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TREATMENT MODALITIES OF ACUTE LUNG INJURY WITH SPECIAL REFERENCE TO AIRWAY PRESSURE RELEASE VENTILATION

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ACADEMIC DISSERTATION

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“Put me back on my bike…”

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ABSTRACT

Background: Acute lung injury (ALI) is a stereotypic inflammatory reaction of the lung to various insults. Acute lung injury and its more severe form, acute respiratory distress syndrome (ARDS), cause respiratory failure, the most common organ failure leading to intensive care. Treatment modalities of ALI remain mainly supportive. One of the most widely used pharmacological treatments is the use of glucocorticosteroids. Glucocorticosteroids during the initial phase of ALI have been shown to be potentially harmful, but during the later fibroproliferative phase several studies indicate a potential benefit. Benefits of this concept have not been investigated with a homogenous group of ALI patients. In ALI, the mainstay of supportive therapy is ventilatory treatment. Ventilatory settings aimed at protecting the lung from possible iatrogenic injury may improve outcome of ALI patients. The use of prone positioning (PP) is a non-ventilatory method which has been shown to improve gas exchange in ALI. Partial ventilatory modes, which allow a patient's spontaneous breathing activity, may improve physiological variables of gas exchange and haemodynamics, particularly with airway pressure release ventilation (APRV), a ventilatory mode with unsupported spontaneous ventilation superimposed on mechanical ventilation. No study has investigated the possible outcome benefit of a ventilatory strategy combining lung protective ventilation, PP, and APRV.

Patients and methods: In all, 89 ALI patients were studied during the years 1996 to 2001 in the mixed intensive care unit of Meilahti Hospital (Helsinki University Central Hospital). Use of APRV together with prone positioning was described in one severe ARDS patient (Study I). In a randomised controlled trial, APRV was compared to another partial ventilatory mode, synchronised intermittent mandatory ventilation (SIMV), with 58 ALI patients (Study II). Prone positioning was part of a standardised treatment protocol, and combined effects of APRV and prone position were investigated during two initial prone position episodes on 33 patients (Study III). Computer tomography (CT) of the lung was performed before inclusion in the trial. Those patients (n = 23) requiring mechanical ventilation after 7 days underwent control CT. Changes in quantitative CT scan were analysed in a subgroup of Study II (Study IV). In the final study, 31 patients with primary ALI and prolonged mechanical ventilation were retrospectively analysed. Of these patients, 16 received steroid treatment for a presumed fibroproliferative reaction. A comparable group of 15 patients was designated as a control group (Study V).

Main results: In the randomised trial comparing APRV to SIMV, the primary endpoint was number of ventilator free-days after randomisation to the study. At day 28, the number of both ventilator-free days (13.4 ± 1.7 in the APRV group and 12.2 ± 1.5 in the SIMV group) and ICU-free days did not differ between the groups. Inspiratory pressure during the first week of study was significantly lower in the APRV group (25.9 ± 0.6 cmH_2O) than in the control group (28.6 ± 0.7 cmH_2O). The 28-day mortality was low in both groups, 17 % in the APRV group and 18 % in the SIMV group (n.s.) (Study II).

Per protocol, PP was applied if PaO_2/FiO_2 decreased below 200 mmHg, and if not contraindicated. The first two episodes were analysed in 33 patients. Oxygenation was significantly better in the APRV group

before the first episode; response to prone positionining in both groups was similar. Before the second episode the PaO_2/FiO_2 ratio was comparable. At the end of the second episode PaO_2/FiO_2 ratio improved more in the APRV group than in the SIMV-group ($p = 0.02$) (Study III).

CT scans in 23 patients showed the decrease in the amount of nonaerated lung to be comparable between the groups: 12.1 ± 4.3 % in the APRV group (n = 13) and 7.2 ± 5.7 % in the SIMV group (n = 10) (Study IV).

In patients with primary ALI, steroid treatment was started 9.7 days (mean) after ICU admission. Values for the controls were recorded on day 10. Within 3 days of this reference point, the PaO_2/FiO_2 ratio improved significantly and C-reactive protein decreased concurrently, together with multiple organ dysfunction score in the group receiving steroids. Neither mortality nor length of stay differed between the groups (Study V).

CONCLUSIONS: This study showed that APRV used as a primary ventilatory mode in ALI is a feasible strategy, and mortality with a group of ALI/ARDS patients is low. No differences appeared in relevant clinical outcome as compared to those with the strategy utilising SIMV. The use of PP together with APRV may have a beneficial, synergistic effect on oxygenation. The effect of ventilatory mode on lung consolidation assessed with CT after 7 days was similar to that of APRV and of SIMV. In primary ALI, steroid treatment instituted after 10 days of the start of the ALI process improves oxygenation, alleviates the inflammatory reaction, and is associated with a decrease in multiorgan dysfunction.

LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following publications. They will be referred to by the Roman numerals I to V.

I Varpula T, Pettilä V, Nieminen H, Takkunen O. *Airway pressure release ventilation and prone positioning in severe acute respiratory distress syndrome.* Acta Anaesthesiol Scand 2001;45:340–4

II Varpula T, Valta P, Niemi R, Takkunen O, Hynynen M, Pettilä V. *Airway pressure release ventilation as a primary ventilatory mode in ARDS.* Acta Anaesthesiol Scand 2004;48;722–31

III Varpula T, Jousela I, Niemi R, Takkunen O, Pettilä V. *Combined effects of prone positioning and airway pressure release ventilation on gas exchange in patients with acute lung injury.* Acta Anaesthesiol Scand 2003;47:516–24

IV Varpula T, Valta P, Markkola A, Pohjanen K, Halavaara J, Hynynen M, Pettilä V. *Assessment of lung aeration with computer tomography:The effects of ventilatory mode in patients with acute lung injury.* (Submitted)

V Varpula T, Pettilä V, Rintala E, Takkunen O, Valtonen V. *Late steroid therapy in primary acute lung injury.* Intensive Care Med 2000;26:526–31

Permission for reprinting was obtained from the publishers of these communications.

ABBREVIATIONS

ACV	Assist/control ventilation
AECC	American-European consensus conference
ALI	Acute lung injury
APACHE	Acute physiology and chronic health evaluation
APRV	Airway pressure release ventilation
ARDS	Acute respiratory distress syndrome
BAL	Bronchoalveolar lavage
BIPAP	Bilevel airway pressure ventilation
CPAP	Continuous positive airway pressure
CT	Computer tomography
DAD	Diffuse alveolar damage
FIO_2	Fraction of inspired oxygen
HFV	High frequency ventilation
HU	Hounsfield unit
ICU	Intensive care unit
IL	Interleukine
IMV	Intermittent mandatory ventilation
IRV	Inverse ratio ventilation
LIP	Lower inflection point
LIS	Lung Injury Score
MOD	Multiple organ dysfunction
MODS	Multiple organ dysfunction score
MOF	Multiple organ failure
MV	Minute ventilation
PAC	Pulmonary artery catheter
PaO_2	Arterial oxygen partial pressure
$PaCO_2$	Arterial carbon dioxide partial pressure
PaO_2/FiO_2 ratio	Ratio of oxygen partial pressure and fraction of inspired oxygen
PCWP	Pulmonary capillary wedge pressure
PEEP	Positive end expiratory pressure
Pinsp	Inspiratory airway pressure
PP	Prone positioning
PS	Pressure support ventilation
PV-curve	Pressure volume curve
Qs/Qt	Intrapulmonary shunt
ROI	Region of interest
SIMV-PC	Synchronized intermittent mandatory ventilation with pressure control
SOFA	Sequential organ failure assessment
UIP	Upper inflection point
VALI	Ventilator-associated lung injury
VFD	Ventilator-free days
VILI	Ventilator induced lung injury
V/Q ratio	Ventilation-perfusion ratio
VT	Tidal volume

1. INTRODUCTION

Acute lung injury (ALI) and its more severe form ARDS represent major causes of acute respiratory failure in critically ill patients (Roupie, et al. 1999). Respiratory failure, "the clinical hallmark" of these syndromes, is the most common cause for admission to an intensive care unit (ICU). Historically, because specialized units equipped to monitor and treat critically ill patients were initially developed to treat patients with acute respiratory insufficiency (Trubuhovich 2004), one can state that respiratory failure and its treatment modalities constitute the essential part of modern critical care.

