of the ventilator consisted of clear water.

**Gas Exchange and Outcome**

The ITPV group sheep were treated on ITPV for 83 ± 54 h (range, 31 to 144 h). All six animals reached a \( PAO_2/FIO_2 \) >280 mm Hg (\( PAO_2 >60 \) mm Hg on room air) (Fig 4, top panel). \( PAO_2 \) was always well maintained within the physiologic range. No sheep developed clinical or radiographic signs of air leak during treatment; the chest tubes previously placed into two sheep during the course of the injury process were removed. Initial chest radiographs showed an increase in opacifications; later there was some clearing.

All control group sheep died after a mean of 50 ± 39 h (range, 15 to 60 h) from progressive hypoxia (Fig 5, top panel) and hypercapnia, with unresponsive cardiovascular failure. Chest radiographs showed progressive pulmonary infiltrates that paralleled worsening of gas exchange and respiratory mechanics. Four of six animals (one of which had a pneumothorax drained during the injury process) developed a pneumothorax that required drainage; air leak from the chest tubes persisted throughout the treatment. There was radiologic evidence of pneumomediastinum, interstitial and subcutaneous emphysema. Dead space before the induction of lung injury was 2.8 ± 1.0 mL/kg and 3.5 ± 0.9 mL/kg in the ITPV group and control group, respec-

### Table 2—Baseline Hemodynamic Variables*

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<tr>
<th></th>
<th>Preinjury</th>
<th>Postinjury</th>
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<tbody>
<tr>
<td></td>
<td>ITPV Group (n = 6)</td>
<td>Control Group (n = 6)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>152 ± 40</td>
<td>152 ± 36</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>117 ± 10</td>
<td>149 ± 141</td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td>16 ± 2</td>
<td>29 ± 2</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>0 ± 2</td>
<td>0 ± 2</td>
</tr>
<tr>
<td>PAWP, mm Hg</td>
<td>5 ± 2</td>
<td>8.5 ± 21</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>3 ± 0.8</td>
<td>3.7 ± 0.5</td>
</tr>
<tr>
<td>SVR, dyne ⋅ s ⋅ cm⁻⁵</td>
<td>1,710 ± 245</td>
<td>1,990 ± 490</td>
</tr>
<tr>
<td>PVR, dyne ⋅ s ⋅ cm⁻⁵</td>
<td>2,601 ± 100</td>
<td>295 ± 118</td>
</tr>
</tbody>
</table>

*Hemodynamic variables at baseline and after injury while on baseline control ventilation at zero end-expiratory pressure (ITPV group and control group). See text for abbreviations. Data are expressed as mean ± SD.

\( \text{fp} < 0.05 \) ITPV group vs control group at baseline and at postinjury.

\( \text{fp} < 0.05 \) comparisons for ITPV group and control group, postinjury vs baseline data.

### Table 3—Hemodynamic Variables Throughout the Course of Treatment*

<table>
<thead>
<tr>
<th></th>
<th>20%</th>
<th>40%</th>
<th>60%</th>
<th>80%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ITPV Group</td>
<td>Control Group</td>
<td>ITPV Group</td>
<td>Control Group</td>
<td>ITPV Group</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>164 ± 26</td>
<td>187 ± 25</td>
<td>171 ± 20</td>
<td>179 ± 25</td>
<td>176 ± 22</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>115 ± 15</td>
<td>120 ± 21</td>
<td>110 ± 10</td>
<td>115 ± 20</td>
<td>114 ± 18</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>4.1 ± 11</td>
<td>3.3 ± 0.5</td>
<td>3.5 ± 11</td>
<td>2.3 ± 0.5</td>
<td>3.7 ± 0.71</td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td>22 ± 41</td>
<td>35 ± 7.0</td>
<td>21 ± 41</td>
<td>34 ± 13</td>
<td>21 ± 40</td>
</tr>
<tr>
<td>CVP, mm Hg</td>
<td>1 ± 3</td>
<td>8 ± 4</td>
<td>1 ± 3</td>
<td>9 ± 3</td>
<td>1 ± 21</td>
</tr>
<tr>
<td>PAWP, mm Hg</td>
<td>5 ± 10</td>
<td>10 ± 1</td>
<td>6 ± 21</td>
<td>14 ± 3</td>
<td>4 ± 11</td>
</tr>
</tbody>
</table>
Figure 4. Changes in VT, PIP, PaO2/FIO2, and RR (mean ± SD) throughout the course of treatment and at baseline in ITPV group. In parentheses, number of animals at each time point.

tively. Vd/Vt before injury did not differ between the two groups (Table 1). Vd/Vt after injury, at the beginning of treatment, at midtreatment, and at the end of treatment, in the ITPV group and control group, is shown in Figure 6. At the beginning of treatment, Vd/Vt averaged about 10% lower in the ITPV group (Table 1, p<0.05). By the end of treatment, Vd/Vt slightly declined in the ITPV group. In the control group, Vd/Vt continued to rise and reached 0.78 ± 0.09 by the end of treatment, at a relatively constant VT (Fig 6). Despite an increase in minute volume, just before death, PaCO2 averaged 33 ± 7 mm Hg.
Lung Pathology and Histology

