

The Use of Airway Pressure Release Ventilation and Open Lung Management for Improving the Outcome of Lung Procurement for Transplantation

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Abstract

One of the most difficult organs to procure for donation is the lung. A detailed understanding of the physiology of mechanical ventilation and its effect on donor lungs is needed to impact on the outcome of lung transplantation. An organized protocol for mechanical ventilation management of the organ donor using the Open Lung Model may positively affect the number of organs that can be procured, and the function of these organs post transplant.

Based on physiologic principles, the use of new modes of ventilation may affect the modulation of cytokines, decrease the transmigration of organisms into the donor lung, and preserve surfactant function in that lung. Therefore, we have developed a protocol guided by physiologic-based parameters and airway pressure release ventilation (APRV), with ongoing feedback from

an advanced respiratory care team to manage donor patients closely.

Setting: 650 bed university hospital and transplant center.

Conclusion: We have developed a physiologic-based protocol, using APRV to achieve lung procurement that can decrease peak pressures and recruit the lungs using less and simultaneously increasing the PaO₂ while using lower FIO₂. This protocol may preserve surfactant function and assist during postoperative management. Additionally, this management mode may protect the donor organs from physiologic decay and even improve the outcomes. Further studies to measure long-term outcome need to be developed to validate physiologically based mechanical ventilation.

Key words: Lung transplantation, Airway Pressure Release Ventilation, open lung concept, cytokine modulation, surfactant.

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Introduction

The incidence of end stage lung disease has grown throughout the world in the last 20 years. (1) A large number of patients awaiting transplantation will not survive due to a large shortage of donor lungs resulting from the decay of many respiratory and physiological parameters while awaiting harvest. Another group of donor lungs does not meet the harvest parameters at the time of brain death or will not undergo the physiologically-based mechanical ventilation protocol required during the highly critical period between declaration of brain death and harvest, thus reducing the chances of a positive outcome. Aggressive management

of these lung donors has been shown to increase the pool of donor lungs available for transplantation (2) by using techniques that only improve blood gases.

The open lung concept (3) of lung recruitment and stabilization using physiological tidal volumes has found a major place in the management of patients in the operating theater and the intensive care unit (ICU). The use of ventilatory management protocols in the critically ill patients in ICU not only impacts the lung's ventilation capacity, but also the systemic inflammatory response. These strategies have evolved from optimizing conventional physiological variables, such as oxygen and carbon dioxide levels, to protecting the lung from injury and decreasing the cytokine modulation in the lung tissue. (4)

Many of these recent studies linked both septicemia and multi-organ failure to mechanical ventilation. It has been shown by our group and others that bacterial translocation can occur in the lung during mechanical ventilation, and it is largely dependent on ventilator setting, has the end product of causing septicemia. (5-7) This large body of literature on ventilation melds well with the literature on lung preservation and the importance of endothelial and alveolar Type II cell integrity and the outcome in transplantation.

We, therefore, discuss some of the physiological changes of mechanical ventilation and how they can benefit donor lung preservation and decrease lung graft dysfunction. We will relate our own simple protocol on the use of airway pressure release ventilation (APRV) and how it can easily be used in this patient population as a starting point for the introduction of physiological principles for these patients.

Physiological Parameters Affected by Mechanical Ventilation

Surfactant Changes

Surfactant alterations have been implicated to contributing significantly to the pathophysiology of transplantation-associated lung injuries. The process of lung transplantation has been shown to reduce surfactant properties after preservation or reperfusion of the graft. (8,9) Studies in pretreatment with surfactant in experimental models has been shown to preserve alveolar morphology and hemodynamics. (10) The depletion of surfactant is similar to findings that

are observed in acute respiratory distress syndrome. (11,12) Therefore, an understanding of how mechanical ventilation and recruitment procedures affect the pulmonary surfactant system may prove crucial for optimal lung preservation.