ALI is an inflammatory reaction of the lungs characterized by activation of several cascades. This complex pathophysiological process results in structural and functional alterations of the lungs characterized by impairment of gas exchange, of respiratory mechanics, and of oxygen delivery. This inflammatory reaction can be initiated by direct pulmonary injury or by indirect systemic insult. In both circumstances, the inflammatory process leads ultimately to diffuse alveolar damage via complex interactions of inflammatory mediators on alveolar epithelial and capillary endothelial cells (Ware and Matthay 2000). Pulmonary inflammation leads to systemic response and development of extrapulmonary organ failure. Progression of end organ dysfunction to multiple organ failure is the main cause of death in ALI patients (Slutsky and Tremblay 1998). Mortality from ALI/ARDS has remained high, ranging from 30 to 70 % (Esteban, et al. 2002, Milberg, et al. 1995).

The most essential part of the supportive treatment of ALI patients is treatment of gas exchange failure. Practically all patients with ALI require assisted positive pressure ventilation in order to reverse respiratory failure. As with any treatment, mechanical ventilation can have side-effects and unwanted consequences. Mechanical ventilation can cause further damage to the lung, exacerbate systemic inflammation, and lead to extrapulmonary organ dysfunction (Dreyfuss and Saumon 1998, Slutsky and Tremblay 1998). Providing ventilatory treatment without causing unnecessary harm improves outcome of ALI (Anonymous 2000), but several aspects, such as ventilatory mode, are still controversial (Tobin 2001). Interfacing with the patient's efforts and with the ventilator's contribution can be arranged in various ways with modern technology (Tobin 2001), enabling the use of partial ventilatory techniques in the early phases of ALI (Cereda, et al. 2000, Putensen, et al. 2001). Achieving satisfactory gas exchange even in severe ARDS patients is feasible with these modes, but benefits of these strategies for outcome are unproven (Cereda, et al. 2000).

The main outcome measure in the interventional trials concerning ALI has been either mortality or a surrogate of mortality, e.g., time of mechanical ventilation or days free of ventilation and being alive after inclusion in the trial (Schoenfeld, et al. 2002). Statistically, demonstrating of the effect of intervention on mortality requires a large and homogenous patient population with a strictly standardised protocol for various aspects of critical care. For smaller groups, physiological outcome variables, related to the pathophysiology of ALI, are needed (Wyncoll and Evans 1999, Vincent 2004). When the effects of ventilatory technique are investigated, variables related to gas exchange are commonly scrutinized, although relationships between gas exchange, extent of lung injury and outcome are not straightforward. Computer-assisted x-ray tomography (CT) is an option for assessing

the extent of lung injury, has proven a good tool in the evaluation of ALI pathophysiology (Gattinoni, et al. 2001a). Several aspects related to lung injury may be measured with CT (Rouby, et al. 2003a).

Historically, very soon after the description of the inflammatory nature of ALI, modulation of the inflammatory reaction was considered as a treatment option (Luce 2002). The most investigated intervention in this sense has been anti-inflammatory drugs, and especially glucocorticosteroids. Although administration of glucocortico-steroids during early phases of ALI has proven to be disadvantageous (Bernard, et al. 1987, Cronin, et al. 1995), several studies have implied that in the late phase of ALI, the inflammatory process is characterised by a fibroproliferative reaction, and glucocorticosteroids may be effective during this phase (Meduri 1999). However, specific indications for glucocorticosteroid treatment and its contribution to outcome in late-phase ALI are still obscure.

In this study, the aim was to evaluate current treatment modalities of ALI, particularly the maintenance of spontaneous ventilation during mechanical ventilation and effects of glucocorticosteroids in the late phase of lung injury. A randomised and controlled study design was used to assess physiological effects and outcome measures comparing two different partial ventilatory modes. Airway pressure release ventilation (APRV), which is a partial ventilatory mode enabling unrestricted unsupported spontaneous breathing superimposed on mechanical ventilation was the primary focus. APRV has not been tested in a randomised, parallel, controlled setting with ALI/ARDS patients. The control mode was the present gold standard syncronised intermittent ventilation (SIMV).

Moderate-dose, prolonged glucocorticosteroid treatment during the late phase of ALI is currently the only clinical treatment option aimed at modulating the inflammatory reaction. The clinical benefit of this strategy was analysed in a homogeneous group of ALI patients.

2. REVIEW OF THE LITERATURE

2.1 Definitions of ALI and ARDS

Acute lung injury was first described as a clinical syndrome by Ashbaugh et al in 1967, who presented a case series of twelve patients with common clinical hallmarks. These signs were acute respiratory distress, hypoxia refractory to oxygen, diffuse bilateral pulmonary infiltrates, reduced compliance of the respiratory system, and requirement of positive pressure breathing. Patients suffered from a variety of serious illnesses and had severe respiratory failure requiring mechanical ventilation (Ashbaugh, et al. 1967). Autopsies of the patients who died, showed hyaline membranes in the airways, atelectasis, microthrombosis, vascular congestion and fibrosis (Wyncoll and Evans 1999). The same investigators proposed the term "adult respiratory distress syndrome" (ARDS), an analogue to the infant respiratory distress syndrome (Petty and Ashbaugh 1971).

To more precisely define this group of patients with strikingly uniform clinical, physiological, radiological, and pathological abnormalities, the original investigators proposed a definition for ARDS. This definition was based on the presence of hypoxia, chest radiographical opacities, decreased mechanical properties of the respiratory system, and exclusion of congestive left heart failure (Petty and Ashbaugh 1971). A very important feature of this and several subsequent definitions has been the presence of a triggering insult or a known risk factor. Almost any critical illness or catastrophic insult to homeostasis is such a risk factor. Table 1 presents common clinical entities associated with ALI. Most definitions of ALI/ARDS have underlined the acute nature of this clinical problem, and the original term "adult respiratory distress syndrome" has been replaced with the term "acute respiratory distress syndrome" (Bernard, et al. 1994b). Another reason is the fact that ALI/ARDS also affects paediatric patients.

The definition advocated by Murray et al incorporated a quantitative scoring system for lung injury with classified variables based on radiographical appearance of the lung on chest x-ray, static lung compliance, positive end expiratory pressure (PEEP) setting, and ratio of arterial partial oxygen pressure and fraction of inspired oxygen (Murray, et al. 1988). The Murray score or Lung Injury Score (LIS) has been widely used in epidemiological studies as well as in several interventional studies. The benefit of this definition is that the severity of lung injury can be quantified, and LIS can be used to compare patients at different time points. In the original work by Murray et al ARDS was defined as a LIS over 2.5, and mild to moderate injury as values between 0.1–2.5 (Murray, et al. 1988). LIS scoring is presented in Table 2.

The final value is obtained by dividing the

Table 1. Clinical entities associated with acute lung injury. (Modified from Ware and Matthey 2000).