At autopsy, the lungs in the ITPV group showed atelectasis not exceeding 20%, mostly in the dependent areas, and small pleural effusions. In the control group, the lungs were purplish throughout, with atelectasis that exceeded 50% of both lungs. There were blebs, fibrin exudate, and pleural effusions. Gross lung injury was rated between 1 and 2 in the ITPV group (light to moderate), and between 2 and 3 in the control group (moderate to severe). Histologic scores are shown in Table 4; the values shown are averages within each group. Interobserver differences in scoring of lung damage were <6%. Total lung weight and body weight ratio was 1.7 ± 0.2% and 2.9 ± 0.2% in the ITPV group and the control group, respectively (p<0.05) (normal, 1.02 ± 0.15%).

**Table 4—Postmortem Histology**

<table>
<thead>
<tr>
<th>Lung Histology</th>
<th>ITPV Group (n = 24)</th>
<th>Control Group (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Emphysematous changes</td>
<td>1.2 ± 0.4</td>
<td>1.0 ± 0.4</td>
</tr>
<tr>
<td>2. Alveolar hemorrhage</td>
<td>1.1 ± 0.3</td>
<td>1.4 ± 0.6</td>
</tr>
<tr>
<td>3. Alveolar neutrophil infiltration</td>
<td>1.4 ± 0.7</td>
<td>2.5 ± 0.5†</td>
</tr>
<tr>
<td>4. Alveolar macrophage</td>
<td>2.0 ± 0.6</td>
<td>2.2 ± 0.4</td>
</tr>
<tr>
<td>Proliferation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Type II cell proliferation</td>
<td>2.1 ± 0.6</td>
<td>2.4 ± 1.0</td>
</tr>
<tr>
<td>6. Hyaline membrane formation</td>
<td>1.2 ± 0.5</td>
<td>2.3 ± 0.8‡</td>
</tr>
<tr>
<td>7. Organization of alveolar exudate</td>
<td>2.7 ± 0.6</td>
<td>2.6 ± 1.0</td>
</tr>
<tr>
<td>8. Interstitial congestion</td>
<td>2.3 ± 0.5</td>
<td>2.2 ± 0.4</td>
</tr>
<tr>
<td>9. Lymphocyte infiltration</td>
<td>1.6 ± 0.4</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td>10. Interstitial thickening</td>
<td>2.5 ± 0.3</td>
<td>2.5 ± 1.0</td>
</tr>
<tr>
<td>11. Interstitial fibrosis</td>
<td>2.5 ± 0.6</td>
<td>2.1 ± 1.0</td>
</tr>
<tr>
<td>12. Intra-alveolar exudate</td>
<td>1.9 ± 0.5</td>
<td>2.8 ± 0.5†</td>
</tr>
</tbody>
</table>

*Data are expressed as mean ± SD (see text). In parentheses, number of lung sections examined.
†p < 0.05, control group vs ITPV group.

**Discussion**

In the current study, we wished to explore long-term effects of a nonrecruiting ventilatory approach on acutely injured lungs with a nonhomogenous pattern, ventilating the remaining healthier parts of the lungs (of relatively normal compliance), with a proportionally lower Vt, hence, still maintaining normal PIP and targeting a “physiological” gas exchange. Specifically, we wished to direct ventilation to the remaining healthy 5 to 8% of lungs and to, per chance, other relatively healthy regions of the remaining parenchyma, without recruitment.

Our experimental model of ARF in the present study was based on MV at a PIP of 50 cm H2O for approximately 2 days. We chose a ventilator-induced lung injury model because of our extensive prior experience14,17,19 and because barotrauma remains one of the major complications of MV. This model is reproducible and characterized by functional impairment and pathologic lesions not unlike those found in early clinical ARF.

The continuous flow of gas through an intratracheal catheter results in tidal ventilation because the expiratory resistance of the ventilator functions as a shutter, as also described by others.20–25 Initial PaO2/FIO2 in the ITPV group upon starting treatment was slightly lower compared with the control group. We ascribe this to the initial loss in mean lung volume that occurred during transition from high-pressure MV to lower airway pressure with ITPV. However, after a few hours of such ventilation, PaO2 gradually rose, along with signs of recovery in compliance that allowed us to reduce RR and to slightly increase Vt, with no change in airway pressures. At the highest RR used in the ITPV group, the maximal measured auto-PEEP was about 0.5 cm H2O. The lack of auto-PEEP suggests that the improvement in oxygenation cannot be ascribed to undetected hyperinflation phenomena.

