VENTILATORY STRATEGY IN ARDS FOCUSING ON PRESSURE CONTROLLED VENTILATION

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VENTILATORY STRATEGY IN ARDS FOCUSING ON PRESSURE CONTROLLED VENTILATION

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CONTENTS

PREFACE

After 30 years of experimental studies and clinical experience, the application of the best mechanical ventilation mode in acute respiratory distress syndrome (ARDS) is still a subject of controversy. The aims of full or partial ventilatory support in ARDS can be summarized as follows:

1. Achievement of optimal arterial oxygenation and adequate alveolar ventilation;

2. Avoidance of damage to pulmonary parenchymal structures by high inflation pressures;

3. Prevention of cardiovascular system depression by high intrapulmonary airway pressures.

Conventional volume controlled ventilation with positive end expiratory pressure (PEEP) has been successfully used for years to treat hypoxemia in ARDS. However, high peak inspiration pressure caused by this mode has stimulated researchers to introduce other ventilatory approaches which fulfill the above-mentioned requirements. Various high frequency ventilation modes have been used to avoid high peak inspiration pressures. Alternatively, pressure controlled inverse ratio ventilation has shown to provide good oxygenation, normocapnia with low peak inspiration pressure and intrapulmonary pressure amplitude.

In some sophisticated medical centers, low frequency positive pressure ventilation

with extracorporeal carbon dioxide removal is used to reduce the ventilation of the lungs, avoid high peak inspiration pressure and allow the lungs to rest.

Many studies have been performed to show superiority of various ventilation modes. However, no prospective randomized study exists to relate any type of ventilatory support with reduced mortality.

This thesis focuses on comparison of different modes of ventilation in animals and patients with ARDS. The aim is to determine the immediate advantages of one mode over the other in terms of gas exchange, airway pressures, hemodynamics and ventilation inhomogeneity.

OVERVIEW OF THE STUDY

Chapter 1 reviews the pathophysiological and pathological changes and diagnostic and therapeutic strategies of ARDS. Lung lavage is presented as a useful animal model of acute respiratory failure.

Chapter 2 reviews conventional volume controlled ventilation with PEEP and pressure conrolled inverse ratio ventilation in relation to intrapulmonary pressure swings, gas exchange, hemodynamics and ventilation inhomogeneity. Special attention is given to the indications and the adjustment of parameters in pressure controlled inverse ratio ventilation.

In *Chapter 3* an animal model of acute respiratory failure is investigated. In this work, the possible advantages of low frequency positive pressure ventilation with extracorporeal carbon dioxide removal are compared with volume controlled ventilation with PEEP and pressure regulated volume controlled ventilation with inspiration/expiration (I/E) ratio 4:1 investigating differences in arterial oxygenation, lung mechanics and hemodynamics.

The same modes of ventilation as used in the studies in Chapter 3 are studied in *Chapter 4* in pigs with surfactant depleted lungs; their effects on intracranial pressure are investigated.

High frequency ventilation is reported to be another mode of ventilation preventing lung injury and providing adequate gas exchange. In *Chapter 5* superimposed expiratory high frequency ventilation on pressure regulated volume controlled ventilation with an I/E ratio 4:1 is applied to surfactant depleted rabbit lungs, and its influence on gas exchange and lung mechanics is compared with volume controlled ventilation with PEEP and

pressure regulated volume controlled ventilation.

Application of inert gas techniques and computerized tomography demonstrated the heterogeneous distribution of the lung pathology in ARDS. In *Chapter 6* a newly developed apparatus is used to measure the ventilation inhomogeneity and functional residual capacity of pig lungs after surfactant depletion caused by lung lavage. Furthermore, it is hypothesized that activities of 5 hydroxytryptamine (5HT) might be initiated in the lungs accompanying the hypoxia of acute respiratory failure in this model, leading to vaso- and bronchospastic effects such as pulmonary hypertension and ventilation inhomogeneity. Therefore, the effect of a specific 5HT antagonist, ketanserine, is investigated in the treatment of pulmonary vasoconstriction and ventilation inhomogeneity of surfactant depleted pig lungs.

In *Chapter 7*, 38 ARDS patients are ventilated randomly with volume controlled ventilation with PEEP and pressure regulated volume controlled ventilation with I/E ratios 2:1, 3:1 and 4:1 to determine the possible advantages of one mode over the other. The oxygenation is evaluated in relation to the intrapulmonary pressure swings. Special attention is given to high intrapulmonary pressure amplitudes and peak inspiratory pressure.

The work in *chapter 8* focuses on the existing controversy regarding the best approach to weaning from mechanical ventilation. In this work, 40 mechanically ventilated patients with acute respiratory failure are studied in two groups and the effects of pressure support ventilation and intermittent mandatory ventilation are compared during weaning of long-term ventilation.

CHAPTER 1

GENERAL INTRODUCTION

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Adult respiratory distress syndrome (ARDS) is a type of acute respiratory failure resulting from altered ventilation-perfusion ratios and leading to hypoxemia, hypo- or hypercapnia and decreased lung compliance. Asbaugh and Petty (1) used the term ARDS for the first time in 1967 to describe the clinical picture of diffuse pulmonary infiltration on chest X-ray, impairment of oxygenation and pulmonary congestion. However, the existence of this syndrome was already reported after the first World War by Weed and McAfee (2) who discussed the respiratory failure as a sequela of wound shock.

Other names such as congestive atelectasis, wet lung syndrome, shock lung, pump lung, transfusion lung, post-traumatic pulmonary insufficiency and Danang lung have also been used to identify this entity. Due to the increased lung water in ARDS, the syndrome has also been referred to as non-cardiogenic pulmonary edema or interstitial pulmonary edema.

Although lung injury associated with shock was recognized many years ago, it is only during the last 25 years that ARDS has been recognized as a serious problem in intensive care patients. Various disorders such as shock, chest trauma, non-thoracic trauma, abdominal or extra-abdominal sepsis, acute pancreatitis, bacterial or viral pneumonia, aspiration pneumonia, head injury, smoke inhalation, drug overdose, radiation pneumonitis etc. have been identified as the initiating events of this pathological entity. Serious hypoxemia and pulmonary edema without pulmonary venous hypertension are uniformly characteristic, regardless of the etiology.

Pathophysiology of ARDS

Respiratory failure follows either a primary lung disease or extra-thoracic injury of many origins. Primary lung injury damages the alveolar cells and results in impaired surfactant

activity. Alveolar macrophages are activated and they liberate chemotactic substances which promote granulocyte micro-aggregation in the lung capillaries. Secondary lung damage is due to extra-thoracic injuries where damaged tissues liberate blood-borne mediators which in turn leads to micro-aggregate formation in the pulmonary micro-vasculature (polymorphonuclear cells, platelets, etc.). An interaction occurs between micro-aggregation and humoral substances (blood-borne but also produced by the micro-aggregates) in the pulmonary capillaries. This interaction causes capillary endothelial injury in the lungs, particularly of capillary basement membranes resulting in increased permeability of these membranes. This situation is also called "capillary leak syndrome". Accumulation of fluid and cells in the interstitium and in the alveoli leads to loss of surfactant activity and hypoxemia and ARDS (3-5).

Pathological changes in the lung

In order to have an efficient gas exchange, a minimum diffusion distance between alveolar air and blood, and a large surface area of well-perfused micro-vasculature exposed to air is required. This blood-gas barrier is extremely delicate and highly vulnerable; damage to this barrier in the acute stage of ARDS leads to increased permeability and flooding of the alveolar space with blood constituents.

Pathologically, ARDS is divided into an early exudative phase which, after about one week, develops into a proliferative phase and eventually into fibrosis (6,7). Changes can be grouped into three stages:

acute ARDS : alveolar edema with fibrin and leukocyte debris, damage to type I pneumocytes and endothelial cells;

sub-acute ARDS: persistent capillary endothelial damage, type II cell proliferation and

the beginning of squamous transformation;

chronic ARDS: thickening of the interstitium by an increased number of type II cells and fibrosis (8,9).

Early ultrastructural changes may occur during the course of ARDS (10-13). Based on a series of 200 human autopsies, Blaisdell and Lewis (14) reported the timing of pathological events in ARDS as follows:

1. First 6 hours: minimal congestion of capillaries and fibrin with platelet and leukocyte aggregates in pulmonary arteries 25-250 microns in diameter.
2. At 12 hours: marked capillary congestion.
3. Between 16-19 hours: periarterial hemorrhage.
4. At 24 hours: severe congestion and interstitial hemorrhage.
5. At 72 hours: generalized consolidation with thrombi and emboli and the appearance of hyaline membranes.
6. Later in the first week: inflammatory cell changes resembling bronchopneumonia.
7. Between the second and sixth week: progressive fibrosis.

Clinical presentation and diagnosis of ARDS

The clinical presentation of patients with ARDS has hardly changed since its original description in 1967 and consists of a history of preceding noxious event; a symptom-free interval lasting hours to days; the subsequent progression of severe hypoxemia, decreased lung compliance and diffuse non-cardiogenic pulmonary edema. An accurate definition of the syndrome is essential for the standardization of the entry criteria into various clinical stages. Variable diagnostic criteria are used by different investigators during the last 25 years. These criteria include chest X-ray, presence or absence of PEEP, specific values for

the alveolar-arterial oxygen tension gradient, pulmonary shunt fraction, FiO_2 and pulmonary compliance. However, these criteria are not universally accepted and vary widely among investigators (Table 1).

Therapeutic strategies

During recent years, there has been a growing tendency to consider mechanical ventilation as a supportive measure rather than therapeutic in the treatment of ARDS. The lack of prospective randomized studies comparing the mortality in ARDS patients ventilated with different modes of mechanical ventilation is probably the main reason for this concept. The immediate therapeutic aim in ARDS is to treat hypoxemia, which in most cases is marked by sophisticated ventilatory support. Of concern is the possibility that ARDS may be a response to barotrauma and that the use of high airway pressures to ventilate patients with ARDS may itself result in injury and morphological changes similar to ARDS, in formerly uninvolved parts of the lung (16-20).

To prevent further barotrauma, techniques such as pressure controlled inverse ratio ventilation (PC-IRV) (16), high frequency ventilation (HFV) (21-24) and low frequency positive pressure ventilation with extra corporeal carbon dioxide removal (LFPPV-$ECCO_2R$) (25) have been used during the last 15 years. The aims of these techniques are to treat hypoxemia, but simultaneously avoid high peak inspiratory pressures and intrapulmonary pressure swings while keeping the alveoli open. Furthermore, remembering the sequence of the pathological changes in the ARDS lungs it is important to apply a suitable mode of ventilation as early as possible to provide maximum opening of the alveoli and to keep them open, as consolidation is reported to occur already at 72 hours after the initiation of the respiratory failure (14).

Table 1. Diagnostic criteria used to define acute respiratory failure and ARDS*

Investigators and study	Criteria used in diagnosis
Ashbaugh et al (1967)	Dyspnoea, tachypnea, refractory hypoxaemia, reduced pulmonary compliance and bilateral alveolar infiltrationon CXR
Pontoppiddan et al (1985)	Four categories of respiratory failure: (i) *At risk:* one or more risk factors, no/minimal changes on CXR, oxygen by face mask for short periods only (ii) *Mild:* minimal diffuse or lobar changes on CXR with or without intubation and CPAP with an $FiO_2 < 0.5$ (iii) *Moderate:* panlobar alveolar infiltrates of one or both lungs of CXR, intubated for more than 24 hours, requiring positive airway pressure (CMV, IMV, PEEP, CPAP) with an $FiO_2 > 0.5$ (iv) *Severe:* bilateral panlobar alveolar infiltrates on CXR, intubated, requiring CMV and PEEP, $PaO_2 < 50$ mmHg with FiO_2 of 1.0 for 8 hours or more, or $FiO_2 > 0.6$ for more than 48 hours
Bartlet et al (1986)	Endotracheal intubation and positive airway pressure for at least 24 hours with an $FiO_2 > 0.50$ Five diagnostic categories defined: pneumonitis, capillary leak syndromes (ARDS), high-pressure oedema, thromboemboli and chronic airways obstruction
Zapol et al (1979)	Fast or slow ECMO entry criteria: (i) *Fast entry:* $PaO_2 < 50$ mmHg for more than 2 hours with an FiO_2 of 1.0 and PEEP > 5 cmH_2O (ii) *Slow entry:* despite maximal medical therapy for 48 hours, $PaO_2 < 50$ mmHg for more than 12 hours when measured on an $FiO_2 > 0.6$ and PEEP > 5 cmH_2O with a pulmonary shunt $> 30\%$ measured on PEEP with an FiO_2 of 1.0
Holcroft et al (1986)	Patients with ARDS requiring mechanical ventilation with an $FiO_2 > 0.4$ and PEEP > 5 cmH_2O 'not responding to conventional therapy'
The Upjohn European multicentre trial of prostaglandin E_1 in ARDS	Patients with postoperatieve ARDS or associated with sepsis or trauma requiring mechanical ventilation, with: an $FiO_2 > 0.5 \pm$ PEEP in two or more determinations at least 2 hours apart in the preceding 24 hours giving a $PaO_2 < 75$ mmHg or an alterial-alveolar ratio < 0.3 with a pulmonary arterial occlusion pressure < 18 mmHg
European Society of Intensive Care study of acute respiratory failure	Patients with respiratory distress and a CXR of diffuse bilateral pulmonary infiltrates and severe hypoxaemia defined by: $PaO_2 < 75$ mmHg with an $FiO_2 > 0.5$ and PEEP 5 cmH_2O for at least 24 hours
Murray et al (1988)	Four independent variables such as CXR, hypoxemia, PEEP and respiratory system compliance were used and each were assigned with a score between 0 and 4. Three diagnostic categories were defined. No lung injury — Score 0 Mild to moderate lung injury — Score 0.1-2.5 Severe lung injury (ARDS) — Score > 2.5

*Modified from Artigas et al (15) CXR, chest X-ray; PaO_2, arterial oxygen tension; FiO_2, inspired fraction of oxygen; CMV, continuous mandatory ventilation; IMV, intermittent mandatory ventilation.

An understanding of the biochemical alterations that take place in the lungs of patients with ARDS has led to evaluation of the therapeutic use of cyclo-oxygenase inhibitors, antibodies directed against endotoxin or C5a, surfactant replacement therapy and antiprotease and antioxidant therapy. However, no specific therapy for ARDS is yet available other than ventilatory and, if necessary, circulatory support measures.

Lung lavage as an animal model of ARDS

Lung lavage has been introduced by Lachmann (26) in 1980 as an experimental guinea-pig model for studying the treatment of respiratory distress syndrome (RDS). In this study, he reported that this model was important in initiating the dominant pathogenetic factor of RDS (surfactant deficiency) without severe damage to the alveolar structures. The repeated lung lavage was shown in this study to cause surfactant depletion with focal to widespread atelectasis and desquamation of bronchial and bronchiolar epithelium. These epithelial lesions were usually accompanied by hyaline membranes. Additionally, the animals showed peribronchial inflammatory changes, characterized by edema and infiltration of polymorphonuclear leukocytes and eosinophils. Electron microscopic examination revealed alveolar epithelial lesions consisting mainly of necrosis and desquamation of membraneous pneumocytes. In some areas interstitial edema of alveolar and bronchiolar walls were observed.

These findings indicated that a condition similar to ARDS can be induced in guinea pigs by repeated lung lavage to study parameters such as blood gases, pulmonary mechanics and various morphological features.

Lung lavage was also performed in rabbit, dog and pig models with equal success. This resulted in significant reduction of FRC and thorax-lung compliance and increased the

permeability of the alveolo-capillary membrane (27), imitating the early phase of ARDS. Furthermore, the model is known to produce RDS persisting for at least for 8 h and is reproducible. Thus, this lung lavage model is particularly favorable for studies as presented in this thesis where the significance of different ventilatory settings are evaluated, compared to models produced by paraquat, HCL installation, oil injection and injection of serum against lung tissue.

Concluding remarks

The results of various studies summarized in this chapter indicate that ARDS is caused by multiple factors consisting of primary or secondary lung damage. A complex mediator cascade is activated leading to the "capillary leak syndrome", pathological changes in the lungs varying from alveolar edema with fibrin and leucocyte debris, to fibrosis and clinical symptoms such as severe hypoxemia and decreased lung compliance. In spite of extensive work done in this field, successful therapeutic measures are still limited to mechanical ventilation. However, ventilatory support, being the treatment of hypoxemia in ARDS, may itself cause lung damage and pathological changes similar to ARDS in healthy parts of the lungs, if applied with high intrapulmonary pressure swings. Considering the pathological changes occurring in ARDS, a ventilation mode opening the lung and keeping it open with the lowest possible pressure swings should be applied as early as possible in the course of ARDS.

Lung lavage is an ideal and stable RDS model in animals to compare the effects of different ventilatory settings, as it initiates the acute stage of ARDS without severely damaging the lungs. Different ventilator modes can be applied after lung lavage and their effects on oxygenation, airway pressures, hemodynamics and ventilation inhomogeneity can

be evaluated.

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CHAPTER 2

ADVANTAGES AND RATIONALE FOR PRESSURE CONTROLLED VENTILATION

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INTRODUCTION

Asbaugh and colleagues (1) in 1969 have used low levels of positive end expiratory pressure (PEEP) with volume controlled ventilation (VCV) (5-10 cm H_2O) in the treatment of hypoxemia in adult respiratory distress syndrome (ARDS). They also indicated that higher levels of PEEP could cause barotrauma, decrease in cardiac output (CO) and therefore a decrease in O_2 transport although PaO_2 is increased. Falke and co-workers (2) defined in 1972 the "optimal PEEP" as a level of PEEP which provided a $PaO_2 > 100$ mmHg with an $FiO_2 \leq 0.5$. In 1975 Suter and colleagues (3) accepted the "optimal PEEP" as a value providing best oxygen transport and lung compliance, which could be obtained with PEEP up to 12 cm H_2O. Application of PEEP has been reported to lower CO (3,4), but Qvist (5) demonstrated in 1975 that the adverse hemodynamic effects of PEEP could be limited by additional fluid administration.