Direct lung injury or pulmonary ALI	
	Pneumonia
	Gastric content aspiration
	Pulmonary contusion
	Inhalation of toxic gases
	Near-drowning
Indirect lung injury or extrapulmonary ALI	
	Sepsis
	Pancreatitis
	Multiple transfusions
	Severe trauma
	Severe burns
	Drug overdose
	Cardiopulmonary by-pass

Table 2. Lung injury score (LIS). (Adapted from Murray et al 1988).

Component	0	1	2	3	4
Chest X-ray (Alveolar infiltrates)	No	1 quadrant	2 quadrants	3 quadrants	4 quadrants
Hypoxaemia (PaO_2/FiO_2, mmHg)	≥300	225–299	175–224	100–174	≤100
PEEP (PEEP-setting, cmH_2O	≤5	6–8	9–11	12–14	≥15
Compliance (Static, mL/cmH_2O)	≥80	60–79	40–59	30–39	≤29

sum of these individual component scores by 4.

The lack of uniform criteria which could form the basis of epidemiological and interventional studies and a better stratification of patients served as the initiative for the American-European Consensus Conference (AECC) to create a simple and a widely accepted definition (Bernard, et al. 1994b). This definition incorporated the term "Acute Lung Injury" (ALI). According to this concept, ALI is considered to be "a syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiological, and physiological abnormalities that cannot be explained, but may coexist with congestive heart failure or pulmonary capillary hypertension". An essential part of the AECC definition is that the onset of the insult must be acute, but no exact time frame for acute illness has yet been presented. According to the AECC criteria, ARDS is an extreme manifestation of ALI, and degree of hypoxemia separates ARDS patients from those with ALI (Bernard, et al. 1994b). The AECC criteria are presented in Table 3.

Comparision of AECC and LIS classifications yielded similar estimates of the incidence of ARDS, although with a discrepancy between the classifications, and neither had any prognostic value (Meade, et al. 2001).

The aim of the development of AECC criteria was to simplify and to make easier clinical application of the definition of ALI/ARDS. A critique of straightforward evaluation of the oxygenation defect in the AECC criteria has been presented. It has been suggested that this evaluation should be with a determined specific PEEP or with otherwise optimised respiratory settings (Villar, et al. 1999). Application of or increase in PEEP can easily, for example, turn an ARDS patient with a Pa_2/FiO_2 ratio of just below 200 mmHg into an ALI patient or even increase the PaO_2/FiO_2 ratio above 300 mmHg (Villar, et al. 1999). To emphasise the inflammatory nature of ALI, incorporation of biochemical markers of inflammation into the definition of ALI has also been suggested (Abraham, et al. 2000). Making the definition more specific may require more a precise definition of radiographical criteria or the use of computed tomography of the lung (Roupie, et al. 1999).

Table 3. AECC criteria for ALI and ARDS (Bernard, et al. 1994a).

1. Acute onset
2. Bilateral infiltrates on chest radiography
3. Pulmonary artery wedge pressure <18 mmHg or the absence of clinical evidence of left atrial hypertension
4. Failure of oxygenation
   a. Acute lung injury considered to be present if PaO_2/FiO_2 is ≤300 mmHg
   b. Acute respiratory distress syndrome considered to be present if PaO_2/FiO_2 is ≤200 mmHg

2.2 Epidemiology of ALI/ARDS

Since the time of the description of ALI/ARDS, it has been difficult to estimate the incidence of this clinical syndrome. A precise and uniform definition is of outmost importance for epidemiological studies. Earlier epidemiological reports have used ambiguous definitions, and the reported incidence of ARDS has varied between 1.5 (Villar and Slutsky 1989) and 60 (Anonymous 1977) cases per 100 000 inhabitants. In more recent prospective cohort studies which have used the AECC criteria, the reported incidence of ALI has ranged from 34 to 64.2 cases per 100 000 and for ARDS 28 cases per 100 000/year (Bersten, et al. 2002) (Goss, et al. 2003). In a Nordic cohort study, the reported incidences of ALI and ARDS were much lower, with only 17.9 per 100 000/year for ALI and 13.5 per 100 000/year for ARDS (Luhr, et al. 1999). In that study, only those patients who were mechanically ventilated over 24 hours were screened. This could have led to underestimation of the incidence. In a recent multicenter survey prevalence of acute lung injury was 7.1 % in a sample of European ICUs (Brun-Buisson, et al. 2004).

The only Finnish study reporting the incidence of ARDS is the study conducted by Valta et al. (Valta, et al. 1999). By using strict criteria for ARDS, and by demanding a PaO_2/FiO_2 ratio below 150 mmHg with FiO_2 >0.5, PEEP >5 cmH_2O, and LIS score >2.5, the incidence of ARDS in Savonia was 4.9 per 100 000/year (Valta, et al. 1999).

The role of the underlying condition and its risk of progression to ALI is a poorly understood issue. Only a few studies have tried to identify patients at risk for ALI/ARDS and tried to determine the incidence of development of ARDS in these clinical situations. No study has used AECC criteria (Hudson, et al. 1995). Clinical situations related to ARDS are so diverse that studies including enough patients in defined groups are difficult to conduct.

2.3 Pathogenesis of ALI

2.3.1 Pathogenetical features of lung injury

The clinical course of ALI can usually be divided into three phases with typical clinical, physiological, and histological patterns (Ware and Matthay 2000). However, as the triggering insults are variable, the typical presentation and progression of the syndrome is difficult to define. Also, especially after the initial phase of the inflammatory reaction, considerable heterogeneity exists in the pathogenesis and clinical progression. For reasons related to underlying disorders, patient-related factors, and treatment or all of these, not all patients progress through all the phases (Weinacker and Vaszar 2001).

The basic pathology of ALI/ARDS during the initial phase comprises a non-specific pattern of lung injury leading to increased permeability of the endothelial and epithelial barriers of the lung, with accumulation of the protein-rich oedema fluid in the interstitium and alveoli. This initial phase or early ARDS is therefore called the exudative phase (Ware and Matthay 2000). The fluid accumulation is accompanied by neutrophil sequestration and migration as a result of chemotactic stimuli released within the lung and the activation of neutrophils by local and circulating inflammatory mediators (Pittet, et al. 1997). Histologically, injury or even necrosis of alveolar type I epithelial cells may be seen. This pattern of injury is described as diffuse alveolar damage (DAD) (Luce 1998). Numerous cascades of mediators, modulators, and inflammatory cells are involved in this process (Pittet, et al. 1997). The relative importance of these components is unknown, and the pathogenesis of lung injury may involve several alternative pathways. Some of the basic pathways involved during initial phase of ALI are summarized in Figure 1.

