

Ventilatory Strategies for Acute Respiratory Distress Syndrome

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Abstract

Acute respiratory distress syndrome (ARDS) is a severe condition that has a high mortality. Mechanical ventilation is required and concepts have evolved over the last few decades as to the methods and principles guiding such ventilatory support. In particular, volutrauma as a feature of ventilator-associated lung injury has been well documented, leading to pressure-limited strategies with consequent permissive hypercapnia. Such an approach is in direct contrast to traditional ventilatory teaching of high tidal volumes and normal PaCO₂. Current strategies therefore emphasise lower tidal volumes, adequate positive end-expiratory pressure (PEEP), minimum FiO₂, and the use of pressure-control modes (plus or minus inverse-ratio ventilation). Hypercapnia is allowed to develop, and adjunctive methods are employed to improve oxygenation in order to minimise the 'pressure-cost' of maintaining adequate oxygenation. With such an approach, overall mortality is reported to be around 40%.

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Introduction

Acute respiratory distress syndrome (ARDS) was first described by Ashbaugh et al in 1967.¹ The original authors detailed the presence of tachypnoea, hypoxaemia, decreased respiratory compliance, bilateral pulmonary infiltrates and reported a survival rate of 42%. Current outcome data have also shown a survival at around the 40% range.² The definition of ARDS has varied from study to study. This lack of diagnostic precision has hampered direct comparisons between different treatment protocols from different centres and epochs. This was addressed at the American-European Consensus Conference in 1994³ which recommended the following for the diagnosis of ARDS: acute onset, PaO₂/FiO₂ <200, bilateral pulmonary alveolar infiltrates, and no evidence of capillary hypertension.

In this review we shall describe the evolution of concepts in the ventilation of patients with ARDS, review the latest clinical evidence from randomised controlled studies and propose a practical approach based upon our personal experience and the current available evidence. We will only focus on the various aspects of mechanical ventilation in ARDS. Ancillary support modalities are beyond the scope of this review.

The Evolution of "Lung Rest" Strategy

Patients placed on artificial ventilation were traditionally supported with positive end-expiratory pressure (PEEP) and tidal volumes of 10 to 15 ml/kg. This attempt to achieve normal arterial blood gases was almost invariably associated with high peak airway pressures in patients with ARDS due to decreased compliance of the respiratory system. This resulted in alveolar over distension and consequent barotrauma. The incidence of air-leak in a recent report in which patients with ARDS were receiving mechanical ventilation with conventional pressures and volumes was 10.6% in 725 patients.⁴ Besides the overt air-leak, many animal studies have established the presence of capillary leak (lung injury) with alveolar over distension even in normal lungs.⁵⁻⁷ Thus, acute lung injury can develop from the very ventilatory support that was meant to keep the patient alive. Furthermore, computer tomographic (CT) examination of the lungs of patients with ARDS showed that, unlike the homogeneous alveolar pattern seen on the chest radiograph, the lungs were affected in a heterogeneous distribution.⁸ Thus, there were widely dispersed collapsed, partially collapsed, and normal lung units in different regions of the lungs. During positive pressure breathing, ventila-

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tion is preferentially distributed to normal lung units with relatively low time constants (resistance multiplied by compliance). As the disease progresses, the proportion of normal lung units will decrease and the respiratory system will then function like a “baby lung”. Applying high distending volumes (and thus high inflation pressures) to such “baby” lungs would therefore increase the risk for developing barotrauma or volutrauma, in addition to cardiorespiratory depression. The recognition that ventilator-support itself may lead to further lung injury has led to the concept of lung rest as well as pressure-limited strategies with permissive hypercapnia.