Two primary mechanisms of surfactant inactivation by mechanical ventilation have been described. The first is whereby mechanical ventilation has been shown to enhance surfactant release from the Type II pneumocyte into the alveolus. (13,14) This material is subsequently lost into the small airways as a result of compression of the surfactant film when the surface of the alveolus becomes smaller than the surface occupied by surfactant molecules. (15,16)

The second mechanism to describe the surfactant changes associated with mechanical ventilation is based on the observation that the alveolar surface area changes result in the conversion of surface active large surfactant aggregates into non-surface active small surfactant aggregates. (17,18)

It has been shown surfactant changes due to mechanical ventilation are reversible as a result of a metabolically active process involving de novo production of surfactant. (12) This balance between secretion and production of large aggregates and uptake clearance and reconversion of small aggregates in the Type II pneumocyte.

The use of modes of ventilation that preserve surfactant levels will naturally pretreat the donor organ to deal with preservation and transplant phases. This will maintain alveolar morphology. Airway Pressure Release Ventilation (APRV), which was first introduced by Downs and a co-workers, (19) has a clear benefit. By maintaining the alveoli open, it prevents surfactant depletion caused by the cyclic opening and closing of alveolar beds. (20) Spontaneous breathing with APRV in experimentally induced lung injury was associated with less atelectasis formation as measured in CT scans. (21) This may affect surfactant turnover and provide a more robust surfactant rich lung for transplant.

Ventilation-induced Mediator Release

The modulation of the immune system by the transplanted organ is a major aspect in the care of the patient post operatively. Unlike the transplanted heart or kidney, lung tissue is particularly sensitive to ischemia because of the

delicate alveolar capillary network. (22) The proposed sequence is as follows: when ischemic pulmonary endothelium is reperfused with whole blood, leukocytes, which normally roll along the vascular endothelium, become weakly attached due to activation of adhesion molecules. (23) This weak binding triggers stronger adhesion as a result of induction of ICAM-1 on the endothelium and ligands in the leukocytes. Firmly attached leukocytes then extravasate across the endothelial wall, migrating into tissues along a concentration gradient of cytokines such as interleukins-8 that are secreted by injured endothelial cells.

Activated leukocytes release humoral mediators such as oxygen-free radicals, various cytokines and proteases. Resulting in exposure of the thrombogenic basement membrane and ultimately manifested as an inflammatory response in the transplanted lung.

The transplant literature has various reports to use controlled reperfusion and leukocyte filtration to decrease this immune lead prior to transplantation. (22,23) It is well-known that mechanical ventilation and alveolar collapse can lead to immune modulation and cytokine release.

A study by Tremblay and co-workers in isolated lungs investigated the effect of different ventilation strategies on lung inflammatory mediator expression and production of cytokines TNF- α , IL-1 β , IL-6, IL-10, MIP-2 and γ -IFN in the presence and absence of a preexisting inflammatory stimulus. (24) High peak inspiratory lung volumes and not using PEEP that leads to alveolar collapse during mechanical ventilation having a synergistic effect on the release of pro-inflammatory mediators from the lung tissue into the airway. Thus, the application of the open lung concept and APRV to decrease inspiratory pressures will decrease the cytokine load in the donor lung, which in concert with leukocyte filtration, greatly decreases the ischemia-reperfusion injury.

Ventilation-induced Bacterial Translocation

Infection is the leading cause of death after lung transplantation; accounting for more than 25% of all post-transplant deaths. (25) Studies have suggested that bloodstream infections frequently occur in transplant

recipients with considerable morbidity and mortality. The most common source of infection was pulmonary, accounting for 70% of infections.

Mechanically ventilated patients often develop pneumonia and there are many national and organizational guidelines to decrease ventilator-associated pneumonia (VAP).

One of the most important aspects in the prevention of VAP is an understanding of how mechanical ventilation affects bacterial translocation. It is conceivable that bacteria can thus gain access to the circulation from damaged lung parenchyma than from previously normal lung tissue. (26,27) This physiology leads to loss of “compartment” where bacteria can migrate both in and out of the lung.

