Chapter 1

Introduction

Casper W. Bollen,

Cuno S.P.M. Uiterwaal,

Adrianus J. van Vught

Introduction

High frequency ventilation is a relatively new technique to ventilate patients. Based on experimental evidence it was postulated that high frequency ventilation compared with conventional mechanical ventilation would result in a more favorable clinical outcome. In this thesis the clinical evidence for this supposition is examined.

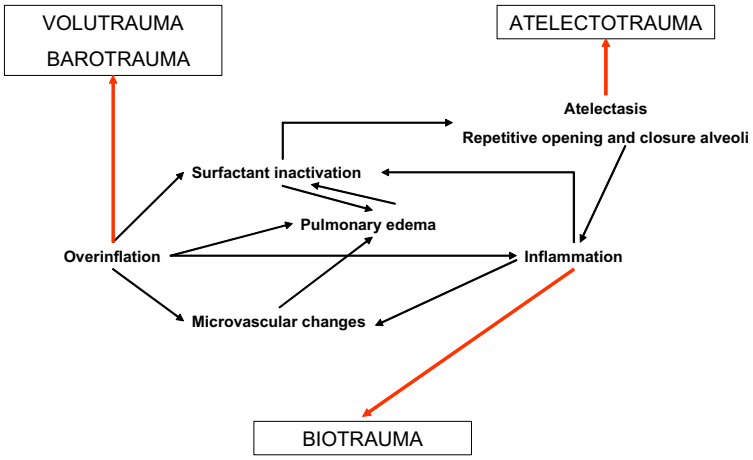
Mechanical ventilation and lung injury

One of the main treatment principles in medicine is 'primum non nocere'. Mechanical ventilation is a basic and commonly applied life supporting modality in neonatal, pediatric and adult intensive care. Mechanical ventilation is not a treatment in the sense that application of mechanical ventilation will cure pulmonary disease, but has to be regarded as a bridge to recovery. A prime requisite to initiate mechanical ventilation should be that the underlying cause of respiratory insufficiency is curable. The purposes of mechanical ventilation, supplying oxygen and removing carbon dioxide, have to be combined with prevention of side effects. The growing recognition that mechanical ventilation in itself can be an independent cause of pulmonary disease puts the principle of primere non nocere at an even more prominent level [1;2].

One of the most important deleterious side effects of mechanical ventilation has been designated as Ventilator Induced Lung Injury (VILI) [3;4]. VILI is a concept that has been extensively investigated in experimental studies [3]. It represents a complex disorder that is caused by a number of factors. The main explanatory mechanisms consist of barotrauma or more importantly volutrauma, atelectotrauma and biotrauma (Figure 1) [3;5-7].

Historically, attention was focused on clinically apparent barotrauma, represented by air leak syndromes [8]. Webb et al. were the first to demonstrate experimental evidence that high airway pressures alone could lead to increased capillary permeability, non-hydrostatic pulmonary edema and tissue damage in rats subjected to positive pressure ventilation [9]. Subsequent studies showed that ventilation with large tidal volumes had more impact on the occurrence of VILI than high airway pressure on itself [10-12]. Therefore, it has been advocated to replace the term 'barotrauma' by 'volutrauma' [6]. The basic premise is that high tidal volumes (volutrauma) cause overdistension of the lungs which is associated with increased capillary permeability, pulmonary edema and histological damage [11;13-16]. Another putative mechanism causing VILI is the concept of 'atelectotrauma' [3]. In the same study by Webb et al., that showed VILI as a result of high airway pressures, a protective effect was found of positive end expiratory pressure (PEEP) as compared with zero end expiratory pressure [9]. Atelectotrauma is thought to be caused by repetitive opening and closing of alveoli resulting in shear stress and mechanical damage, especially in diseased parts of the lungs [17-19]. Overdistension of compliant alveoli in the healthy parts of the lungs can cause additional damage (volutrauma) [20]. Finally, prolonged injurious ventilation results in microscopic abnormalities with inflammatory infiltrates that are indistinguishable from Acute Respiratory Distress Syndrome (ARDS) in humans [21;22]. Experimental studies showed a distinctive effect of ventilatory strategies on cytokine concentrations in lung lavage of isolated unperfused rat lungs [23]. The more harmful ventilatory strategies were associated with major increases in cytokine concentrations. The term biotrauma has been coined to describe potentially injurious local and systemic inflammatory response to physical stress [24;25]. Putting it all together, the sequence of events resulting in VILI can be described as depicted in Figure 1.

