Acute Respiratory Failure induced by Mechanical Pulmonary Ventilation at a Peak Inspiratory Pressure of 40 cmH_2O

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The effects of high pressure mechanical pulmonary ventilation at a peak inspiratory pressure of 40 cmH_2O were studied on the lungs of healthy newborn pigs (14–21 days after birth). Forty percent oxygen in nitrogen was used for ventilation to prevent oxygen intoxication. The control group (6 pigs) was ventilated for 48 hours at a peak inspiratory pressure less than 18 cmH_2O and a PEEP of 3–5 cmH_2O with a normal tidal volume, and a respiratory rate of 20 times/min. The control group showed few deleterious changes in the lungs for 48 hours. Eleven newborn pigs were ventilated at a peak inspiratory pressure of 40 cmH_2O with a PEEP of 3–5 cmH_2O and a respiratory rate of 20 times/min. To avoid respiratory alkalosis, a dead space was placed in the respiratory circuit, and normocarbia was maintained by adjusting dead space volume. In all cases in the latter group, severe pulmonary impairments, such as abnormal chest roentgenograms, hypoxemia, decreased total static lung compliance, high incidence of pneumothorax, congestive atelectasis, and increased lung weight were found within 48 hours of ventilation. When the pulmonary impairments became manifest, 6 of the 11 newborn pigs were switched to the conventional medical and ventilatory therapies for 3–6 days. However, all of them became ventilator dependent, and severe lung pathology was found at autopsy. These pulmonary insults by high pressure mechanical pulmonary ventilation could be occurring not infrequently in the respiratory management of patients with respiratory failure.
(Key words: mechanical pulmonary ventilation, high peak inspiratory pressure, acute respiratory failure, barotrauma)

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Soon after mechanical pulmonary ventilation (MV) first became popular in the clinical management of patients with respiratory failure caused by poliomyelitis or other neuromuscular disorders, then by pulmonary diseases, the side effects of MV began to attention. There were debates concerning the expression "Respirator Lung", which implied that MV caused pulmonary damage. Nash et al.[1] performed MV on healthy goats at a peak inspiratory pressure (PIP) of 13 cmH_2O for 3 to 4 days, and concluded "The Respirator Lung was a misnomer". Indeed, MV usually does not cause severe pulmonary complications on patients with healthy compliant lungs, as was the case in poliomyelitis and patients undergoing general anesthesia

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for minor surgery. In these cases, a low PIP, as Nash used in his experiment, is enough to get adequate pulmonary gas exchange.

However, a high PIP is often necessary during MV for patients with respiratory distress syndrome (RDS) with low compliant lungs. The pulmonary effects of long-term MV with a high PIP have not been studied in detail. Therefore, we have studied the effects of high pressure MV at a PIP of 40 cmH_2O for 48 hours on the healthy lungs of newborn pigs.

Methods

Seventeen newborn pigs, 14 to 21 days after birth, weighing 3.72 ± 0.30 kg, were intubated orotracheally under sodium pentobarbital anesthesia and placed on a mechanical ventilator. The anesthesia was switched to 1–2% halothane in nitrous oxide and oxygen for the following operation. One small catheter was inserted into the left external jugular vein for IV infusion, and another into the right external jugular vein for continuous heparin infusion. The right carotid artery was also cannulated for blood pressure monitoring and blood sampling. Two T-shaped silicone chest tubes were installed into the bilateral chest cavities, and they were continuously drained with a negative pressure of cmH_2O to prevent sudden death from tension pneumothorax. A urinary catheter was placed into the bladder transabdominally. Tracheostomy was done, and the orotracheal tube was replaced with a spiral tracheostomy tube.

After all was finished, the pigs were put in a prone position. Anesthesia and paralization were maintained throughout the experiments with sodium pentobarbital and pancuronium bromide. The pigs were mechanically ventilated by a Newport 100E ventilator (NMI, USA) with a tidal volume (V_T) of 13 ml/kg, a respiratory rate (RR) of 20 times/min, and a PIP less than 18 cmH_2O with a positive end-expiratory pressure (PEEP) of 3–5 cmH_2O. A humidified gas mixture of 40% oxygen in nitrogen, warmed to 38°C, was used throughout the experiments. After 2 hours of MV with the above mode, arterial blood gases, total static lung compliance (TSLC), and a chest roentgenogram were taken as control values.

