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# Intratracheal Pulmonary Ventilation *versus* Conventional Mechanical Ventilation in a Rabbit Model of Surfactant Deficiency

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## ABSTRACT

Intratracheal pulmonary ventilation (ITPV) enhances the clearance of $CO_2$ from dead space and lungs by a bias flow of gas administered in the distal trachea. ITPV flow is continuously administered through a separate catheter placed within an endotracheal tube (ETT). After exiting from catheter's tip in the distal trachea, the flow of gas is redirected outward *away* from the lungs. We hypothesized that, compared with conventional mechanical ventilation (CMV), ITPV may increase minute $CO_2$ clearance ($\dot{V}co_2$), reduce the partial pressure of $CO_2$ dioxide in arterial gas ($Paco_2$), and reduce distal tracheal peak inspiratory pressure (dPIP). We induced surfactant deficiency in 15 adult rabbits by lung lavage with 10 mL/kg normal saline. Animals were ventilated through a double-lumen 4.0 ETT, inserted through a tracheotomy incision. dPIP, distal positive end expiratory pressure, and distal mean airway pressure were monitored, and the mean exhaled $CO_2$ concentration was measured. For ventilator rates (respiratory rate) of 30, 45, and 70 breaths/min, the study included two phases: phase I compared $CO_2$ clearance and $Paco_2$ between ITPV and CMV using similar ventilatory pressures; phase II evaluated the effectiveness of ITPV in reducing dPIP and tidal volume ($V_t$), compared with CMV, while maintaining eucapnea. When comparing ITPV and CMV, the following results (mean ± SD) were achieved at respiratory rate of 30, 45, and 70 breaths/min, respectively. Phase I ITPV resulted in mean percent reduction of $Paco_2$ by 31.4 ± 10%, 37.1 ± 9.7% and 38.3 ± 9%; mean percent increase in $\dot{V}co_2$ by 61.3 ± 29%, 56 ± 23%, and 98 ± 40%, compared with CMV. Phase II ITPV resulted in mean percent reduction of dPIP by 35.5 ± 14%, 38 ± 10.8%, and 37.2 ± 13.7%, and mean percent reduction in $V_t$ by 34.7 ± 12.9%, 36.4 ± 15%, and 52.7 ± 10.7%, compared with CMV. The changes in $Paco_2$, $\dot{V}co_2$ (phase I), and dPIP and $V_t$ (phase II) were all significantly more than 25% ($p < 0.05$). Oxygenation and pH were not significantly different between ITPV and CMV. We conclude that, in a surfactant deficiency rabbit model, ITPV is an efficient mode of assisted ventilation that increases $CO_2$ clearance and reduces ventilator pressures required for adequate ventilation. We speculate that ITPV can minimize lung barotrauma associated with mechanical ventilation. (***Pediatr Res* 38: 878–885, 1995**)

**Abbreviations**

**CMV,** conventional mechanical ventilation
**$dP_{aw}$,** distal mean airway pressure
**dPEEP,** distal positive end expiratory pressure
**dPIP,** distal peak inspiratory pressure
**ETT,** endotracheal tube
**ITPV,** intratracheal pulmonary ventilation
**PFT,** pulmonary function test
**RR,** respiratory rate
**$Vco_2$,** minute $CO_2$ clearance
**$V_D$,** dead space volume
**$V_t$,** tidal volume
**$Paco_2$,** partial pressure of $CO_2$ in arterial gas
**$Pao_2$,** partial pressure of $O_2$ in arterial gas
**$Fio_2$,** fraction of inspired $O_2$
**I:E ratio,** inspiratory:expiratory ratio
**$F_ECO_2$,** mean exiting $CO_2$ concentration
**$\dot{V}_E$,** expiratory minute volume
**$T_I$,** inspiratory time
$T_E$, expiratory time
**ECMO,** extracorporeal membrane oxygenation

Intratracheal pulmonary ventilation is a new mode of ventilation developed by Kolobow *et al.* (1–5). ITPV involves the introduction of humidified air/oxygen flow through a small catheter with a diffuser at its distal end, inside a small plastic sleeve which redirects the gas *away* from the lungs (Figs. 1 and

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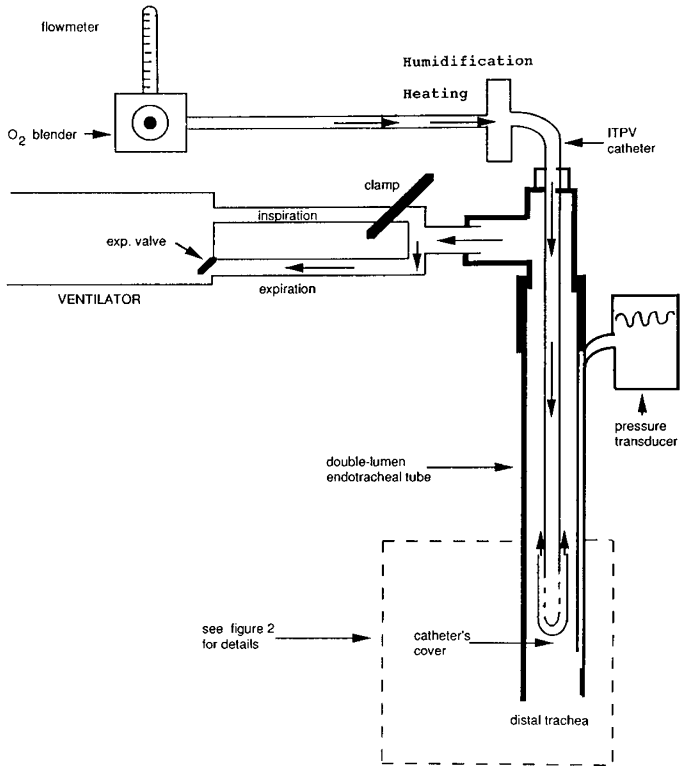


**Figure 1.** ITPV system. The inspiratory flow from the ventilator is blocked (*clamp*). Gas flows to the patient exclusively through the ITPV catheter (*continuous flow*). The ventilator serves for setting the respiratory rate, I:E ratio, PEEP, and for timed exhalations via its expiratory valve.