Pressure controlled inverse ratio ventilation (PC-IRV) was used for the first time by Reynolds (6) in 1971 in the respiratory distress syndrome (RDS) of the newborn. It was suggested to improve oxygenation probably due to an increased mean airway pressure and a more equal distribution of gas. In the late seventies and early eighties Lachmann and colleagues (7-9) studied PC-IRV in ARDS models as well as in ARDS patients. They reported excellent gas exchange at reduced peak inspiratory pressure (PIP) compared to volume controlled ventilation with PEEP (VCV-PEEP) without additional depression on cardiocirculatory parameters in comparison to VCV-PEEP at the same oxygenation level. Morphological studies in animals also showed that the lungs were better preserved after PC-IRV than after conventional ventilation with PEEP. Brief reports and studies performed for a short period of time (10,11) followed the initial studies. Lain and colleagues (12)

compared PC-IRV with VCV-PEEP in 18 ARDS patients, and reported a decrease of PIP, no pneumothorax and better oxygenation with PC-IRV. East and coworkers have designed a computerized protocol for the clinical management of PC-IRV in ARDS patients in 1992 (13). In spite of all these reports, no randomized study exists to evaluate the outcome in ARDS patients ventilated with PC-IRV.

In this chapter the effects of VCV-PEEP and PC-IRV will be reviewed concerning intrapulmonary pressure swings, gas exchange, hemodynamics and ventilation inhomogeneity. Furthermore, the indications and the adjustments of parameters in PC-IRV will be discussed.

VCV-PEEP VERSUS PC-IRV

The aim of ventilatory therapy in ARDS is to provide adequate gas exchange, while avoiding complications such as progressive lung injury and hemodynamic depression. These goals can be achieved by keeping PIP to the minimum acceptable level, as PIP over 40-50 cm H_2O is associated with an increased risk of barotrauma and morphological changes in the lungs and airways (14).

In accordance with the pathophysiology of ARDS, ventilatory support should provide a persistent positive alveolar pressure to balance the high retractive forces due to diminished surfactant system. To maintain this balance it would be ideal to maintain a constant alveolar pressure. Therefore, in ARDS, when artificial ventilation is required, it is logical to control pressure rather than volume since the physical and therapeutic effects of intermittent positive pressure ventilation are closely linked to positive airway pressures. This concept implies that insufflation pressure is responsible for stabilization of lung units

while release of this pressure during the expiratory phase is responsible for ventilation.

This is in contradiction to VCV-PEEP, where tidal volume (V_T) maintains ventilation and PEEP prevents airway closure. However, clinically used levels of external PEEP will never stabilize all the alveoli as there is no homogeneous distribution of the lung damage in ARDS (15,16).

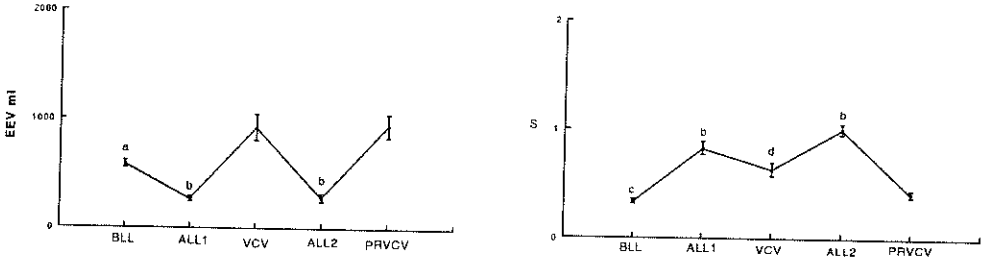

Fig.1. End expiratory volume (EEV) and ventilation inhomogeneity index (S) obtained with the application of ventilation modes. Higher S values indicate higher ventilation inhomogeneity. BLL= before lung lavage; ALL= after lung lavage; VCV= volume controlled ventilation with PEEP; PRVCV= pressure regulated volume controlled ventilation (PCV) with I/E ratio 4:1; a= significantly different from ALL, VCV and PRVCV ($P<0.05$); b= significantly different from VCV and PRVCV ($P<0.05$); c= significantly different from ALL and VCV ($P<0.05$); d= significantly different from PRVCV ($P<0.05$).

In an editorial Lachmann (17) stressed that, a preset external PEEP will only balance the increased retractive forces of a part of the damaged lungs preventing their collapse during the expiration of the ventilatory cycle, but will still not be sufficient to keep all parts of the lungs open. Highly damaged lung regions will only be aereated at the end of inspiration and gas exchange may be highly decreased due to the short time of insufflation, whereas during the same period capillary perfusion is reduced by the high intra-alveolar pressure. Moreover, the applied external PEEP may probably lead to capillary compression

and ventilation/perfusion mismatching in the healthy regions of the lungs, which will be more prominent during the inspiration. Thus, in ARDS, the ventilatory support should open up closed units and keep them open and should avoid local hyperinflation. Once the alveoli are opened at PC-IRV, the PIP can be set at the level that balances elastic recoil caused by the increased surface forces. Ventilation is then achieved by briefly releasing that pressure so that expiration takes place without leaving time for alveolar collapse. By applying this concept the lung will be kept optimally open and be ventilated with a smaller intrapulmonary pressure amplitude compared to VCV-PEEP.

By studying ventilation inhomogeneity, as described by Huygen and colleagues (18), we recently demonstrated in an ARDS model that PC-IRV with inspiration/expiration (I/E) ratio of 4:1 provided significantly more homogeneous ventilation compared to VCV-PEEP, almost equal to the control values of the healthy lungs (fig. 1) (Kesecioglu J, Gültuna I, Ince C et al. 1993). These results confirm the beneficial effect of prolonged inspiration in stabilizing the airways and the alveoli and resulting in homogeneous ventilation.

Impact of high intrapulmonary pressure amplitude on barotrauma

In a mathematical modelling of the lung, Mead and colleagues (19) stated in 1970: "At a transpulmonary pressure of 30 cm H_2O, the pressure tending to expand an atelectatic region surrounded by a fully expanded lung would be approximately 140 cm H_2O". Such forces may well be a prime reason for structural damage to the bronchiolar and alveolar epithelium, as is typical for ARDS in the adult, and may not only form the basis for the formation of hyaline membranes but may also cause the release of mediators from the disrupted parenchyma - triggering the pathophysiological mechanisms of ARDS (17).

This hypothesis supported by clinical obeservation of Reynolds and coworkers (20)

who reported a decrease of mortality in neonates with RDS ventilated with pressure controlled ventilation (PCV) when PIP and intrapulmonary pressure amplitude were kept lower. Similarly improved survival is reported in ARDS patients ventilated with low V_T and intrapulmonary pressure amplitude (21) or when low frequency positive pressure ventilation with extracorporeal carbon dioxide removal method is used to provide lung rest and reduce ventilation (22).

Relation between ventilation pressure and alveolar pressure

There is a growing tendency of accepting end inspiratory plateau pressure (EIPP) as a more important determinant of barotrauma compared to PIP (23). There is a drop of pressure in the lungs from the first to the 23rd generation of airways as long as flow exists. Thus, PIP measured at the ventilator does not reflect the intra-alveolar pressure exactly in VCV-PEEP. On the other hand, the exact values of this pressure distribution during the inspiration phase, apart from the driving pressure from the ventilator and the EIPP is also not known. ARDS is a non-homogeneously distributed disease in the lungs, composed of healthy and a varying degree of damaged alveoli. Therefore, a large difference may exist in the pressure distribution within the lung during inspiration. Non-collapsed alveoli will receive the pressure early. The collapsed alveoli will be re-aereated at different times and this recruitment will partly continue during the inspiration pause. The pressures in the alveoli will decrease at end inspiration due to re-aereation of the atelectatic parts of the lung ("pendelluft"). Therefore at constant flow ventilation (VCV-PEEP) it is possible for some alveoli to receive higher pressures during the inspiration than the plateau pressure at end inspiration. As mentioned, this behaviour can take place only in VCV with an end inspiratory pause. In contrast, during PCV in no parts of the lung (independent of time and

re-aereation) can the pressure be higher than the preset pressure. In other words, at PCV "pendelluft" cannot occur.

The authors believe that the effects of PIP should not be underestimated as a cause of morphological damage (barotrauma), as this occurs not only in the alveoli but also in the higher airways. A good example of this is the hyaline membrane disease seen in neonates. In an animal model it has been shown that during mechanical ventilation the distal conducting airway rather than the alveolus may become the most compliant portion of the respiratory tract, and that interstitial emphysema, pseudocyst formation and pneumothorax appear to be a consequence of airway rather than alveolar rupture (24). Moreover, broncho-pulmonary dysplasia seen in mechanically ventilated neonates is closely related to morphological changes occurring in the mucosa and submucosa of the bronchi and bronchioles when high ventilation pressures are used (25).

Dependence of PaO_2 on ventilatory setting

Most studies report an improvement of oxygenation when PC-IRV is applied in severe ARDS patients already ventilated with VCV-PEEP (8-12). We have recently performed a prospective randomized controlled study on 38 ARDS patients comparing the effects of VCV-PEEP with PCV with different I/E ratios (Kesecioglu J, Lachmann B, Telci L et al. 1993). During the first 10 minutes of application of PCV a PIP of about 50 cm H_2O was applied to re-aereate atelectatic lung regions. Significant increases of PaO_2 values were obtained with increased I/E ratios at PCV (fig 2). Furthermore, a marked decrease of PIP, (from 48 cm H_2O to 30 cm H_2O) and intrapulmonary pressure amplitude (from 34 cm H_2O to 17 cm H_2O) was measured when switching from VCV to PCV mode with I/E 4:1 (Table 1).

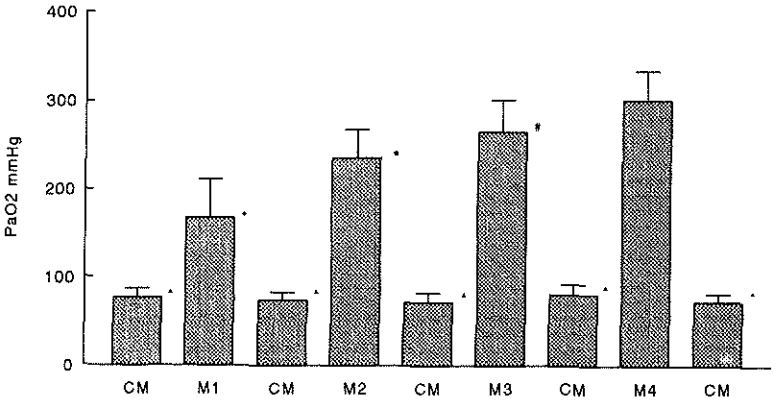

Fig.2. PaO_2 values obtained with the application of ventilation modes. CM= control mode; M= mode; M1=VCV-PEEP; M2=PCV with I/E 2:1; M3= PCV with I/E 3:1; M4= PCV with I/E 4:1; ▲= significantly different from M1, M2, M3 and M4 ($P<0.01$); += significantly different from M2, M3 and M4 ($P<0.01$); *= significantly different from M3 and M4 ($P<0.01$); #= significantly different from M4 ($P<0.01$).

Table 1. Parameters measured during the administration of trial modes of ventilation (mean±SD).

M	CM	M1	M2	M3	M4
n	38	38	38	38	38
PIP (cm H_2O)	33.8 ± 6.8	47.8 ± 10.3[a]	34.3 ± 4.0[b]	32.2 ± 4.5	30.4 ± 4.6
mPaw (cm H_2O)	9.2 ±4.3[c]	19.5 ± 6.1[d]	25.2 ± 3.6	26.5 ± 4.4	27.0 ± 3.7
EIPP (cm H_2O)	26.61 ±4.6	37.5 ± 5.3[a]	34.3 ± 4.0[b]	32.2 ± 4.5	30.4 ± 4.6
$PEEP_T$ (cm H_2O)	4[c]	14.2 ± 3.0[e]	8.5 ± 1.3[f]	10.5 ± 1.2	13.4 ± 1.1[e]
ΔP (cm H_2O)	28.3±3.1[c]	33.7±4.2[d]	26.3±2.1[f]	21.7±1.9	17.2±1.8[e]

n= number of patients; CM= control mode; M= mode; M1= VCV-PEEP; M2= PCV with I/E 2:1; M3= PCV with I/E 3:1; M4=PCV with I/E 4:1; PIP= peak inspiratory pressure; mPaw= mean airway pressure; EIPP= end inspiratory plataeu pressure; $PEEP_T$= total PEEP; ΔP= intrapulmonary pressure amplitude; values shown in CM, M1 are external PEEP and in M2, M3 and M4 are external PEEP+auto-PEEP. [a]= different from CM, M2, M3 and M4. [b]= different from M4. [c]= different from M1, M2, M3 and M4. [d]= different from M2, M3 and M4. [e]= different from M2 and M3. [f]= different from M3.

One of the explanations of these diseased lungs being succesfully ventilated with such a small intrapulmonary pressure amplitude can be explained by the law of La Place, $P = 2\gamma/r$ (P = pressure, γ = surface tension, r = radius), by assuming the presence of a high constant surface tension in these diseased lungs. In a recent editorial Lachmann (17)) also referred to this law as an explanation why surfactant-depleted ARDS-like lungs with a high and constant surface tension at the air liquid interface could be adequately ventilated with a low intrapulmonary pressure amplitude. "Since critical opening pressure is inversely proportional to alveolar unit size, it follows that progressive recruitment of air spaces requires a continuously rising pressure during inflation which is observed as high PIP and the pressure necessary to induce some volume changes depends on the initial radius. In other words, to get a certain volume change in a larger alveoli, the necessary pressure changes are much smaller compared to the alveolus which is collapsed or contains lower volume. It can further be derived from the law of La Place that the pressure necessary to keep the alveoli open is smaller at a high functional residual capacity (FRC) level. Therefore the PEEP necessary to stabilize the end expiratory collapse can be minimized if the lungs are totally opened up to an FRC level of a healthy lung". On the contrary, Lessard and colleagues (27) showed a decrease in PaO_2 with PC-IRV with I/E ratio 2:1 compared to VCV-PEEP. The application of a pressure in PC-IRV which is lower than the opening pressure can never recruit collapsed alveoli and therefore can never increase gas exchange, as explained in the previous paragraph.

Hemodynamic effects of different ventilatory settings

Any mode of mechanical ventilation is likely to cause a decrease in CO, when high intrapulmonary pressures are used. Several investigations have reported adverse

hemodynamic effects of PEEP in experimental animals (5) and ARDS patients (3,28). Others either found no significant changes in CO and right ventricular end diastolic volume (RVEDV) with up to 15 cm H_2O PEEP suggesting that RVEDV has no relationship to intra-alveolar distending pressures (29), or have reported that mean values for cardiac index (CI), systemic arterial blood pressure and systemic vascular resistance (SVR) do not correlate with the level of PEEP applied (30). Ellman and Dembrin (31) found no changes in CO with the application of up to 20 cm H_2O PEEP in ARDS patients. Similar controversies exist for the hemodynamic effects of inverse ratio ventilation. In our previously mentioned study on ARDS patients, we did not observe any deleterious effect of the used ventilatory settings with a proper fluid management combined with positive inotropic drugs. However, Cole and coworkers (32) observed a decrease in CO and oxygen delivery with I/E ratio of 4:1 but not with I/E ratios of 1.1:1 of 1.7:1. On the contrary no reduction of CO was observed by Lain and colleagues (12) with PC-IRV with I/E ratios up to 4:1. Poelaert and coworkers (33) even observed an increase in CI with I/E ratio of 4:1.

Several factors may contribute to the avoidance of hemodynamic depression during the ventilation of patients with ARDS. Extra fluid administration has been suggested to limit the adverse hemodynamic effects of PEEP (5). This procedure will prevent preload reduction and a decrease in CO. Inotropic drugs can also be used as an additional measure to maintain an optimal CO. Moreover, the high retractive forces in the ARDS lungs may also limit the airway pressures being transmitted to the pulmonary vasculature, which normally would result in a decreased preload.

To study the hemodynamic effects of different ventilatory settings, we have performed a study on 15 pigs with surfactant depleted lungs and compared the effects of VCV-PEEP, PCV with I/E 4:1 and low frequency positive pressure ventilation with

extracorporeal carbondioxide removal (LFPPV-ECCO$_2$R), (34). At the beginning of PCV and LFPPV-ECCO$_2$R modes high PIP of about 45 cm H_2O was applied for about 5 min to open the alveoli. Total-PEEP ($PEEP_T$ = external PEEP + auto PEEP) (about 15 cm H_2O) and mean airway pressures were kept almost identical in all modes. PaO_2 > 350 mmHg was achieved with all three modes.

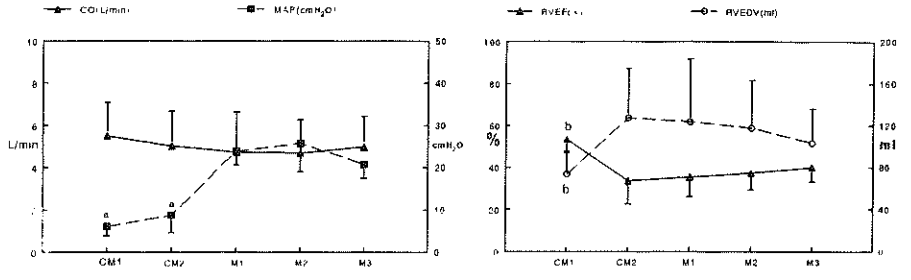

Fig.3. Hemodynamic changes observed with the application of different modes. CO= cardiac output; MAP= mean airway pressure; RVEF= right ventricular ejections fraction; RVEDV= right ventricular end diastolic volume; CM1= control mode before lung lavage; CM2= control mode after lung lavage; M1= VCV-PEEP; M2= PCV with I/E 4:1; M3= LFPPV-ECCO$_2$R; a= significantly different from M1, M2 and M3 ($P<0.01$); b= significantly different from CM2, M1, M2 and M3 ($P<0.01$).