After the control values were taken, the pigs were assigned to either control group A or experimental group B. Group A (n = 6) was ventilated for 48 hours as in the control period described above. Group B (n = 11) was ventilated 20 times/min with a PIP elevated to 40 cmH_2O by increasing V_T. A PEEP of 3–5 cmH_2O was the same as in Group A. An adjustable dead space tube was placed in the respiratory circuit to avoid respiratory alkalosis due to hyperventilation. High pressure mechanical ventilation (HPMV) was performed for 48 hours or until the Pa_{O_2} fell to less than 60 mmHg at an F_{IO_2} 0.4. Then, 5 pigs were sacrificed for autopsy (Group B-1). In the remaining 6 pigs (Group B-2), when they reached the terminal criteria as in Group B-1, conventional MV for the treatment of acute respiratory failure (ARF) was started and continued for 3–6 days. During the management of conventional MV, the respiratory dead space was removed, and adequate V_T, PEEP, F_{IO_2} and other medical efforts were taken for life-saving.

Arterial blood gases were analyzed every hour and TSLC was measured every four hours. TSLC was measured by stepwise inflation of the lungs with air, with an increment of 25 ml by using a large syringe, until the maximal intratracheal pressure reached 20 cmH_2O. The intratracheal pressure was measured with a pressure transducer (Gould P23 ID, USA) at the proximal end of the endotracheal tube. When the base excess fell under −5 mEq/L, $NaHCO_3$ was given to correct the arterial pH. Half saline (2.5% dextrose and 0.45% NaCl) was continuously given intravenously at the rate of 5 ml/kg/h. KCl was also given intermittently to maintain the serum K^+ within 3.5–4.5 mEq/L. Massive thrombosis was frequently found in the superior and inferior caval veins of pigs mechanically ventilated with a high PIP in a preliminary experiment, but this problem was avoided by the intravenous administration of heparin. Therefore, heparin

Table 1. Arterial Blood Gases and Total Static Lung Compliance during Mechanical Pulmonary Ventilation

		Control	2 h	4 h	8 h	12 h	16 h	20 h	24 h	32 h	40 h	42 h	Terminal
pHa	Group A	7.521 ±0.063 (6)	7.466 ±0.076 (6)	7.509 ±0.068 (6)	7.476 ±0.054 (6)	7.464 ±0.044 (6)	7.424 ±0.025 (6)	7.409 ±0.055 (6)	7.432 ±0.068 (6)	7.481 ±0.033 (6)	7.474 ±0.027 (6)	7.432 ±0.052 (6)	7.462 ±0.085 (6)
	Group B	7.492 ±0.084 (11)	7.492 ±0.114 (11)	7.446 ±0.104 (11)	7.381 ±0.098 (11)	7.412 ±0.107 (11)	7.365 ±0.101 (6)	7.381 ±0.106 (5)	7.553 ±0.117 (2)	7.266* ±0.025 (2)	7.216* ±0.006 (2)	7.286* ±0.033 (2)	7.318* ±0.061 (11)
Pa_{O_2}	Group A	172.8 ± 24.1	162.2 ± 29.1	176.0 ± 24.2	167.8 ± 22.0	174.4 ± 15.4	171.6 ± 20.8	167.3 ± 21.5	170.2 ± 25.0	178.5 ± 20.5	181.9 ± 34.3	176.2 ± 28.9	184.3 ± 23.0
	Group B	183.7 ± 21.8	178.1 ± 29.7	171.5 ± 37.5	149.4 ± 41.2	127.2 ± 62.3	146.4 ± 41.4	124.1 ± 63.7	137.7 ± 9.8	105.3* ± 12.9	74.6* ± 17.4	53.2* ± 0.1	55.3* ± 9.8
Pa_{CO_2}	Group A	32.3 ± 3.3	34.1 ± 6.3	28.6 ± 2.8	30.2 ± 3.5	28.8 ± 2.8	30.7 ± 2.2	31.3 ± 5.0	31.0 ± 6.1	27.7 ± 4.2	28.0 ± 4.2	30.8 ± 4.5	29.2 ± 2.8
	Group B	31.9 ± 5.1	32.3 ± 7.8	34.3 ± 7.8	39.6* ±. 8.6	36.3* ± 4.9	40.1* ± 2.9	37.7 ± 4.4	36.1 ± 2.2	45.8* ± 1.3	37.9* ± 1.2	38.1 ± 4.0	36.5* ± 3.4
TSLC	Group A	1.656 ±0.344	1.661 ±0.158	1.658 ±0.360	1.615 ±0.272	1.693 ±0.254	1.826 ±0.286	1.657 ±0.152	1.548 ±0.235	1.606 ±0.253	1.502 ±0.250	1.552 ±0.382	1.862 ±0.496
	Group B	1.545 ±0.439	2.351* ±0.539	2.295 ±0.736	1.975 ±0.872	1.698 ±0.977	2.110 ±0.916	2.000 ±1.038	2.255* ±0.474	1.805 ±0.191	1.490 ±0.028	1.430 ±0.057	1.213 ±0.719