One method of preventing ventilator-associated lung injury was to stop ventilating the lungs entirely or only do it infrequently. In order to “rest the lungs” in this fashion, extracorporeal methods were employed to maintain oxygenation or ventilation. This took the form of extracorporeal membrane oxygenation (ECMO), or extracorporeal carbon dioxide removal (ECCO₂R).⁹ This is similar to the cardiopulmonary bypass machine employed in open-heart surgery, and can support oxygenation and the circulation completely if the set-up is venous-arterial ECMO. However, in the North American NIH trial of ECMO, there was no improvement in survival¹⁰ and similarly there was no significant outcome difference with ECCO₂R when contemporaneous controls were employed in the study from Salt Lake City.¹¹ Lower mortality rates have only been reported from centres utilising ECMO that did not incorporate a control group and recruited a large proportion of young patients with ARDS following trauma. Extracorporeal methods are therefore currently only used in selected cases. Another strategy has been to utilise intravascular oxygenation. This utilises a bundle of microporous polypropylene hollow fibres with gas on the inside and blood outside the hollow fibre pathway, and the whole device is placed in a major vessel (usually inferior vena cava through the femoral vein via a surgical cut down). Initial Phase I trials have shown it to be safe with some bleeding and decrease in platelet count, while effecting O₂ and CO₂ transfer.¹² Further trials are underway to determine its utility for the treatment of ARDS.

Pressure-limited strategies led to reductions in tidal volumes (6 to 8 ml/kg) with consequent hypercapnia. A retrospective analysis by Hickling et al¹³ showed that by employing permissive hypercapnia ARDS mortality was reduced to 16%. Despite the lack of a prospective randomised protocol, the data from Hickling et al had been widely quoted and used as a premise for the current strategy. Pressure-control modes were thus re-introduced to limit airway pressures (over distension), along with inverse-ratio ventilation. This was shown to improve oxygenation while reducing peak airway pressures.¹⁴ However, it was soon recognised that the im-

provement in oxygenation was secondary to increased mean airway pressures from the development of intrinsic PEEP.¹⁵ A further theoretical advantage of pressure-controlled over volume control ventilation is that, with its decelerating flow (with a blunted instead of square wave inspiratory pressure profile), the pressure control mode may improve the distribution of gas-flow between inhomogeneous lung units with different time constants, the gradual fall in late inspiratory pressure may enhance distribution of inspired air to lung units with longer time constants thus allowing better overall alveolar recruitment. Inverse-ratio ventilation [reversal of the normal inspiratory:expiratory duty cycle (the I:E ratio)] allows a higher mean airway pressure to be achieved for a lower peak airway pressure. Intrinsic PEEP may develop with the reduction in expiratory time, and it is thus important to monitor cardiac output for any impairment with the use of a pulmonary artery catheter.

The dogma of “lung protection” became widely accepted in the 1990s and led to recommendations to limit plateau pressures to 35 cm H₂O with lower tidal volumes. Contraindications to hypercapnia include raised intra-cranial pressure, or significant haemodynamic instability. In order to aid CO₂ clearance, tracheal gas insufflation has been employed.¹⁶ This provides intermittent or constant gas flow via a cannula into the lower trachea in order to flush the CO₂-containing gas out of the large airways, thereby reducing anatomic deadspace and reducing PaCO₂. During permissive hypercapnia, TGI becomes even more effective as the CO₂ content of the tracheal gas is higher. Difficulties with this technique include cannula placement, humidification, tidal volume compensation, and possible irritation or abrasion of the lower trachea. Other means were also employed to improve oxygenation and thus limit alveolar overdistension: prone position,¹⁷ inhaled nitric oxide,¹⁸ and nebulised prostacyclin.¹⁹ Patients in the intensive care unit are usually nursed in the supine position. Computer tomographic examination showed that in the supine position, most of the collapsed and consolidated lung units in ARDS are localised to the dependent dorsal paravertebral and basal regions. Switching from a supine to prone position results, in many cases, in improved ventilation to and recruitment of these diseased regions. The distribution of pulmonary blood flow is, however, less affected by such changes in position. Thus, prone positioning reduces intra-pulmonary shunting and improves ventilation-perfusion matching in ARDS. A study by Chatte et al²⁰ showed that 78% of their severely acute respiratory failure patients had improvement in oxygenation (PaO₂/FiO₂ improved by 20 torr or greater), and this improvement persisted in 57% even after return to the supine position. The improvement in gas-exchange function was achieved promptly on assuming the prone position and was associated with minimal

side-effects. This appears to be a relatively cost-effective manoeuvre and should be incorporated in ventilatory protocols for ARDS.