2); the catheter is placed within an ETT or a tracheostomy tube. The tip of the ITPV catheter is positioned proximal to the distal end of the ETT. Gas flow-through the catheter is continuous. A timed expiratory valve sets the I:E ratio and RR ranging from

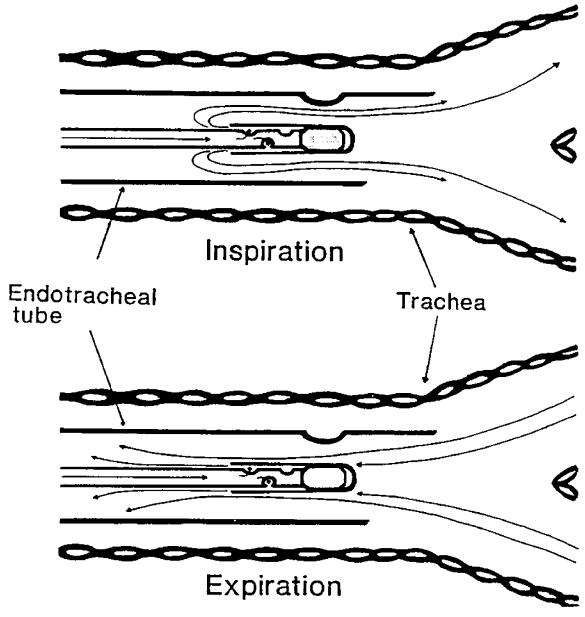


**Figure 2.** ITPV. Direction of intratracheal gas flow during inspiration and expiration (printed with permission from Kolobow T. 1991 Introduction to Intratracheal Pulmonary Ventilation (ITPV). In: ITPV Training Manual, unpublished.)

20 to 120 breaths/min; when the ventilator's exhalation valve is closed, gas flows into the lungs, and when the valve is open, gas flows upward entraining the alveolar gas, thus, facilitating exhalation and reducing dead space ventilation (Figs. 1 and 2).

ITPV was designed to ventilate areas of the lungs that are patent but not collapsed alveoli or atelectatic areas. Therefore an improvement in $Po_2$ is not anticipated if there is a sufficient ventilation/perfusion mismatch with significant intrapulmonary shunt. On the other hand, $CO_2$ clearance is expected to increase with ITPV. ITPV is optimally applied by using tidal volumes and peak inspiratory pressures which are lower than those used in CMV. However, patients who require large tidal volumes for achieving adequate gas exchange can benefit from ITPV combined with CMV (hybrid ventilation). The potential advantages of ITPV compared with CMV are: *1*) lower PIP and $V_t$, thus, avoiding pulmonary barotrauma; *2*) lower dead space ventilation, promoting $CO_2$ removal; and *3*) ability to use higher respiratory rates without the risk of developing inadvertent PEEP.

The common feature of all intratracheal ventilation techniques, ITPV and non-ITPV, is the displacement of the gas-exchange *interface* closer to the lungs (from the mouth-nose/proximal end of ETT *to* the distal trachea), thus partially bypassing the dead space. However, ITPV and non-ITPV techniques for intratracheal ventilation differ in the direction of the intratracheal gas flow. In the non-ITPV studies, the bias flow of gas is administered into the trachea or in a bronchus (6–8), with the gas directed forward into the lungs and/or to the sides. ITPV is unique in its special way of clearing the upper dead space from $CO_2$, *i.e.*, the *reversed* flow of gas in the distal trachea is directed *away* from the lungs, thus flushing the proximal dead space from $CO_2$ and partially avoiding $CO_2$ rebreathing.

Although the experience with ITPV is still limited and no controlled human studies have been reported, ITPV has been proven to be an effective form of ventilation in two animal trials: reduced lung volume (2) and diffuse parenchymal lung disease (4). In addition, ITPV was successfully used in three humans: two cases with congenital diaphragmatic hernia (1) and one case with adult respiratory distress syndrome (5).

In this study, we tested the effectiveness of ITPV in adult rabbits with surfactant deficiency induced by lung lavage with normal saline. Rabbits were chosen for this study because they have comparable weight, respiratory mechanics, and lung volumes to those of newborn infants (9, 10). We hypothesized that ITPV would be superior to CMV in terms of $CO_2$ clearance and that lower ventilatory support would be needed with ITPV to maintain adequate ventilation and oxygenation.

## METHODS

### Animal Preparation

The study was approved by the Animal Care Committee at Childrens Hospital Los Angeles. We used 15 New Zealand white adult female rabbits with a body weight of 3.4–4.7 kg. Atropine (0.04 mg/kg) was given s.c. as premedication. For induction of anesthesia, we used intramuscular ketamine (50 mg/kg/dose) and Rompun (xylazine) (8.8 mg/kg/dose). Anes-

thesia was maintained by i.v. Innovar-vet (0.22 mg/kg/dose). Pain control and paralysis were maintained by fentanyl and pancuronium bromide. Body temperature of 38.5°C was maintained by keeping each rabbit on a heating blanket. Maintenance fluid was delivered via the marginal ear vein as dextrose 5% in water with 0.45% saline at a rate of 8–10 mL/kg/h. All of the animals were treated by i.v. ampicillin (100 mg/kg every 6 h) and gentamicin (2.5 mg/kg every 12 h). Urinary drainage was accomplished by an indwelling Foley catheter in the urinary bladder. The middle auricular artery was catheterized, and systemic blood pressure was measured by a fluid-filled pressure transducer (Viggo-Spectramed, Oxnard, CA). Vital signs (heart rate, respiratory rate, temperature, and blood pressure) were monitored continuously. Arterial blood gas values were measured every 30 min. The endotracheal tube was a double-lumen ETT no. 4.0 ($ETCO_2$ tracheal tube, Sheridan Catheter Corp., Argyle, NY).