Figure 1



Pathogenesis of Ventilator Induced Lung Injury. During mechanical ventilation lung tissue may be damaged by several mechanisms, classified as volutrauma, barotrauma, atelectotrauma and biotrauma. There is a reinforcing interaction between the different mechanisms leading to a number of viscious circles. See text for further explanation.

Volutrauma on the one side and atelectotrauma on the other side result in surfactant inactivation, pulmonary edema and tissue damage. Pulmonary edema fluid inhibits surfactant activity [26]. Moreover, alveolar distension and repetitive opening and closing of alveoli causes inflammation, further aggravating pulmonary edema and tissue damage. Thus, a number of vicious circles ensue.

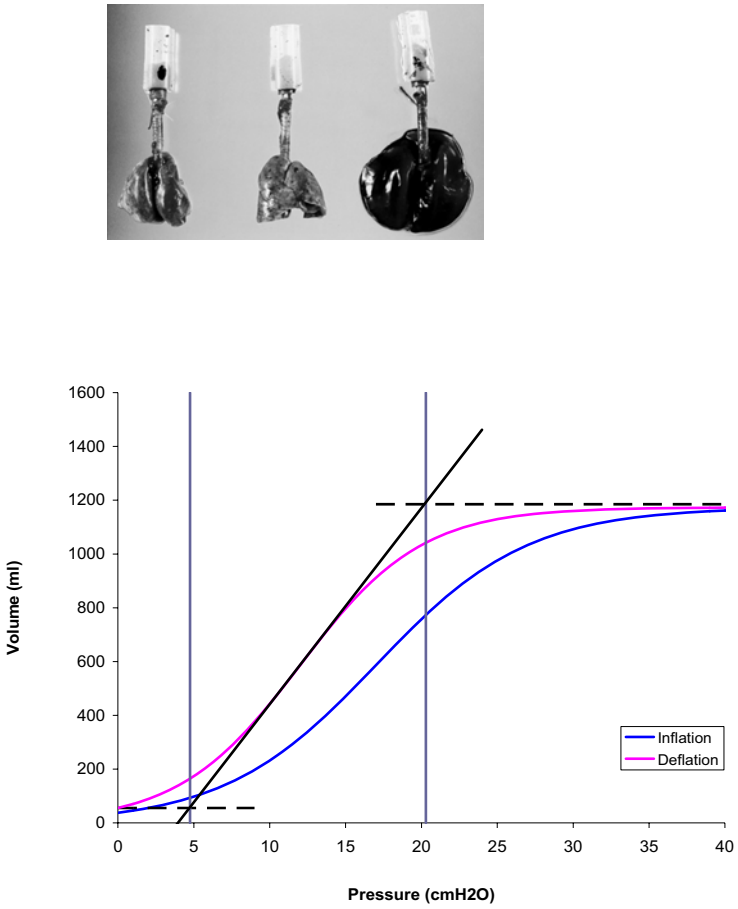
The possibility that mechanical ventilation can actually worsen acute lung disease is now widely accepted [7]. The clinical counterpart of VILI has been described as Ventilator Associated Lung Injury (VALI) [27;28]. VALI has been implicated in the causation of Acute Lung Injury (ALI) and subsequently ARDS [29]. ALI and ARDS are both clinical entities that are diagnosed exclusively by definition [30]. ALI has been defined as acute onset of bilateral infiltrates on chest radiograph and a ratio of partial pressure of arterial oxygen (PaO2) divided by fraction of inspired oxygen (FiO2) of

less than 300 without evidence of left ventricular heart failure. ARDS uses the same definition except that PaO2/FiO2 fraction has to be less than 200. Mortality in ARDS is high and in two recent studies was estimated to be 0.46 in adults and 0.22 in children [31;32]. The exact causative mechanism through which VALI contributes to mortality is not known. It has been postulated that in conjunction to and aggravated by VALI, multiple organ failure can develop with ultimately death [33]. It is thought that this is caused by immunologic active products of lung damage that spill over to the systemic circulation resulting in a systemic inflammatory reactive syndrome with subsequent organ damage [34;35]. However, the importance of an independent role of VALI in multiple organ failure and death by immunological mediators has been debated [36;37].