Current Evidence

In line with the current move for evidence-based medicine, prospective controlled studies were designed to test the apparent promise of such a pressure-limited approach to ARDS ventilation. Amato et al²¹ demonstrated in a small group of patients ($n = 28$), that utilising a pressure-limited ventilation strategy led to better evolution of lung function (compliance and $\text{PaO}_2/\text{FiO}_2$ ratio), but no improvement in outcome. They extended the study to 53 patients and there was a significant reduction in 28-day mortality (38% versus 71%).²² This study has been criticised for relatively small number of patients and a much higher than expected mortality for the control group. Two other subsequent multi-centre trials have also been reported. One study from Europe²³ studied 108 patients with ARDS and no other organ system failure, comparing 2 ventilatory strategies: standard (tidal volumes ≥ 10 mL/kg, PaCO_2 38 to 42 torr, and $P_{\text{peak}} < 60$ cmH₂O), versus limited pressure ($P_{\text{plat}} = 25$ cmH₂O). They showed no significant difference in 60-day mortality (41% versus 48%), incidence of pneumothorax (13% versus 15%), or the development of secondary organ failure. Another study from North America involving 120 patients²⁴ also demonstrated no difference in outcome using $P_{\text{peak}} \leq 30$ cmH₂O, tidal volume ≤ 8 mL/kg, and PEEP 5 to 20 cmH₂O. The two later studies concur with each other and differ from that of Amato et al.²¹ These suggest that the sole application of a pressure-limited strategy may not have a major impact on outcome in ARDS, although most intensivists follow this practice.

These trials have therefore failed to show any significant impact of the “lung protection” strategy on outcome, although difficulties were encountered attempting to apply these ventilatory strategies to diverse groups of patients and to the different centres involved in the trial. Other considerations include the potential of hypoventilation in such patients, utilising a P_{plat} limit alone, when transalveolar pressure should be the true limit.²⁵ Hence, in situations where chest wall and abdominal compliance are decreased, P_{plat} may be increased but transalveolar pressure will be low. Furthermore, these studies may have recruited too few patients to show a mortality difference. One of the benefits of reduced alveolar distension, may be a reduced likelihood of depressed cardiac output, and hence, maintenance of oxygen delivery.

New Modes

Despite the lack of positive outcome results, such pressure-limited strategies have spawned newer modes

of ventilation, including airway pressure release ventilation,²⁶ high-frequency oscillatory ventilation,²⁷ and liquid ventilation.²⁸ Airway pressure release ventilation is based on an intermittent decrease in airway pressure and lung volume. It was designed to augment alveolar ventilation as an adjunct to spontaneous breathing with CPAP. The tidal volume depends on lung compliance, airway resistance, the magnitude of airway pressure release, and the duration of pressure release. The potential advantage of this mode is therefore low peak airway pressure, low intrathoracic pressure, and improved matching of ventilation and perfusion. High-frequency oscillators operate with a to-and-fro application of pressure on the airway opening. Fresh gas is supplied as “bias flow”. Tidal breaths are small and gas exchange occurs other than with conventional bulk flow transportation. Liquid ventilation utilises fluorocarbon liquids to support gas exchange. This substance is inert with low surface tensions that are excellent solvents for O_2 and CO_2 . By eliminating active surface active forces, liquid ventilation may minimise risk of further barotrauma. These newer methods have yet to be applied universally, and studies are ongoing to resolve the utility of such new modalities. Bovine surfactant replacement has also been attempted and been shown to improve oxygenation when instilled but with no difference in outcome.²⁹

Positive End-expiratory Pressure (PEEP)