## Study Plan

The study was conducted as follows: *1*) sedation, anesthesia, and insertion of both venous and arterial catheters; *2*) tracheotomy, insertion of the ETT through the tracheotomy incision, bagging the animal briefly, and securing the ETT by a tie around the trachea to avoid any leak of gas around the ETT; *3*) paralyzing the animal and mechanical ventilation with a pressure-controlled mode, using a 900-C Servo ventilator (Siemens, Elma, Sweden) (settings: $Fio_2$ = 0.3, RR = 30 breaths/min, I:E ratio = 1:2, PIP = 13 cm $H_2O$, PEEP = 3 cm $H_2O$); *4*) measuring arterial blood gas values and first (baseline) pulmonary function test (PFT); *5*) Induction of surfactant deficiency by lavage with normal saline; *6*) arterial blood gas and a second PFT 45 min later; *7*) comparison of CMV and ITPV according to a preset ventilation protocol, while keeping dPEEP of 4–5 cm $H_2O$ and I:E ratio of 1:2 constant through the study (Table 1). Adequate ventilation and oxygenation was defined as pH = 7.37–7.43, $Paco_2$ = 37–43 mm Hg, and $Pao_2$ = 80–100 mm Hg. At the end of the planned experiment, the animal was killed by an overdose of pentobarbital (120 mg/kg).

**Table 1.** *Ventilation protocol for the comparison of ITPV and CMV*

| Phase | Goal of phase | Ventilation mode | Method |
|---|---|---|---|
| I | Comparison of $CO_2$ clearance on similar dPIP | Step 1. CMV | Adjust RR and dPIP to deliver $V_t$ of 7–9 ml/kg |
| | | Step 2. ITPV | Measure $Paco_2$ and $Vco_2$ at RR and dPIP similar to those in step 1 |
| II | Comparison of dPIP and $V_t$ needed for normalizing $Paco_2$ | Step 3. CMV | Maintain normal $Paco_2$ by adjusting dPIP without changing RR |
| | | Step 4. ITPV | Maintain normal $Paco_2$ by adjusting ITPV flow and increasing RR by 10–20 breaths/min |

## Induction of Surfactant Deficiency

We used a variation of known techniques for induction of surfactant deficiency in animals (11, 12): lung lavage by intratracheal instillation of warm (37°C) normal saline 10 mL/kg followed by positive pressure ventilation by bagging for 3 min (Fio2 = 1.0, RR = 30 breaths/min, PIP = 15 cm $H_2O$). The saline was then recovered by aspiration through the ETT.

## Pulmonary Function Tests

In this study, PFT were used to assess the severity of induced surfactant deficiency in terms of lung compliance. The prelavage PFT were performed on ventilatory settings of $Fio_2$ = 0.3, RR = 30 breaths/min, I/E ratio = 1:2, PIP = 13 cm $H_2O$, PEEP = 3 cm $H_2O$. PFT was repeated 45 min after lavage on ventilatory settings of $Fio_2$ of 1.0, RR of 40 breaths/min, and PIP of 16–24 cm $H_2O$. Compliance was determined by using the SensorMedics 2600 pulmonary function cart (SensorMedics Corporation, Yorba Linda, CA). Flow-volume loops were measured through a Hans Rudolph 4500 series pneumotach while the rabbit was ventilated with the Siemens Servo ventilator. Static compliance was determined by a single breath occlusion technique (13). Tidal breathing volume loops were obtained. After at least eight loops were stored, the occlusion valve was activated for the measurement of respiratory system compliance. The mean of 10 occlusions was used for analysis. Passive respiratory system compliance was calculated by dividing the total passive expiratory volume by the airway pressure measured at the endotracheal tube adaptor during a brief end-inspiratory occlusion (200 ms).

## Ventilation Techniques

***CMV.*** A Servo ventilator was used in a pressure control mode. This ventilator has modules for continuous display of $V_t$ (inspiratory and expiratory), proximal PIP, proximal $P_{aw}$, proximal PEEP, and exhaled minute ventilation. During CMV, the inspiratory tidal volume displayed in the Servo ventilator (inspired $volume_{displayed}$) was recorded as the $V_t$.

***ITPV.*** ITPV was performed using the 900-C Servo ventilator and a reversed-thrust ITPV catheter as recommended by Kolobow *et al.* (1–5) (Figs. 1 and 2). A reversed flow 5-F catheter (COOK Critical Care, Inc.) was inserted into the ETT, with its tip 1 cm proximal to the distal end of the ETT. ITPV gas mixture (air and/or oxygen) was heated (Anamed Humitube Controller, Las Vegas, NV) and humidified (modification of the Simplex Humitube heated wire circuit). The ITPV flow was continuous with gas exiting from the narrow annular orifice of the catheter and following the Teflon catheter outward (away from the direction of the carina) (Fig. 1). The reversed flow in the distal trachea produces a Venturi effect and may lower tracheal PEEP. Possible decrease of tracheal PEEP (dPEEP) below a preset value of 4 cm $H_2O$ was avoided by raising the proximal PEEP in the ventilator.

The ventilator was set up for the standard pressure mode and primarily used for timed expirations (Fig. 1). The disposable corrugated tubing of the ventilator was replaced with less compliant Tygon tubing to withstand the back pressure gener-

ated by the ITPV flow. The inspiratory limb of the tubing circuit was clamped during ITPV, so that all the inspiratory flow came from the ITPV intratracheal catheter (Fig. 1). Because of the reverse flow of gas up the ETT, the proximal airway pressures did not reflect pressures at the carina. Therefore, the side port of the Sheridan ETT was connected to a separate pressure monitor to measure distal tracheal pressures (Pneumogard, Novametrix, model no. 1200).

Distal to the Servo's exhalation valve, we continuously measured the mean *exiting* $CO_2$ concentration ($F_ECO_2$) (End Tidal $CO_2$ Monitor, Novametrix, model 1260), at the outlet of a mixing chamber draining the exhaled gas from the Servo ventilator. $F_ECO_2$ was recorded immediately after initiating ITPV (within 1 min). We calculated $CO_2$ production as follows: $\dot{V}co_2 = \dot{V}_E \times F_ECO_2$, where $\dot{V}_E$ was the expiratory minute volume *displayed* by the Servo ventilator. During ITPV, $\dot{V}_E$ expressed two components: *1*) the exhaled gas from the lungs and *2*) the reversed fresh gas flow (outward) originating from the ITPV catheter during expiration.