It has been established that preserving end-expiratory lung volume keeping the lung recruited with PEEP has a beneficial effect on the course of infection in terms of reducing bacterial counts recovered from lung tissue after prolonged mechanical ventilation of lungs inoculated with bacteria. (28) It is important to realize that avoiding high peak transpulmonary pressures and preserving an open lung with end-expiratory volume with PEEP, can reduce translocation of *Pseudomonas aeruginosa*, (27) *Klebsiella pneumoniae*, (29) and *Escherichia coli* (30) from the lung into the bloodstream and from the systemic circulation into the lung. It is interesting that some of these organisms are very common bloodstream isolates after lung transplantation. (25)

This data suggests that ventilation-induced changes in barrier function of the lung epithelium and/or endothelium to bacteria to ascertain extent may contribute to the development of bacteremia and endotoxemia seen post-transplant. The maintenance of lung volume through close ventilator management with APRV and monitoring to keep the lung open prior to transplant may keep bacterial counts low and prevent VAP prior to transplantation.

The APRV Protocol

The APRV protocol to maintain lung volume and maintain an open lung model was developed at the University of Rochester (31) after review of several lung procurement protocols that did not match the standards of physiologic-

based ventilation. The majority of these protocols used older means of ventilation, for example, tidal volumes of 10-15 ml/kg on volume-based platforms, which do not follow the current practice of ventilation in critically ill patients in the ICU.

We introduced the use of APRV, (32) which is a mode commonly used in our trauma ICU, where the majority of organ donors are admitted. The University of Rochester has been using the open lung practice, developed in collaboration with Erasmus University in Rotterdam for over 20 years, (33) so the entire staff was familiar with such physiologically based ventilation.

All patients placed on APRV were placed on FIO₂ of .40 and a P high to maintain a tidal volume of 6-8 ml/kg. If a P/F ratio was >300 with these ventilator settings, the patient was considered a candidate for lung procurement. In a pilot study, (31) all nine patients had a 37% increase in PaO₂ without changing FIO₂ (Figure 1) on the ventilator. This was due to the lung recruitment and stabilization and the control of peak pressures due to the mode of ventilation. Six of the nine patients were used for transplantation, and none were rejected for primary pulmonary reason; but for other criterion reason, two were not used due to prolonged time on ventilator (3 weeks) and the other for possible aspiration

around the time of trauma.

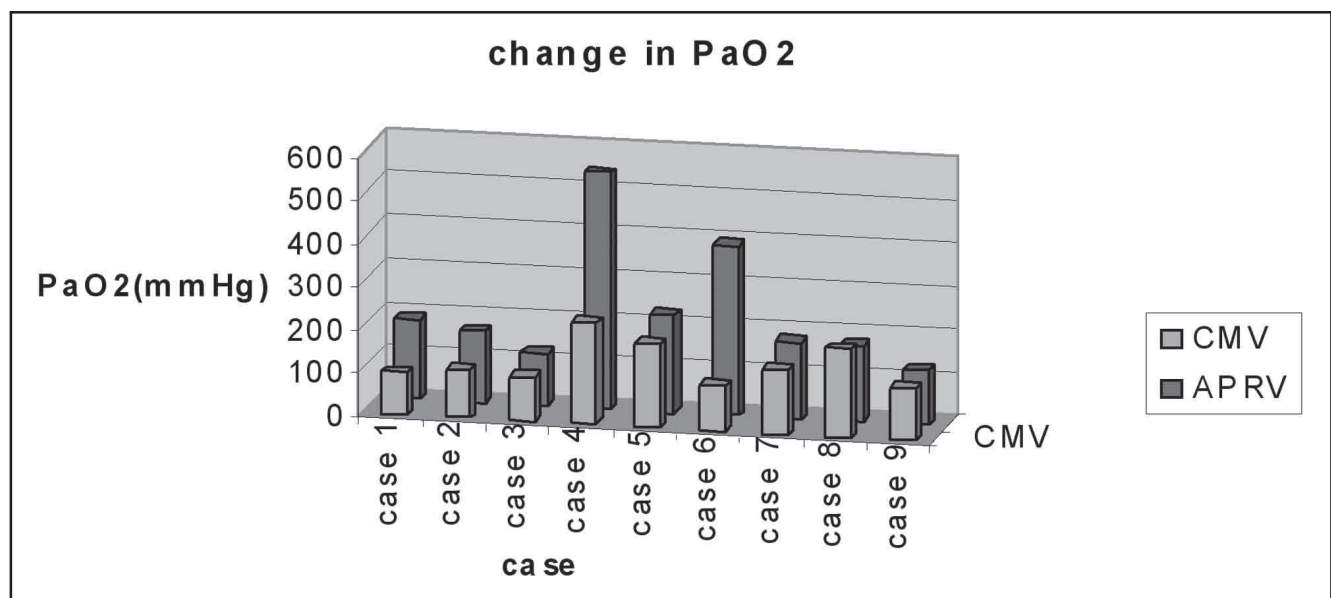
We have been shown that using APRV in the use of lung procurement can decrease peak pressure and recruit the lungs using less pressure, but also increased PaO₂ using the lower lung protective FIO₂. Projecting the data derived from multiple studies in mechanical ventilation, lung protective modes may also preserve surfactant, decrease cytokine modulation and bacterial location.