Lung protective ventilation strategies

As there is abundant experimental and clinical evidence that mechanical ventilation can cause lung damage, avoidance of VALI must be of prime concern while ventilating patients. Obviously, volutrauma can be prevented by use of low tidal volumes. However, this could be in disagreement with the objective to prevent atelectasis [38]. Studies showed that ventilation at very low lung volumes with low level of PEEP caused a significant decrease in lung compliance and progression of lung injury [9;17]. The combined effort of limiting tidal volumes with recruitment of lung alveoli and preventing alveoli to collapse has been designated as the open lung concept [39]. The rationale behind this approach can be described graphically by the pressure volume curve (Figure 2). The pressure volume curve during mechanical ventilation follows a specific pattern [40-42]. During the inflation phase pressure builds up while lung volume only increases slightly. At a specific point the relative volume gain, in response to pressure, increases and follows a more or less linear a more horizontal

Figure 2



Inflation and deflation pressure-volume curve (PV Curve). These curves were calculated by the equation V = a + b / (1 + e-(P-c)/d) (40). V = Lung volume (ml). P = Airway pressure (cmH2O). The lower and upper corner pressures (Pcl, Pcu) are defined by the intersect of the tangent at the steepest part of the curve with the tangent of the more horizontal parts of the curve. The part between the lower and upper corner pressure could be regarded as a safe window between atelectasis and overdistension.

course. The expiration limb of the curve follows a different route. Considerable less pressure is needed to maintain a certain amount of lung volume compared with the inspiration limb of the pressure volume curve. This increase in compliance is caused by recruitment of alveoli and is

called ‘pulmonary hysteresis’ [43]. The upper and lower corner pressures are defined as the points were the slopes of the curves change abruptly [42]. It is generally thought that the lower corner pressure signifies the point of the critical opening pressure of alveoli and that the upper corner pressure is related to start of overdistension [44]. Therefore, protective ventilation strategies should theoretically be dictated by these corner pressures that are specific for individual patients. The zone between these corner pressures has been designated as safe window [45]. However, this model has been differentiated and modified in the fact that the inflation characteristics of the PV curve have been shown not to be simply related to successive alveolar recruitment and overdistension [40]. Between the lower and upper corner point, a substantial number of alveoli may still not be recruited, while, at the same time, already recruited alveoli develop overexpansion. Therefore, the safe window may not be an exactly definable range.

Lung protection with conventional mechanical ventilation

Normal lungs are less susceptible to VALI while gas exchange can be easily achieved within physiological airway pressure and tidal volume limits [46]. In diseased lungs, mechanical ventilation is confronted with a number of problems:

- Gas exchange is disturbed.
- Compliance is decreased.
- Disease activity in the lungs is heterogeneously distributed.

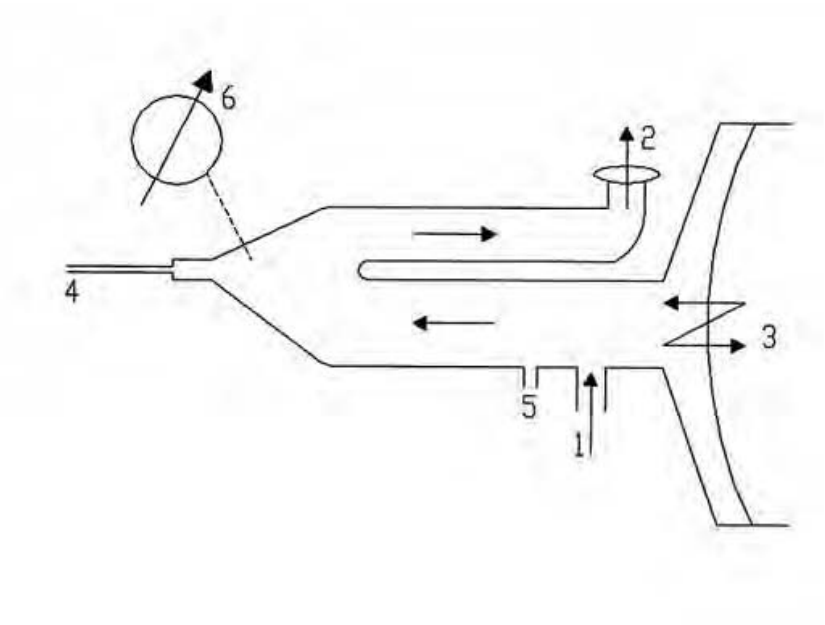
To achieve a lung protective ventilation strategy, limiting tidal volumes on the one hand and applying sufficient PEEP on the other hand have to be combined with maintaining adequate gas exchange. Limiting tidal volumes