PEEP improves oxygenation by recruiting collapsed lung units and reducing shunt.³⁰ If alveoli are allowed to collapse at end-expiration as may happen in units with surfactant dysfunction, there is an increase in shear stress to re-open the lung units with positive-pressure ventilation that eventually leads to lung injury. Hence, a certain level of minimum PEEP is recommended which is taken to be above the “knee” (P flex inflection) point on the pressure-volume curve for the lungs (Fig. 1). Too high a level of PEEP is also detrimental, leading to overdistension (lung injury) and increased dead-space ventilation besides haemodynamic consequence.³¹ Thus, “minimally effective” PEEP is usually defined as the level below which the pressure-volume curve starts to plateau off (P flex in Figure 1), while “best” PEEP is the level when the beneficial and potential harmful effects of PEEP is balanced. There is no consensus however on which is the “best” PEEP to administer in patients with ARDS. Amato et al²² kept the PEEP 2 cmH₂O above P flex and reported a reduced mortality in their study group. There is no collaborative evidence from other studies however that one method of defining “best PEEP” is superior to any other.^{23,24} Super-PEEP has also been alluded to that would decrease intrapulmonary shunt below 15% of cardiac output. This may be as high as 57 cmH₂O.³² Another factor to consider is intrinsic PEEP,

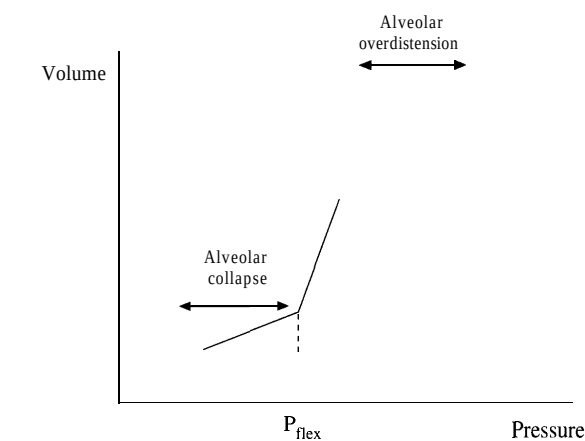


Fig. 1. Pressure-volume graph to demonstrate the lower inflection point (P_{flex}), above which optimal PEEP should be set.

which frequently develops with inverse-ratio ventilation.³³ This is the result of inadequate emptying, especially in the setting of inverse-ratio ventilation. A mixture of applied PEEP and intrinsic PEEP may allow individualisation of total PEEP to compensate for the different time constants in the diseased lung, and maintain a better distribution of ventilation. Otherwise, in ARDS lungs any increase in ventilated lung volume by applied PEEP not only reduces intrapulmonary shunt but equally also hyperventilates non-compressed lung areas. On a practical level, PEEP is usually maintained between a level of 5 to 15 cmH₂O. With inverse ratio ventilation, this usually leads to a mean airway pressure of 20 to 25 cmH₂O.

Oxygen Concentration .

High concentrations of oxygen should be avoided if possible, to limit oxygen toxicity,^{34,35} while maintaining a PaO₂ ≥60 mmHg (pulse oximetry ≥92%). Inhaled NO by improving oxygenation may aid in this process, besides a potential anti-inflammatory action. Shunt fraction is reduced as blood flow is redistributed in the lungs to the better ventilated units with inhaled NO.¹⁸ Patients with pulmonary hypertension will have improvement in cardiac outputs in certain cases that will also lead to improved oxygenation.³⁶

A Practical Approach (Table I)

Start with a tidal volume of 6 to 8 mL/kg and a rate between 16 and 20 breaths/minute. Use the assist control mode with a PEEP of 10 cmH₂O. A ramp waveform is preferable, with a normal I to E ratio, and a FiO₂ of up to 100% if necessary. Ensure the patient is deeply sedated and preferably paralysed. The use of neuromuscular blockade is to facilitate patient-machine synchrony and reduce respiratory muscle work. This becomes more important if inverse-ratio ventilation is contemplated. Assess the arterial blood gas in 30 minutes and follow the pulse oximetry (keep >90%). Monitor the peak air-

TABLE I: PRESSURE-LIMITED STRATEGY

Tidal volume	6 to 8 mL/kg
Peak airway pressure	35 cm H ₂ O
PaCO ₂	Allow to rise up to 100 torr if pH > 7.2
FiO ₂	FiO ₂ <0.6 (if possible)
Positive end-expiratory pressure (PEEP)	5 to 15 cm H ₂ O
Mean airway pressure (MAP)	18 to 25 cm H ₂ O
I:E ratio	1:2 to 2: 1 (method of increasing MAP)
Mode	Pressure-control or volume control with decelerating flow