Some patients recover quickly within a few days after the initial defect of alveoli-endothelial permeability and do not enter the subsequent phases of inflammatory injury. Some patients, however, move after

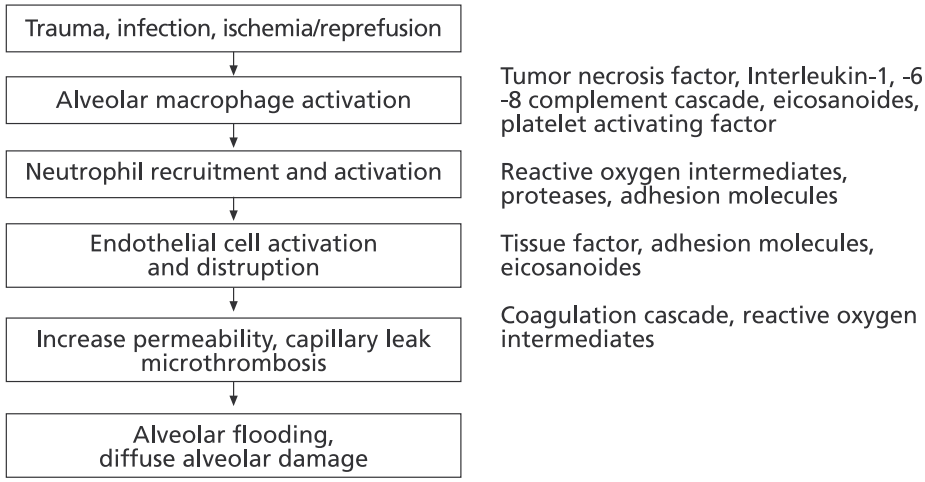
5 to14 days to the second or proliferative phase of lung injury, a phase characterized by marked proliferation of fibroblasts in the alveoli. The proliferation of alveolar type II cells leads to interstitial fibrosis, and the obstruction and destruction of the pulmonary capillary circulation (Lee and Jain 2002). Recent data suggest that the fibroproliferative response may begin early in the course of ALI (Marshall, et al. 2000). In some patients the proliferative phase evolves to a third phase, the chronic fibrotic phase of ALI. This phase, commonly referred to as late ARDS, usually develops beyond 10 days after the initial insult and is characterized by extensive fibrosis with obliteration of the normal lung structure, development of emphysematous lung regions, and bulla (Artigas, et al. 1998).

The basic mechanisms that control the progression of ongoing lung injury and the factor, which regulates inflammatory process are not yet fully understood (Bellingan 2002). Extremely complex interactive regulatory signals pose a significant challenge to developing treatments which would have beneficial effects on the course of the inflammatory reaction and outcome.

2.3.2 Ventilator-induced lung injury

Treatment of ALI, and especially the application of mechanical ventilation, have several consequences for the pathophysiology of lung injury. Besides being life-saving supportive treatment of respiratory failure, just as with any treatment, mechanical ventilation also has side-effects. After only 3 years after the description of ARDS, came the first reports speculated that mechanical ventilation may cause iatrogenic injury to the lungs through the non-uniform expansion of the injured lung (Mead J 1970). Barotrauma, the leakage of air due to disruption of the airspace wall, and haemodynamic compromise due to decrease of cardiac filling are complications recognised ever since the development of positive pressure breathing (Pontoppidan, et al. 1972). Subtler, iatrogenic injury caused to the lung by mechanical ventilation is a concept that is defined as "ventilator-associated lung injury" (VALI) (Pinhu, et al. 2003). When induced in an animal model by injurious mechanical ventilation alone, the term ventilator-induced lung injury (VILI) is recommended (Anonymous 1999). The contri-

Figure 1. (Modified from Bulger et al 2001).



bution of VALI to the pathogenesis of lung injury is inseparable and indistinguishable from the underlying disorder (Dreyfuss and Saumon 1998).

The underlying mechanisms contributing to VILI are well established in several experimental investigations (Dreyfuss and Saumon 1998). Factors involved in this process include high inspired oxygen concentration, high pressure and volumes, tidal collapse, and reinflation of the lung during mechanical ventilation. It has been suggested that these factors should be categorised into five distinct components: barotrauma, volutrauma, atelectotrauma, biotrauma, and toxic effects of oxygen (Pinhu, et al. 2003).

Although the toxic effects of oxygen due to increased formation of oxygen free radicals have been demonstrated in several experimental models (Dreyfuss and Saumon 1998), the threshold for pulmonary oxygen toxicity in humans and particularly those with ALI is unknown. However, the lowest possible concentration of oxygen that relieves tissue hypoxia is commonly recommended (Jenkinson 1993). In patients with normal lungs, even prolonged exposure to high oxygen concentrations has not been associated with increased markers of lung injury (Capellier, et al. 1998). A high oxygen concentration may cause atelectasis formation due to absorption in areas with a low ventilation-perfusion ratio and hence may worsen the gas-exchange (Hedenstierna 1999). To avoid hypoxia, high concentrations of oxygen are, however, usually needed in ventilatory treatment of ALI. The relationship between toxic effects of oxygen and detrimental effects of hypoxia remain unknown.

High airway pressure was initially considered the major factor causing unfavourable side-effects related to mechanical ventilation. Macroscopic accumulation of extra-alveolar air is a gross manifestation of barotrauma. Clinically, this kind of barotrauma presents as pneumothorax, pneumomediatinum, pneumatocele, subcutaneous emphysema, and even gas embolism, but no correlation between clinical barotraumas and airway pressure has been firmly established (Weg, et al. 1998). Airway pressure is not a particularly good surrogate for alveolar pressure, and peak airway pressure in partcular highly influenced by several factors affecting lung and chest wall mechanics. Because airway pressure is dependent on mechanical properties of the respiratory system, barotrauma and volutrauma may be viewed as two aspects of the same phenomenon (Gattinoni, et al. 2003).

The term volutrauma was suggested to indicate that the critical factor causing injury at cellular level is excessive volume rather than high transpulmonary pressure (Dreyfuss and Saumon 1998). This was demonstrated by strapping the chest wall of experimental animals and ventilating them at high pressures, but low tidal volumes. In this setting, lung injury remained moderate, but similar airway pressures without strapping and the inevitable high tidal volumes can lead to increased permeability and pulmonary oedema. Several other experimental trials have shown that overstretching of the lung's fibroskeleton causes direct physical damage to alveolar-capillary structures, leading to increased permeability and disruption of alveolar and endothelial structures (Dreyfuss and Saumon 1998). Molecular pathways involved in signal transduction in this process are complex and still poorly understood. Regional transpulmonary pressures control distribution of overstretching. Lung weight promotes the collapse of dependent areas, causing a marked decrease in regional transpulmonary pressure (Gattinoni, et al. 1993). Chest wall derangements, the weight of mediastinal structures, and increased intra-abdominal pressure may also lead to regional variation in transpulmonary pressure. Distribution of ventilation is determined by this regional variation, and ventilation has a preference for the areas of least intrapleural pressure such as the anterior parts of the thorax in a supine patient. Hence, these areas are prone to volutrauma. Proof of this injury caused by overdistension is evident radiologically and histologically.

Cystic changes in lung parenchyma, bulla, and fibrosis have a tendency to develop into anterior parts of the lung (Desai, et al. 1999).

Atelectotrauma refers to shearing injury caused by recruitment and de-recruitment within the respiratory cycle (Dreyfuss and Saumon 1998). Mechanical force generated at the junction of areas with different mechanical properties is called shear stress. Traction forces generated between collapsed alveoli and adjacent expanded lung units have been predicted in a mathematical model to exceed 100 cmH_2O (Marini 2001). Prevention of lung collapse by applying PEEP or by using measures aimed at recruiting the lung can theoretically reduce this shearing stress and alleviate mechanical strain on lung structures (Lachmann 1992). The independent contribution of each component: baro-, volu- or atelectotrauma, on development of VILI is unknown (Pinhu, et al. 2003). In the experimental setting, the least injurious type of positive pressure ventilation is a combination of low tidal volume and high PEEP aiming to avoid overdistension and repetitive opening and closing of alveoli (Dreyfuss and Saumon 1998). In a clinical setting, this type of ventilatory strategy has been called the open lung approach or lung protective ventilation (Amato, et al. 1998, Lachmann 1992). Clinical trials on mechanical ventilation will be discussed later.