will inevitably result in hypercapnia and respiratory acidosis. How much hypercapnia is acceptable is not clear [47]. However, accepting a certain amount of hypercapnia has been associated with better outcome [48]. Another change in pulmonary disease is loss of compliance. This is displayed by the downward displacement of the pressure volume curve. Loss of recruitable lung segments due to lower compliance results in a smaller lung available for ventilation, the so called 'baby lung' [49]. This further limits tidal volumes. Experimental studies showed an exponential increase in VILI when harmful ventilation strategies were combined with prior lung injury compared with prior lung injury alone or injurious ventilation strategies alone [23]. The heterogeneous nature of clinical lung disease further aggravates atelectasis of diseased parts of the lung and overdistension of healthy parts of the lung [50-52]. Yet, a sufficient level of positive end-expiratory pressure has to be maintained to keep the lung open. It can be hypothesized that at a certain point tidal volumes delivered by conventional ventilation superimposed on a level of PEEP sufficient to keep the lung open will fail to stay in the safe window on the pressure volume curve. A specific type of ventilator combining very small tidal volumes with a continuous distending airway pressure is the high frequency ventilator.

Lung protection with high frequency ventilation

High frequency ventilation is a collection of ventilation modes that combines very small tidal volumes at high frequency with a high continuously distending airway pressure. Examples of techniques are high frequency oscillatory ventilation, high frequency jet ventilation, and high frequency flow interruption ventilation. The most commonly used device is the high frequency oscillatory ventilator (HFOV) (Figure 3). Like the other modalities, HFOV employs respiratory frequencies that are significantly

Figure 3



Schematic view of the high frequency oscillatory ventilator. Mean airway pressure is regulated by controlling the inflation of the balloon valve (2) in the expiratory limb of the circuit. As inflation pressure inside the balloon increases, the outflow of gas is restricted, providing mean airway pressure. Superimposed on this mean airway pressure are tidal volumes delivered by electronically driven membrane displacements (3). This Figure was kindly provided by Elmer J. van Vught.

(180-2000 breaths/min) higher and tidal volumes that are markedly lower (1-5 ml/kg) than conventional mechanical ventilation (CMV) [53;54]. The first application of HFOV can be traced back to Lunkenheimer et al. [55].The major difference between HFOV and other forms of high frequency ventilation is the active expiratory phase. A membrane causes oscillating movements of air with a frequency typically ranging from 5 – 10 Hz. These small movements, tidal volumes, are superimposed on a continuously distending pressure. As the movement of air progresses through the respiratory system and airways, the amplitude of airway movement is attenuated to very small tidal volumes at the alveolar level [56-58]. Gas exchange is probably achieved by a complicated diffusion and

convection process rather than by delivery of tidal volumes [59]. Early HFOV devices were only suitable for ventilating infants and small children, because of their limited power. At the present time HFOV devices are marketed that can be used to ventilate adults as well. HFOV has been extensively tested in animals with different models of lung disease. Invariably, these tests showed a reduction in lung damage as compared with CMV. This has been demonstrated both at a physiological level as by histopathological examination of ventilated lungs in animal models (Figure 4) [60-68]. However, evidence in humans is less unequivocal. The majority of trials have been performed in premature neonates with respiratory distress syndrome [69]. Recently two trials have been conducted in adult patients with acute respiratory distress syndrome [70;71].

Analysis of clinical evidence of HFV compared with CMV

This thesis can be divided into two main sections. The first part of the thesis relates to the evidence comparing high frequency ventilation with CMV in premature neonates with IRDS. In the second part of this thesis, evidence comparing HFOV with CMV in adults with ARDS is assessed. In four out of five studies in this thesis meta-analytic techniques were used to provide answers to the research questions that were raised. Meta-analysis can be used to pool results from randomized trials to obtain more precise estimates [72]. Three different forms of meta-analysis were used to summarize the evidence of clinical trials. First, cumulative meta-analysis was performed to determine the progression of evidence over time [73;74]. This enabled us to identify specific sources of heterogeneity between studies. Secondly, meta-regression analysis was used to calculate quantitative effects of important determinants on the relative treatment effect of high frequency ventilation compared with CMV. Furthermore,