Group A: conventional mechanical ventilation with a peak inspiratory pressure less than 18 cmH_2O. Group B: high pressure mechanical ventilation with a peak inspiratory pressure of 40 cmH_2O. Numbers in parenthesis: numbers of subjects at each measure point.
Pa_{O_2} and Pa_{CO_2} are expressed in the unit of mmHg, and TSLC in the unit of $ml/cmH_2O/kg$ of body weight.
* $P<0.05$, compared with Group A at each measure point

of 5 mg/kg/h was administered continuously both in Groups A and B. Additional chest roentgenograms were taken whenever it seemed necessary, and at the end of each experiment. The last data were taken just before the end of each experiment as the terminal values.

The pigs were sacrificed by an intravenous bolus injection of pentobarbital. At autopsy, the chest was opened, and the gross lung findings were graded according to our scoring system. A comparative assessment was based on inspection immediately after opening the chest, and before the attempts at manual inflation of the lungs. The right lung was removed for a light microscopic study, and the left lung was removed to measure the wet lung weight (WLW g/kg of body weight), dry lung weight (DLW g/kg of body weight), and lung water volume (WLW-DLW g/kg of body weight). Four other pigs (Group C), which were not treated by any medical managements, were sacrificed by intravenous administration of pentobarbital for light microscopic and weighing studies of the lung.

Data are expressed as mean ± SD. For a statistical evaluation of the results, Student's t-test was used, with $P<0.05$ as the limit of significance.

Results

The control values in Groups A and B were in the normal ranges, and there was no significant difference between both groups. All animals in Group A were mechanically ventilated for the entire 48 hours with no significant changes in V_T, TSLC, and arterial blood gases (table 1). Arterial pH was well controlled without any supplementation of $NaHCO_3$. Any significant alteration of the ventilator settings was not necessary to maintain Pa_{CO_2} within the normal or hyper-eliminated range. Pa_{O_2} was also stable, and there were no significant changes in the entire course of the experiment. There was no case of pneumothorax in this group. Chest roentgenograms showed no abnormalities. At autopsy, the lungs appeared pink, well aerated, with a few small or moderate sized areas of atelectasis, and no pleural effusions were found (table 2). WLW, DLW, and WLW-DLW in Group A were not significantly different from those in Group C (table 3).

Table 2. Degree of Pulmonary Impairments at Autopsy

		Insignificant	Moderate	Severe
Group A	(n=6)	4/6	2/6	
Group B-1	(n=5)			5/5
Group B-2	(n=6)			6/6
Group C	(n=4)	4/4		

Legends: refer to Table 1 and text.
Insignificant: lungs generally pink except for rare spotty areas of atelectasis less than 5% in any one single lobe; no pleural effusion.
Moderate: pulmonary atelectasis between 5–20% in any one single lobe.
Severe: atelectasis over 20% in all lobes of the lungs, or pneumothorax, with pleural effusion and numerous blebs.

The animals in Group B were ventilated for 12 to 43 hours with a mean of 22.0 ± 11.1 hours to reach the terminal criteria. With the start of HPMV, the V_T in Group B rose to about 5 times that of the control value (12.7 ± 1.9 ml/kg) to maintain the PIP at 40 cmH_2O. In a few hours of HPMV, the V_T increased to the maximum of 65.5 ± 7.6 ml/kg to keep the same PIP of 40 cmH_2O. After several hours in a stable state, the V_T decreased gradually and fell toward the terminal value of 38.4 ± 16.9 ml/kg ($P<0.05$, compared with the maximum value). The TSLC also increased after the start of HPMV, and the value at 2 hours was significantly higher than the value at 2 hours of Group A (table 1). After a transient increase, however, the TSLC decreased gradually and the terminal value became significantly lower than the values at 2 hours, 4 hours, and 8 hours ($P<0.05$).