With ITPV, $V_t$ was calculated as follows: $V_t = [(\text{expiratory volume} - \text{inspiratory volume})_{\text{displayed}}] \times [T_I/(T_I + T_E)]$, where $T_I$ and $T_E$ are inspiratory and expiratory times, respectively. The displayed expiratory volume of each breath included the gas originating from the ITPV catheter during expiration *and* gas coming from the lungs (previously from the ITPV catheter during inspiration). With ITPV, all the inspiratory flow of gas to the animal's lungs originated from the separate ITPV gas source. In this study I:E ratio was kept constant at 1:2, and the displayed inspiratory volume was zero because of clamping the inspiratory limb of the ventilator's tubing circuit. Therefore, the calculated $V_t = (\text{expiratory volume}_{\text{displayed}})/3$ .

### Protocol for Comparison of ITPV and CMV

After induction of surfactant deficiency, the ventilation plan included two phases and each phase had two 30-min steps (Table 1). dPEEP and I:E ratio were kept constant. Phase I (steps 1 and 2) compared $\dot{V}co_2$ and $Paco_2$ between ITPV and CMV, using similar RR and dPIP. Phase II (steps 3 and 4) compared the dPIP, $dP_{aw}$, and $V_t$ required in either CMV or ITPV to maintain normal $Paco_2$, while adjusting ITPV flow rate and using a 10–20/min higher RR with ITPV. Our aim in increasing RR by 10–20 breaths/min in phase II was to allow the use of ITPV in optimum and achieve further reduction of $V_t$ and PIP while still keeping eucapnea. The ventilation protocol at each of the four steps was repeated at RR of 30, 45, and 70 breaths/min.

### Statistical Analysis of Data

All of the parameters that might be affected by the use of ITPV ($\dot{V}co_2$, $Paco_2$, dPIP, $dP_{aw}$, $V_t$, $Pao_2$, and pH), were compared between ITPV and CMV in phase I and phase II of the study. The *mean percent change* in each parameter between the two ventilation modes was the variable that we tested for statistical significance, using a one-sample *t* test, for each ventilator rate of 30, 45, and 70 breaths/min. For statistical significance, the mean percent change in each parameter was compared against a preset change of 25%. We chose a change of 25% for comparisons because we thought that changes significantly more than 25% will be accepted by almost all clinicians as valid results. However, that does not imply that changes of 10–24%, if significantly achieved, are not clinically important.

To test for possible differences between the means of the percent change in the above parameters studied ($\dot{V}co_2$, $Paco_2$, dPIP, $dP_{aw}$, $V_t$, $Pao_2$, and pH) between different RR of 30, 45 and 70 breaths/min, we used one-way analysis of variance (repeated measures). Values are presented as mean ± SD. A *p* value of 0.05 or less was statistically significant.

## RESULTS

### Induction of Surfactant Deficiency

Before lung lavage, while sedated and paralyzed, all animals required low ventilator settings ($Fio_2 = 0.3$, PIP = 13 cm $H_2O$, RR = 30 breaths/min) and had normal $Pao_2$ and $Paco_2$. Surfactant deficiency was successfully induced as evidenced by clinical signs and the extent of ventilatory support in all animals, and by changes in blood gas values and in respiratory system compliance in most animals. After lung lavage with normal saline, most animals became hypoxemic in spite of ventilation with higher ventilatory settings ($Fio_2 = 1.0$, PIP = 16–24 cm $H_2O$, RR = 40 breaths/min). Eleven of the 15 animals studied remained hypoxemic ($Pao_2 < 80$ mm Hg), whereas 4 of 15 animals had a $Pao_2$ of 80–130 mm Hg. Four animals became hypotensive and required i.v. normal saline boluses. Forty-five minutes after lung lavage, the static lung compliance in 13 of 15 animals decreased by 17–62% (Table 2). Lung compliance did not change in one animal and slightly increased by 4.2% in another animal. No additional measurements of lung compliance were performed during phase I, phase II of the study, or after completion of the study.

### Comparison of ITPV and CMV

Induction of surfactant deficiency and PFT was performed in 15 animals. Two of those animals died immediately after

**Table 2.** *Static lung compliance before and 45 min after lung lavage*

| Animal no. | Compliance (mL/cm $H_2O$/kg) | | Change in compliance (%) |
|---|---|---|---|
| | Prelavage | Postlavage | |
| 1 | 0.72 | 0.53 | −26.38 |
| 2 | 0.72 | 0.48 | −33.33 |
| 3 | 1.00 | 0.80 | −20.00 |
| 4 | 0.97 | 0.39 | −59.79 |
| 5 | 0.85 | 0.42 | −50.58 |
| 6 | 0.60 | 0.59 | −1.00 |
| 7 | 0.56 | 0.32 | −42.85 |
| 8 | 0.80 | 0.53 | −33.75 |
| 9 | 1.12 | 0.75 | −33.03 |
| 10 | 1.20 | 1.25 | +4.16 |
| 11 | 0.73 | 0.50 | −31.50 |
| 12 | 0.99 | 0.37 | −62.62 |
| 13 | 1.00 | 0.44 | −56.00 |
| 14 | 0.88 | 0.36 | −59.09 |
| 15 | 0.79 | 0.65 | −17.72 |

starting phase I of the ventilation protocol (CMV, step 1) from sudden severe air leak syndrome (pneumothorax and pneumoperitoneum and s.c. emphysema).

***Application of ITPV.*** All four steps of the ventilation protocol were completed in the 13 animals at RR of 30 and 45 breaths/min. ITPV flow of 2.6–10.9 L/min (phase I) and 2–11.1 L/min (phase II) was required in this study (Table 3). In most animals, increasing the respiratory rate mandated the use of higher ITPV flow rates. CMV was started first in seven animals, whereas ITPV was started first in six animals. Comparisons on RR of 70 breaths/min were completed only in 10 animals, because 3 of the 13 animals left died later on during ventilation at RR of 70 breaths/min. One animal died due to accidental venous air emboli. The other two animals who died developed pulmonary hemorrhage immediately after lung lavage, survived part of the study, and died during ventilation at a RR of 70 breaths/min. The mechanism of the pulmonary hemorrhage is not clear, and histopathologic studies of the lungs were not performed.