The term biotrauma refers to a local and systemic inflammatory response associated with lung injury caused by mechanical ventilation (Dreyfuss and Saumon 1998). This inflammatory response has been tested in several laboratory models as well as in clinical settings (Slutsky 1999). These studies have shown marked increases in the release of inflammatory mediators such as proinflammatory cytokines, TNF-alfa, IL-6, IL-1beta, and several others (Dreyfuss and Saumon 1998). Associated with an injurious type of ventilation, the pulmonary production of these mediators rises, and high concentrations may be detected in the bronchoalveolar lavage (BAL) (Ranieri, et al. 1999). Increased production of these mediators exacerbates pre-existing lung damage and results also in spillover into the systemic circulation. Systemic effects of proinflammatory mediators can initiate and cause propagation of a systemic inflammatory response leading to detrimental effects on several end-organ functions and ultimately to multiple organ failure (MOF). This pathophysiological pathway is in parallel with the fact that patients with ALI/ARDS usually die from MOF and not from hypoxemia. Hence, it has been postulated that mechanical ventilation may be an important contributing factor to the development of the vicious cycle leading to MOF (Slutsky and Tremblay 1998).

2.3.3 Clinical and physiological features of ALI

During the initial exudative phase, the clinical presentation of ALI is characterized by progressive dyspnoea, tachypnea, hypoxemia, and worsening of the lung's mechanical properties. Life-threatening respiratory failure usually develops within 24 hours after the underlying precipitating insult. The evolution from this initial exudative phase to the proliferative phase ensues within 2 to 5 days. The proliferative phase is characterised by a hyperdynamic metabolic state and signs of multiple organ dysfunction. If the patient does not recover, progression to the fibroproliferative phase usually takes place within 5 to 14 days. During this fibroproliferative phase, the lung's mechanical properties worsen further due to fibrosis. If resolution and recovery do not occur, patients die, usually due to progression of MOF, recurrent sepsis, or refractory hypoxemia (Ware and Matthay 2000).

Accumulation of protein-rich fluid into the interstitium leads to increase in lung weight. Increased pressure in the dependent lung causes alveolar collapse in dorsal and posterior parts (Gattinoni, et al. 1986a). Fluid accumulation is accompanied by surfactant dysfunction, which further favours atelectasis formation (Nicholas, et

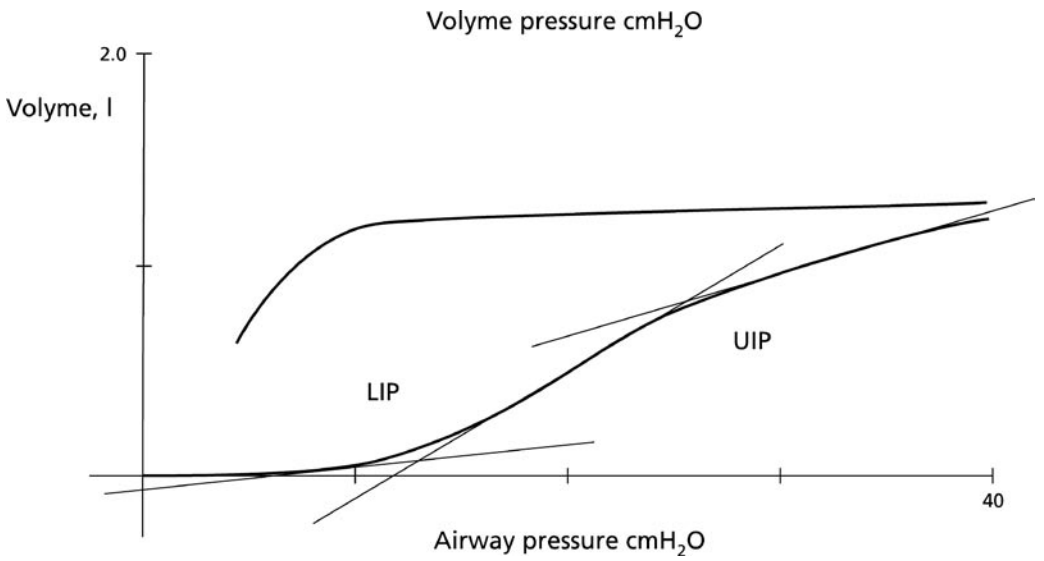
al. 1997), which is worsened by absorption of oxygen into the pulmonary circulation, especially when the inspired gases have a high oxygen concentration (Rothen, et al. 1998). Increased pressure in the abdominal cavity may also cause compression tof the posterior parts of the lung. Alveolar collapse and filling of the airspaces with oedema and inflammatory debris causes intrapulmonary shunting and formation of areas of poor ventilation. Alveolar and endothelial damage also activates the coagulation cascades, leading to thrombus formation in the pulmonary circulation (Welty-Wolf, et al. 2002). The inflammatory response alters the responses of the pulmonary vasculature, and normal hypoxic pulmonary vasoconstriction is lost.

These changes cause increased intrapulmonary shunting and mismatching in ventilation-perfusion, and refractory hypoxemia thus ensues. Alveolar fluid accumulation may block gas diffusion; later fibrotic changes worsen this problem. Perfusion inequality causes increase in dead space ventilation, thus hampering carbon dioxide elimination. Development of fibrosis leads to a further increase in dead space ventilation. Increase in dead space during the initial phase of ALI correlates with poor outcome (Nuckton, et al. 2002).

Due to fluid accumulation, alveolar collapse, and fibrosis, mechanical properties of the lung deteriorate. Airway resistance and elastance of the lung and are markedly increased. Analysis of respiratory system mechanics usually involves reconstructing a pressure/volume diagram. The total respiratory system of an ALI patient has a typical sigmoid shape: The initial part of the curve is a very gentle slope reflecting low compliance at lung volumes below functional residual capacity. The point, where the slope of the curve increases has been called as the lower inflection point, LIP. The slope of the curve is increased after LIP, and the compliance is greater. When pressure is further increased, a transition to lower compliance is observed at a point called the upper inflection point, UIP (Stenqvist 2003). Figure 2 presents the typical PV curve of one ALI patient.

The physiological correspondence and clinical utility of mechanical measurements in guidance of ventilator treatment has been under intense research. The traditional interpretation of the PV curve suggests that LIP is the critical pressure at which the al-

Figure 2. PV curve for one ALI/ARDS patient by a slow-flow inflation method.
LIP = Lower inflection point. UIP = Upper inflection point.



veoli collapse occurs during expiration and re-open during inspiration. At the linear part of the PV curve, no further recruitment occurs, and the decrease in compliance at UIP indicates overdistension of the alveoli. In accordance with this interpretation, setting the respiratory cycle to occur in the linear part between LIP and UIP would be the most lung-protective strategy. However, because this traditional interpretation of PV tracings has several problems, the concept has been challenged (Hickling 2002, Stenqvist 2003). It seems obvious that LIP does not represent a single point of recruitment, but rather an increased rate of alveolar opening (Stenqvist 2003). Similarly, UIP is not a reliable indicator of overdistension (Hickling 2002).

A PV curve can be traced by several different methods. Original methods were truly static measurement with a supersyringe (Gattinoni, et al. 1987a) or multiple occlusion with a ventilator (Rossi, et al. 1985). These methods are cumbersome and rarely utilized in daily practice. A method using single inflation with a ventilator using a constant, very slow flow is easier to perform in ICU (Lu, et al. 1999). PV curves obtained with slow-inflation or semi-static methods correlate well with the supersyringe method (Lu, et al. 1999). Both static and semi-static methods require the patient to be myorelaxed or heavily sedated. Cessation of normal tidal breathing, oxygen uptake during measurement, and compression of gases may create artefacts (Stenqvist 2003). Measurement of lung mechanics during tidal breathing (dynamic measurement) combined with direct tracheal pressure monitoring avoids some of these problems and can be used for continuous monitoring (Karason, et al. 2001).