In Group B, metabolic acidosis progressed in spite of frequent administrations of $NaHCO_3$. Pa_{CO_2} was maintained in the normal range by decreasing the dead space volume from the maximum value of 62.1 ± 15.5 ml/kg in a few hours from the start

Table 3. Body Weight and Left Lung Weight

	BW (kg)	WLW/BW (g/kg)	DLW/BW (g/kg)	(WLW-DLW)/BW (g/kg)
Group A (n=6)	3.91 ± 0.41	6.13 ± 1.01	1.08 ± 0.14	5.05 ± 0.87
Group B-1 (n=5)	3.55 ± 0.19	9.45 ± 1.75*‖	1.48 ± 0.17*‖	7.98 ± 1.62*‖
Group B-2 (n=6)	3.64 ± 0.14	18.79 ± 9.46*‖	2.25 ± 0.93*‖	16.53 ± 9.57*‖
Group C (n=4)	3.36 ± 0.88	5.62 ± 1.00	1.13 ± 0.24	4.49 ± 0.78

WLW: wet weight of left lung, DLW: dry weight of left lung, WLW-DLW: water volume of left lung, Right lungs were used for microscopic study.
* $P<0.05$, compared with Group A, ‖ $P<0.05$, compared with Group C

of HPMV to the minimum value of 29.5 ± 26.2 ml/kg at the terminal ($P<0.05$). The respiratory dead space volume had to be adjusted according to the change in V_T. Pa_{O_2} was stable for several hours from the start of HPMV; however, it started to fall gradually, or sometimes rapidly, and the terminal value was significantly lower than in Group A (table 1).

Pneumothorax occurred in 7 pigs (63.6%) of Group B. Chest roentgenograms showed progressive pulmonary infiltrates over the course of the study. Pulmonary atelectasis, pleural effusion, and numerous blebs were seen in all the pigs at autopsy (table 2). WLW, DLW, and WLW-DLW in Group B-1 were significantly heavier than those in Groups A and C (table 3).

The animals in Group B-2 were treated with conventional respiratory and medical therapies for 3–6 days after they reached the terminal criteria. All of them became ventilator dependent. At the end of the experiment, arterial blood gases showed pH 7.338 ± 0.147, Pa_{O_2} 85.9 ± 6.3 mmHg, Pa_{CO_2} 39.8 ± 3.0 mmHg, and BE −3.7 ± 10.7 mEq/L under the ventilator settings of F_{IO_2} 0.74 ± 0.22, RR 23.6 ± 12.5 times/min, PIP 38.2 ± 3.4 cmH_2O, and PEEP 11.8 ± 3.5 cmH_2O. Pulmonary atelectasis and pleural effusion were more severe than those in Group B-1. WLW, DLW, and WLW-DLW in Group B-2 were significantly heavier than those in Groups A and C (table 3).

Discussion

Acute pulmonary impairments of overinflation of the lugns even for a few hours with a high intratracheal pressure have often been reported. Greenfield et al.[2] found severe atelectasis and an abnormal increase in the surface tension of the lungs 24 hours after MV at a PIP of 28 to 32 cmH_2O and only 2 hours of duration. MV for 20 min at a PIP of over 42 cmH_2O increased the microvascular permiability of the isolated and blood-perfused lung[3]. It occurred in some cases at a PIP as low as 30 cmH_2O. Rats, mechanically ventilated for 1 hour at a PIP of 30 to 45 cmH_2O, developed perivascular and alveolar edema, hypoxemia, decrement of dynamic compliance in the lungs, and died[4].

In ventilator therapy for patients with acute respiratory failure, high airway pressure is often necessary to get adequate pulmonary gas exchange. The necessity usually lasts several days, or weeks, not several hours. However, the effects of long-term HPMV have not been studied in detail. It should have been studied before the wide clinical application of MV.

This experiment was planned to examine the effect of HPMV at a PIP of 40 cmH_2O for 48 hours on the lungs of healthy newborn pigs. Since 40% oxygen was used for the inspired gas, oxygen intoxication could be ruled out, and the control group A showed few deleterious changes after 48 hours of MV. On the other hand, pulmonary impairments were found in all pigs of Group B. Conventional MV could not return the pulmonary pathology in Group B-2 as a model of acute respiratory fail-

ure. Pulmonary pathology in Group B-2 was worse than that in Group B-1. The parameters, such as Pa_{O_2} and TSLC, were usually better for several hours from the beginning of HPMV than the control values. If we had stopped the experiment within several hours, the results would have misled us to conclude that "Respirator Lung is a misnomer". The pulmonary dysfunctions and impairments induced by a high intratracheal pressure and/or hyperinflation[5] may be attributable to the disturbance of the pulmonary surfactant system[6,7], an increment of pulmonary capillary permiability[3], and a direct insult on the integrity of pulmonary parenchyma consisting of over 80 cell lines.