Further physiological studies to quantify the level of lung protection in donor lungs to measure surfactant levels and cytokine modulation should be done. Also, outcome studies in patients who have received these lungs should evaluate the rate of infections and complications to historic controls.

Conclusions

APRV and open lung strategy improves oxygenation and may improve post transplant outcomes. Physiologically based ventilatory strategy may play an important role in transplantation by preventing the donor organ decaying in multiple aspects of its function gas exchange and immunomodulation being the most important.

Figure 1. Improved Oxygenation with APRV and Lung Recruitment



References

1. Current estimates from the National Health Interview Survey 1993. *Vital Health Stat* 10 1994;190:1-221.
2. Straznicka M, Follette DM, Eisner MD, Roberts PF, Menza RL, Babcock WD. Aggressive management of lung donors classified as unacceptable: excellent recipient survival one year after transplantation. *J Thorac Cardiovasc Surg* 2002;124:250-8.
3. Papadakos PJ, Lachmann B. Ventilatory strategies to reduce pulmonary morbidity and mortality in intensive care. *J Organ Dysfunction* 2007;3:95-99.
4. Uhlig S, Ranieri M, Slutsky AS. Biotrauma hypothesis of ventilator-induced lung injury. *Am J Respir Crit Care Med* 2004;169:314-5.
5. Verbrugge SJ, Sorm V, van 't Veen A, Mouton JW, Gommers D, Lachmann B. Lung overinflation without positive end-expiratory pressure promotes bacteremia after experimental *Klebsiella pneumoniae* inoculation. *Intensive Care Med* 1998;24:172-7.
6. Cakar N, Akinci O, Tugrul S, Ozcan PE, Esen F, Eraksoy H, et al. Recruitment maneuver: does it promote bacterial translocation? *Crit Care Med* 2002;30:2103-6.
7. Haitsma JJ, Uhlig S, Göggel R, Verbrugge SJ, Lachmann U, Lachmann B. Ventilator-induced lung injury leads to loss of alveolar and systemic compartmentalization of tumor necrosis factor- α . *Intensive Care Med* 2000;26:1515-22.
8. Klepetko W, Lohninger A, Wisser W, Mueller MR, Khünl-Brady G, Windisch A, et al. Pulmonary surfactant in bronchoalveolar lavage after canine lung transplantation: effect of L-carnitine application. *J Thorac Cardiovasc Surg* 1990;99:1048-58.
9. Andrade RS, Solien EE, Wangenstein OD, Tsai MY, Kshetry VR, Bolman RM 3rd. Surfactant dysfunction in lung preservation. *Transplantation* 1995;60:536-41.
10. Koletsis E, Chatzimichalis A, Fotopoulos V, Kokkinis K, Papadimitriou E, Tiniakos D, et al. Donor lung pretreatment with surfactant in experimental transplantation preserves graft hemodynamics and alveolar morphology. *Exp Biol Med* 2003;228:540-5.
11. Hallman M, Spragg R, Harrell JH, Moser KM, Gluck L. Evidence of lung surfactant abnormality in respiratory failure. Study of bronchoalveolar lavage phospholipids, surface activity, phospholipase activity, and plasma myoinositol. *J Clin Invest* 1982;70:673-83.
12. Haitsma JJ, Papadakos PJ, Lachmann B. Surfactant therapy for acute lung injury/acute respiratory distress syndrome. *Curr Opin Crit Care* 2004;10:18-22.
13. Massaro GD, Massaro D. Morphologic evidence that large inflations of the lung stimulate secretion of surfactant. *Am Rev Respir Dis* 1983;127:235-6.
14. McClenahan JB, Urtnowski A. Effect of ventilation on surfactant, and its turnover rate. *J App Physiol* 1967;23:215-20.