No change of CO and RVEF was observed with increasing mPaw in the treatment groups compared to the control modes (fig 3). Similar to the results of our clinical study, PIP values were significantly lower with PCV and LFPPV-ECCO$_2$R (around 31 cm H_2O) compared to VCV-PEEP (around 45 cm H_2O).

These data support the results of other investigators who reported no deterioration of hemodynamics with the application of PEEP up to 20 cm H_2O.

Clinical applications

Three important questions remain in the clinical application of PC-IRV. First, when to apply it during the course of ARDS. Second, what are the rules for opening up the lung and keep it open and third how long to continue with PC-IRV. Our policy during recent years has been to apply PC-IRV at the earliest possible moment, preferably immediately after the diagnose of ARDS (within the first 24 hours), to achieve maximum recruitment with the lowest PIP and smallest intrapulmonary pressure amplitude.

In detail, we apply an I/E ratio of 2:1-4:1 with a frequency between 15-20 breaths/min at FiO_2 1.0. An external PEEP 4-6 cm H_2O is applied to get a higher $PEEP_T$. Under the these conditions we frequently measure arterial blood gases and increase PIP in steps of 3-4 cm H_2O to look for a dramatic improvement of PaO_2. If PaO_2 increases significantly it is assumed that most of the alveoli are recruited. At this opening procedure of the alveoli the cardiovascular system may be strongly affected due to high PIP and end-expiratory intra-alveolar pressures and therefore use of additional volume substitutes and/or positive inotropic drugs may be necessary. Once a dramatic increase of PaO_2 is observed after a period of 3-5 min we decrease the PIP to the lowest possible level to keep the alveoli open. This level is also monitored by PaO_2 measurement. It is important to realise that there is a delicate balance between opening and closing pressures of alveoli. In other words decreasing the PIP by 1-2 cm H_2O too much, can lead to a dramatic decrease in PaO_2. In case this happens one has to go back to the previous opening pressure. Then, knowing the pressure necessary to balance the increased retractive forces in the inspiratory phase, one has to look for the auto-PEEP which prevents end-expiratory collapse of the whole lung. By keeping the PIP constant we reduce the auto-PEEP either by decreasing the frequency or I/E ratio or external PEEP as long as PaO_2 remains constant. Once again if

PaO_2 deteriorates one has to repeat the whole procedure. Thus, if one follows this whole procedure, than it is possible to ventilate the patients with acute respiratory failure with intrapulmonary pressure amplitudes of 12-20 cm H_2O only, as demonstrated in Table 1. After the whole procedure we decrease the FiO_2 stepwise to a level to have a PaO_2 around 100 mg Hg.

Alternatively, those who have more experience with VCV-PEEP, can use this mode with standard V_T around 12 ml/kg. One can begin with 4 cm H_2O PEEP and increase it with 2 cm H_2O increments until a dramatic increase of PaO_2 is obtained (alveolar recruitment). The PIP observed at this PEEP level is accepted as our alveolar opening pressure for the collapsed parts of the lung. Then, one can switch to PC-IRV with the prefered I/E ratio and frequency, with PIP set above the level obtained with VCV-PEEP The PIP can be reduced thereafter as previously described.

When the pulmonary condition begins to improve inspiration time should be shortened and/or PIP should be lowered to avoid the airway pressure being transmitted to the capillary bed. This situation can be recognised as an improvement of compliance, increased MPAP and/or decreased CO and systemic blood pressure.

CONCLUSION

VCV-PEEP can provide adequate oxygenation in recruitable lungs with ARDS. However, it results in a high PIP. On the other hand, the results obtained in a number of studies discussed in this chapter stress the importance of the use and immediate effects of PC-IRV. It provides significant improvement of oxygenation and homogeneous ventilation. It does not depress hemodynamic functions when applied carefully in ill patients. Avoiding high

PIP and intrapulmonary pressure amplitude, it seems to be a safe form of management reducing the risk of barotrauma. However, the limited application periods in the studies performed so far, prevent further discussion on the effects of this mode over progressive lung injury or weaning of the patient from the ventilator, stressing the necessity for further randomized studies.

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CHAPTER 3

RESPIRATORY AND HEMODYNAMIC EFFECTS OF CONVENTIONAL VOLUME CONTROLLED PEEP VENTILATION, PRESSURE REGULATED VOLUME CONTROLLED VENTILATION AND LOW FREQUENCY POSITIVE PRESSURE VENTILATION WITH EXTRACORPOREAL CARBON DIOXIDE REMOVAL IN PIGS WITH ACUTE ARDS

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INTRODUCTION

Mechanical ventilation is an essential treatment strategy to relieve immediate hypoxemia in the adult respiratory distress syndrome (ARDS). While it is necessary to obtain optimal partial oxygen pressures in the arterial blood, it is even more important to deliver this oxygen to the tissues. This delivery, partly dependent on cardiac output (CO), is reported to be negatively affected by high intrapulmonary pressures applied during mechanical ventilation (1,2). Furthermore, some ARDS patients develop pulmonary hypertension, which leads to an increase of right ventricular (RV) afterload, progressing further to disturbances in left ventricular (LV) performance due to decreased preload and compliance (3).

Several mechanisms, including decreased venous return (4-8), increased RV afterload (9-11), decreased myocardial blood flow (12,13) and decreased LV compliance (14) have been described to explain the decrease in CO during the application of conventional volume controlled ventilation (VCV) with positive end-expiratory pressure (PEEP). On the other hand, some studies on ARDS patients fail to reveal negative effects of PEEP on CO (15-17).

Pressure controlled inverse ratio ventilation (PC-IRV) is described by Lachmann and colleagues as a good alternative to VCV with PEEP, providing alveolar stabilization by auto-PEEP (18). Furthermore, peak inspiratory pressure (PIP) can be kept at a lower level, thus minimizing the risk of barotrauma.

Low frequency positive pressure ventilation with extracorporeal carbon dioxide removal (LFPPV-ECCO$_2$R) was applied successfully by Gattinoni and co-workers in patients with ARDS (19). This mode allowed a reduction in the minute ventilation and PIP,

whilst adequately oxygenating the patient. Although ventilatory management is only partly performed with this method and CO_2 is removed by extracorporeal circulation, relatively high levels of PEEP (15-25 cm H_2O) are used during bypass and can have the same negative effects on CO due to the mechanisms mentioned above. There are many studies in which hemodynamic depression is caused by a high mean alveolar pressure (mPaw) or a high level of PEEP during conventional ventilation (6, 7, 10, 11). However, no studies on the effects of LFPPV-$ECCO_2R$ on the cardiovascular system have yet been reported. Morris and colleagues recently reported no difference in the survival rate of ARDS patients treated with LFPPV-$ECCO_2R$ or with continuous positive pressure ventilation with passive hypercapnia (20).

The aim of this study was to investigate whether there is any advantage of LFPPV-$ECCO_2R$ compared to VCV with PEEP and compared to PRVCV regarding arterial oxygenation, lung mechanics and hemodynamics in an animal model of acute respiratory failure when PEEP and tidal volume (V_T) had to be adjusted to keep $PaCO_2$ around 5.3 kPa and PaO_2 above 47 kPa.

METHODS

This study was performed at the Medical Faculty of Istanbul University. Approval of the local Animal Investigation Committee was obtained.

Fifteen adult male pigs, 43.81 ± 5.69 kg (range 35-50 kg) were premedicated with midazolam (0.5 $mg.kg^{-1}$) intramuscularly. Anesthesia was induced with thiopentone (2-4 $mg.kg^{-1}$), given through a 20 G cannula placed into an ear vein. Tracheostomy was performed and a portex tube ID 7 mm was inserted. The tube was fixed to the trachea with

stitches and the cuff was inflated to avoid air leakage. Thereafter, the lungs were ventilated with a Servo 900C ventilator (Siemens-Elema, Solna, Sweden). Anesthesia was maintained by infusion of midazolam (0.2 $mg.kg^{-1}.min^{-1}$) and fentanyl (2 $\mu g.kg^{-1}.min_{-1}$). Pancuronium bromide infusion (0.08 $mg.kg^{-1}.min^{-1}$) was administered for muscle relaxation after an initial bolus of 0.2 $mg.kg^{-1}$.

A 7 Fr three lumen catheter (Abbott Critical Systems, Chicago, USA) for fluid replacement and a modified 7.5 Fr pulmonary artery catheter equipped with a fast response thermistor (93A-431H, Edwards Lab, Santa Anna, USA) allowing measurement of right ventricular ejection fraction (RVEF) were inserted in the right internal jugular and femoral veins respectively.

Two 20 Fr canulas (Cook, Ontario, Canada) were inserted in the left internal jugular and in a femoral vein for the administration of extracorporeal circulation. A femoral artery was cannulated for blood sampling and invasive blood pressure monitoring. An 18 Fr Foley urine catheter was placed into the bladder by cystostomy to monitor urinary output.

Mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP) and central venous pressure (CVP) were evaluated at the end of expiration by Viggo Spectramed transducers on a Horizon 2000 (Mennen Medical, Rehovot, Israel) as well as the heart rate (HR). CO and RVEF were measured by the thermodilution technique with a Baxter REF1 computer (Edwards Lab, Santa Anna, USA) by means of two to four 10-ml injections of cold ($<8°C$) saline given randomly during the ventilatory cycle (21). The following formulas were used for calculation of the hemodynamic parameters: stroke volume (SV) (ml) = CO x 1000/HR; stroke index (SI) $ml.m^{-2}$ = SV/body surface area (BSA) (using a scale prepared for humans); left ventricular stroke work index (LVSWI) ($g.cm.m^{-2}$) = 0.0136 (MAP - PCWP)

x SI; right ventricular stroke work index (RVSWI) ($g.cm.m^{-2}$) = 0.0136 (MPAP - PCWP) x SI; systemic vascular resistence (SVR) ($dyn.s.cm^{-5}$) = 80 (MAP - CVP)/CO and pulmonary vascular resistence (PVR) ($dyn.s.cm^{-5}$) = 80 (MPAP - PCWP)/CO.

Arterial blood gases were determined by the ABL 300 (Radiometer, Copenhagen, Denmark). Respiratory system compliance (C_{RS}) and best-PEEP were measured and calculated with a computer, Compli 80 System (Kontron, Milan, Italy). In this system, a pressure-volume curve was determined after disconnecting the pigs from the ventilator and allowing the lungs to collapse (zero PEEP). Then an automatically driven syringe (1.5 L) inflated the lungs by stepwise movements of 100 ml air, to a total volume of 10 ml/kg body weight. C_{RS} was calculated by the computer as the ratio between the inspiratory volume and the pressure difference. Best-PEEP was calculated by the computer as the minimal pressure at which the pressure-volume curve became linear and corresponds to the pressure at which PEEP must be set to increase functional residual capacity (22). A centrifugal pump (Biomedicus, Minneapolis, USA) and membrane lungs (SciMed, Minneapolis, USA) were used for $ECCO_2R$. The membrane lungs were each ventilated with 10 l of humidified pure O_2.

After completing baseline measurements, respiratory failure was induced by surfactant depletion by lung lavage repeatedly performed with 50 $ml.kg^{-1}$ of warm saline solution at 5-10 min intervals until a PaO_2 < 13 kPa was achieved (23). Before lavage [control mode (CM 1)], during and after lung lavage (CM2) lungs were ventilated with VCV with a preset static-PEEP (PEEPs) of 4 cm H_2O, V_T 8-12 $ml.kg^{-1}$, frequency (f) 12 $breaths.min^{-1}$, I/E ratio 1:2 (25% I, 10% pause) and FiO_2=1.0.

After a stabilization period of about 15 min randomly applied modes of ventilation to achieve PaO_2 >47 kPa and $PaCO_2$ about 5.3 kPa were as follows:

Mode 1 (M1): VCV with measured best-PEEP, V_T 8-12 ml.kg^{-1}, f 12 breaths.min^{-1} and I/E ratio 1:2 (25% I, 10% pause).

M2: PRVCV with PEEPs 4 cm H_2O, f 12 breaths.min^{-1}, PIP adjusted to get a V_T 8-12 ml.kg^{-1} and I/E ratio 4:1 (80% I). Around 45 cm H_2O PIP was applied during the first 5 min to open the alveoli.

M3: LFPPV with measured best-PEEP, tidal V_T 5 ml.kg^{-1}, f 5 breaths.min^{-1} and I/E ratio 1:2 (25% I, 10% pause); 1-2 l.min^{-1} O_2 given through a catheter (ID 1 mm) inserted through the tracheal tube and advanced to the level of the carina; $ECCO_2R$ with a pump speed of 20-30% of the CO measured during CM2 and membrane lungs with a surface area of 7 m^2 (19) were used. V_T was adjusted to achieve a PIP of 45 cm H_2O during the first 5 min to open the alveoli.

Fluid was administered to keep CVP between 7-14 mmHg. Measurements were made 60 min after changing the ventilatory mode. Total-PEEP ($PEEP_T$ = PEEPs + auto-PEEP) of M2 displayed by pressing the end-expiratory hold button, PIP and mPaw of all modes displayed by the ventilator were recorded. Intrapulmonary pressure amplitude (ΔP), defined as the difference between $PEEP_T$ or PEEPs and PIP, were recorded. Before the use of different ventilatory settings, CM2 was applied for 30 minutes to investigate whether any changes in gas exchange had occurred over time.

Data were compared by a two-way analysis of variance (ANOVA) test. All data are expressed as mean $\pm$ SD. Student's t-test was used for pair-wise comparisons. Significance was considered at $P < 0.01$.

RESULTS

PaO_2 and $PaCO_2$ values are shown in figures 1 and 2. No statistical significance was observed between the PaO_2 values of all CM2 modes of ventilation that were applied before changing to a different mode. During M3 significantly higher PaO_2 values compared to M1 were obtained. No statistically significant difference was observed in $PaCO_2$ values between the groups.

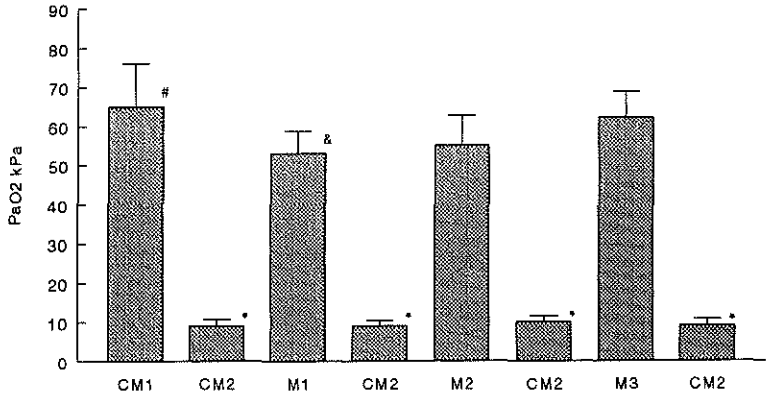

Figure 1: Changes in PaO_2 during the application of modes. For legends see text.

#= significantly different from CM2 and M1 ($P<0.01$); *= significantly different from CM1, M1, M2 and M3 ($P<0.01$); &= significantly different from M3 ($P<0.01$).

The values of lung mechanics including PIP, mPaw, $PEEP_T$, ΔP, C_{RS} and expired minute ventilation (V_E) measured during the application of each mode, together with the baseline measurements, are listed in Table 1. PIP values with M2 and M3 were significantly lower compared to those with M1. No difference in mPaw values was observed between M1, M2 and M3; however these values were significantly higher compared to CM1 and CM2. ΔP was significantly lower with M2 and M3 compared to

M1.

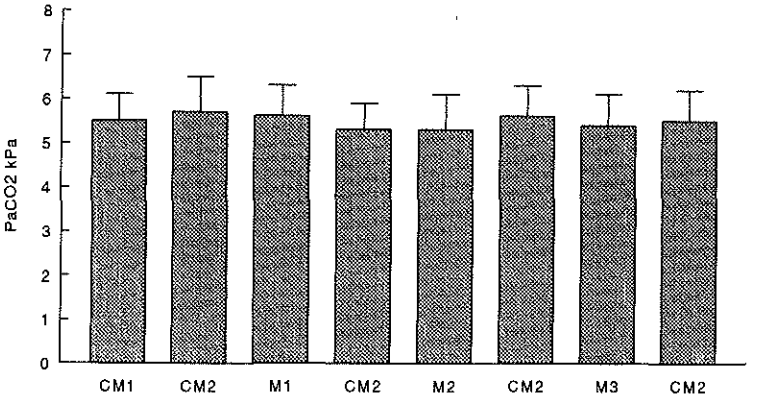

Figure 2: $PaCO_2$ values measured during the study. For legends see text. No difference was observed between any of the groups.

Data on the changes in hemodynamic parameters are given in Table 2. Although a slight decrease in CO was observed with the treatment groups compared to CM1 and CM2, this difference was not significant. The pump speed adjusted according to the CO at the CM2 was 1.0 ± 0.1 l in M3. A significant decrease in RVEF and a significant increase in MPAP, PVR and RVSWI were observed after lung lavage. PCWP increased significantly with the administration of the treatment modes. No significant changes were observed between groups concerning the other measured hemodynamic variables.

DISCUSSION

The basic principle of respiratory support in ARDS should be to administer adequate

pressure in the lungs during the inspiratory phase to overcome the critical opening pressure of the collapsed alveoli and by maintaining this pressure to prevent their closure during expiration (24). In order to obtain optimal gas exchange in ARDS the use of high intrapulmonary pressures are usually necessary. However, if not meticulously controlled these pressures may lead to a disturbance of cardiovascular functions which will be followed by a further impairment of O_2 transport to the tissue. This situation may give rise to a conflict between the concept of providing gas exchange and the simultaneous need to protect against hemodynamic depression and barotrauma.