The mechanism of thrombus formation in the animals ventilated with a high PIP during the preliminary study has not been clear. However, it is suggested that some hematologic changes could occur by hyperventilation[8,9]. It might play some role in the thrombus formation, and might cause the pulmonary impairments.

Since the adult respiratory distress syndrome (ARDS) was first recognized by Ashbaugh et al.[10] in 1967, the pathogenesis of ARDS has been studied, but it is not understood enough and still under debate. The mortality rate of ARDS is still as high as about 50%, and has not decreased in these 10 years, despite current supportive therapy[11]. Once ARDS occurs, whatever the cause may be, patients are put on mechanical ventilatory support as the state of the art. And a high PIP is usually used to get seemingly good pulmonary gas exchange. The complication of HPMV has been well recognized as barotrauma, such as subcutaneous and mediastinal emphysema, and pneumothorax. Recently, also recognized as barotrauma are pulmonary interstitial air cysts, interstitial emphysema, and bronchopulmonary dysplasia in adults[12–14]. However, we have been emphasizing the importance of a much earlier recognition of the insulting effects of a high intratracheal pressure and hyperinflation on healthy lung parenchyma. So called barotrauma nowadays, such as pneumothorax and other impairments, could be the latest stage of HPMV. The impaired lugns, as in ARDS, still have healthy areas with good compliance, as well as damaged areas with low compliance. When they are mechanically ventilated with an equal pressure, the healthy areas are over inflated and will be injured.

Comparing the weights of the lungs in acute respiratory failure, Nash et al.[15] found that 46% of the mechanically ventilated lungs weighed over 1800 g, but this was only 7% when the lungs were not mechanically ventilated. They also found in the mechanically ventilated lungs the typical light microscopic features defined as ARDS nowadays. The gross and light microscopic findings of the lungs in this experiment, though they are not presented in this paper, were very similar to ARDS, consisting of a destruction of the alveolar lining, hyaline membrane formation, interstitial edema, bleeding and inflammatory cell infiltration into the alveoli. HPMV is frequently used in clinical respiratory care, and might be blamed for contributing to the aggravation of ARDS.

Positive end-expiratory pressure (PEEP) is often used to improve pulmonary oxygenation in the management of ARDS. However, PEEP, combined with a conventional MV, might not contribute to the improvement of the overall survival rate of ARDS, but just prolong the life for several days[16], if due attention is not paid to the proper PIP. The higher the PEEP or mean airway pressure, usually the higher the arterial blood oxygen tension becomes. However, the higher PEEP necessitates a higher PIP and overly expands lung parenchyma, resulting in a faster and a more severe lung damage. We should not treat the patient by only looking at the numbers in laboratory data, such as Pa_{O_2}, but we should treat the impaired lung itself. Even in animal experiments, the effectiveness of respiratory care should be assessed considering the histological recovery of the impaired lungs and/or the net results of survival.

There is no definitive therapeutic method yet to cure the impaired lungs, especially in

ARDS. Therefore, it will become important, at least, not to disturb the natural healing of the damaged lung, and not to insult the healthy areas that still exist in the damaged lung. On this point, we are interested in the report of Kolobow et al.[17]. The patients with ARDS which met the NIH-ECMO criteria and had a TSLC of over 30 ml/cmH_2O were treated only by continuous positive airway pressure (CPAP). They saved 90% of the patients, who would normally have died under the management of conventional MV[18]. Apneic oxygenation, MV with a small tidal volume, or high frequency ventilation, all with a PEEP, might be also helpful for the natural healing of the impaired lugns, if we avoid overinflation and keep the PIP within 30 cmH_2O[19–21]. These types of ventilatory support will often face the problem of insufficient pulmonary gas exchange. However, this problem can be solved by applying a veno-venous (V-V) bypass with an artificial membrane lung, so called extracorporeal CO_2 removal ($ECCO_2R$)[22].

High pressure MV with a PIP of over 40 cmH_2O has insulting effects on the healthy lung. It might disturb the natural healing of the damaged lung areas, and further insult the healthy areas still remaining even in the lungs of ARDS. This could be the early stage of barotrauma. Pneumothorax, pneumomediastinum, and interstitial emphysema could be the latest stage of barotrauma. CPAP might help, or at least not disturb, the natural healing of the impaired lung. When pulmonary gas exchange is not sufficient by CPAP alone, $ECCO_2R$ will be available as a supplementary means. We must consider not only the problems of gas exchange in the lung, but also the best possible way to promote the natural healing process in the lung as well.