Figure 4

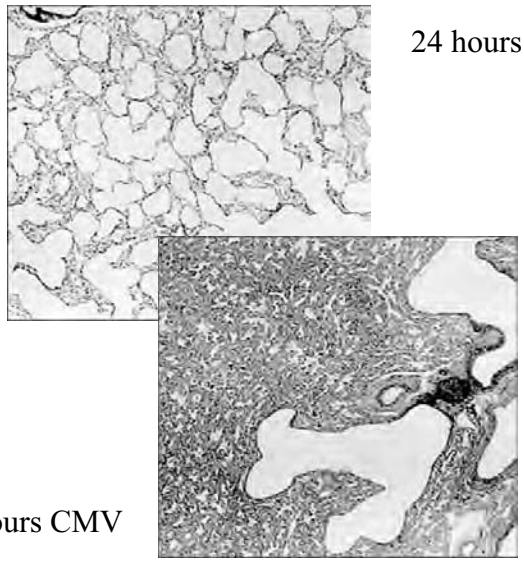


Figure used with permission from Meredith et al. (66). Histological specimens are shown from lungs of premature baboons with hyaline membrane disease ventilated 24 hours with positive pressure ventilation versus HFOV.

meta-regression analysis was used to identify determinants of mortality in HFOV treated adult patients with ARDS. Finally, sequential meta-analysis was applied with trials as unit of analysis to determine the number of trials needed to be conducted to establish the effect of high frequency ventilation on pulmonary outcome [75;76].

Outline of this thesis

Studies in premature neonates

The studies presented in this thesis were initiated to answer the following general question: Is high frequency ventilation better than CMV? The majority of clinical trials have been performed in premature neonates with IRDS due to limitations posed by available high frequency ventilators at that time. Therefore, the following research questions were formulated:

1. Does elective use of high frequency ventilation in premature neonates with IRDS result in better clinical outcome than conventional mechanical ventilation?

In Chapter 2 trials were stratified by different high frequency ventilators and by different ventilatory strategies. In addition, a cumulative meta-analysis was performed within relevant strata, which allowed for examination of development of available evidence over time and assessment of sources of remaining heterogeneity

2. What factors determine the relative treatment effect of high frequency ventilation compared with CMV?

A meta-regression analysis was conducted in Chapter 3 to obtain unbiased estimates of the effects of possible covariates that explained heterogeneity between trials that investigated the elective use of high frequency ventilation compared with CMV in premature neonates with IRDS.

3. Is there enough evidence to establish whether or not high frequency ventilation confers clinical benefit over CMV, or do more clinical trials need to be performed?

Chapter 4 presents a sequential meta-analysis to determine whether or not and at what point in time additional trials comparing high frequency ventilation with CMV, still contributed to available evidence.

Studies in adult patients

Published randomized trials in adults were limited to one study. The remainder of clinical studies comprised observational studies. All research in adult patients presented in this thesis was performed in patients with ARDS. An additional multi-center randomized trial was analyzed and a meta-analysis of observational research was conducted to answer the following questions:

4. Is high frequency oscillatory ventilation as safe and effective as conventional mechanical ventilation in adults with ARDS?
Chapter 5 shows the results of a multi-center randomized trial that compared early treatment with HFOV of ARDS in adult patients with the use of conventional ventilation.

5. What factors determine mortality in adult patients with ARDS treated with HFOV?
In Chapter 6 a meta-analysis of observational research was conducted. Determinants of mortality in HFOV treated ARDS patients were identified using meta-regression analysis.

Reference List

1. Albert RK. Least PEEP: primum non nocere. *Chest* 1985;**87**:2-4.

2. Ricard JD. Manual ventilation and risk of barotrauma: primum non nocere. *Respir.Care* 2005;**50**:338-9.

3. Dreyfuss D,.Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am.J.Respir.Crit Care Med.* 1998;**157**:294-323.

4. Pingleton SK. Complications of acute respiratory failure. *Am.Rev.Respir.Dis.* 1988;**137**:1463-93.

5. Plotz FB,.van Vught AJ. [Lung damage due to mechanical ventilation]. *Ned.Tijdschr.Geneeskd.* 1999;**143**:133-6.

6. Dreyfuss D,.Saumon G. Barotrauma is volutrauma, but which volume is the one responsible? *Intensive Care Med.* 1992;**18**:139-41.

7. Parker JC, Hernandez LA, Peevy KJ. Mechanisms of ventilator-induced lung injury. *Crit Care Med.* 1993;**21**:131-43.

8. Macklin MT,.Macklin CC. Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions: an interpretation of the clinical literature in the light of laboratory experiment. *Medicine* 1944;**23**:281-352.

9. 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.* 1974;**110**:556-65.

10. Dreyfuss D, Soler P, Saumon G. Spontaneous resolution of pulmonary edema caused by short periods of cyclic overinflation. *J.Appl.Physiol* 1992;**72**:2081-9.