***Phase I: Comparison of step 2 (ITPV) and step 1 (CMV) on similar dPIP.*** When the same dPIP and RR were used, ITPV compared with CMV resulted in increased $VCO_2$ and decreased $Paco_2$, at all RR studied (Fig. 3). The mean percent increases in $\dot{V}co_2$ achieved with ITPV, compared with CMV, ranged from 56.4 to 98.4% and were significantly more than 25%. Significantly more $CO_2$ was removed on RR of 70 breaths/min than on either RR of 30 breaths/min or RR of 45 breaths/min ($p < 0.05$). The mean percent reductions in $Paco_2$ achieved with ITPV, compared with CMV, ranged from 31.4 to 38.3% and were significantly more than 25%. Comparison of ITPV and CMV on similar dPIP did not result in significant differences in inspiratory $V_t$, $Pao_2$, $dP_{aw}$, or pH. In five animals oxygenation increased by up to 20%, did not change in seven animals, and decreased by 10% in one animal (data not shown).

Figure 4 shows a distal tracheal pressure tracing (Hewlett Packard 78304A) during phase I of the study on similar ventilatory settings: dPIP = 24 cm $H_2O$, dPEEP = 4 cm $H_2O$, $dP_{aw}$ = 11 cm $H_2O$, I:E 1:2, RR = 45 breaths/min, and

**Table 3.** *ITPV flow (L/min) used in phase I and phase II*

| | RR (breaths/min) | | | | | |
|---|---|---|---|---|---|---|
| | 30 | | 45 | | 70 | |
| Animal no. | Phase I | Phase II | Phase I | Phase II | Phase I | Phase II |
| 1 | 5.8 | 5.6 | 9.0 | 5.4 | 7.1 | 6.9 |
| 2 | 3.3 | 4.3 | 5.6 | 5.7 | 5.7 | 6.0 |
| 3 | 3.6 | 4.2 | 3.9 | 5.0 | 5.5 | 8.0 |
| 4 | 2.6 | 3.6 | 5.6 | 4.5 | 7.7 | 8.6 |
| 5 | 3.4 | 3.1 | 5.4 | 5.5 | 7.2 | 8.5 |
| 6 | 3.0 | 4.6 | 5.7 | 7.9 | 10.9 | 11.1 |
| 7 | 3.4 | 2.3 | 7.0 | 9.0 | N/A | N/A* |
| 8 | 3.8 | 7.8 | 9.0 | 8.1 | 8.9 | 11.0 |
| 9 | 3.7 | 3.2 | 5.3 | 2.0 | 8.7 | 3.9 |
| 10 | 3.8 | 3.9 | 6.7 | 9.3 | N/A | N/A† |
| 11 | 4.0 | 3.8 | 5.6 | 3.4 | 8.8 | 3.8 |
| 12 | 5.0 | 4.9 | 6.9 | 6.9 | N/A | N/A† |
| 13 | 3.1 | 2.5 | 4.3 | 2.7 | 5.5 | 3.2 |

* Died at phase I (RR = 70 breaths/min) due to accidental air emboli.

† Died at phase I (RR = 70 breaths/min) due to severe pulmonary hemorrhage.

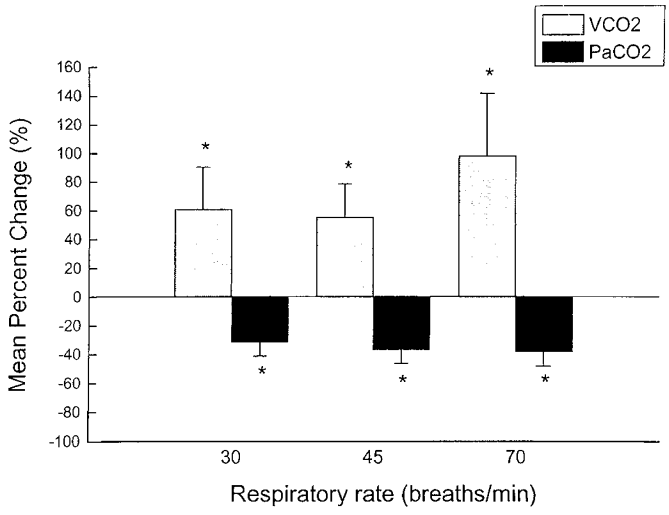


**Figure 3.** Percent changes (mean ± SD) in $\dot{V}co_2$ and $Paco_2$ during phase I of the study: comparison of step 2 (ITPV) and step 1 (CMV), at RR of 30, 45, and 70 breaths/min. *$p < 0.05$ compared with a change of 25%. The mean percent changes of $\dot{V}co_2$ with ITPV compared with CMV, at RR of 30, 45, and 70 breaths/min, respectively: 61.3 ± 29, 56.4 ± 23.5, and 98.4 ± 40.7. The mean percent changes of $Paco_2$ with ITPV compared with CMV, at RR of 30, 45, and 70 breaths/min, respectively: −31.4 ± 10, −37.1 ± 9.7, and −38.3 ± 9.9.

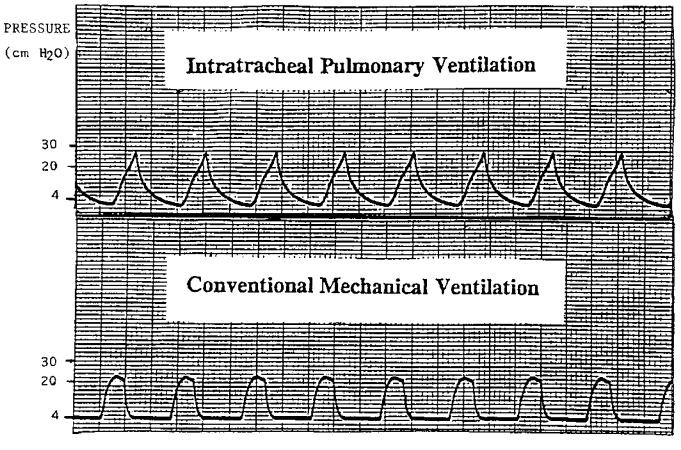


**Figure 4.** Distal tracheal pressure tracing during phase I of the study: (step 2) (ITPV) *vs* step 1 (CMV), Hewlett Packard 78304A: speed = 10 mm/s, dPIP = 24 cm $H_2O$, dPEEP = 4 cm $H_2O$, $dP_{aw}$ = 11 cm $H_2O$, I:E 1:2, RR = 45 breaths/min, and $ITPV_{flow}$ = 7 L/min. Note the gradual increase of dPIP and the decelerating pattern of dPEEP with ITPV, compared with CMV.