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References

1. Nash G, Bowen JA, Langlinais PC: "Respirator Lung" A Misnomer. Arch Path 21:234–240, 1971
2. Greenfield LJ, Ebert PA, Benson DW: Effect of positive pressure ventilation on surface tension properties of lung extracts. Anesthesiology 25:312–316, 1964
3. Parker JC, Townsley MI, Rippe B, Taylor AE, Thigpen J: Increased microvascular permeability in dog lungs due to high peak airway pressures. J Appl Physiol 57:1809–1816, 1984
4. Webb HH, Tierney DF: Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. Am Rev Respir Dis 110:556–565, 1974
5. Mascheroni D, Kolobow T, Fumagalli R, Moretti M, Chen V, Buckhold D: Acute respiratory failure following induced hyperventilation. Am Rev Respir Dis 131:A333, 1985
6. Wyszogrodski I, Kyei-Aboagye KH, Taeusch W Jr, Avery ME: Surfactant inactivation by hyperventilation: conservation by end-expiratory pressure. J Appl Physiol 38:461–466, 1975
7. McClenahan JB, Urtrowski A: Effect of ventilation on surfactant, and its turnover rate. J Appl Physiol 23:215–220, 1967
8. Staubli M, Stauble UP, Waber U, Straub PW: Hyperventilation-induced changes of the blood picture. J Appl Physiol 58:1170-1175, 1985
9. Staubli M, Ott P, Waber U, Stauble UP, Jeanneret C, Peheim E, Straub PW: Erythrocyte adenosine triphosphate depletion during voluntary hyperventilation. J Appl Physiol 59:1196–1200, 1985
10. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE: Acute respiratory distress in adults. Lancet 2:319–323, 1967
11. Rinaldo JE, Rogers RM: Adult respiratory distress syndrome. Changing concepts of lung injury and repair. N Engl J Med 306:900–909, 1982
12. Pratt PC, Vollmer RT, Schelburne JD, Crapo JD: Pulmonary morphology in a multihospital collaborative extracorporeal membrane oxygenation project. Light microscopy. Am J Pathol 95:191–214, 1979
13. Albelda SM, Gefter WB, Kelley MA, Epstein DM, Miller WT: Ventilator-induced subpleural air cysts: Clinical, radiographic, and pathologic significance. Am Rev Respir Dis 127:360–365, 1983
14. Churg A, Golden J, Fligiel S, Hogg JC: Bronchopulmonary dysplasia in the adult. Am Rev Respir Dis 127:117–120, 1983

15. Nash G, Blennerhassett JB, Pontoppidan H: Pulmonary lesions associated with oxygen therapy and artificial ventilation. N Engl J Med 276:368–374, 1967
16. Springer RR, Stevens PM: The influence of PEEP on survival of patients in respiratory failure: A retrospective analysis. Am J Med 66:196–200, 1979
17. Kolobow T, Gattinoni L, Fumagalli R, Arosio P, Pesenti A, Solca M, Chen V: Carbon dioxide and the membrane artificial lung: Their roles in the prevention and treatment of respiratory failure. Trans Am Soc Artif Intern Organs 28:20–23, 1982
18. National Heart Lung and Blood Institute, Division of Lung Diseases. Extracorporeal support for respiratory insufficiency. Bethesda, Md: National Institutes of Health 1979
19. Hamilton PP, Onayemi A, Smyth JA, Gillan JE, Cutz E, Froese AB, Bryan AC: Comparison of conventional and high-frequency ventilation: Oxygenation and lung pathology. J Appl Physiol 55:131–138, 1983
20. Pesenti A, Kolobow T, Buckhold DK, Pierce JE, Huang H, Chen V: Prevention of hyaline membrane disease in premature lambs by apneic oxygenation and extracorporeal carbon dioxide removal. Intensive Care Med 8:11–17, 1982
21. Tsuno K, Prato P, Kolobow T: Acute respiratory insufficiency induced by high pressure mechanical ventilation at a peak inspiratory pressure of 30 cmH_2O. Am Rev Respir Dis 131:A154, 1985
22. Gattinoni L, Pesenti A, Pelizzola A, Gaspani ML, Iapichino G, Agostoni A, Damia G, Kolobow T: Reversal of terminal acute respiratory failure by low frequency positive pressure ventilation with extracorporeal removal of CO_2 (LFPPV-ECCO$_2$R). Trans Am Soc Artif Intern Organs 27:289–293, 1981