11. Carlton DP, Cummings JJ, Scheerer RG, Poulain FR, Bland RD. Lung overexpansion increases pulmonary microvascular protein permeability in young lambs. *J.Appl.Physiol* 1990;**69**:577-83.

12. Hernandez LA, Peevy KJ, Moise AA, Parker JC. Chest wall restriction limits high airway pressure-induced lung injury in young rabbits. *J.Appl.Physiol* 1989;**66**:2364-8.

13. Dreyfuss D, Basset G, Soler P, Saumon G. Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. *Am.Rev.Respir.Dis.* 1985;**132**:880-4.

14. Kim KJ,.Crandall ED. Effects of lung inflation on alveolar epithelial solute and water transport properties. *J.Appl.Physiol* 1982;**52**:1498-505.

15. 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* 1984;**57**:1809-16.

16. Parker JC, Hernandez LA, Longenecker GL, 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.

17. Muscedere JG, Mullen JB, Gan K, Slutsky AS. Tidal ventilation at low airway pressures can augment lung injury. *Am.J.Respir.Crit Care Med.* 1994;**149**:1327-34.

18. Sohma A, Brampton WJ, Dunnill MS, Sykes MK. Effect of ventilation with positive end-expiratory pressure on the development of lung damage in experimental acid aspiration pneumonia in the rabbit. *Intensive Care Med.* 1992;**18**:112-7.

19. Taskar V, John J, Evander E, Robertson B, Jonson B. Surfactant dysfunction makes lungs vulnerable to repetitive collapse and reexpansion. *Am.J.Respir.Crit Care Med.* 1997;**155**:313-20.

20. Dreyfuss D, Soler P, Saumon G. Mechanical ventilation-induced pulmonary edema. Interaction with previous lung alterations. *Am.J.Respir.Crit Care Med.* 1995;**151**:1568-75.

21. Kawano T, Mori S, Cybulsky M, Burger R, Ballin A, Cutz E *et al*. Effect of granulocyte depletion in a ventilated surfactant-depleted lung. *J.Appl.Physiol* 1987;**62**:27-33.

22. Tsuno K, Miura K, Takeya M, Kolobow T, Morioka T. Histopathologic pulmonary changes from mechanical ventilation at high peak airway pressures. *Am.Rev.Respir.Dis.* 1991;**143**:1115-20.

23. 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.

24. Dos Santos CC,.Slutsky AS. The Contribution of Biophysical Lung Injury to the Development of Biotrauma. *Annu.Rev.Physiol* 2005.

25. Halbertsma FJ, Vaneker M, Scheffer GJ, van der Hoeven JG. Cytokines and biotrauma in ventilator-induced lung injury: a critical review of the literature. *Neth.J.Med.* 2005;**63**:382-92.

26. Lachmann B. The role of pulmonary surfactant in the pathogenesis and therapy of ARDS. *Update in intensive care and emergency medicine*, pp 123-34. Springer-Verlag, 1987.

27. Pinhu L, Whitehead T, Evans T, Griffiths M. Ventilator-associated lung injury. *Lancet* 2003;**361**:332-40.

28. International consensus conferences in intensive care medicine: Ventilator-associated Lung Injury in ARDS. This official conference report was cosponsored by the American Thoracic Society, The European Society of Intensive Care Medicine, and The Societe de Reanimation de Langue Francaise, and was approved by the ATS Board of Directors, July 1999. *Am.J.Respir.Crit Care Med.* 1999;**160**:2118-24.

29. Rouby JJ, Lherm T, Martin de LE, Poete P, Bodin L, Finet JF *et al*. Histologic aspects of pulmonary barotrauma in critically ill patients with acute respiratory failure. *Intensive Care Med.* 1993;**19**:383-9.

30. Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L *et al*. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am.J.Respir.Crit Care Med.* 1994;**149**:818-24.

31. Flori HR, Glidden DV, Rutherford GW, Matthay MA. Pediatric acute lung injury: prospective evaluation of risk factors associated with mortality. *Am.J.Respir.Crit Care Med.* 2005;**171**:995-1001.

32. Gong MN, Thompson BT, Williams P, Pothier L, Boyce PD, Christiani DC. Clinical predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion. *Crit Care Med.* 2005;**33**:1191-8.

33. Plotz FB, Slutsky AS, van Vught AJ, Heijnen CJ. Ventilator-induced lung injury and multiple system organ failure: a critical review of facts and hypotheses. *Intensive Care Med.* 2004;**30**:1865-72.

34. Ranieri VM, Suter PM, Tortorella C, De TR, Dayer JM, Brienza A *et al*. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 1999;**282**:54-61.