The strategy of implementing PV curves as a basis for ventilator setting has been tested in one randomised clinical trial (Amato, et al. 1998), which showed beneficial effects in the group using ventilator settings between LIP and UIP as compared to the control group with conventional tidal and conventional PEEP settings (Amato, et al. 1995). Lung mechanics were also used in a clinical trial utilizing inflammatory markers as an endpoint for VALI (Ranieri, et al. 1999). Concentrations of proinflammatory markers in BAL and in the systemic circulation decreased in the treatment group in which lung mechanics were measured and used in the setting of the ventilator as compared to control group values (Ranieri, et al. 1999).

2.4 Imaging in ALI

Due to fluid accumulation and airway collapse during the initial phase of ALI, anterior chest x-ray reveals bilateral alveolar infiltrates. Asymmetrical patchy consolidations with pleural effusions are typically present. An airbronchogram may become visible. Alveolar oedema resembles cardiogenic oedema, but with no signs of left atrial hypertension or cardiac enlargement. Differential diagnosis of this widespread airspace opacification is difficult. Often fluid accumulation between hydrostatic forces or exudation due to a permeability disorder is indistinct, based on chest x-ray (Desai and Hansell 1997). As the disease progresses, reticular opacities often become evident as a sign of increased fibrosis. With resolution of ALI, radiological findings ultimately disappear (Desai 2002, Desai and Hansell 1997).

CT studies have revealed several pathophysiological features of ALI. One notable feature is the reduction in aerated lung volume and its replacement by fluid and tissue. The volume of a functional, aerated lung can fall to only 20 to 30 % of its normal volume (Gattinoni, et al. 1987a). Another distinct feature is the distribution of alterations seen on CT. In contrast to that on the anterior x-ray, opacifications and loss of gas volume are not homogenous in CT scanning, but are distributed mostly in the gravity-dependent areas of the lung (Gattinoni, et al. 1991).

CT changes in ALI may be defined on the basis of morphology. Fleishner Society Nomenclature is a widely used definition in which CT findings are categorised as

ground-glass opacification, consolidation, or a reticular pattern (Austin, et al. 1996). Pathophysiologically, ground-glass opacification represents an active inflammatory process in the interstitium and alveoli, with alveoli incompletely filled with oedema fluid, cellular debris, and inflammatory cells. Consolidation refers to complete or almost complete loss of gas due to the complete filling of alveoli or total collapse of the lung area. Reticular pattern refers to the thickening of interstitial structures due to fibrosis, oedema, or inflammation (Austin, et al. 1996).

CT findings at different clinical phases of ALI are dissimilar. During the early exudative phase, typical findings include normal regions in the anterior, ground glass opacification in the middle, and consolidation in the dorsal parts of the lung (Gattinoni, et al. 1986a). This distribution is determined largely by gravity on the basis of progressive bronchiolar collapse towards the dependent zones due to the weight of the overlying pulmonary parenchyma (Gattinoni, et al. 1986a). There is also a cephalocaudal gradient; lower lobes are more extensively opacified than are upper lobes (Malbouisson, et al. 2000, Puybasset, et al. 1998). In the later phases of ALI, a reticular pattern due to fibrosis dominates in CT findings. Densities are also more evenly distributed, and usually resolution of dependent consolidation begins. Complications such as bullae and extra-alveolar air appear with the protracted course. Distribution of air cysts and bronchiectasises prevail in nondependent areas (Treggiari, et al. 2002). After the acute phase, fibrotic changes occur in the lung parenchyma. The predominantly ventral distribution of these changes indicates that they may be related to VALI rather than to the inflammatory process itself (Nobauer-Huhmann, et al. 2001). In a long term follow-up, fibrosis also occurs, mainly in the anterior portion (Desai, et al. 1999).

The CT appearance of ALI depends on the type of lung injury. A direct insult results in densities which are more asymmetric, with both dense parenchymal opacifications and ground glass opacifications. In an indirect insult, CT scanning shows more symmetric dorsal consolidations and ground glass opacifications (Goodman, et al. 1999). A French study provides two opposite radiological presentations, corresponding to different lung morphologies (Rouby, et al. 2003a). In patients with focal CT attenuations, frontal chest radiography generally shows bilateral opacities in the lower quadrants; these may remain normal, particularly when the lower lobes are entirely atelectatic. In patients with diffuse CT attenuations, the typical radiological presentation is “white lung” (Rouby, et al. 2003a). However, in these studies no correlation existed with type of lung injury (Puybasset, et al. 2000).

This distinction between focal versus diffuse loss of aeration has been suggested as a guide in the selection of optimal PEEP level (Rouby, et al. 2002). In an earlier study, CT alterations in the direct injury subgroup showed a more homogenous distribution, and there was more overlap between morphological findings (Rouby, et al. 2000); in that study, the pattern of lung morphology correlated with prognosis (Rouby, et al. 2000).

CT enables the determination of tissue density in a given voxel. Tissue CT densities called Hounsfield units (HU), range from –1000 HU (gas) to 1000 HU (bone). Water has a HU value of 0. Most investigators studying ALI have used a categorisation into lung that are nonaerated (tissue absorption between 0 and –100 HU), poorly aerated (–100 to –500 HU), normally aerated (–500 to –900 HU), and hyperinflated (–900 to –1000 HU) (Gattinoni, et al. 2001a). In a given region of interest (ROI), the distribution of voxels by the CT number frequency can be displayed. This technique makes it possible to measure the amount of gas within the lungs, the amount of lung tissue, and the relation between tissue mass and volume (Gattinoni, et al. 2001a).

The CT densitometric technique allows investigation of the pathophysiology of ARDS and especially the effects of different

treatment modalities. These measurements have correlated with several physiological variables in several studies. Extent of nonaerated tissue has correlated well with pulmonary shunt fraction and hypoxemia (Gattinoni, et al. 1988, Goodman, et al. 1999, Pelosi, et al. 2001). Respiratory compliance correlates with the amount of normally aerated lung (Gattinoni, et al. 1987b). The concept of "baby lung" means that decrease in compliance is not due to rigidity of the lung, but the small volume of normally aerated lung (Gattinoni, et al. 1987a). Quantitative analysis of CT served in investigation of the effects of PEEP (Gattinoni, et al. 1986a), body position (Gattinoni, et al. 1991), recruitment manoeuvres (Bugedo, et al. 2003, Lim, et al. 2003b), and ventilatory mode (Prella, et al. 2002).

Most CT studies in ALI/ARDS patients have involved only a few CT slices. Earlier, slow scan acquisition , and even at present exposure to radiation have limited the number of slices to be performed, especially in studies requiring repeated scans (Brochard 2001). Recently, a French group has developed a new technique based on multidetector helical scanners (Malbouisson, et al. 2001b, Puybasset, et al. 1998), allowing the whole lung to be scanned within 3 to 8 seconds, providing 1.5 mm slices that enable reconstruction of the whole lung. By manually outlining each section and with the aid of special software (Lungview ®), this system allows volumetric measurement of overinflated, normally aerated, poorly aerated, and nonaerated lungs. In addition, lung recruitment can be measured as the amount of gas that penetrates poorly aerated and nonaerated lung regions after ventilatory intervention (Malbouisson, et al. 2001b, Rouby, et al. 2003a). The method is laborious and is still considered experimental. Clinical studies utilising it are still few.