Table 1. Respiratory parameters during the administration of ventilatory modes.

n=15	CM1	CM2	M1	M2	M3
PIP (cmH_2O)	16.8 ± 4.4^a	32.3 ± 8.7	45.4 ± 8.5^b	31.5 ± 7.7	30.7 ± 6.0
mPaw (cmH_2O)	6.1 ± 2.2^c	8.8 ± 4.1^c	23.9 ± 3.4	25.7 ± 6.7	20.5 ± 3.3
$PEEP_T$ (cmH_2O)	4^c	4^c	14.1 ± 3.9	15 ± 3.3	16.9 ± 2.9
ΔP (cmH_2O)	13.1 ± 3	27.8 ± 3.4^d	31.2 ± 3.3^d	15.7 ± 3.4	15.4 ± 3.2
C_{RS} ($ml.cmH_2O^{-1}$)	47.3 ± 5.8^a	25.7 ± 4.4^c	30.9 ± 3.8	32.2 ± 3.0	34.8 ± 3.7
V_E ($l.min^{-1}$)	5.0 ± 1.1	5.0 ± 0.9	4.8 ± 0.9	4.9 ± 1.0	1.0 ± 0.4^e

Values are presented as mean $\pm$ SD. For legends see text. a=significantly different from CM2, M1, M2 and M3 ($P<0.01$); b=significantly different from CM2, M2 and M3 ($P<0.01$); c=significantly different from M1, M2 and M3 ($P<0.01$); d=significantly different from CM1, M2, and M3 ($P<0.01$); e= significantly different from CM1, CM2, M1 and M2 ($P<0.01$).

Application of PEEP is the therapeutic modality usually considered when investigating the effect of mechanical ventilation on gas exchange or on the cardiocirculatory system in ARDS. The PEEP level used did not differ significantly in all our treatment modes. In VCV, measurement of best-PEEP described by Gattinoni and

colleagues (22) was used to get the required oxygenation. However, the needed ventilation to keep $PaCO_2$ around 5.3 kPa resulted in a high PIP of around 45 cm H_2O, which is known to be associated with a risk of barotrauma due to high shear forces leading to morphological damage of the lungs (25-30). In PRVCV, high mPaw was obtained by increasing the inspiratory time to 80% of the respiratory cycle leading to an auto-PEEP of around 11 cm H_2O.

Table 2. Hemodynamic parameters during the administration of ventilation modes.

n=15	CM1	CM2	M1	M2	M3
CO ($l.min^{-1}$)	5.5±1.6	5±1.6	4.7±1.9	4.7±1.9	5±1.4
RVEF (%)	53.4±5.7[a]	33.6±11.1	35.2±9.2	37.3±8.2	39.9±6.8
HR ($beats.min^{-1}$)	164±23	156±34	160±15	154±20	150±22
SV (ml)	38.0±8.7	39.2±11.4	38.0±13.0	38.3±13.7	39.9±17.3
RVSWI ($g.cm.m^{-2}$)	7.8±2[a]	12.5±4.3	11.8±3.8	11.4±3.8	10.4±2.7
LVSWI ($g.cm.m^{-2}$)	66.4±21.6	60.8±17.8	58.8±23.3	56.0±17.7	54.6±18.1
MPAP (mmHg)	25.8±4.4[a]	35.1±4.1	32.2±5.1	35.4±4.6	34.8±4.2
PCWP (mmHg)	12.7±5.9	14.9±5.2	17.9±4.6	16.6±4.2	16.8±4.4
CVP (mmHg)	9.8±2.9	10.1±2.3	11.0±2.2	11.7±2.1	12.5±2.7
MAP (mmHg)	130±17	133±22	125±19	120±22	121±15
PVR ($dyn.s.cm^{-5}$)	208±165[a]	374±220	406±245	400±245	394±246
SVR ($dyn.s.cm^{-5}$)	1757±488	1711±551	1623±488	1600±499	1590±506

Values are presented as mean±SD. For legends see text. a=significantly different from CM2, M1, M2 and M3 ($P<0.01$).

In spite of technical differences, the concept of increased mPaw is also true for LFPPV-ECCO$_2$R. By applying PEEP of around 17 cm H_2O almost the same PIP as with PRVCV was obtained. However, V_T was restricted to 5 ml/kg, thus elevation of PIP to above 35-40 cm H_2O was avoided. The slightly higher PaO_2 values obtained with LFPPV-ECCO$_2$R was probably due to the ventilation of the membrane lungs with O_2 in addition to the intrapulmonary administration of oxygen (via the catheter).

ARDS is characterized by an increase in permeability of the pulmonary microvascular bed and pulmonary hypertension eventually leading to disturbances in RV function, even with a normal myocardium (31). The results of this study show that induction of respiratory failure by lung lavage produces a significant decrease in RVEF. Parallel to this finding, MPAP and PVR increased significantly, indicating an increase in afterload and a deterioration in the right ventricular performance, thereby producing a suitable ARDS model (similar to the clinical findings) for the evaluation of the hemodynamic effects of mechanical ventilation.

No further deterioration in hemodynamic parameters was observed after surfactant depletion with the application of the treatment modes compared to CM2. In spite of the sustained depression of RV performance seen after lung lavage, LV functions were well preserved. The changes in CO and LVSWI were non-significant, perhaps due to keeping CVP levels around 10-13 mmHg, thereby preventing preload reduction and a significant decrease in CO.

Our data concerning hemodynamic functions are in accordance with those of Ellman and Dembrin (17) who also reported no changes in these parameters with the application of up to 20 cm H_2O PEEP in ARDS patients. They related their findings to the application of ventilation in the assist mode, avoidance of the use of sedatives and narcotics, and

avoidance of hypovolemia. Controlled ventilation, sedative and narcotic drugs were used in our study but hypovolemia was also avoided, which might explain the similar results.

Contrary to our findings, several investigators have reported adverse hemodynamic effects of PEEP in experimental animals (6) and ARDS patients (2,14). No further change seen in already deteriorated RV functions in our study supports the findings of Schulman and colleagues (32), who reported a very small decrease in RVEF with up to 20 cm H_2O PEEP in patients with deteriorated baseline RV functions. Similarly, other studies have reported either no worsening of the already decreased LV compliance after the administration of PEEP (33), or found no significant changes in CO and RVEF with up to 15 cm H_2O PEEP in patients after thorocotomy (34), or have reported that mean values for cardiac index, systemic arterial blood pressure and systemic vascular resistance (SVR) do not correlate with the level of PEEP applied (15). On the other hand, Downs and colleagues (16) demonstrated an increase in CO in most of the patients with the application of up to 20 cm H_2O PEEP, which was reflected by an decrease in the difference between arterial blood O_2 content (CaO_2) and pulmonary arterial blood O_2 content (CvO_2).

VCV with best-PEEP provides adequate oxygenation. However, it results in high PIP. On the other hand PRVCV with an I/E ratio of 4:1 and LFPPV-ECCO$_2$R have comparable results with respect to gas exchange, airway pressures and hemodynamic parameters with low PIP. However important differences exist between these two modes. LFPPV-ECCO$_2$ is more than just a ventilation mode. It is invasive, expensive, needs additional equipment, and involves special training of and attention from the attending medical staff. While the latter two factors also apply to PRVCV, it is still only another form of ventilation which can be used more routinely rather than in specialized centers. The period of investigation was limited to 1 hour with each mode and it is still difficult to

speculate about the long term effects of the techniques used in this study. However, considering the results obtained, it is concluded that in this animal model of acute ARDS in whom most of the alveoli are recruitable, PRVCV is an adequate form of treatment without necessitating further invasive measures.

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CHAPTER 4

EFFECTS OF DIFFERENT MODES OF VENTILATION ON OXYGENATION AND INTRACRANIAL PRESSURE OF PIGS WITH SURFACTANT DEPLETED LUNGS

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INTRODUCTION

In cases where the diseased state of the patient is caused or further complicated by a brain injury, conflict can arise between the need to provide adequate gas exchange and the simultaneous need for protection of the brain against a possible increase of intracranial pressure (ICP) due to the ventilatory modes used.

The effect of positive end-expiratory pressure (PEEP) on ICP has been reported by various investigators, without any consensus being reached (1-10). While the application of PEEP resulted in increases in ICP in some studies (1,2), other researches failed to demonstrate an increase of this parameter with a clinical consequence (3). Because of this reason volume controlled ventilation (VCV) with PEEP, pressure regulated volume controlled ventilation (PRVCV) with an inspiratory/expiratory (I/E) ratio of 4:1 and low frequency positive pressure ventilation with extracorporeal CO_2 removal (LFPPV-ECCO$_2$R) were compared in normovolemic isocapnic pigs in supine posture, with surfactant depleted lungs. The aim of the study was to investigate the influence of these different modes of gas exchange on ICP.

METHODS

This study was performed at the Medical Faculty of Istanbul University. Approval of the local Animal Investigation Committee was obtained.

Six male pigs, 41.2 ± 2.7 kg were premedicated with midazolam (0.5 mg/kg) intramuscularly. Anesthesia was induced with thiopentone (2-4 mg/kg), given through a 20 G cannula placed into an ear vein. Tracheostomy was performed and a portex tube with an

internal diameter of 7 mm was inserted. The tube was fixed to the trachea with stitches and the cuff was inflated to avoid air leakage. Lungs were ventilated with a Servo 900C (Siemens-Elema, Solna, Sweden) ventilator thereafter. Anesthesia was maintained by infusion of midazolam (0.2 mg/kg/min) and fentanyl (2 μg/kg/min). Pancuronium bromide (0.08 mg/kg/min) infusion was administered after a bolus of 0.2 mg/kg for muscle relaxation.

A 7F three lumen catheter for adequate fluid replacement to avoid hypovolemia and a 7F thermodilution catheter for hemodynamic monitoring were inserted to the surgically exposed right and left internal jugular veins respectively. The needle and the Seldinger guide wire provided with the system were used for insertion and the ligature of the vessels was avoided in order not to obstruct venous flow.

Two 20F cannulae were inserted to the right and left femoral veins for the administration of extracorporeal circulation. The femoral artery was cannulated for blood sampling and invasive blood pressure monitoring. An 18F urine catheter was placed into the bladder by cystostomy to monitor urine output.

ICP was monitored by a 22G catheter introduced to the ventricule through a twist drill hole, 2 cm lateral to the midline and 1 cm posterior to the coronary suture. ICP and cardiac output (CO) measurements were made on a Horizon 2000 (Mennen Medical, Rehovot, Israel) monitor.

Arterial blood gases were determined by ABL 300 and OSM Hemoximeter (Radiometer, Copenhagen, Denmark). Total static lung compliance (TSLC) and best-PEEP were measured with the Compli 80 System (Kontron, Milan, Italy). In this system, the pressure-volume curve was determined by using a stepwise inflation of the lungs (100 ml per step), starting at atmospheric pressure and continuing to a total volume of 10 ml/kg

inflation. TSLC was computed as the ratio between the volume from the inflation limb of the pressure-volume and the corresponding pressure difference. Best-PEEP was computed as the minimum pressure at which the slope of the pressure-volume curve became linear. Total PEEP [$PEEP_T$ = static-PEEP (PEEPs) + auto-PEEP] of PRVCV mode was displayed by the ventilator by pressing the end-expiratory hold button. A centrifugal pump (Biomedicus, Minneapolis, U.S.A.) and membrane lungs (SciMed, Minneapolis, U.S.A.) were used for $ECCO_2R$. The membrane lungs were each ventilated with 10 l/minute of humidified O_2.

After completing baseline measurements the pigs were subjected to lung lavage; 50 ml/kg of warm saline solution was used to establish a model of ARDS. PaO_2 < 100 mm Hg at CM 2 was accepted as ARDS.

Thereafter different modes of ventilation were applied:

CM 1: VCV with a preset PEEPs 4 cm H_2O, V_t 10-15 ml/kg, frequency (f) 12 breaths/min and I/E ratio 1:2 (25% I, 10% pause).

CM 2: As CM 1. After lung lavage.

Mode (M) 1: VCV with measured best-PEEP, V_t 10-15 ml/kg, f 12 breaths/min and I/E ratio 1:2 (25% I, 10% pause).

M 2: PRVCV with PEEPs 4 cm H_2O, PIP adjusted to get a V_t 10-15 ml/kg, f 12 breaths/min and I/E ratio 4:1 (80% I).

M 3: LFPPV with measured best-PEEP, V_t 5 ml/kg, f 5 breaths/min and I/E ratio 1:2 (25% I, 10% pause) 1-2 l/min O_2, given through a catheter (ID 1 mm), inserted through the tracheal tube and advanced to the level of the carina; $ECCO_2R$ with a pump speed of 20-30% of the CO measured during CM2 and two membrane lungs with a surface area of 3.5 m^2 each.

FiO_2 was 1.0 in all modes. Measurements were made 60 minutes after changing the ventilatory mode. The ventilation modes were adjusted to get an equal $PaCO_2$ values and PaO_2 values above 350 mm Hg. After lavage ARDS was reconfirmed when switching from one mode to the other by repeating CM as an intermediate step. Pigs which became hemodynamically unstable at any time during the course of the study were excluded.

Data were compared among the groups by two way analysis of variance (ANOVA) test. All data are expressed as mean ± SD. Student's t-test was used for pairwise comparisons. Significance was considered at $P<0.01$.

RESULTS

The arterial blood gas values PaO_2 and $PaCO_2$ are shown in figures 1 and 2. Higher PaO_2 values were obtained with the application of M3. $PaCO_2$ values were kept similar in all modes of both groups.

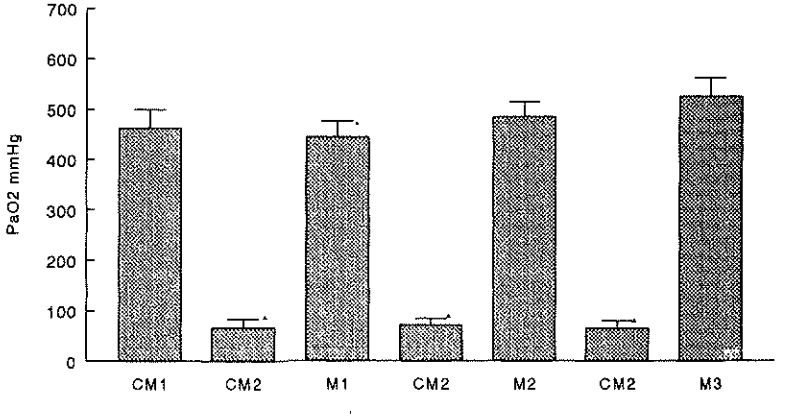

Figure 1. PaO_2 data of the trial modes. ▲ significantly different from CM1, M1, M2 and M3 ($P<0.01$); * significantly different from M3 ($P<0.01$). For legends see text.

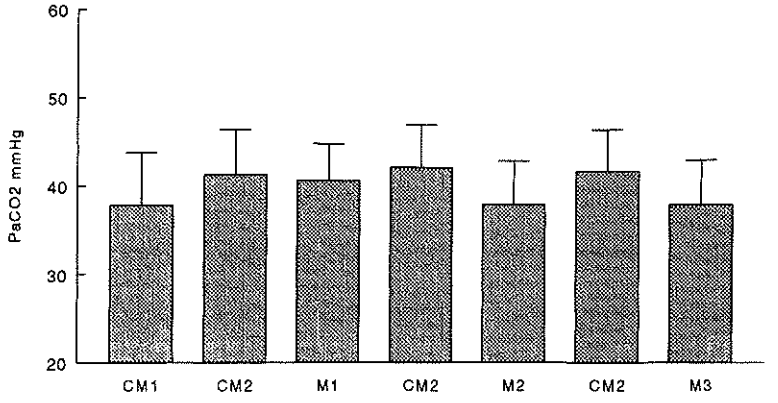

Figure 2. $PaCO_2$ data of the trial modes. No differences were found between the groups.

For legends see text.

Changes in ICP and CO during the application of each mode along with the baseline measurements in both groups are shown in figure 3. No significant change of ICP and CO was observed with the treatment modes compared to the control mode after lung lavage. No differences were observed between the effects of M1, M2 and M3 on ICP and CO in both groups.

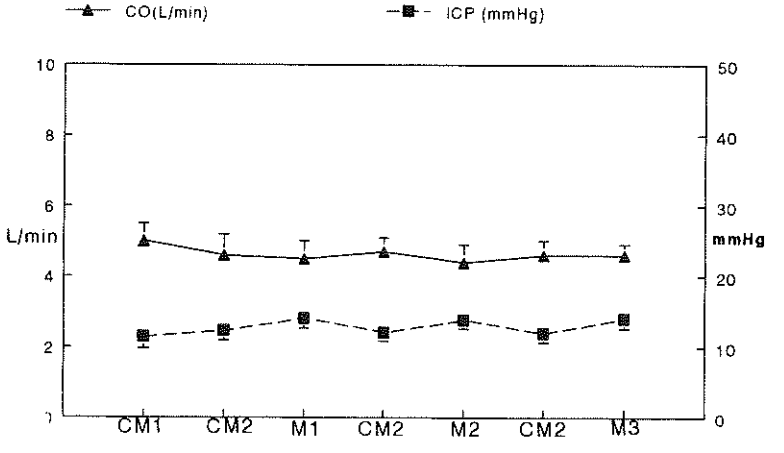

Figure 3. ICP and CO data of the trial modes. No differences were found between the groups. For legends see text.

Data on $PEEP_T$ and TSLC are depicted in Table 1. No difference was observed between the $PEEP_T$ levels in M1, M2 and M3. TSLC was decreased significantly after the application of lung lavage.