35. Ranieri VM, Giunta F, Suter PM, Slutsky AS. Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. *JAMA* 2000;**284**:43-4.

36. Dreyfuss D, Ricard JD, Saumon G. On the physiologic and clinical relevance of lung-borne cytokines during ventilator-induced lung injury. *Am.J.Respir.Crit Care Med.* 2003;**167**:1467-71.

37. Pugin J. Is the ventilator responsible for lung and systemic inflammation? *Intensive Care Med.* 2002;**28**:817-9.

38. Dreyfuss D,.Saumon G. Should the lung be rested or recruited? The Charybdis and Scylla of ventilator management. *Am.J.Respir.Crit Care Med.* 1994;**149**:1066-7.

39. Lachmann B. Open up the lung and keep the lung open. *Intensive Care Med.* 1992;**18**:319-21.

40. Markhorst DG, van Genderingen HR, van Vught AJ. Static pressure-volume curve characteristics are moderate estimators of optimal airway pressures in a mathematical model of (primary/pulmonary) acute respiratory distress syndrome. *Intensive Care Med.* 2004;**30**:2086-93.

41. van Genderingen HR, van Vught AJ, Jansen JR. Estimation of regional lung volume changes by electrical impedance pressures tomography during a pressure-volume maneuver. *Intensive Care Med.* 2003;**29**:233-40.

42. Venegas JG, Harris RS, Simon BA. A comprehensive equation for the pulmonary pressure-volume curve. *J.Appl.Physiol* 1998;**84**:389-95.

43. Escolar JD, Escolar MA, Guzman J, Roques M. Pressure volume curve and alveolar recruitment/de-recruitment. A morphometric model of the respiratory cycle. *Histol.Histopathol.* 2002;**17**:383-92.

44. Matamis D, Lemaire F, Harf A, Brun-Buisson C, Ansquer JC, Atlan G. Total respiratory pressure-volume curves in the adult respiratory distress syndrome. *Chest* 1984;**86**:58-66.

45. Froese AB. High-frequency oscillatory ventilation for adult respiratory distress syndrome: let's get it right this time! *Crit Care Med.* 1997;**25**:906-8.

46. Taskar V, John J, Evander E, Wollmer P, Robertson B, Jonson B. Healthy lungs tolerate repetitive collapse and reopening during short periods of mechanical ventilation. *Acta Anaesthesiol.Scand.* 1995;**39**:370-6.

47. Feihl F,.Perret C. Permissive hypercapnia. How permissive should we be? *Am.J.Respir.Crit Care Med.* 1994;**150**:1722-37.

48. Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Med.* 1990;**16**:372-7.

49. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M. Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. *Am.Rev.Respir.Dis.* 1987;**136**:730-6.

50. Tsang JY, Emery MJ, Hlastala MP. Ventilation inhomogeneity in oleic acid-induced pulmonary edema. *J.Appl.Physiol* 1997;**82**:1040-5.

51. Gattinoni L, D'Andrea L, Pelosi P, Vitale G, Pesenti A, Fumagalli R. Regional effects and mechanism of positive end-expiratory pressure in early adult respiratory distress syndrome. *JAMA* 1993;**269**:2122-7.

52. Victorino JA, Borges JB, Okamoto VN, Matos GF, Tucci MR, Caramez MP *et al*. Imbalances in regional lung ventilation: a validation study on electrical impedance tomography. *Am.J.Respir.Crit Care Med.* 2004;**169**:791-800.

53. Drazen JM, Kamm RD, Slutsky AS. High-frequency ventilation. *Physiol Rev.* 1984;**64**:505-43.

54. Froese AB,.Bryan AC. High frequency ventilation. *Am.Rev.Respir.Dis.* 1987;**135**:1363-74.

55. Lunkenheimer PP, Rafflenbeul W, Keller H, Frank I, Dickhut HH, Fuhrmann C. Application of transtracheal pressure oscillations as a modification of "diffusing respiration". *Br.J.Anaesth.* 1972;**44**:627.

56. Gerstmann DR, Fouke JM, Winter DC, Taylor AF, deLemos RA. Proximal, tracheal, and alveolar pressures during high-frequency oscillatory ventilation in a normal rabbit model. *Pediatr.Res.* 1990;**28**:367-73.

57. van Genderingen HR, Versprille A, Leenhoven T, Markhorst DG, van Vught AJ, Heethaar RM. Reduction of oscillatory pressure along the endotracheal tube is indicative for maximal respiratory compliance during high-frequency oscillatory ventilation: a mathematical model study. *Pediatr.Pulmonol.* 2001;**31**:458-63.