15. Faridy EE. Effect of ventilation on movement of surfactant in airways. *Respir Physiol* 1976;27:323-34.
16. Wyszogrodski I, Kyei-Aboagye K, Tausch HW Jr, Avery ME. Surfactant inactivation by hyperventilation: conservation by end-expiratory pressure. *J Appl Physiol* 1975;38:461-6.
17. Veldhuizen RA, Marcou J, Yao LJ, McCaig L, Ito Y, Lewis JF. Alveolar surfactant aggregate conversion in ventilated normal and injured rabbits. *Am J Physiol* 1996;270:L152-8.
18. Verbrugge SJ, Böhm SH, Gommers D, Zimmerman LJ, Lachmann B. Surfactant impairment after mechanical ventilation with large alveolar surface area changes and effects of positive end-expiratory pressure. *Br J Anaesth* 1998; 80:360-4.
19. Stock MC, Downs JB, Frolicher DA. Airway pressure release ventilation. *Crit Care Med* 1987;15:462-6.
20. Burchardi H. New strategies in mechanical ventilation for acute lung injury. *Eur Respir J* 1996;9:1063-72.
21. Wrigge H, Zinslerling J, Neumann P, Defosse J, Magnusson A, Putensen C, et al. Spontaneous breathing improves lung aeration in oleic acid-induced lung injury. *Anesthesiology* 2003;99:376-84.
22. Novick RJ, Menkis AH, McKenzie FN. New trends in lung preservation: a collective review. *J Heart Lung Transplant* 1992;11:377-92.
23. Novick RJ, Gehman KE, Ali IS, Lee J. Lung preservation: the importance of endothelial and alveolar type II cell integrity. *Ann Thorac Surg* 1996;62:302-14.
24. Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS. Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. *J Clin Invest* 1997;99:944-52.
25. Palmer SM, Alexander BD, Sanders LL, Edwards LJ, Reller LB, Davis RD, et al. Significance of bloodstream infection after lung transplantation: analysis in 176 consecutive patients. *Transplantation* 2000;69:2360-6.
26. Seidenfeld JJ, Mullins RC 3rd, Fowler SR, Johanson WG Jr. Bacterial infection and acute lung injury in hamsters. *Am Rev Respir Dis* 1986;134:22-6.
27. Johanson WG Jr, Higuchi JH, Woods DE, Gomez P, Coalson JJ. Dissemination of *Pseudomonas aeruginosa* during lung infection in hamsters. Role of oxygen-induced lung injury. *Am Rev Respir Dis* 1985;132:358-61.
28. Tilson MD, Bunke MC, Smith GJ, Katz J, Cronau L, Barash PG, et al. Quantitative bacteriology and pathology of the lung in experimental *Pseudomonas pneumonia* treated with positive end-expiratory pressure (PEEP). *Surgery* 1977;82:133-40.
29. Verbrugge SJ, Sorm V, van 't Veen A, Mouton JW, Gommers D, Lachmann B. Lung overinflation without positive end-expiratory pressure promotes bacteremia after experimental *Klebsiella pneumoniae* inoculation. *Intensive Care Med* 1998;24:172-7.
30. Nahum A, Hoyt J, Schmitz L, Moody J, Shapiro R, Marini JJ. Effect of mechanical ventilation strategy on dissemination of intratracheally instilled *Escherichia coli* in dogs. *Crit Care Med* 1997;25:1733-43.
31. Koch R, Papadakos PJ. The use of airway pressure release ventilation for improving the outcome of lung procurement for transplantation. *Am Rev Respir Dis* 2008;177:A123.
32. Putensen C. Airway pressure release ventilation. In: Papadakos PJ, Lachmann B, editors. *Mechanical Clinical Applications and Pathophysiology*. Philadelphia (PA): Elsevier; 2008. p. 266-75.
33. Papadakos PJ, Lachmann B. The open lung concept of alveolar recruitment can improve outcome in respiratory failure and ARDS. *Mt Sinai J Med* 2002;69:73-7.