$ITPV_{flow}$ = 7 L/min. The gradual increase of dPIP and the decelerating dPEEP with ITPV differ from those displayed with CMV where dPIP has a more abrupt increase and dPEEP is constant. In spite of the different shape of the pressure/time curves with ITPV and CMV, the areas under the curve with both ventilation modes look comparable.

***Phase II: Comparison of step 4 (ITPV with 10–20 breaths/min higher RR) and step 3 (CMV) with normalization of Paco2.*** When dPIP and RR were adjusted to normalize $Paco_2$, significantly lower dPIP and lower $V_t$ were required with ITPV than with CMV, at all RR studied. The mean percent reductions in dPIP achieved with ITPV, compared with CMV, ranged from 35.5 to 38% and were significantly more than 25% ($p < 0.05$) (Fig. 5). There was no significant advantage of any of the different RR used on the extent of the reduction in dPIP.

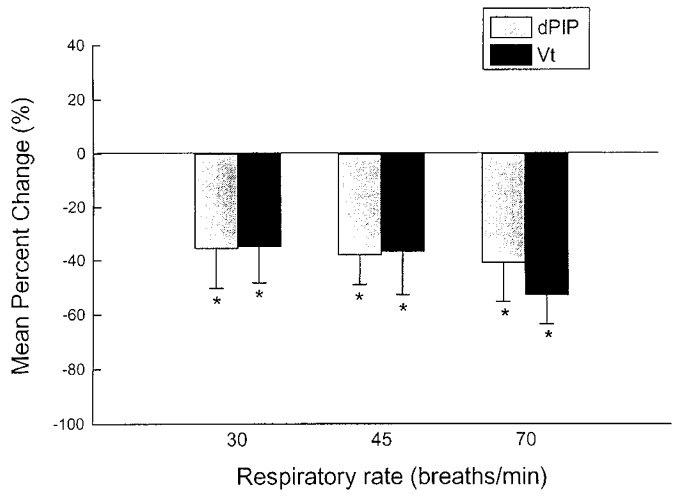


**Figure 5.** Percent changes (mean ± SD) in dPIP and $V_t$ during phase II of the study: comparison of step 3 (CMV) at RR of 30, 45, and 70 breaths/min and step 4 (ITPV with 10–20/min higher RR). *$p < 0.05$ compared with a change of 25%. The mean percent changes of dPIP with ITPV compared with CMV, at RR of 30, 45, and 70 breaths/min, respectively: −35.5 ± 14.1, −38 ± 10.8, and −37.2 ± 13.7. The mean percent changes of $V_t$ with ITPV compared with CMV, at RR of 30, 45, and 70 breaths/min, respectively: −34.7 ± 12.9, −36.4 ± 15, and −52.8 ± 10.

The mean percent reductions in $V_t$ achieved with ITPV, compared with CMV, ranged from 34.7 to 52.8% and were significantly more than 25% ($p < 0.05$) (Fig. 5). Comparison of $V_t$ reductions (step 4 *versus* step 3) between different RR showed that ITPV with higher RR (80–90 breaths/min) allowed the use of the lowest $V_t$ possible, while still achieving normal $Paco_2$. The mean percent reductions in $dP_{aw}$ with ITPV, compared with CMV, did not achieve our preset change of 25% but still were significantly more than 10% at RR of 45 and 70 breaths/min ($p < 0.05$) (Table 4). During this phase of the study, pH was not significantly different between ITPV and CMV (data not shown). Compared with CMV, $Pao_2$ decreased with ITPV in most animals especially on RR of 30 breaths/min; however, this decrease did not reach statistical significance (Table 5).

## DISCUSSION

Our study showed that, compared with CMV, more $CO_2$ was cleared from the lungs by ITPV and that ITPV allowed the use of significantly lower dPIP and $V_t$ to maintain normal ventilation and comparable oxygenation.

In this study, the effectiveness of ITPV was tested against that of CMV in two different settings. The aim of the first setting (phase I) was to test whether more $CO_2$ could be removed with ITPV compared with CMV on the same dPEEP, dPIP, I:E ratio, and RR. Our results show that clinically significant mean reductions in $Paco_2$ of 31.4–38.3% and mean increases in $\dot{V}co_2$ of 56.4–98.4% were achieved with ITPV compared with CMV, at similar ventilatory settings. During this phase of the study, neither oxygenation nor blood pressure were significantly different between ITPV and CMV. Maintenance of comparable oxygenation during this phase of the study was mainly due to the use of similar $dP_{aw}$ with ITPV and CMV.

The level of the proximal PEEP required by the Servo ventilator was the most important indicator for the impact of the reversed ITPV flow on the distal tracheal pressure. The higher the ITPV flow rate, the higher the proximal PEEP needed to keep dPEEP from dropping. On one hand, the decelerating pattern of dPEEP, during ITPV, helps to avoid the risk of inadvertent PEEP observed during CMV at high RR (Fig. 4). On the other hand, this decelerating pattern of PEEP may lead to lung atelectasis if high ITPV flow rates are used. To prevent such potential risk of ITPV, distal tracheal PEEP should be continuously monitored and kept constant.