58. van Genderingen HR, van Vught AJ, Duval EL, Markhorst DG, Jansen JR. Attenuation of pressure swings along the endotracheal tube is indicative of optimal distending pressure during high-frequency oscillatory ventilation in a model of acute lung injury. *Pediatr.Pulmonol.* 2002;**33**:429-36.

59. Chang HK. Mechanisms of gas transport during ventilation by high-frequency oscillation. *J.Appl.Physiol* 1984;**56**:553-63.

60. Hamilton PP, Onayemi A, Smyth JA, Gillan JE, Cutz E, Froese AB *et al*. Comparison of conventional and high-frequency ventilation: oxygenation and lung pathology. *J.Appl.Physiol* 1983;**55**:131-8.

61. McCulloch PR, Forkert PG, Froese AB. Lung volume maintenance prevents lung injury during high frequency oscillatory ventilation in surfactant-deficient rabbits. *Am.Rev.Respir.Dis.* 1988;**137**:1185-92.

62. deLemos RA, Coalson JJ, Gerstmann DR, Null DM, Jr., Ackerman NB, Escobedo MB *et al*. Ventilatory management of infant baboons with hyaline membrane disease: the use of high frequency ventilation. *Pediatr.Res.* 1987;**21**:594-602.

63. Imai Y, Kawano T, Miyasaka K, Takata M, Imai T, Okuyama K. Inflammatory chemical mediators during conventional ventilation and during high frequency oscillatory ventilation. *Am.J.Respir.Crit Care Med.* 1994;**150**:1550-4.

64. Kolton M, Cattran CB, Kent G, Volgyesi G, Froese AB, Bryan AC. Oxygenation during high-frequency ventilation compared with conventional mechanical ventilation in two models of lung injury. *Anesth.Analg.* 1982;**61**:323-32.

65. Matsuoka T, Kawano T, Miyasaka K. Role of high-frequency ventilation in surfactant-depleted lung injury as measured by granulocytes. *J.Appl.Physiol* 1994;**76**:539-44.

66. Meredith KS, deLemos RA, Coalson JJ, King RJ, Gerstmann DR, Kumar R *et al*. Role of lung injury in the pathogenesis of hyaline membrane disease in premature baboons. *J.Appl.Physiol* 1989;**66**:2150-8.

67. Takata M, Abe J, Tanaka H, Kitano Y, Doi S, Kohsaka T *et al*. Intraalveolar expression of tumor necrosis factor-alpha gene during conventional and high-frequency ventilation. *Am.J.Respir.Crit Care Med.* 1997;**156**:272-9.

68. von der HK, Kandler MA, Fink L, Schoof E, Dotsch J, Brandenstein O *et al*. High frequency oscillatory ventilation suppresses inflammatory response in lung tissue and microdissected alveolar macrophages in surfactant depleted piglets. *Pediatr.Res.* 2004;**55**:339-46.

69. Henderson-Smart DJ, Bhuta T, Cools F, Offringa M. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane.Database.Syst.Rev.* 2003;CD000104.

70. Bollen CW, van Well GT, Sherry T, Beale RJ, Shah S, Findlay G *et al*. High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: a randomized controlled trial [ISRCTN24242669]. *Crit Care* 2005;**9**:R430-R439.

71. Derdak S, Mehta S, Stewart TE, Smith T, Rogers M, Buchman TG *et al*. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. *Am.J.Respir.Crit Care Med.* 2002;**166**:801-8.

72. Egger M, Smith GD, Sterne JA. Uses and abuses of meta-analysis. *Clin.Med.* 2001;**1**:478-84.

73. Conti CR. Clinical decision making using cumulative meta-analysis. *Clin.Cardiol.* 1993;**16**:167-8.

74. Ioannidis JP, Contopoulos-Ioannidis DG, Lau J. Recursive cumulative meta-analysis: a diagnostic for the evolution of total randomized evidence from group and individual patient data. *J.Clin.Epidemiol.* 1999;**52**:281-91.

75. Henderson WG, Moritz T, Goldman S, Copeland J, Sethi G. Use of cumulative meta-analysis in the design, monitoring, and final analysis of a clinical trial: a case study. *Control Clin.Trials* 1995;**16**:331-41.

76. Pogue JM,.Yusuf S. Cumulating evidence from randomized trials: utilizing sequential monitoring boundaries for cumulative meta-analysis. *Control Clin.Trials* 1997;**18**:580-93.