way pressure and the mean airway pressure. Close monitoring of the haemodynamics is required (an arterial line is mandatory for blood pressure monitoring and frequent blood draws). Increase the PEEP to 15 cmH₂O if the oxygen saturation by pulse oximetry is still <90%. If the peak airway pressure is high (>35 cmH₂O) change to pressure control mode and consider increasing inspiratory time. Set PEEP at 10 cmH₂O and preset pressure at 25 cmH₂O with a respiratory rate of 20 and an I to E ratio of 1:1. Neuromuscular blockade is absolutely important when this is performed. Mean airway pressure should be increased to between 20 and 25 cmH₂O. If oxygen saturation remains poor, consider prone positioning at this point. Hypercapnia may result and can usually be tolerated up to a pH of 7.2. A high index of suspicion for pneumothorax should be maintained, especially if there are sudden increases in peak airway pressure on volume modes or a fall in tidal volume on pressure modes, plus hypotension.

When the patient improves, titrate the FiO₂ to keep oxygen saturation >90%. Assist control mode can be utilised again with a normal I to E ratio. From then onwards, the normal weaning protocols can be resumed.

Conclusion

In summary, ventilation of a patient with ARDS requires close attention to airway pressures (peak and mean can be higher if chest wall or abdominal compliance is decreased), utilising adequate PEEP and the minimum amount of oxygen for adequate oxygen saturation (90%). Besides ventilatory strategies, adjunct measures (prone position, inhaled NO) to improve oxygenation without increasing alveolar distension should be attempted. Immunomodulatory methods (e.g. steroids) in “late” ARDS³⁷ may also aid recovery of the lungs. Careful attention to haemodynamics, and all other aspects of critical care may lead to better outcome.