ITPV was previously evaluated in two sheep models of lung disease: *reduced lung volume* after progressive pneumonectomies (2) and *diffuse parenchymal lung disease* after barotrauma to airways and lungs (4). In lambs, Muller *et al.* (2) reduced

**Table 4.** *Phase II (comparison of CMV and ITPV* while aiming for eucapnea): change in $dP_{aw}$ (cm $H_2O$)*

| | Respiratory rate (breaths/min) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 30 | | | 45 | | | 70 | | |
| Animal no. | CMV | ITPV | Change (%) | CMV | ITPV | Change (%) | CMV | ITPV | Change (%) |
| 1 | 15.9 | 11.4 | −28 | 11.8 | 10.4 | −6.7 | 12.0 | 9.5 | −20.0 |
| 2 | 13.5 | 14.2 | −10.3 | 14.2 | 11.5 | −19.0 | 14.6 | 11.1 | −23.0 |
| 3 | 7.8 | 4.3 | −45.0 | 10.1 | 7.8 | −23.0 | 9.5 | 7.0 | −16.0 |
| 4 | 9.5 | 7.2 | −24.0 | 9.6 | 8.0 | −16.0 | 11.3 | 9.6 | −15.0 |
| 5 | 10.0 | 6.0 | −40.0 | 8.9 | 7.1 | −30.0 | 10.8 | 6.3 | −41.0 |
| 6 | 10.7 | 10.2 | −4.6 | 12.7 | 11.5 | −9.4 | 13.4 | 12.3 | −8.2 |
| 7 | 11.7 | 10.9 | −6.0 | 13.9 | 14.0 | −0.7 | N/A† | N/A† | |
| 8 | 11.7 | 11.9 | +1.7 | 11.5 | 10.9 | −5.2 | 10.2 | 10.4 | +2.0 |
| 9 | 8.2 | 5.2 | −36.0 | 8.3 | 5.0 | −40.0 | 8 | 4.6 | −42.0 |
| 10 | 8.0 | 6.7 | −16.2 | 11.7 | 11.0 | −6.0 | N/A‡ | N/A‡ | |
| 11 | 7.7 | 6.6 | −13.0 | 7.3 | 6.1 | −19.0 | 8.2 | 5 | −39.0 |
| 12 | 11.6 | 10.6 | −8.6 | 14.3 | 12.5 | −14.0 | N/A‡ | N/A‡ | |
| 13 | 8.2 | 5.8 | −29.0 | 7.7 | 4.2 | −42.0 | 6.0 | 3.6 | −40.0 |
| Mean ± SD | | | −18.3 ± 16.8 | | | −17.6 ± 13.2 | | | −24.2 ± 15.3 |

* During this phase of the study, ITPV was performed using 10–20/min higher respiratory rates than with CMV.

† Died at phase I (RR = 70 breaths/min) due to accidental air emboli.

‡ Died at phase I (RR = 70 breaths/min) due to severe pulmonary hemorrhage.

**Table 5.** *Phase II (comparison of CMV and ITPV* while aiming for eucapnea): change in $Pao_2$ (mm Hg)*

| | Respiratory rate (breaths/min) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 30 | | | 45 | | | 70 | | |
| Animal no. | CMV | ITPV | Change (%) | CMV | ITPV | Change (%) | CMV | ITPV | Change (%) |
| 1 | 48 | 49 | −6.0 | 54 | 40 | −26.0 | 46 | 49 | +6.0 |
| 2 | 49 | 41 | −16.3 | 52 | 35 | −32.0 | 60 | 32 | −46.0 |
| 3 | 151 | 82 | −45.3 | 104 | 84 | −19.0 | 101 | 110 | +8.9 |
| 4 | 67 | 55 | −18.0 | 54 | 37 | −31.5 | 31 | 30 | −3.2 |
| 5 | 60 | 64 | +6.6 | 53 | 49 | −5.7 | 37 | 29 | −22.0 |
| 6 | 32 | 22 | −31.0 | 32 | 26 | −13.7 | 33 | 27 | −18.0 |
| 7 | 55 | 38 | −31.0 | 39 | 29 | −23.0 | N/A† | N/A† | |
| 8 | 37 | 27 | −37.0 | 43 | 40 | −7.0 | 47 | 67 | +42.0 |
| 9 | 146 | 142 | −27.0 | 222 | 237 | +6.7 | 233 | 228 | −2.0 |
| 10 | 132 | 133 | +0.8 | 28 | 30 | +7.1 | N/A‡ | N/A‡ | |
| 11 | 149 | 81 | −37.5 | 100 | 158 | +58 | 100 | 100 | 0.0 |
| 12 | 42 | 28 | −33.0 | 41 | 37 | −9.7 | N/A‡ | N/A‡ | |
| 13 | 115 | 328 | +186.0 | 313 | 375 | +20.0 | 358 | 460 | +28.0 |
| Mean ± SD | | | −4.2 ± 59.9 | | | −6.3 ± 24.9 | | | −0.63 ± 24.9 |

* During this phase of the study, ITPV was performed using 10–20/min higher respiratory rates than with CMV.

† Died at phase I (RR = 70 breaths/min) due to accidental air emboli.

‡ Died at phase I (RR = 70 breaths/min) due to severe pulmonary hemorrhage.

lung volume by excluding one or more lobes of the lungs by ligating the respective bronchi and pulmonary arteries. Lambs ventilated with 12.5% remaining lung (right upper lobe alone) could no longer be adequately ventilated or oxygenated with CMV, and died of respiratory failure. Use of ITPV, with the right upper lobe alone, allowed weaning of lambs to room air within 2 h, at PIP 9–14 cm $H_2O$, and RR of 60–120 breaths/min. The same lambs were then ventilated with CMV and died within 12 h of severe respiratory failure. In our surfactant deficiency model, we also observed that with ITPV, adequate removal of $CO_2$ could be achieved at significantly lower dPIP and $V_t$, compared with CMV.

In sheep with induced acute respiratory failure after mechanical ventilation at high PIP, Aprigliano *et al.* (4) applied ITPV at RR from 40 to 70 breaths/min, with $V_t$ from 1.5 to 3 mL/kg at zero PEEP and a resulting PIP from 7 to 10 cm $H_2O$. The $Fio_2$ was adjusted to keep the $Pao_2$ above 100 mm Hg. As lung function improved over time, RR was reduced with eventual weaning. Our study ended 6 h after induction of surfactant deficiency. However, in a prolonged experiment lung function and oxygenation might improve over time, as previously described by Aprigliano *et al.* (4).

In the second setting (phase II), we applied ITPV in its most effective way (step 4 of our protocol), on 10–20 breaths/min higher RR than CMV, and with the lowest dPIP, $V_t$, and $dP_{aw}$ possible that allowed the maintenance of normal $Paco_2$. Our results show that, while keeping normal $Paco_2$ of 37–43 mm $H_2O$, ITPV allowed clinically significant mean reductions of 35.5–38% in dPIP compared with those required with CMV. In addition, this step of ITPV allowed clinically significant mean reductions of 34.7–52.8% in inspiratory $V_t$, and mean reductions of 17.6–24.2% in $dP_{aw}$. Those significant reductions in dPIP, $V_t$, and $dP_{aw}$ were consistent with all RR studied. Blood pressure was not significantly different between ITPV and CMV. With ITPV, oxygenation decreased in most animals; however, this decrease was not statistically significant. We believe that the decrease in oxygenation during phase II of the study was due to the use of lower $dP_{aw}$ with ITPV compared with CMV.