Table 1. TSLC and PEEPi values measured during the administration of trial modes of ventilation (mean ± SD)

	TSLC (ml/cm H_2O)	PEEPi (cm H_2O)
CM1	44.9±4.6[a]	4[b]
CM2	21.5±3.9[b]	4[b]
M1	33.1±2.6	12.9±1.7
CM2	22 ±3.4[b]	4[b]
M2	33 ±2.5	13.6±1.4
CM2	21.8±3.7[b]	4[b]
M3	35.1±2.1	14.3±1.3

TSLC= total static lung compliance; $PEEP_T$= total-PEEP; values shown in CM1, CM2, M1 and M3 are static-PEEP and in M2 is static-PEEP + auto-PEEP.
a= significantly different from CM2,M1, M2 and M3 ($P<0.01$)
b= significantly different from M1, M2 and M3 ($P<0.01$)

DISCUSSION

The aim of ventilatory therapy in ARDS is to provide oxygenation and opening of the recruitable alveoli. A critical pressure has to be applied to the alveoli in order to achieve these goals. A meticulous selection of ventilatory mode and pressures are essential to avoid complications such as barotrauma, hemodynamic depression or increased ICP (11). On the other hand serious depression of circulation or increase in ICP should not be expected as long as the applied pressure is precisely adjusted to balance the surface tension and preventing its transmission to the vascular bed (12).

In this study best-PEEP measurements allowed us to apply the desired amount of end expiratory pressure to provide adequate gas exchange without an elevation of ICP.

The results of this study show that PRVCV and LFPPV-ECCO$_2$R yielded higher PaO_2 values compared to VCV with PEEP. Minimal changes in ICP and CO were observed after lung lavage suggesting the existence of a protective mechanism of the ARDS in this model. This protection was probably due to a significant decrease in TSLC due to the surfactant depletion caused by lung lavage.

PRVCV and LFPPV-ECCO$_2$R proved to be superior modes compared to VCV with PEEP since in addition to the lack of their negative effect on ICP and hemodynamics they provided better oxygenation, suggesting their use in ARDS patients with elevated ICP and deteriorated surfactant system.

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CHAPTER 5

EFFECTS OF DIFFERENT MECHANICAL VENTILATION MODES ON OXYGENATION IN SURFACTANT DEPLETED RABBIT LUNGS

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INTRODUCTION

Application of conventional volume controlled ventilation (VCV) with positive end-expiratory pressure (PEEP) is usually a successful immediate therapy to relieve hypoxemia in acute respiratory failure (ARF) (1). However, this form of ventilation is associated with high tidal volumes (V_T) and high peak inspiratory pressures (PIP) which are suggested to cause barotrauma and morphological changes in the lungs (2-5).

Pressure controlled inverse ratio ventilation (PC-IRV) is reported (6,7) as a method providing better oxygenation with lower PIP, compared to VCV with PEEP.

High frequency ventilation (HFV) is another model preventing further lung injury due to a low V_T and its successful use in providing gas exchange are reported (8,9). However, HFV has some limitations in application in humans as monitoring of the respiratory variables, alarm systems and humidification of gases are sometimes not suitable for long-term use.

On the other hand, superimposing HFV on the expiratory phase of pressure regulated volume controlled ventilation (PRVCV) with an inspiration/expiration (I/E) ratio 4:1, is expected to provide a further increase of mean airway pressure (mPaw) and auto-PEEP leading to an improvement of oxygenation and CO_2 elimination, while an increase in PIP levels are avoided.

Therefore aiming to achieve a PaO_2 level above 300 mmHg by adjusting preset static-PEEP ($PEEP_S$) and PIP levels, and almost constant expiratory minute volumes (V_E), VCV with PEEP, PRVCV with an I/E ratio 4:1 and superimposed expiratory HFV on PRVCV with an I/E ratio 4:1 (SEHFV-PRVCV) were investigated in this study, concerning their influence on gas exchange and lung mechanics in surfactant depleted rabbit lungs.

METHODS

The study protocol was approved by the Animal Care Committee of Erasmus University Rotterdam, The Netherlands.

Six male New Zealand rabbits, 2.8±0.2 kg (range 2.6-3.2 kg), were used in this study. Anesthesia was induced with pentobarbital given intravenously through a 22 G cannula placed into an ear vein. Tracheostomy was performed and a tube ID 3 mm with two additional side entrances for HFV and airway pressure monitoring was inserted. The tube was fixed tightly to the trachea to avoid air leakage. Anesthesia was maintained with infusion of pentobarbital and fentanyl. Pancuronium bromide was administered for muscle relaxation. The lungs were ventilated with Servo 900C (Siemens-Elema, Solna, Sweden). SEHFV was performed with a high Frequency Unit 970 (Siemens-Elema, Solna, Sweden) connected to and triggered by the Servo ventilator 900C.

A catheter was placed in the femoral artery for invasive arterial blood pressure monitoring and blood sampling. Cardiovascular monitoring was done by means of a Marquette monitor system 7000™ (Marquette Electronics Inv. Milwaukee, Ws, USA) and printed directly with a Marquette monitor printer 7100. Arterial blood gases were measured with the blood gas analyzer ABL 330 (Radiometer, Copenhagen). Total PEEP [$PEEP_T$ = static-PEEP (PEEPs) + auto PEEP] were displayed by pressing the end-expiratory hold button of the ventilator, PIP and mPaw as displayed by the ventilator and intrapulmonary pressure amplitude (ΔP), defined as the difference between PIP and $PEEP_T$, or PEEPs were recorded.

After completing baseline measurements, respiratory failure was induced by surfactant depletion by lung lavage performed four times with 100 ml warm saline (2) to

produce a PaO_2 between 40 and 70 mmhg. Before lavage [control mode (CM) 1], during and after lung lavage (CM2) the lungs were ventilated with VCV with a preset PEEPs of 4 cm H_2O V_T 12 ml/kg, frequency (f) 30 breaths/min and I/E ratio 1:2 (25% I, 10% pause).

After a stabilization period of 15 min randomly applied modes (M) of ventilation to achieve a PaO_2 above 300 mmHg and constant V_E were as follows:

M 1: VCV with a $PEEP_S$ between 8 and 14 cm H_2O to achieve PaO_2 above 300 mmHg, f 30 breaths/min, V_T 12 ml/kg and I/E ratio of 1:2 (25% I, 10% pause).

M 2: PCVRV with f 30/min and I/E ratio of 4:1 (80% I). 35 cm H_2O PIP was applied during the first 5 minutes of artificial ventilation for alveolar recruitment. PIP was then reduced to a level of 1-2 cm higher then the opening pressure of the alveoli. PEEPs was adjusted to keep V_T at 12 ml/kg.

M 3: PCVRV with f 30/min and I/E ratio of 4:1 (80% I). 35 cm H_2O PIP was applied during the first 5 minutes of artificial ventilation for alveolar recruitment. PIP was then reduced to a level of 1-2 cm higher then the opening pressure of the alveoli. PEEPs was adjusted to keep V_T at 12 ml/kg. Additionally an open system was connected to flush the airways with SEHFV with a f 15 Hz, V_T 0.3 ml/kg and pulse duration of 20%.

FiO_2 was 1.0 in all modes. The rabbits were treated 30 minutes with each mode and the measurements were made thereafter. Before the use of different ventilatory settings CM2 was applied for 30 min to investigate whether any changes in gas exchange occurred over time.

Data were compared by two-way analysis of variance (ANOVA) test. All data are

expressed as mean ± SD. Student's t-test was used for pair-wise comparisons. Significance was considered at $P < 0.05$.

RESULTS

With the same minute ventilation, PRVCV increased oxygenation significantly compared to control modes and M1. M3 also improved PaO_2 values but SEHFV in this mode did not produce significant changes compared to M2 (Figure 1). $PaCO_2$ decreased significantly with the application of M2 and M3. SEHFV did not further effect CO_2 elimination (figure 2).

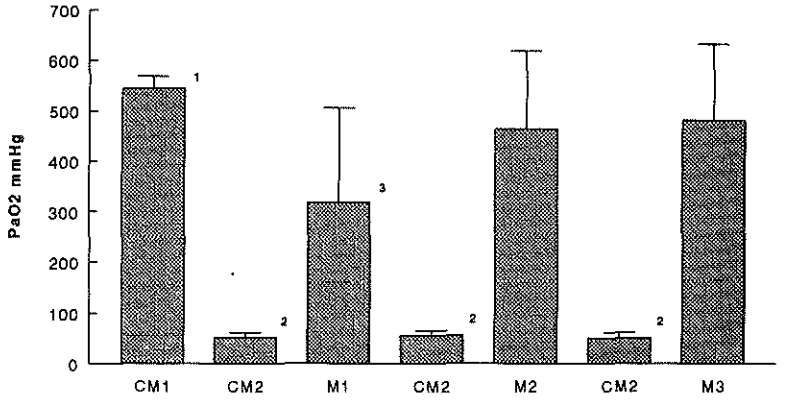

Figure 1. PaO_2 values observed during the study. For legends see text. 1= significantly different from CM2 and M1 ($P<0.05$); 2= significantly different from M1, M2 and M3 ($P<0.05$); 3= significantly different from M2 and M3 ($P<0.05$).

PEEPs in M1 and $PEEP_T$ measured in M2 and M3 were similar and no statistical significance was observed between groups. ΔP was significantly higher M1 compared to M2 and M3. PIP values were significantly lower and mPaw values were significantly higher in M2 and M3 compared to the VCV with PEEP (Table 1).

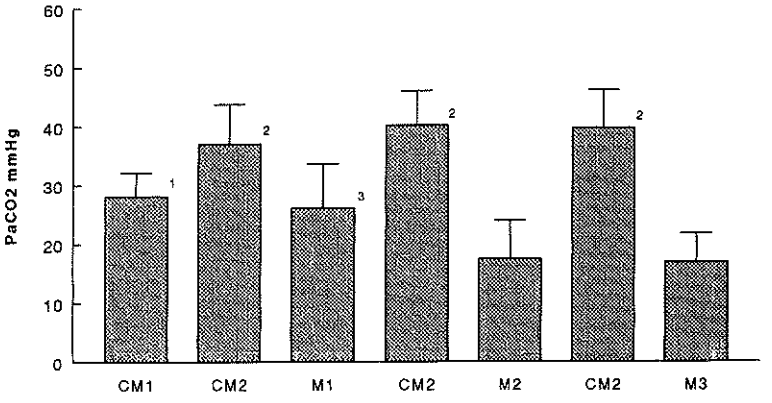

Figure 2. $PaCO_2$ values observed during the study. For legends see text. 1= significantly different from CM2, M2 and M3 ($P<0.05$); 2= significantly different from M1, M2 and M3 ($P<0.05$); 3= significantly different from M2 and M3 ($P<0.05$).

Table 1. Lung mechanics parameters during the application of ventilatory modes (mean±SD).

n= 9	PIP (cm H_2O)	mPaw (cm H_2O)	$PEEP_T$ (cm H_2O)	ΔP (cm H_2O)
CM1	15.8 ± 1.3[a]	6.8 ± 1.0[a]	4[c]	11.2 ± 0.9[a]
CM2	26.3 ± 3.0	8.7 ± 0.8[c]	4[c]	22.8 ± 1.7[d]
M1	37.1 ± 7.0[b]	17.2 ± 4.4[d]	13.2 ± 1.8	24.3 ± 5.4[d]
CM2	24.3 ± 3.2	8.7 ± 0.9[c]	4[c]	20.9 ± 1.8[d]
M2	28.5 ± 2.3	23.8 ± 2.1	13.4 ± 2.1	14.6 ± 2.0
CM2	25.9 ± 2.8	8.0 ± 0.9[c]	4[c]	21.3 ± 2.3[d]
M3	28.7 ± 3.7	24.9 ± 2.1	14.2 ± 2.3	14.7 ± 2.6

For legends see text. a= Significantly different from CM2, M1, M2 and M3 ($p<0.05$).
b= Significantly different from CM2, M2 and M3 ($p<0.05$).
c= Significantly different from M1, M2 and M3 ($p<0.05$).
d= Significantly different from M2 and M3 ($p<0.05$).

DISCUSSION

The results of this study show that best oxygenation was achieved with PRVCV and SEHFV-PRVCV, yet PIP values maintaining constant minute ventilation were lower with

these modes. Considerably higher PIP was necessary to provide the desired gas exchange in VCV with PEEP compared to M2 and M3, although the PaO_2 achieved was much lower than in the other treatment modes.

In a recent review article Lachmann (10) stated that during the application of VCV with clinically used PEEPs levels the set PEEPs will only balance the retractive forces of some parts of the damaged lungs and only these parts of the lung will not collaps during the whole respiratory cycle leading to improved blood gases. However, PEEPs will not be enough to keep all parts of the lungs open. Highly damaged lung regions will be aerated only at the end of the inspiratory phase. Additionally, perfusion will decrease due to the high intra-alveolar pressure of end inspiration limiting the contribution of affected lung regions to gas exchange. On the other hand, healthy regions of the lungs can also have capillary compression and a ventilation/perfusion mismatching due to the applied PEEPs which will be even more prominent during the inspiration phase, causing the over-distension of these parts.

On the other hand at PRVCV if the PIP is adjusted only to compensate for the retractive forces of the whole lung, overdistension of the alveoli can never occur. An auto-PEEP can be created by either increasing the I/E ratio at constant frequency or increasing the frequency at a constant I/E ratio (or both). This will establish an expiration time too short to allow complete emptying of the lung. Therefore even the stiffest parts of the lung will have no time to recollapse, will be kept open and can be ventilated with a smaller ΔP compared to VCV with PEEP.

In this study SEHFV-PRVCV did not affect oxygenation or CO_2 elimination significantly compared to PRVCV. Earlier reports show improvement of these parameters with HFV combined with conventional ventilation (11-14). However, in those studies

superimposed HFV on conventional ventilation was compared with VCV with PEEP or continuous positive airway pressure (CPAP). Moreover, from experimental results in pigs with acute respiratory failure, it is known that the reason for these findings may be the increased PIP and mPaw pressures during superimposed HFV. A remarkable improvement in gas exchange is observed with combined ventilation compared to M1 in this study, but when the results of M2 are considered, this change is obviously due to PRVCV rather than HFV. In a similar study Lachmann and colleagues (15) superimposed HFV to the expiratory phase of VCV and achieved improved CO_2 elimination. However, their impression was that this form of ventilation was inferior to PCIRV with a prolonged inspiratory cycle up to 80%. Our results confirm their impression as no additional CO_2 elimination is observed with the application of SEHFV. This lack of further CO_2 elimination was probably due to the adequate CO_2 elimination from the large airways during the application of PRVCV.

In conclusion VCV with PEEPs provided adequate oxygenation, but it resulted in high PIP. Although the PIP levels remained low, SEHFV-PRVCV did not further increase the PaO_2 or $PaCO_2$ elimination in this animal model of acute respiratory failure suggesting no additional advantages with this mode over M2. In this study PRVCV with a prolonged inspiratory cycle of 80% is found to be a adequate ventilatory mode, not necessitating further combinations.

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CHAPTER 6

EFFECT OF KETANSERINE ON OXYGENATION AND VENTILATION INHOMOGENEITY IN PIGS WITH ARDS

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INTRODUCTION

The lungs in ARDS consist of units with different impedance characteristics (resistance and compliance) due to the nonhomogenous distribution of gas exchange abnormalities and mechanical alterations also under influence of bronchial obstruction. While some parts of the lungs are normal others are affected to varying degrees resulting in a difference in time required for alveolar volume and pressure in different lung units to reach equilibrium. In other words, unequal distribution of pressure and volume is observed leading to ventilation inhomogeneity . A multi breath indicator gas washout technique has been recently reported to quantify this inhomogeneity (1).

Acute respiratory failure is frequently accompanied by bronchospasm and pulmonary hypertension. Platelets are thought to have an important place in the etiology of these lung abnormalities (2-4). They may cause vaso- and bronchospastic events due to their 5 hydroxytryptamine (5HT) releasing activity. 5HT is a smooth muscle constrictor which may partly be involved in bronchoconstriction (5,6) and pulmonary hypertension in acute respiratory failure (7-9).

Ketanserin is expected to reverse the effects of 5HT as a specific antagonist. Therefore, in acute respiratory failure its administration may be followed by pulmonary vaso- and bronchodilation resulting in significant changes in ventilation parameters.

In this study lung lavage was used to create surfactant depletion in pig lungs, aiming to assess the ventilation inhomogeneity caused by this acute respiratory distress syndrome (ARDS) model. It is hypothesized that 5HT induced effects might be initiated in this model, leading to vaso- and bronchospastic events such as pulmonary hypertension and ventilation inhomogeneity and that the effect of a specific 5HT antagonist, ketanserin may be beneficial

in the treatment of pulmonary vasoconstriction and ventilation inhomogeneity of surfactant depleted pig lungs.

METHODS

Seven pigs (19-22kg) were investigated in this study. Anesthesia was induced with 30 mg/kg ketamine given intramuscular. The trachea was intubated with a portex tube with an internal diameter of 7 mm and the cuff was inflated to avoid air leakage. The lungs were ventilated with a Servo 900C (Siemens-Elema Solna, Sweden) ventilator fitted with an indicator gas injector (1). Anesthesia was maintained by infusion of midazolam (0.02 mg/kg/min) and ketamine (0.05 mg/kg/min). Pancuronium bromide infusion (0.08 mg/kg/min) was adminstered after a bolus dose of 4 mg for muscle relaxation. A catheter for fluid replacement and a 7F Swan-Ganz thermodilution catheter for hemodynamic monitoring were inserted through the right and left internal jugular veins respectively. The carotid artery was cannulated for blood sampling and invasive blood pressure monitoring. An 18F urine catheter was placed into the bladder by cystostomy to monitor urine output.

Mean arterial blood pressure, mean pulmonary artery pressure and pulmonary capillary wedge pressure were measured at the end of expiration. Cardiac output was measured by the thermodilution technique. Arterial blood gases were determined by an AVL 945 automatic bloodgas system.

Peak inspiration pressure, mean airway pressure and expired minute ventilation were electronically recorded.

A multiple breath indicator gas washout test using 2% SF_6 was performed to calculate end expiratory volume (EEV) and an index for ventilation inhomogeneity (S) as

described by Huygen and colleagues (1). The indicator and the metabolic gases were continuously measured by a mass-spectrometer (Airspec MGA 3000, UK) and EEV and S were calculated.