In the control group, we observed major cardiovascular impairment. Terminally, sheep became oliguric and unresponsive to either fluid loading or furosemide, along with a slow and progressive fall in BP and CO. In the ITPV group, there was a greater hemodynamic stability with a small positive fluid balance. The average urine output was greater in the ITPV group sheep, without diuretics, and was maintained throughout the course of treatment. In the
latter group, two sheep developed systemic hypotension and required catecholamines either during the injury process or during the early part of treatment. Both were weaned off vasopressors. The lung injury process was uniform in all randomized sheep with respect to lung function, although it is difficult to interpret the postinjury hemodynamic differences among the two groups. The postinjury difference in Vd/Vt might be explained with the slightly greater Vt and the lower CO in the control group sheep.

Our study was not specifically designed to deal with the controversial issues related to patients with ARF. Currently, the physician can implement permissive hypercapnia (PHC), and limit VTs and pressures to reduce the risk of ventilator-related lung injury.20 Recent studies have shown continuous TGI at moderate catheter flows a helpful adjunct to MV to decrease Paco₂ in hypercapnic patients with ARF.24,25,27

In the ITPV groups, we ventilated lungs at a Vt as low as 2.5 mL/kg, and maintained PIP <20 cm H₂O. By decreasing the anatomic dead space, Paco₂ remained within the physiologic range, with Vt well below values commonly used with PHC, and avoiding overdistention of lung units. Of great interest was the collection of copious quantities of turbid, viscous liquid in the water trap of the expiratory line of the ventilator. We believe this was the result of the rapid stream of gas emerging from the RTC catheter, in a direction out of the tracheal tube that expelled mucus from the ETT.

One may hence wonder to what degree early use of a low PEEP-low Vt strategy could affect the evolution of the initial underlying disease process in any patient with ARF, who is now treated with MV using standards of care of today, with PIP between 30 and 35 cm H₂O. We believe those pressures may be inherently injurious.28 A recent work by Roupie and colleagues in patients with ARDS points to the importance of titrating Vt and limiting plateau pressures based on the P-V curve.

Amato and colleagues have shown that a previously practiced ventilatory approach applied to patients with early ARDS can delay lung recovery. More recently, the same group extended their study to the overall mortality of a large population of patients with ARDS.29 Their results showed that setting a respiratory PEEP above the lower inflection point of the P-V curve, while limiting Vt excursions and allowing CO₂ to rise, significantly improved survival, compared with a group treated with minimum PEEP and Vt of 12 mL/kg. In a prospective multicenter trial on PHC conducted by Brochard et al.,30 a “control” group was treated at the same PEEP as the PHC group, with a Vt >10 mL/kg, to achieve normocapnia, and limiting PIP to 60 cm H₂O. The group treated with PHC, to target a plateau pressure of approximately 25 cm H₂O to avoid overdistention, did not show better morbidity or mortality. The two studies taken together suggest that prevention of ongoing atelectasis with repeated alveolar opening and closure may be a determinant factor affecting outcome. Further randomized clinical studies are needed to explore this issue. Whether PEEP simply adds to the end-expiratory volume of lung units that are already open or maintains patency of unstable alveoli may depend on the stage of injury and the location of the alveolus within the injured lungs. The relatively high pressures applied to recruit collapsed lung units may transiently improve overall compliance, but those pressures may be far too high for the already opened lung units.

In our study, the significant increase in lung weight in the control group reflects more extensive histopathologic abnormalities found in this group. This correlated with finding of hyaline membranes, cellular infiltrates, and fluid accumulation, rather than alteration of the pulmonary vessels or the interstitium. The finding of inflammatory cell infiltration in the intra-alveolar space is in line with previous studies with large cyclic volumes.8,9,14,28 Our findings contrast with recent studies reported by Muscedere and colleagues,5 who found a significantly higher incidence of hyaline membrane formation in excised, lavaged rat lungs ventilated for 2 h at PEEP below the inflection point. We believe this can be explained by the different experimental conditions of their study. Dreyfuss and Saumon41 mechanically ventilated rats for 20 min, and found that ventilator-induced pulmonary edema increased with PEEP, at the same Vt. They suggest that lung overinflation was likely the main factor to the formation of pulmonary edema.

While in this experimental setting, a low PEEP-low Vt ventilatory strategy was shown to be successful compared to a strategy with PEEP targeted to gas exchange without limit of Vt; this study considered only one of the two possible lung protective ventilatory options. We did not explore a high PEEP-low Vt lung ventilatory strategy with atelectasis reversal as normocapnia was a primary goal. If we were to remove that restriction, the ITPV group could likely have been ventilated at a PIP <15 cm H₂O. Further studies are needed to investigate the latter option. Preliminary clinical studies with ITPV or hybrid-ITPV have been successful in patients with ARF in uncontrolled clinical trials, but its use has been limited.32,33

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REFERENCES