Human experience with ITPV is currently limited to three case reports. Wilson *et al.* (1) reported two term neonates with congenital diaphragmatic hernia meeting the criteria for >90% mortality on the basis of ventilatory index. The patients could not be weaned from ECMO therapy by using CMV. ITPV was effective in weaning from ECMO, alleviating post-ECMO hypercapnia, and achieving better alveolar ventilation at lower PIP than CMV with substantial decrease in dead space volume. The second report on the use of ITPV in humans came from Raszynski *et al.* (5) who weaned a 16-y-old patient from ECMO by using hybrid ITPV (ITPV with standard positive pressure ventilation), after failure of conventional ventilatory weaning methods. The patient suffered from severe surfactant deficiency, needed maximal ventilatory support on CMV, developed severe pulmonary air leak syndrome and necrotizing tracheitis, and eventually was placed on venoarterial ECMO. After 11 d of ECMO support the patient could not be weaned without significant ventilatory support. Initiation of ITPV allowed immediate weaning from ECMO. The ITPV course lasted 12 d with tidal volumes of 2–3 mL/kg and carinal PIP < 25 cm $H_2O$. The air leaks ceased, and the post-ITPV bronchoscopy displayed a dramatically improved tracheitis with normal airways observed. The significant reduction of $V_t$ that was demonstrated in our study by using ITPV conforms with the results of Kolobow and Raszynski (5). This reduction in $V_t$ can potentially decrease barotrauma.

Regarding oxygenation, ITPV neither improved nor worsened oxygenation when adequate $dP_{aw}$ was maintained (phase I), but ITPV led to a slight decrease in oxygenation when $dP_{aw}$ dropped (phase II). Using ITPV for longer periods (days) may reduce barotrauma to the respiratory system, may allow faster and better recovery of diseased alveoli, and thus may improve oxygenation (5).

In terms of cost effectiveness, ITPV is inexpensive when compared with nonconventional methods of ventilation such as high frequency oscillatory ventilation or ECMO. In addition to the conventional ventilator, the application of ITPV requires the specific-reversed-thrust catheter, a second source of gas flow and pressure monitoring devices. Furthermore, ITPV is easier to handle and administer than high frequency oscillatory ventilation and is far less invasive than ECMO. In terms of safety, ITPV may be a safe technique for assisted ventilation, as long as high rates of gas flow are avoided, proper positioning of the ITPV catheter's tip is maintained, and distal PEEP is monitored. Nonetheless, further safety measures should be addressed in future studies including the need for a pressure limit pop-off valve on the incoming ITPV bias flow and discontinuing ITPV whenever suctioning of the airway is performed.

Our hypothesis that ITPV, compared with CMV, leads to better $CO_2$ removal and reduction of $Paco_2$, was proven. ITPV also allowed the use of significantly lower dPIP, $dP_{aw}$, and $V_t$, while achieving eucapnea. We speculate that ITPV can be beneficial in lung diseases where $CO_2$ retention is the major problem. We also speculate that ITPV can minimize barotrauma to the lungs associated with CMV.

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## REFERENCES

1. Wilson JM, Thompson JR, Schnitzer JJ, Bower LK, Lillehei CW, Pearlman ND, Kolobow T 1993 Intratracheal pulmonary ventilation and congenital diaphragmatic hernia: a report of two cases. J Pediatr Surg 28:484–487
2. Muller EE, Kolobow T, Mandava S, Jones M, Vitale G, Aprigliano M, Yamada K 1993 How to ventilate lungs as small as 12:5% of normal: the new technique of intratracheal pulmonary ventilation. Pediatr Res 34:606–610
3. Kolobow T, Muller E, Mandava S, Jones M, Vitale G, Aprigliano M 1991 Intratracheal pulmonary ventilation (ITPV). A new technique. Pediatr Res 29:31A(abstr)
4. Aprigliano M, Kolobow T, Rossi N, Tsuno K, Lee KH 1992 Intratracheal pulmonary ventilation (ITPV) in the management of acute respiratory failure (ARF). Am Rev Respir Dis 145:A4559(abstr)
5. Raszynski A, Hultquist KA, Latif H, Sussmane J, Wolfsdorf J, Kolobow T. Rescue from pediatric ECMO with prolonged intratracheal pulmonary ventilation. ASAIO Trans 1993;39:M681–M685
6. Gavriely N, Eckmann D, Grotberg JB 1992 Gas exchange by intratracheal insufflation in a ventilatory failure dog model. J Clin Invest 90:2376–2383
7. Nahum A, Ravenscarft SA, Nakos G, Burke WC, Adams AB, Marcy TW, Marini JJ 1992 Tracheal gas insufflation during pressure-control ventilation. Am Rev Respir Dis 146:1411–1418
8. Burke WC, Nahum A, Ravenscarft SA, Adams AB, Nakos G, Marcy TW, Marini JJ 1992 Phase specific intratracheal gas insufflation augments alveolar ventilation. Am Rev Respir Dis 145:A4559(abstr)
9. Tran N, Lowe C, Sivieri EM, Shaffer TH 1980 Sequential effects of acute meconium obstruction on pulmonary function. Pediatr Res 14:34–38
10. Crofill ML, Widdicombe JG 1961 Physical characteristics of the chest and lungs and the work of breathing in different mammalian species. J Physiol 158:1–14
11. Lachman B, Robertson B, Vogel J 1980 *In vivo* lung lavage as an experimental model of the respiratory distress syndrome. Acta Anaesthesiol Scand 24:231–236
12. Schindler M, Seear M 1991 The effect of lung mechanics on gas transport during high-frequency oscillation. Pediatr Pulmonol 11:335–339
13. LeSouef PN, England SJ, Bryan AC 1984 Passive respiratory mechanics in newborns and children. Am Rev Respir Dis 129:552–556