Pigs were subjected to lung lavage to establish a model of ARDS (10). They were ventilated before lung lavage, after lung lavage and after ketanserine administration with volume controlled ventilation with PEEP 4 cm H_2O tidal, volume 8-12 ml/kg, frequency 12 breaths/min, inspiration / expiration ratio 1:2 and FiO_2 at 1.0. Minute ventilation was kept almost constant in all modes and ventilation parameters were not changed during the whole course of the study. After completing baseline measurements lung lavage was performed with 150 ml/kg of warm saline solution to induce severe respiratory failure. PaO_2 < 100 mm Hg after lung lavage was accepted as ARDS and measurements were repeated after allowing a stabilization period of at least 2 hours. Ketanserin was given thereafter as an intravenous bolus dose of 0.2 mg/kg. The same set of measurements were done 5 minutes after the administration of the drug.

All data expressed as mean $\pm$ SEM were compared between groups by pairwise t-tests. Significance was considered at $p \leq 0.05$.

RESULTS

No data of the experiments were deleted from the study. A significant decrease in EEV and increase in S were observed after lavage ($P < 0.05$). The administration of ketanserin improved S significantly ($P < 0.05$). No effect of ketanserine was seen on EEV (fig. 1).

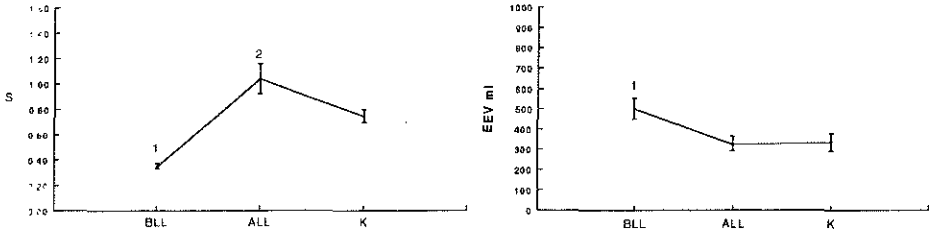

Figure 1. Ventilation inhomogeneity and end expiratory volume observed in the study. S= ventilation inhomogeneity index; EEV= end expiratory volume; BLL= before lung lavage; ALL= after lung lavage; K= after ketanserine administration. 1= significantly different from ALL and K ($P<0.05$); 2= significantly different from K ($P<0.05$).

PaO_2 values decreased significantly after lavage compared to before lung lavage ($P<0.05$). No significant change was observed between measurements after lung lavage and after ketanserin. $PaCO_2$ increased significantly with surfactant depletion compared to before lung lavage ($P<0.05$). No significant change in $PaCO_2$ was observed after ketanserine administration. (Table 1).

Peak inspiration pressure and mean airway pressure increased significantly after lung lavage ($P<0.05$). No change was observed with these parameters with the administration of ketanserin (Table 1). Minute ventilation remained unaltered during the whole study. No changes in cardiac output were observed during the study period. Mean pulmonary artery pressure and pulmonary capillary wedge pressure increased and mean arterial blood pressure decreased significantly after lung lavage ($P<0.05$). After ketanserine there was no

significant change in these parameters (Table 1).

Table 1. Respiratory and hemodynamic parameters observed during the study (mean ± sem).

n = 7	BLL	ALL	K
PaO_2 mmHg	525 ± 34[1]	70 ± 5	87 ± 6
$PaCO_2$ mmHg	46 ± 0.6[1]	58 ± 4.3	58 ± 3
meanPaw cmH_2O	7.1 ± 0.4[1]	13.6 ± 0.6	13.8 ± 0.7
PIP cmH_2O	20.2 ± 0.5[1]	43.8 ± 3.5	41.3 ± 0.2
V_E	4.4 ± 0.1	4.8 ± 0.1	4.9 ± 0.2
CO L/min	3.6 ± 0.3	3.3 ± 0.5	3.4 ± 0.6
MPAP mmHg	19.9 ± 1.6[1]	37 ± 3.6	36.1 ± 14
PCWP mmHg	9.9 ± 1.5[1]	16.4 ± 2.1	16.7 ± 1.5
MABP mmHg	109 ± 6[1]	85 ± 6	72 ± 6

BLL= before lung lavage; ALL= after lung lavage; K= after the administration of ketanserine; meanPaw= mean airway pressure; PIP= peak inspiration pressure; V_E minute ventilation; CO= cardiac output; MPAP= mean pulmonary artery pressure; PCWP= pulmonary capillary wedge prssure; MABP= mean arterial blood pressure;[1] significantly different from ALL and K ($P<0.05$).

DISCUSSION

Huygen and colleagues (1) have recently introduced multi-breath indicator gas washout test in postoperative intensive care patients and stressed the importance of the index S as a

sensitive diagnostic parameter for the assessment of ventilation inhomogeneity in conjunction with the assesment of EEV. The use of this washout test enabled us to investigate functional properties of the lung in the ARDS model used in this study.

Lung lavage is an acute respiratory failure model which is known to produce surfactant depletion, alveolar collapse and hypoxemia. This model, introduced by Lachmann and co-workers (10), imitates the early phase of ARDS and high S values obtained in this study combined with a typical decrease in EEV confirms it as a good ARDS model providing ventilation inhomogeneity. However the exact cause of this ventilation inhomogeneity in this ARDS model needs further explanation.

Activation of platelets and their pulmonary entrapment with subsequent release of the smooth muscle constrictor 5HT is thought to occur during the early phase of ARDS resulting in pulmonary hypertension and airway constriction (2-9). 5HT is also known to cause peripheral bronchospasm in airways less than 3 mm in diameter.[5] This constriction may play an important role in the ventilation inhomogeneity of the ARDS lungs.

The results of this study show that ketanserin improved the ventilation inhomogeneity caused by lung lavage without significant changes in EEV. Although some pigs showed improved PaO_2 values, the mean value over the whole group remained unchanged. In contrast to previous studies, no changes in mean pulmonary artery pressure and other hemodynamic parameters were observed after the administration of ketanserin.

The significant improvement of ventilation inhomogeneity with a specific 5HT antagonist in the lung lavage model indicates involvement of local 5HT receptors causing bronchoconstriction at the level of the distal airways. Administration of ketanserin has probably resulted in bronchodilation of constricted small airways and better distribution of ventilation to these areas. However, the lack of a significant improvement of oxygenation

can be attributed to the still existing alveolar collapse and low EEV due to surfactant depletion.

An increase in pulmonary shunt could be expected after ketanserin administration due to its vasodilator effect, resulting in impairment of PaO_2, but no effect of ketanserin was observed in this study on pulmonary vasoconstriction. Vincent and collegues[11] also observed no changes in PaO_2 and related this to the comparable increase in ventilation as well as perfusion due to the antagonism of airway constriction caused by ketanserin. Huet and co-workers (12) reported even an improved oxygenation with ketanserin in pulmonary embolism and related this either to the redistribution of perfusion to well ventilated lung units or improved ventilation to normally perfused lung tissue due to decreased bronchoconstriction. Olson (13) has also suggested that ketanserin might relieve airway constriction in hypoventilated lung areas.

Ketanserin is reported to decrease pulmonary hypertension which is partly mediated by 5HT release by activated platelets in patients with ARDS (11,14). The lack of antagonist effect of ketanserin on pulmonary hypertension in this experimental model of ARDS, suggests the involvement of other vasoconstrictive agents than 5HT to be responsible for the increase in mean pulmonary artery pressure.

In conclusion, according to the multi-breath indicator gas washout test used in this study, lung lavage seems to offer a good respiratory failure model to investigate ventilation inhomogeneity. In this model of ARDS, ventilation inhomogeneity is probably caused partly by constriction of the distal small airways due to 5HT reflex activity and it is reversed by a specific 5HT antagonist ketanserin, resulting in better distribution of ventilation in the lungs. However, no effect of ketanserine was seen on oxygenation, pulmonary hypertension and as expected on EEV.

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CHAPTER 7

PRESSURE REGULATED VOLUME CONTROLLED VENTILATION WITH DIFFERENT I/E RATIOS COMPARED WITH CONVENTIONAL VOLUME CONTROLLED PEEP VENTILATION IN PATIENTS SUFFERING FROM ARDS

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INTRODUCTION

Positive end expiratory pressure (PEEP) was suggested to be the therapy of choice of adult respiratory distress syndrome (ARDS) by Asbaugh and colleagues (1). Recent literature indicate that any type of ventilatory management is a supportive measure to provide adequate gas exchange and has little effect on treatment of the underlying pathology (2,3). The main immediate therapeutic goal in ARDS is to overcome hypoxemia and mechanical ventilation is the only way to provide a major improvement of oxygenation. This improvement can be accomplished by adjusting ventilation in several ways. Slowly but steadily insight has grown that the process of ventilation (i.e. application of pressure to the lungs) may be associated with secondary lung damage, especially in patients with ARDS. For that reason new mechanical ventilatory approaches have been introduced in the last two decades, aiming to provide adequate gas exchange in the lungs by maintaining aeration of as large parts of the lung as possible without hyperdistension, expiratory lung collapse or barotrauma (4).

In the literature sufficient evidence exists to indicate the adverse effects of high peak inspiratory pressure (PIP) and large tidal volume (V_T) which can cause barotrauma or progressive lung injury (5-11). Gattinoni and colleagues (12) have applied partial extracorporeal CO_2 removal for a reduction in minute ventilation meanwhile avoiding high PIP. However, in only a minority of intensive care units this sophisticated and expensive form of treatment can be performed. Seeking for an alternative, Hickling and coworkers (13) have recently shown decreased mortality in ARDS by avoidance of large V_T and limiting PIP. Lee and colleagues (14) have also demonstrated the safe use of low tidal volumes in selected patients. However, this type of ventilation with permissive hypercapnia

can prove harmful to some patients with, for example, high intracranial pressure, ischemic heart disease or hypertension.

Lachmann and coworkers (4) have reported better oxygenation, normocapnia, in some cases even hypocapnia, reduced alveolar-arterial end expiratory carbon dioxide (A-aDCO_2), lower PIP and intrapulmonary pressure amplitude (ΔP) with pressure controlled inverse ratio ventilation (PC-IRV). Several case reports and studies have been published reporting the benefits of PC-IRV in infants with respiratory distress syndrome of the newborn (15) and patients with ARDS (4,16-18). However, no study exists in which the benefits of these types of ventilatory settings have been evaluated in patient study groups and a recent review article of Blanch and coworkers have stressed the necessity of a well-designed, prospective, randomized comparison of PC-IRV and VCV (19). In this study, VCV with PEEP was compared with pressure regulated volume controlled ventilation (PRVCV) mode (which is in fact pressure controlled ventilation) with almost constant expired minute ventilation (V_E) at three different inspiration/expiration (I/E) ratios in patients with ARDS to determine the possible advantages of one mode over the other. Oxygenation was evaluated in relation to the intrapulmonary pressure swings.

PATIENTS AND METHODS

A group of 38 patients (male: 22, female: 16) with polytrauma, within 24 h after being admitted to the intensive care unit with respiratory failure, were studied after they were hemodynamically stabilized. During this period, the patients were mechanically ventilated with a mean airway pressure (mPaw) of around 15-25 cm H_2O to correct hypoxemia and fluid was administered in case of hypovolemia. After stabilization sufficient oxygenation

was obtained with FiO_2 1.0 and PEEP 4 cm H_2O and these ventilation settings were used as control mode (CM). The protocol was approved by the ethical committee on human research of the University of Istanbul, Medical Faculty where the study was performed. Patients were included after informed consent of their families had been obtained, when the following criteria were fulfilled:

1) Being in a disease category known potentially to cause ARDS,

2) Diffuse infiltrates in more than 2 quadrants on the chest X-ray,

3) PaO_2/FiO_2 ratio $<$ 100 mm Hg with PEEP of 4 cm H_2O at CM.

According to the lung injury score by Murray (20) each patient had a score above 2.5 (severe lung injury).

Intravascular pressures, systemic arterial blood pressure, central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) were monitored and all tracings were displayed on a Horizon 2000 monitor (Mennen Medical, Rehovot, Israel). A 7Fr pulmonary artery catheter was inserted in each patient. Cardiac output (CO) was measured by thermodilution and hemodynamic parameters were calculated on the Horizon 2000 monitor. Arterial blood gases and O_2-saturation were measured with ABL 300 and OSM 2 (Radiometer, Copenhagen, Denmark).

All patients were sedated with appropriate doses of benzodiazepines and paralysed for the duration of the trial with nondepolarizing muscle relaxants (pancuronium bromide or vecuronium bromide). Narcotics (morphine) were used to provide analgesia. Adequate fluid was administered to keep pulmonary capillary wedge pressure (PCWP) values of the patients above 10 mm Hg, during the whole study period.

The patients were ventilated with a Servo 900C (Siemens Elema, Solna, Sweden).

PIP, end inspiratory pressure (EIP), mPaw and total PEEP ($PEEP_T$) displayed by the ventilator (by pressing the end-expiratory hold button) were recorded. ΔP was defined as the difference between PIP and $PEEP_T$ values. The V_T in VCV mode and PIP at PRVCV modes were adjusted to keep minute ventilation constant at unchanged frequency (f). The randomly applied modes of ventilation with FiO_2 at 1.0 were as follows:

CM: VCV with static-PEEP 4 cmH_2O, V_T 10-12 ml/kg (adjusted according to the expiratory value in all modes), f 12/min and I/E ratio 1:2 (25% I, 10% pause).

mode (M) 1: VCV with static-PEEP > 10 cm H_2O, V_T 10-12 ml/kg, f 12/min and I/E ratio 1:2 (25% I, 10% pause).

M2: PRVCV with static-PEEP 4 cm H_2O, f 12/min and I/E ratio 2:1 (67% I, 0% pause). Around 50 cm H_2O PIP was applied during the first 10 min to open the alveoli. This was confirmed by an increase in PaO_2. PIP was slowly reduced to get a V_T 10-12 ml/kg thereafter.

M3: PRVCV with static-PEEP 4 cm H_2O, f 12/min and I/E ratio 3:1 (67% I, 5% pause). Around 50 cm H_2O PIP was applied during the first 10 min to open the alveoli. This was confirmed by an increase in PaO_2. PIP was slowly reduced to get a V_T 10-12 ml/kg thereafter.

M4: PRVCV with static-PEEP 4 cm H_2O, f 12/min and I/E ratio 4:1 (80% I, 0% pause). Around 50 cm H_2O PIP was applied during the first 10 min to open the alveoli. This was confirmed by an increase in PaO_2. PIP was slowly reduced to get a V_T 10-12 ml/kg thereafter.

Patients were ventilated in the CM before the beginning of the trial and prior to conversion from one mode to the other for 30 minutes. Blood gas measurements were

performed thereafter to detect changes in gas exchange. All other modes were applied for 2 hours each, FiO_2 being 1.0 during the last 30 minutes, prior to the measurements. All patients were given 5-10 μg/kg/min dopamine at the beginning of the trial (CM) to keep CO above 4 l/min and this dose was unchanged for each patient during the whole study period.

Data were compared with each other by a two way analysis of variance (ANOVA) test. All data are expressed as mean $\pm$ SD. Significance was considered at $P \leq 0.01$.

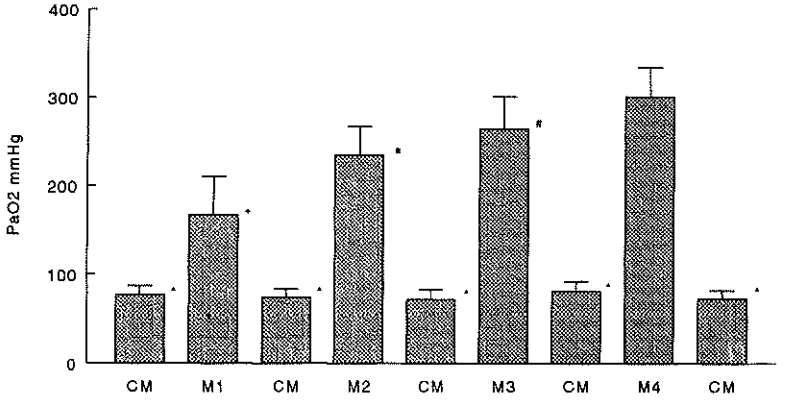

Fig. 1. PaO_2 values obtained with the application of ventilatory modes. CM= control mode; M= mode; ▲ significantly different from M1, M2, M3 and M4 ($P<0.01$); + significantly different from M2, M3 and M4 ($P<0.01$); * significantly different from M3 and M4 ($P<0.01$); # significantly different from M4 ($P<0.01$).

RESULTS

The mean age and weight of the patients were 36.3 ± 15.5 yrs and 65.9 ± 17 kg. Mean PaO_2/FiO_2 ratio measured at the beginning of the study was 76.9 ± 10.2 mm Hg. The mean

lung injury score of the patient population was 3.1±0.2.

On admission, sixteen patients had unilateral or bilateral chest tubes due to traumatic pneumothorax. An additional pneumothorax was detected in four patients during application of VCV with high PEEP during the trial. In these patients, minute volume and static-PEEP were readjusted during CM to get the previous PIP.

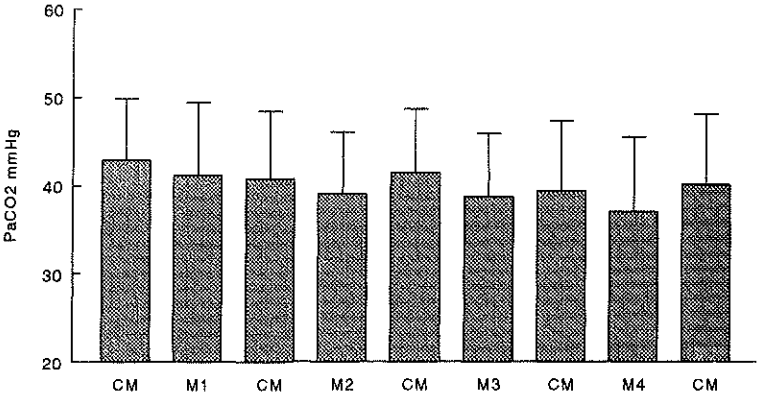

Fig. 2. $PaCO_2$ values obtained with the application of ventilatory modes.