REFERENCES

1. Ashbaugh D G, Bigelow D B, Petty T L, Levine B E. Acute respiratory distress in adults. *Lancet* 1967; ii:319-23.

2. Villar J, Slutsky A. Is the outcome from acute respiratory distress syndrome improving? *Curr Opin Crit Care* 1996; 2:79-87.
3. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al and the Consensus Committee. The American-European Consensus Conference on ARDS. *Am Rev Respir Dis* 1994; 149:818-24.
4. Weg J G, Anzueto A, Balk R A, Wiedemann H I, Pattishall E N, Schork A, et al. The relation of pneumothorax and other air leaks to mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338:341-6.
5. Webb H H, Tierney D F. Experimental pulmonary edema due to intermittent positive-pressure ventilation with high inflation pressure. Protection by positive end expiratory pressure. *Am Rev Respir Dis* 1974; 110:556-65.
6. Parker J C, Hernandez L A, Longnecker G L, Peevy K, Johnson W. Lung edema caused by high peak inspiratory pressures in dogs. Role of increased microvascular filtration pressure and permeability. *Am Rev Respir Dis* 1990; 142:321-8.
7. Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *Am Rev Respir Dis* 1988; 137:1159-64.
8. Pelosi P, Crotti S, Brazzi L, Gattinoni L. Computed tomography in adult respiratory distress syndrome: what has it taught us? *Eur Respir J* 1996; 9:1055-62.
9. Gattinoni L, Pesenti A, Masheroni D, Marcolin R, Fumagalli R, Rossi F, et al. Low-frequency positive-pressure ventilation with extracorporeal CO₂ removal in severe acute respiratory failure. *JAMA* 1986; 256:881-6.
10. Zapol W M, Snider M T, Hill J D, Fallat R J, Bartlett R H, Edmunds L H, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. *JAMA* 1979; 242:2193-6.
11. Morris A H, Wallace C J, Menlove R L, Clemmer T P, Orme J F, Weaver L K, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO₂ removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1994; 149:295-305.
12. High K M, Snider M T, Richard R, Russell G B, Stene J K, Campbell D B, et al. Clinical trials of intravenous oxygenation in patients with adult respiratory distress syndrome. *Anesthesiology* 1992; 77:856-63.
13. Hickling K G, Henderson S J, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Medicine* 1990; 16:372-7.
14. Gurevitch M J, Van Dyke J, Young E S, Jackson K. Improved oxygenation and lower peak airway pressure in severe adult respiratory distress syndrome. Treatment with inverse ratio ventilation. *Chest* 1986; 89:211-3.
15. Kacmarek R, Hess D. Pressure-controlled inverse-ratio ventilation: Pna-acea or auto-PEEP? *Respiratory Care* 1990; 35:945-8.
16. Ravenscraft S A, Burke W C, Nahum A, Adams A B, Nakos G, Marcy T W, et al. Tracheal gas insufflation augments CO₂ clearance during mechanical ventilation. *Am Rev Respir Dis* 1993; 48:345-51.
17. Langer M, Mascheroni D, Marcolin R, Gattinoni I. The prone position in ARDS patients: a clinical study. *Chest* 1988; 94:103-7.
18. Rossaint R, Falke K J, Lopez F, Slama K, Pison U, Zapol W M. Inhaled nitric oxide in adult respiratory distress syndrome. *N Engl J Med* 1993; 328:399-405.
19. Zwissler B, Kemming G, Habler O, Kleen M, Merkel M, Haller M, et al. Inhaled prostacyclin (PGI₂) versus inhaled nitric oxide in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1996; 154:1671-7.
20. Chatte G, Sab J M, Dubois J M, Sirodot M, Gaussorgues P, Robert D. Prone position in mechanically ventilated patients with severe acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1997; 155:473-8.
21. Amato M B P, Barbas C S V, Medeiros D M, Schettino G D I, Filho G L, De Carvalho C R R. Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1995; 152:1835-46.
22. Amato M B I, Barbas C S V, Medeiros D M, Lorenzi F G, Kairalla R A, Deheinzelin D, et al. Effect of protective ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; 338:347-54.
23. Brochard L, Roudot-Thoraval F and the collaborative group on VT reduction. Tidal volume (V_t) reduction in acute respiratory distress syndrome (ARDS): A multicenter randomized study. *Am J Respir Crit Care Med* 1997; 155:A505.
24. Stewart T E, Meade M O, Granton J, Lapinsky S, Hodder R, McLean R, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. *N Engl J Med* 1998; 338:355-61.
25. Manning H L. Peak airway pressure: Why the fuss? *Chest* 1994; 105:242-7.
26. Rasanen J, Cane R D, Downs J B, Hurst J M, Jousela I T, Kirby R R, et al. Airway pressure release ventilation during acute lung injury: A prospective multicenter trial. *Crit Care Med* 1991; 19:1234-41.
27. Froese A B. A reappraisal of high-frequency ventilation in the critical care setting. *Curr Opin Crit Care* 1996; 2:54-9.
28. Lachmann B, Verbrugge S. Liquid ventilation. *Curr Opin Crit Care* 1996; 2:60-6.
29. Gregory T J, Steinberg K I, Spragg R, Gadek J E, Hyers T M, Longmore W J, et al. Bovine surfactant therapy for patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1997; 155:1309-15.
30. Suter P M, Fairly H B, Isenberg M D. Optimum end-expiratory airway pressure in patients with acute pulmonary failure. *N Engl J Med* 1975; 292:284-9.
31. Jardin F, Farcot J, Boissante L, Curien N, Margairaz A, Bourdarias J I. Influence of positive end-expiratory pressure on left ventricular performance. *N Engl J Med* 1981; 304:387-92.
32. Downs J B, Klein E F, Modell J H. The effect of incremental PEEP on PaO₂ in patients with respiratory failure. *Anesth Analg* 1973; 52:210-5.
33. Pepe P E, Marini J J. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction: the auto-PEEP effect. *Am Rev Respir Dis* 1982; 126:166-70.
34. Moran J F, Robinson L A, Lowe J E, et al. Effects of oxygen toxicity on regional ventilation and perfusion on the primate lung. *Surgery* 1981; 89:575-81.
35. Wolf W G, Ebert P A, Sabiston D C. Effects of high oxygen tension on mucociliary function. *Surgery* 1972; 72:246-52.
36. Fierobe L, Brunet F, Dhainaut J F, Monchi M, Belghith M, Mira J P, et al. Effect of inhaled nitric oxide on right ventricular function in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 1995; 151:1414-9.
37. Meduri G U. Late adult respiratory distress syndrome. *New Horizons* 1993; 1:563-77.