2.5 Pharmacological treatment in ALI

2.5.1 Pharmacological treatment options

Several pharmacological interventions have been tested in the treatment of ALI. Proposed therapies include anti-endotoxin immunotherapy, cyclo-oxygenase inhibitors, antagonists of pro-inflammatory cytokines, platelet-activating factor inhibitors and receptor antagonists, pentoxifylline, lipid mediators, several antioxidants, antiproteases, anti-adhesion molecules, and surfactant replacement therapy (Artigas, et al. 1998). For most of these approaches, the evidence is from experimental settings and from small-scale physiological trials. A few of these proposed pharmaco-therapies have entered phase III clinical trials, but unfortunately with negative results. None among these therapies is recommended outside investigational use at present.

Besides these therapies are inhaled vasodilators. Inhaled nitric oxide in partcular has been investigated. A universal pathophysiological finding in ALI is elevated pulmonary resistance. Inhaled NO may selectively reduce pulmonary artery pressure and improve oxygenation (Rossaint, et al. 1993), and several studies have tested the possible outcome benefit of inhaled NO, all with negative results (Dellinger, et al. 1998), meaning that, neither can inhaled NO be recommended as a standard therapy for ALI.

2.5.2 Glucocorticosteroids in ALI

Glucocorticosteroids are at present the most widely used immunomodulative drug therapy (Tasaka, et al. 2002). By binding to cytoplastic glucocorticoid receptors, they exert broad inhibitory effects on cytokine transcription factors and production of proinflammatory cytokines (Thompson 2003). Glucocorticosteroids may also block cytokine receptors and antagonize cytokine-mediated activation of transcription factors.

Fibroproliferative response has been shown to be modulated by the mediators tumor necrosis factor alfa, interleucin-1 and -8, and tumor growth factor (Luce 2002). By reducing the effects of these mediators, steroids may interfere with the fibroproliferative process (Meduri, et al. 1994). Glucocorticosteroids may also prevent collagen deposition and increase collagen breakdown in several fibrotic diseases.

Due to their broad anti-inflammatory properties, glucocorticosteroids have been assumed to have a potential benefit in the treatment and prevention of ALI/ARDS. Administration of a short course of large doses of glucocorticosteroids in the early phase of ARDS or to septic patients at high risk for ARDS was tested in several large scale multicenter trials (Luce, et al. 1988, Bernard, et al. 1987, Bone 1989). Two meta-analyses concluded that this concept is not beneficial for ARDS patients in terms of mortality or reversal of ARDS, and that glucocorticosteroids lead to an increased number of nosocomial infections (Cronin, et al. 1995, Lefering and Neugebauer 1995). In sepsis and septic shock, early treatment with anti-inflammatory doses of steroids may even worsen outcome (Cronin, et al. 1995, Lefering and Neugebauer 1995).

Increased understanding of the pathogenesis of ALI and regulation of the host-defence response the during fibroproliferative phase of ALI has created a new interest in testing the effects of glucocorticosteroids in the late phase of ALI/ARDS (Meduri 2002). A fibroproliferative host response is the lungs' stereotypical reaction to tissue injury (Meduri, et al. 1995a). Alveolar and epithelial cells are replaced by mesenchymial cells, which produce collagen, collagen precursors, and extracellular matrix. As a consequence, alveolar and interstitial scarring, capillary obliteration, and distortion of lung architecture occur. As a marker of collagen accumulation, the procollagen aminoterminal propolypeptides type I and III are observed in BAL and the systemic circulation (Meduri 1996). Severity of fibrosis and mortality correlate with levels of these markers in BAL and the systemic circulation (Clark, et al. 1995). Although the cause and exact mechanism regulating the development of fibrosis are not fully understood, several anti-inflammatory cytokines are known to be necessary to terminate this response (Meduri 1996). Clinical manifestations of fibroproliferation are diverse, and differential diagnosis from the pneumonia and extrapulmonary infection is very difficult. Clinical findings of fibroproliferation suggested in various studies are summarised in Table 4.

The response of the biological markers of fibroproliferation to corticosteroid treatment has been investiged in several studies by Meduri et al., who found that prolonged corticosteroid treatment was associated with rapid decrease in the procollagen aminoterminals propolypeptides type I and III, and these effects were parallel to clinical benefits (Meduri, et al. 1998b).

This theoretical background and clinical experience suggest that moderate-dose glucocorticoid treatment during the late phase of ALI may be beneficial (Biffl, et

Table 4. Clinical manifestations of the proliferative phase of ALI.

Fever >38.8 °C
Leucocytosis >10 x 10^3/l
Diffuse alveolar or interstitial infiltrates
Fibrotic changes in CT or x-ray
Increased dead space ventilation
Neutrophila in BAL
Positive clinical response to glucocorticosteroids

al. 1995, Hooper and Kearl 1990, Keel, et al. 1998). The first reports were anecdotal case studies, but some of these were later expanded to larger case series with historical or concurrent controls. These studies consistently showed improvement in lung function and reduction in associated organ dysfunction. In addition, investigators reported lower mortality than for historical controls, a shortened use of mechanical ventilation, and a briefer ICU stay (Biffl, et al. 1995, Hooper and Kearl 1990, Keel, et al. 1998). Meduri et al have conducted the only prospective study on late steroids in ARDS. They included patients with LIS of >2.5 and mechanical ventilation for 7 days. Methylprednisolone 2 mg/kg/day in four doses was given to the intervention group. The study protocol allowed crossover from control arm to intervention arm when no improvement was observed after 10 days of inclusion trial. Four patients were crossed over, leaving only 4 in the control group (Meduri, et al. 1998a). The study was terminated after 24 randomised patients, due to significant reduction in ICU mortality in the steroid group. This study has recieved criticism, but the results have raised interest in the late-steroid concept in ARDS (Brun-Buisson and Brochard 1998).

2.6 Ventilatory treatment of ALI

2.6.1 Lung-protective ventilation

The most appropriate method of mechanical ventilation and its physiological targets have been a subject for debate since the description of ALI/ARDS (Moloney and Griffiths 2004). Classically, the aim has been the normalisation of arterial oxygen and carbon dioxide partial pressures. To achieve these targets in ALI patients with increased dead space, tidal volumes between 12 to 15 ml/kg have been conventionally used (Tobin 1994). This is considerably higher than the normal resting tidal volume for humans or for a wide variety of mammals (Tenney SM 1963). Concerns about ventilator-induced lung injury have led to development of ventilatory strategies aimed at avoiding the increased mechanical stress which can cause further injury to the lungs. The first reports were case series and non-controlled cohorts, which showed benefit from a gentler ventilatory strategy (Gentilello, et al. 1995, Hickling, et al. 1994, Lewandowski, et al. 1995). These reports and experimental evidence led to formation of a consensus statement on ventilatory treatment by the American European Consensus Conference in 1998 (Artigas, et al. 1998). On the basis of expert opinion, this statement suggests that airway plateau pressure should be limited to below 25 to 30 cmH_2O; no strict values for tidal volumes or guidelines for PEEP setting were recommended (Artigas, et al. 1998). Although vague, the term "lung protective ventilation" was advocated by several authors (Amato, et al. 1995). The elements of lung-protective ventilation are limitation of tidal volume or transpulmonary pressure or both. This usually leads to limitation of carbon dioxide elimination which is accompanied by hypercarbia, often referred to "permissive hypercapnia" (Hickling, et al. 1994). To reduce pulmonary collapse, the use of high PEEP or recruitment manoeuvres or both are usually emphasised as an essential part of lung protection. Sometimes this type of strategy has been called the open lung approach (Lachmann 1992).