CM= control mode; M= mode. No significant differences were found between the groups.

PaO_2 and $PaCO_2$ values obtained with each ventilation mode are shown in figures 1 and 2. Increased I/E ratios resulted in significant increases in PaO_2 values. Furthermore, similar PaO_2 values obtained during CM, applied between modes, indicated that the diseased state did not change, eliminating the possibility of improving lung functions during the trial period. $PaCO_2$ values were similar and no statistically significant differences were observed between any of the modes. The applied PEEP for VCV mode was 14.2±3.0 cm H_2O. $PEEP_T$ values increased with increasing I/E ratios in a statistically significant manner (Table 1).

Table 1. Parameters measured and calculated during the administration of trial modes of ventilation (mean±SD).

	CM	M1	M2	M3	M4
n	38	38	38	38	38
PIP (cm H_2O)	33.8 ± 6.8	47.8 ± 10.3[a]	34.3 ± 4.0[b]	32.2 ± 4.5	30.4 ± 4.6
mPaw (cm H_2O)	9.2 ±4.3[c]	19.5 ± 6.1[d]	25.2 ± 3.6	26.5 ± 4.4	27.0 ± 3.7
EIP (cm H_2O)	26.61 ±4.6	37.5 ± 5.3[a]	34.3 ± 4.0[b]	32.2 ± 4.5	30.4 ± 4.6
$PEEP_T$ (cm H_2O)	4[c]	14.2 ± 3.0[e]	8.5 ± 1.3[f]	10.5 ± 1.2	13.4 ± 1.1[e]
ΔP (cm H_2O)	28.3±3.1[c]	33.7±4.2[d]	26.3±2.1[f]	21.7±1.9	17.2±1.8[e]
CO (L/min)	7.29 ± 3.16	7.11 ± 3.27	6.95 ± 2.77	7.17 ± 2.83	7.21 ± 2.81
MPAP (mm Hg)	22.45 ± 7.29[d]	26.77 ± 8.44[g]	28.12 ± 7.65	29.81 ± 5.66	31.65 ± 5.78
PCWP (mm Hg)	10.45 ± 5.42[g]	13.44 ± 5.21[g]	13.76 ± 5.82	15.43 ± 4.63	16.32 ± 3.84
MAP (mm Hg)	85.24 ± 19.47	83.39 ± 22.93	81.61 ± 16.66	82.37 ± 17.26	79.78 ± 12.87

For legends see text. [a]=significantly different from CM, M2, M3 and M4 ($P<0.01$). [b]= significantly different from M4 ($P<0.01$). [c]= significantly different from M1, M2, M3 and M4 ($P<0.01$). [d]= significantly different from M2, M3 and M4 ($P<0.01$). [e]= significantly different from M2 and M3 ($P<0.01$). [f]= significantly different from M3 ($P<0.01$). [g]= significantly different from M3 and M4 ($P<0.01$).

Airway pressure changes that occurred when switching from one mode to the other showed a remarkable decrease of PIP with PRVCV modes and an increase of mPaw was seen with the inverse I/E ratios (Table 1). EIP decreased significantly with M3 and M4 compared to M1. ΔP decreased progressively and significantly with the increase of I/E during the application of PRVCV modes (Table 1). According to the protocol V_E was kept constant in all modes.

Data concerning the hemodynamic parameters are summarized in Table 1. Increases of mean pulmonary artery pressure (MPAP) and PCWP were observed in PRVCV modes compared to CM and M1. The patients received their routine maintenance fluid during the study and about 500 ml of extra colloids were given at the beginning of the study when CM was randomly switched to any of the trial modes. After approximately 5 hours, this was repeated. An average of 6.7 ± 0.4 μg/kg/min dopamine was given to the patients during the trial.

DISCUSSION

The aim of ventilatory therapy in ARDS is to provide adequate gas exchange and to obtain recruitment of functioning alveolar units, while avoiding complications such as barotrauma, progressive lung injury and hemodynamic depression. These goals can be achieved by keeping PIP to the minimum acceptable level, as PIP over 40-50 cm H_2O is associated with an increased risk of barotrauma (21) and by providing optimal CO and vascular pressures to enable adequate oxygen transport to the tissue.

In this study, the modes M2-M4 were pure pressure controlled time cycled modes of artificial ventilation and are called PRVCV modes because PIP was manually regulated and changed to keep the V_T and V_E constant. The results of this study show that PRVCV yielded higher PaO_2 values and arterial oxygenation improved stepwise progressively, yet PIP values necessary to maintain a constant minute ventilation were decreasing with increasing inspiratory time. Moreover, ventilation on PRVCV mode with I/E ratio of 4:1 could be maintained with the lowest ΔP of around 17 cm H_2O, a value comparable to a pressure amplitude necessary to ventilate healthy lungs. This pressure amplitude was

increased twofold in VCV with PEEP and could result in considerably high shear forces, which accompany the nonhomogenous expansion of the lungs (22,23). One of the explanations of these diseased lungs being ventilated with this small ΔP can be explained by the law of La Place, $P = 2\gamma/r$ (P = pressure, γ = surface tension, r = radius), by assuming the presence of a high constant surface tension in these diseased lungs (23). According to this law critical opening pressure is inversely proportional to alveolar unit size and progressive recruitment of air spaces require a continuously rising pressure during inflation which is observed as high PIP in M1. Therefore, the pressure necessary to induce some volume changes depends on the initial radius of the alveoli. In other words, to get a certain volume change in larger alveoli, the necessary pressure changes are much smaller compared to the alveoli which are collapsed or contain lower volumes. It can further be derived from the law of La Place that the pressure necessary to keep the alveoli open is smaller at a high functional residual capacity (FRC) level. Therefore, the PEEP necessary to stabilize the end expiratory collaps can be minimized if the lungs are totally opened up to a FRC level of a healthy lung. This was confirmed in a recent study of Lichtwarck-Aschoff and collegues (24) who demonstrated that once the lungs are opened they could be adequately ventilated with ΔP of only 16-20 cm H_2O with those ventilator modes which create auto-PEEP.

The almost instantaneous and dramatic effect on PaO_2 when instituting PRVCV reflects a delicate balance between closing and opening forces acting within terminal lung units. This is clearly demonstrated in modes 2 and 4 where PIP difference was only around 4 cm H_2O and mPaw difference was only around 2 cm H_2O. However, these very small differences led to an improvement of arterial oxygenation of around 70 mm Hg in M4. Interaction between adjacent lung units offers one explanation for these dramatic effects.

Open units will contribute to the opening of neighbouring closed units. The opposite is also true, i.e., closed units will promote the closure of nearby units. A kind of "majority rule" then will be in effect. If most units are open, others will follow (22,25).

The use of arterial blood gases as the main endpoint of study in various patterns of ventilation needs some consideration. At an FiO_2 of 1.0, variations of PaO_2 due to mismatching of ventilation/perfusion or a low diffusion capacity will be of minor importance compared to the effect of right-to-left shunting. Therefore, an FiO_2 of 1.0 was always used in this study 30 minutes prior to the measurements. An improvement of PaO_2 can then be due to either a fall of the shunt fraction or to an increase of mixed venous oxygen saturation that occurs when cardiac output increases in relation to metabolic demands. The dramatic increase in PaO_2 was observed at breathing patterns characterized by higher mPaw applied for a large fraction of the breathing cycle which could lead to a decrease of CO. However, CO remained unaltered during the whole study period. Thus an increase in PaO_2 in our study indicates an improvement of lung function, particularly a decrease in shunt fraction.

Our findings in this study are in accordance with those described by Lachmann and colleagues (4,7). Recently, in a review article, Hickling (21) also stressed the importance of high PIP as a cause of barotrauma and pulmonary interstitial emphysema which shows the importance of low PIP during PC-IRV for the prevention of iatrogenic lung damage. Patients in this study group being polytraumatic, a number of them already had unilateral or bilateral thorax drains on admission. Therefore an exact evaluation of the barotrauma caused purely by the ventilation mode itself is difficult. However, pneumothorax was detected in four patients during the application of VCV with PEEP. No additional

pneumothorax was seen during PRVCV. Our data are in contradiction to that of Tharratt and co-workers (26) who reported an overall incidence of 23% pneumothorax during the application of PC-IRV. However in their study, high V_T was delivered to the lungs and therefore, unnecessary high PIP levels were obtained in PC-IRV mode, approximately 46 cm H_2O, equivalent to the PIP reached in this study with VCV with PEEP mode.

It has been suggested by some investigators that high mPaw could be a cause of barotrauma in inverse ratio ventilation (IRV), especially with high I/E ratios (27). To our opinion barotrauma can be prevented if PIP levels are kept under strict control to change the I/E ratios promptly when overinflation of the lungs becomes apparent. This situation can be expected with an improvement of compliance, increased MPAP and/or decreased CO and systemic blood pressure.

High mPaw is suggested to be a cause of hemodynamic compromise by some investigators. Cole and colleagues (16) reported a decrease of CO and oxygen delivery ($\dot{D}O_2$) with I/E ratio of 4:1. Using dopamine and fluid administration as a prophylactic measure during this trial, no negative effects of PRVCV on CO under the described clinical conditions were observed suggesting the use of an appropriate inotropic and fluid therapy to overcome the cardiodepressive effect of high mPaw. Other studies have confirmed the benefits of PC-IRV on PaO_2 and showed that circulation was not seriously depressed as long as only moderately high airway pressures were applied (18,28). Poelaert and coworkers (29) have even observed an increase in cardiac index with I/E ratio of 4:1.

The need for heavy sedation has been claimed to be a disadvantage of IRV (30). However, this mode of ventilation is reserved for a population of patients at the beginning phase of severe respiratory failure until the lungs are opened and stabilized. Another form of mechanical ventilation necessitating less sedation could be considered thereafter. In our

experience the patients in our study group would need heavy sedation with any form of alternative conventional ventilation techniques.

The results obtained in this study, certainly stress the importance of the use and immediate effects of PRVCV, but the limited study period prevents further elaboration on the effects of this mode over progressive lung injury or weaning of the patient from the ventilator, stressing the necessity of further randomized studies.

In summary, PRVCV with prolonged inspiration times provides immediate significant improvement in oxygenation compared to VCV with PEEP in ARDS. Avoiding high PIP and ΔP it may maintain lung integrity and reduce the risk of barotrauma. If can easily be applied but it needs careful monitoring and changing of I/E ratios whenever needed, to avoid transmission of high mPaw to the pulmonary circulation resulting in a decreased CO.

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CHAPTER 8

COMPARISON OF PRESSURE SUPPORT VENTILATION AND INTERMITTENT MANDATORY VENTILATION DURING WEANING IN PATIENTS WITH ACUTE RESPIRATORY FAILURE

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INTRODUCTION

Certain groups of mechanically ventilated patients with acute respiratory failure are difficult to wean from prolonged ventilation despite advanced respiratory support techniques. The common modes for providing support during weaning are intermittent mandatory ventilation (IMV), and spontaneous ventilatory trial (SVT) techniques; such as continuous positive airway pressure (CPAP) and T-piece. Weaning is often initiated with IMV, and a series of SVTs are introduced as the patient tolerates decreasing rates of IMV. However, there is some concern that this strategy of weaning may not be optimal for patient comfort, and muscle reconditioning (1).

Pressure support ventilation (PSV) is a new ventilatory mode which augments a spontaneous breath with a fixed amount of positive pressure. The level of positive pressure is set by the physician, and the patient has control over the respiratory frequency and inspiratory time. In many clinical studies, PSV appeared to be potentially useful during the weaning period by maintaining muscle activity with patient comfort (1,2).

Controversy still exists regarding the best approach to weaning, since there are not enough data to indicate the superiority of one technique over another. This study was designed to compare the effects of PSV and IMV on weaning of long-term artificially ventilated patients with acute respiratory failure (ARF) due to thorax trauma.

METHODS

Fourty mechanically ventilated patients (male:21; female:19) with thorax injury were studied in two groups during the weaning period. Patients fulfilling the following criteria

were included in the study on admission to the ICU:

1. Trauma Score (TS) $\geq$ 5 and $\leq$ 10.
2. PaO_2/FiO_2 ratio of greater than 150.
3. Total static lung compliance (TSLC) > 30 ml/cmH_20
4. Not undergoing abdominal or any other surgical procedure.

All patients received mechanical ventilatory support in a pressure controlled mode with a Servo 900C (Siemens-Elema). The decision to begin weaning a patient was based on the following criteria:

a) A spontaneous respiratory rate > 10/ min, < 36/ min when removed from mechanical ventilatory support.
b) Stable or improving chest radiographs.
c) PaO_2 > 60 mmHg with a FiO_2 < 0.4, $PaCO_2$ < 50 mmHg, PEEP < 5 cmH_2O.
d) Magnitude of inspiratory effort at least - 2 cmH_2O.
e) Hemodynamic stability as evidenced by a regular cardiac rhythm and mean arterial pressure (MAP) higher than 60 mmHg without any vasopressor.

The patients were then randomly assigned to a weaning mode of either PSV (n=20) or IMV (n=20). IMV was set according to clinical guidelines to supply a minute volume (MV) of 12-15 ml/kg/min, and a $PaCO_2$ of less than 50 mmHg. FiO_2 was set to provide a PaO_2 > 60 mmHg. The initial level of PSV was designed to result in a minute volume similar to the IMV group. A pressure of -2 cmH_2O in the inspiratory circuit triggered

inspiratory flow to provide the level of inspiratory pressure. Again FiO_2 was set to provide $PaO_2 > 60$ mmHg.

During the weaning period, the following measurements were made at 2-hourly intervals.

1. Mandatory and spontaneous ventilatory rates (f) and tidal volumes (TV) measured by the expiratory flow in the ventilatory circuit.
2. Peak airway pressure (Peak paw) measured in the inspiratory circuit of the ventilator.
3. Arterial O_2 saturation (SaO_2) determined from Hemoximeter OSM3 (Radiometer). Blood gas analyses were done by ABL300 (Radiometer, Copenhagen).
4. End-tidal CO_2 and O_2 consumption (VO_2) was measured by a Datex-Multicap.
5. Arterial blood pressures were measured from a radial artery catheter using a Viggo-Spectramed transducer and a Horizon 1000 (Mennen Medical) monitor.

The accepted parameters during the weaning procedure were as follows:

1. $PaO_2 > 60$ mmHg.
2. Increase in $PaCO_2 < 10$ mmHg from the baseline value.
3. PH > 7.28 or PH < 7.55
4. Spontaneous respiration rate < 30/ min.
5. Heart rate (HR) < 140/ min.
6. MAP > 60 mmHg.

Patients were excluded from the protocol at any time during weaning when their

parameters did not fulfil the given criteria. The patient was placed on the previous ventilatory support settings when significant deteriorations in SaO_2 or $PaCO_2$ were seen. All patients received endotracheal suctioning when necessary, and no sedatives or narcotics were administered during the weaning trial.

On the first day of weaning the parameters were measured and calculated for mean $\pm$ SD. The patients were then treated by the same protocol until they could be disconnected from the ventilator. Before disconnection, a test was performed so that they should generate a maximal inspiratory effort. During the weaning period, patients were asked how they tolerated the type of the ventilation.

The time from the beginning of weaning until its successful completion was accepted as weaning time (WT), and a successful weaning was defined as 48 hours discontinuation of mechanical ventilation.

Data were compared between the two groups by Student's t-test. Significance was considered at $p < 0.05$.

RESULTS

Both groups of patients were of similar age and sex, and there was no significant difference of trauma scores between the two groups on admission. Characteristics of the PSV and IMV groups along with the mean baseline mechanical ventilation parameters are summarized in Table 1.

Table 1. Data for the patient groups on admission.

	PSV (n= 20)	IMV (n= 20)
Sex M/F	12 / 8	9 / 11
Age (years)	41.65 ± 17.1	43.7 ± 13.4
TS	7.69 ±1.8	7.76 ±1.4
PaO_2/FiO_2	183.8 ± 60.8	182.4 ±61.4
TSLC (ml/cmH_2O)	39.4 ± 8.4	39.9 ± 10
SaO_2 (%)	97.4 ± 2.3	97.9 ± 3.1
$PaCO_2$ (mmHg)	36.2 ± 10.6	34.8 ± 8.4

TS= trauma score; TSLC= total static lung compliance;

Ventilatory parameters, gas exchange, blood pressure, heart rate and VO_2 values during the first day of weaning period in both groups are compared in Table 2. No significant differences were observed in the mean values of SaO_2, $PaCO_2$, arterial pressure, heart rate and VO_2.

Table 2. Ventilatory parameters, gas exchange, and hemodynamic parameters during PSV and IMV during the first day of weaning.

	PSV	IMV
MV (ml/kg/min)	124.8 ± 11.1	122.4 ± 10.9
frequency (/min)	15.1 ± 4.3[a]	23.2 ± 5.6
Peak paw (cmH_2O)	27.0 ± 4.1[a]	33.1 ± 6.1
SaO_2 (%)	97.4 ± 1.5	96.9 ± 1.7
$PaCO_2$ (mmHg)	34.3 ± 11.4	32.7 ± 9.3
MAP (mmHg)	66.9 ± 9.1	67.5 ± 10.5
HR (bpm)	88.8 ± 12.2	87.8 ± 13.4
VO_2 (ml/min)	199.8 ± 26.2	223.8 ± 29.1

[a] $p < 0.05$ between PSV and IMV

MV= minute ventilation; MAP= mean arterial pressure; HR= heart rate; VO_2= oxygen consumption.

Applied peak airway pressure to provide adequate minute volume in the PSV group was ranged between 18 and 32 cmH_2O. It was noted that PSV was associated with a significantly lower peak airway pressure than IMV. Patients were observed to be clearly more comfortable in PSV mode.

Patients who generated a maximum inspiratory pressure of more than -20 cmH_2O with an adequate gas exchange of $PaO_2 > 80$ mmHg with $FiO_2 < 0.35$, were disconnected

from the ventilator. A successful weaning was accepted as 48 hours discontinuation of mechanical ventilatory support. Of the 40 patients, 32 were weaned successfully: 17 in the PSV group and 15 in the IMV group. Although total ventilation time (TVT) prior to weaning was similar in both groups, weaning time was observed to be significantly shorter in the PSV group than in the IMV group (Table 3).

Table 3. Comparison of weaning time and total ventilation time

	PSV	IMV
Weaning time (/day)	6.3 ± 3.1	9.9 ± 2.7[a]
Total ventilation time (/day)	19.1 ± 2.3	22.4 ± 3.1

[a] $p < 0.05$ between PSV and IMV

DISCUSSION

Pressure support ventilation is a recent form of ventilatory assistance, that can be used for mechanical ventilation and weaning. Although no study has yet demonstrated the superiority of this mode over other techniques of weaning, some have shown a number of advantages (1-6).

The main findings of this study demonstrated that inspiratory pressure assist with PSV resulted in lower levels of peak airway pressure with a slower spontaneous ventilatory rate compared to IMV. Patients appeared to tolerate PSV better than IMV and the weaning time was significantly shortened with three and a half days and less unsuccesfull attempts at

disconnection were observed.

Recently, McIntyre and co-workers described the effects of various levels of PSV on airway pressure, gas exchange and patient comfort (1). They found PSV to be a reasonable form of mechanical ventilatory support in patients with spontaneous ventilatory drives. It improved patient comfort and reduced the patient's ventilatory work. In the same study McIntyre found a significant positive correlation between the level of PSV and tidal volume, and a negative correlation with the frequency of spontaneous breathing. These findings are similar to ours, since we measured the same amount of minute volume at a decreased respiratory rate and peak airway pressure in PSV.

Kanak and co-workers described a decrease in oxygen consumption when the mode of ventilatory assistance was changed from IMV to PSV (7). They noted that the patients' respiratory efforts decreased and that the respiratory rate was reduced during PSV. Fahey and coworkers also reported a significant reduction in the O_2 cost of breathing with PSV (8). In their study, they found that PSV prevented diaphragmatic failure by diminishing the patient's work of breathing and total O_2 consumption. Brochard and co-workers showed that O_2 consumption decreased when PSV was added (2). From their data, the work of breathing appeared to be the prime determinant of the O_2 cost of breathing. Extrapolating these results to ours, we noted a lower O_2 consumption in the PSV group. Although not significant, this difference was considerable when compared with IMV.

Prakash and Meij, in their study including 26 patients after aortocoronary bypass grafts, compared the cardiovascular effects of PSV with conventional ventilatory modes, and they found no negative effects of PSV (9). Our results also showed no adverse effects on cardiovascular variables in patients of both groups.

Hurst and co-workers evaluated the effects of adding low levels of PSV in

conjuction with intermittent mandatory ventilation (5). They showed an increase in mean airway pressure and improvement in oxygenation. McIntyre noted that PSV was associated with higher levels of mean airway pressure compared to IMV, however gas exchange was similar during both forms of ventilation (1). Our results showed efficacy of gas exchange in both PSV and IMV groups. We observed slightly and nonsignificantly better gas exchange with higher PaO_2 and lower $PaCO_2$ values in PSV mode.

We conclude that ARF patients can be weaned successfully by either PSV or IMV modes. However, being synchronized with the natural rhythm of breathing and maintaining patient comfort with muscle reconditioning, PSV seems to be more efficient than IMV since it significantly shortens weaning time in ARF patients on long-term ventilatory support with less frustrating failures.

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SUMMARY

In this thesis, the effects of different models of ventilatory support is investigated in animal models and patients with ARDS.

As outlined in *Chapter 1,* ARDS is a type of lung injury which was recognized many years ago, and is associated with shock and trauma. It follows either a primary lung disease or extra-thoracic injury of varying origins, activating a mediator cascade leading to the "capillary leak syndrome". Pathological changes range from alveolar edema to consolidation and fibrosis of the lungs. Many diagnostic criteria are used to define ARDS without a consensus being reached. The therapy of ARDS is limited to ventilatory and cardiocirculatory support and ventilation can itself be dangerous if high intrapulmonary pressures are used. Lung lavage is a stable acute respiratory failure model imitating the early stage of ARDS, and is particularly favorable for studies in which different ventilatory settings are evaluated.

In *Chapter 2* it is stressed that pressure controlled inverse ratio ventilation stabilizes the alveoli and keeps them open. Volume controlled ventilation with PEEP will not be sufficient to achieve this goal. Furthermore, volume controlled ventilation with PEEP will result in higher intrapulmonary pressure amplitudes and peak inspiratory pressures compared to pressure controlled inverse ratio ventilation which may lead to structural damage to the bronchiolar and alveolar epithelium and causes barotrauma. A review of studies indicates an improvement of oxygenation when pressure controlled inverse ratio ventilation is applied in ARDS patients who are already ventilated with volume controlled ventilation with PEEP. Controversial data exist on the hemodynamic effects of both modes. However, application of PEEP up to 20 cm H_2O seems to have no negative effects on

cardiac output if extra measures such as fluid administration and/or positive inotropic drugs are used. The high retractive forces in the ARDS lung may also limit the high pressure being transmitted to the pulmonary vasculature. Furthermore, pressure controlled inverse ratio ventilation must be used at an early stage of ARDS in order to achieve maximum recruitment. A high peak inspiratory pressure must be applied first to open the alveoli and this must be decreased slowly to the lowest possible level to keep the alveoli open. This is monitored by repeated PaO_2 measurements.

Chapter 3 shows that in order to achieve a PaO_2 above 47 kPa, significantly higher peak inspiratory pressure are needed with volume controlled ventilation with PEEP compared to pressure regulated volume controlled ventilation and low frequency positive pressure ventilation with extracorporeal carbon dioxide removal. Furthermore, lung lavage applied to create an ARDS model produces a significant decrease in right ventricular ejection fraction and significant increases in mean pulmonary arterial pressure and pulmonary vascular resistance indicating an extra burden to right ventricular performance. No further deterioration of the hemodynamic parameters in ARDS lungs is observed with the application of any of the ventilation modes with similar PEEP levels.

Controversial results are reported concerning the effects of high intrapulmonary pressures during mechanical ventilation on intracranial pressure. In *Chapter 4*, no changes in intracranial pressure were observed with the application of the ventilation modes with PEEP levels around 13-14 cm H_2O, suggesting a preventive mechanism of ARDS in this model.

Chapter 5 describes that best oxygenation is achieved with pressure regulated volume controlled ventilation and superimposed high frequency ventilation with pressure regulated volume controlled ventilation. Peak inspiratory pressure values are lower with

these modes compared to volume controlled ventilation with PEEP. However, superimposed high frequency ventilation with pressure regulated volume controlled ventilation did not affect gas exchange significantly compared to pressure regulated volume controlled ventilation volume, suggesting no additional advantages of high frequency ventilation in this animal model of acute respiratory failure. Although superimposed high frequency ventilation is reported to improve gas exchange when used in combination with volume controlled ventilation, pressure regulated volume controlled ventilation with an I/E ratio 4:1 is found to be a ventilatory mode not necessitating further combinations.

Lung lavage is an acute respiratory failure model which is known to be stable for several hours. Our results in *Chapter 6* confirm the stability of this model and the great reduction of functional residual capacity following its application. Furthermore, increase in ventilation inhomogeneity demonstrates this method to be a valuable acute respiratory failure model providing non-homogeneous distribution of ventilation as well as impaired gas exchange. Improvement of ventilation inhomogeneity is observed in this work with the use of the specific 5 hydroxytryptamine antagonist, ketanserine. This shows that, in this model, ventilation inhomogeneity is partly caused by constriction of the distal small airways due to 5 hydroxytryptamine reflex activity. The lack of antagonist effect of ketanserine on pulmonary hypertension in this model of ARDS, suggests the activation of other vascular vasoconstrictor mediators in the airways.

The aim of ventilatory therapy in ARDS is to provide adequate gas exchange and to obtain recruitment of functioning alveolar units, while avoiding complications such as barotrauma, progressive lung injury and hemodynamic depression. These goals can be achieved by keeping peak inspiratory pressure to the minimum acceptable level and by providing optimal cardiac output to enable oxygen transport to the tissue. *Chapter 7* shows

that pressure regulated volume controlled ventilation with a prolonged inspiration time provides significant improvement compared to volume controlled ventilation with PEEP in ARDS patients. Furthermore, it avoids a high peak inspiratory pressure and intrapulmonary pressure amplitude and, therefore, reduces the risk of barotrauma. No negative effect of the ventilation modes on cardiac output and oxygen delivery are observed under the described clinical conditions.

In *Chapter 8* pressure support ventilation is shown to be more efficient than intermittent mandatory ventilation since it shortens the weaning time in acute respiratory failure patients on long-term ventilatory support. The gas exchange and oxygen consumption is similar in both groups. However, pressure support ventilation results in a lower peak inspiratory pressure and a lower spontaneous breathing rate compared to intermittent mandatory ventilation.

SAMENVATTING

In dit proefschrift worden de effecten van verschillende beademingsvormen in diermodellen van ARDS en bij patiënten met ARDS onderzocht.

In *hoofdstuk 1* wordt ARDS beschreven als een vele jaren geleden herkend type longbeschadiging geassocieerd met shock en trauma. ARDS treedt op na een primaire longaandoening of na een een scala van extrathoracale letsels en leidt via activatie van een cascade van mediatoren tot het "capillaire lek syndroom". De pathologisch-anatomische veranderingen lopen uiteen van alveolair oedeem tot consolidatie van long en fibrose.
Over de definitie van ARDS bestaat geen consensus; veel verschillende diagnostische criteria worden gehanteerd. De behandeling van ARDS is beperkt tot ventilatoire en hemodynamische ondersteuning. Beademing kan op zichzelf gevaarlijk zijn indien hoge intrapulmonale drukken worden gegenereerd. Longlavage is een stabiel model van acuut respiratoir falen, dat een goede gelijkenis toont met het acute stadium van ARDS en bijzonder geschikt is om verschillende beademingsvormen te vergelijken

In *hoofdstuk 2* wordt betoogd dat "pressure controlled inverse ratio" de alveoli stabiliseert en open houdt. "Volume controlled ventilation" met PEEP is niet in staat dit doel te bereiken. In vergelijking met "pressure controlled inverse ratio ventilation" resulteert "volume controlled ventilation" met PEEP in een hogere intrapulmonale drukamplitude en een hogere inspiratoire piekdruk, leidend tot beschadiging van epitheel van brochioli en alveoli en tot barotrauma. Uit de literatuur blijkt dat overgaan op "pressure controlled inverse ratio ventilation" bij ARDS-patiënten, die beademd worden met "volume controlled ventilation met PEEP", resulteert in betere oxygenatie. Data betreffende de hemodynamische effecten van beide beademingsvormen zijn niet eenduidig. PEEP tot 20

cm water lijkt echter geen nadelig effect te hebben op het hartminuutvolume indien daarnaast extra vocht en positief inotrope farmaca worden gegeven. Ook voorkomen de sterke retractieve krachten in ARDS-longen wellicht transmissie van de hoge pulmonale druk op de longvasculatuur. Bovendien dient "pressure controlled inverse ratio ventilation" in vroeg stadium van ARDS toegepast te worden om maximale recrutering van alveoli te verkrijgen. Aanvankelijk moet een hoge inspiratoire piekdruk worden gebruikt om de alveoli te openen. Daarna wordt deze, op geleide van de PaO_2, langzaam verminderd tot het laagste niveau waarbij de alveoli open blijven.

In *hoofdstuk 3* wordt aangetoond dat significant hoger inspiratoire piekdrukken nodig zijn om een PaO_2 van meer dan 47 kPa te bereiken met "volume controlled ventilation" met PEEP, dan met "pressure regulated volume controlled ventilation" en "low frequency positive pressure ventilation with extracorporeal CO_2-removal". Longlavage, toegepast om een ARDS-model te creëren, resulteert in een significante daling van de ejectiefractie van de rechter ventrikel en een significante toename van de gemiddelde druk in de longslagader en van de longvaatweerstand. Dit wijst op een extra belasting van de rechter ventrikel. Geen van de toegepaste beademingsvormen resulteert in een verdere verslechtering van de hemodynamische parameters.

In de literatuur worden tegenstrijdige resultaten gemeld betreffende het effect van hoge intrapulmonale drukken op de intracraniële druk. In *Hoofdstuk 4* worden geen veranderingen in intracraniële druk gezien als gevolg van beademingsvormen met PEEP van 13 tot 14 cm water, wijzend op een mogelijk effect van ARDS in dit model.

Hoofdstuk 5 beschrijft dat de beste oxygenatie bereikt wordt met "pressure regulated volume controlled ventilation" en "high frequency ventilation gesuperponeerd op pressure regulated volume controlled ventilation". De inspiratoire piekdruk blijft lager dan bij

"volume controlled ventilation" met PEEP. In vergelijking met "pressure regulated volume controlled ventilation" had "high frequency ventilation gesuperponeerd op pressure regulated volume controlled ventilation" echter geen significant effect op de gaswisseling, hetgeen suggereert dat "high frequency ventilation" in dit model van acuut respiratoir falen geen additioneel voordeel biedt. Hoewel "high frequency ventilation gesuperponeerd op volume controlled ventilation" volgens de literatuur de gaswisseling gunstig zou beïnvloeden, blijkt "pressure regulated volume controlled ventilation" met een I:E-verhouding van 4:1 een beademingsvorm te zijn die een combinatie met een tweede beademingsvorm overbodig maakt.

Longlavage is een model voor respiratoir falen, waarvan bekend is dat het gedurende meerdere uren stabiel is. Onze resultaten in *Hoofdstuk 6* bevestigen de stabiliteit van dit model en de forse vermindering van functionele residuele capaciteit, die longlavage veroorzaakt. Daarnaast toont ook de toegenomen inhomogeniteit van de ventilatie aan, dat dit een waardevol model is voor acuut respiratoir falen, dat zowel inhomogene ventilatie als gestoorde gaswisseling heeft. In dit hoofdstuk resulteert de specifieke 5-hydroxytryptamine antagonist ketanserine in een vermindering van ventilatie-inhomogeniteit. Dit wijst erop, dat in dit model, ventilatie-inhomogeniteit deels veroorzaakt wordt door constrictie van distale luchtwegen door 5-hydroxytryptamine reflex-activiteit. Dat ketanserine geen antagonerend effect heeft op de pulmonale hypertensie, suggereert dat in dit model andere vasoconstrictieve mechanismen dat het effect op de luchtwegen geactiveerd worden.

Het doel van beademingsstrategieën bij ARDS is, het verkrijgen van adequate gaswisseling, recruteren van functionerende alveoli en tegelijkertijd het vermijden van complicaties als barotrauma, progressieve longschade en hemodynamische verslechtering. Deze doeleinden worden bereikt door de inspiratiedruk te handhaven op het minimaal

acceptabele niveau en door het hartminuutvolume optimaal te houden teneinde transport van zuurstof naar de weefsel mogelijk te maken. In *Hoofdstuk 7* wordt aangetoond dat "pressure regulated volume controlled ventilation" met een verlengde inspiratietijd bij ARDS-patiënten een significante verbetering geeft ten opzichte van "volume controlled ventilation" met PEEP. Bovendien worden een hoge inspiratoire piekdruk en intrapulmonale drukamplitude vermeden en is het risico op barotrauma minder. In de beschreven klinische situatie worden van de beademingsstrategieën nadelige gevolgen op hartminuutvolume en zuurstoftransport gezien.

In *Hoofdstuk 8* wordt aangetoond dat "pressure support ventilation" efficiënter is dan "intermittent mandatory ventilation" omdat het de periode van ontwenning van de beademing verkort bij patiënten, die na acuut respiratoir falen langdurig beademd zijn. De gaswisseling en het zuurstofverbruik zijn in beide groepen vergelijkbaar. Wel resulteert "pressure support ventilation" in een lagere inspiratoire piekdruk en een lagere spontane ademfrequentie in vergelijking met "intermitttent mandatory ventilation".

Future developments

With increasing knowledge on the pathophysiology of ARDS and the mechanics of alveolar repair, specific therapeutic measures will emerge to prevent the lung injury and promote alveolar repair. It is already known that excess of protolytic enzymes and toxic oxygen metabolites are involved in creating lung injury. Application of anti-proteases and antioxidant substances to the alveoli would be a logical preventive approach. Substances accelerating epithelial cell replication, limiting mesenchymal cell replication and promoting endothelial cell replication and reconstruction would have a valuable therapeutic place in the future in airway alveolar repair. Intratracheal administration of these substances seem to be ideal, as it would maximize their therapeutic effect and minimize their systemic activity.

During the past 25 years the spectrum of ARDS has changed. Few patients die nowadays from the direct sequelae of this lung injury, but they commonly develop a clinical course resulting in multiple organ failure. The source of this development is still unclear. Better understanding of the causes of multiple organ failure is necessary to improve the mortality rate of these patients.

At present, no effective and singular treatment of the varied presentation of ARDS exists. Sophisticated ventilatory and circulatory support are the only currently applicable therapies. Therefore, it is very important to use these measures correctly in order not to harm the patients further. The damaging effects of high intrapulmonary pressures and pressure swings and their relation with various modes of mechanical ventilation are widely discussed in this thesis.

It is demonstrated that almost all modes of mechanical ventilation provide adequate oxygenation in recruitable lungs with ARDS. However, pressure regulated volume controlled ventilation with prolonged I/E ratios and low frequency positive pressure

ventilation with extracorporeal carbon dioxide removal avoid high peak inspiration pressure and intrapulmonary pressure amplitude reducing the risk of barotrauma. Considering our results, in the early phase of ARDS in which most of the alveoli are still recruitable, pressure regulated volume controlled ventilation should be an adequate form of treatment without the use of further invasive methods. However, at a later stage of the disease when only marginal alveolar recruitment is possible, in which no form of ventilation would be effective to provide gas exchange, low frequency positive pressure ventilation with extracorporeal carbon dioxide removal should be considered as the treatment of choice.

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