The lung protective strategies have been tested in five randomised controlled trials (Amato, et al. 1998, Anonymous 2000, Brochard, et al. 1998, Brower, et al. 1999, Stewart, et al. 1998). Each of these studies has used reduced tidal volumes as compared to those of the control group, but volumes and distending transalveolar pressures in both treatment and control groups have varied. Permissive hypercapnia was allowed in some studies, while others tried to maintain normocapnia also in the treatment group. The essential difference in ventilatory protocols between these studies was in the setting of PEEP. The Amato study used titration of PEEP based on lung mechanical measurement (Amato, et al. 1998), while other studies chose a similar protocol

for PEEP in both groups. Interpretation of the results is difficult also because of differences in study design. Pooled absolute risk reduction for mortality during follow-up in these studies was 6 % (95 % CI 1 – 12). In the largest trial, the secondary end-point was ventilator-free days (Anonymous 2000). The difference in means for VFD was 2 days with a 0.5 to 3.5 95 % confidence interval. A summary of these studies is presented in Table 6.

Based on these studies, several meta-analyses and clinical guidelines have been presented (Eichacker, et al. 2002, Petrucci and Iacovelli 2003). Definitive answers for many issues are still open, and the Cochrane Review grades the value of low tidal volume as B (Petrucci and Iacovelli 2003). The issue of PEEP setting is even more open. A large-scale trial by the ARDSnet collaboration tested the use of systematically higher PEEP. Because preliminary results indicated that this approach is not beneficial, the study was discontinued prematurely. Mortality was rate was low (24.9 % vs 27.5 %) in both treatment groups with no difference whether lower or higher PEEP levels were used (Brower, et al. 2004). No firm recommendations conserning the setting of PEEP are stated in recent guidelines (Dellinger, et al. 2004).

2.6.2 Ventilatory treatment options

Several modifications of mechanical ventilation have been developed and brought into clinical use (Tobin 1994). Few of these have been tested in clinical trials to evaluate their impact on outcome in ALI (Räsänen and Downs 1991). Delivery and setting of the inspiratory waveform profile is one aspect of mechanical ventilation. Volume-cycled, constant-flow ventilation has been compared to pressure-controlled ventilation in one randomised trial: In this multicenter study, 79 ARDS patients were randomly assigned to be ventilated with either the pressure-controlled or volume-controlled mode. In both instances, inspiratory plateau pressure was limited to below 35 cm H_2O. Patients with volume control had both a significantly higher in-hospital mortality rate (78 % vs. 51 %) and a higher number of extrapulmonary organ failures. However, multivariate analysis suggested that the outcome was unrelated to ventila-

Table 6. Prospective studies investigating protective ventilatory strategies.

	(Amato, et al. 1998)	(Brochard, et al. 1998)	(Stewart, et al. 1998)	(Brower, et al. 1999)	NIH (Anonymous 2000)
Number of patients	53	116	120	52	861
Tidal volume in control group	12 ml/kg	10.3 ml/kg	10.7 ml/kg	10.5 ml/kg	12 ml/ideal body weight
Tidal volume in intervention group	<6 ml/kg	7.1 ml/kg	7 ml/kg	7.5 ml/kg	6 ml/ideal body weight
PEEP in control group	8.7 cmH_2O	10.7 cmH_2O	7.2 cmH_2O	8.2 cmH_2O	8.6 cmH_2O
PEEP in intervention group	16.4 cmH_2O	10.7 cmH_2O	8.6 cmH_2O	9.5 cmH_2O	9.4 cmH_2O
Mortality in control group	71 %	47 %	46 %	47 %	39 %
Mortality in intervention group	45 %	38 %	50 %	50 %	31 %
ARR % 95 % CI	26 0–52	–8.6 –9–27	3.3 –15–21	–3.8 –23–31	8.8 2–15

ARR = Absolute risk reduction; 95 % CI = 95 % confidence interval.

tory mode (Esteban, et al. 2000a). Smaller trials comparing volume-controlled to pressure controlled ventilation have demonstrated only minor differences between the modes when settings were comparable (Lessard, et al. 1994, Prella, et al. 2002).

Adjustment of the inspiratory-expiratory time-ratio by extending inspiratory time is one modification of conventional ventilation. It is usually referred as inverse ratio ventilation (IRV) (Marcy and Marini 1991). By extending the inspiratory time, peak airway pressure can be reduced, and at the same time mean airway pressure is increased (Marcy and Marini 1991). Increase in mean airway pressure is related to improvement of oxygenation in some studies (Wang and Wei 2002, Zavala, et al. 1998), while most studies show no benefit (Lessard, et al. 1994, Mercat, et al. 1997). The short time allowed for expiration creates the potential for incomplete expiration before the next inspiration, a situation referred to as air trapping or development of intrinsic PEEP. This may lead to hyperinflation, barotraumas, and heamodynamic compromise (Lessard, et al. 1994, Ludwigs, et al. 1997, Valta and Takala 1993). In a physiological study by Valta et al (1993) the effect of reduced expiratory time on end-expiratory lung volume and pressure during volume-controlled IRV was similar to the use of PEEP (Valta and Takala 1993). In a long-term follow-up with CT scanning, the use of IRV was related to an increased amount of reticular, fibrotic changes in anterior parts of the lung among survivors of ARDS (Desai, et al. 1999). No prospective study has compared IRV to the conventional mode in order to test its implications for relevant clinical outcome measures.

High frequency ventilation (HFV) refers to techniques employing much higher breathing frequencies and much smaller tidal volumes than those of conventional mechanical ventilation. Since its first description in 1972, it has been used mainly in paediatric patients, but evidence of its benefits is still controversial (Henderson-Smart, et al. 2003). Theoretically, a ventilatory strategy which combines very low tidal volume and alveolar excursion with high mean airway pressure and good lung recruitment may be ideal to avoid VILI. The clinical benefit of HFV has been tested in one randomised clinical trial involving patients with severe ARDS (Derdak, et al. 2002). This trial showed a trend towards an improved outcome associated with early use of HFV, but it was underpowered to show any benefit for mortality (Derdak, et al. 2002).

2.6.3 Partial ventilatory modes

Interaction between ventilator and patient is another aspect of ventilatory treatment of ALI. Traditionally, mechanical ventilation has been applied with full control of alveolar ventilation by ventilator in order to completely unload the patient from the work of breathing. When improvement of gas exchange and mechanical disturbance allowes, partial ventilatory modes are able to facilitate weaning from respiratory support. Several partial ventilatory modes have been developed to employ various techniques to combine the patient's spontaneous activity and the ventilator´s mechanical assistance. Differences between modes are subtle with clinical benefits still unproven (Räsänen and Downs 1991).

Interaction between spontaneous breathing and mechanical ventilation can serve to categorize partial ventilatory techniques (Putensen, et al. 2002). The first group consists of modes where every spontaneous inspiratory effort is augmented by a response from the ventilator. Assist-controlled ventilation (ACV), pressure support ventilation (PS), and proportional assist ventilation (PAV) belong to this category. The second group comprises types in which minute ventilation is modulated by addition of non-assisted inspirations; intermittent mandatory ventilation (IMV) and its modification, synchronised intermittent mandatory ventilation (SIMV), are examples. The third category comprises ventilatory modes in which unrestricted and unsupported

spontaneous breathing is possible at any phase of the mechanical ventilatory cycle, and switching between two airway pressures provides mechanical part of alveolar ventilation. Airway pressure release ventilation (APRV) and biphasic positive airway pressure ventilation (BIPAP) represent this category. The fourth category comprises various hybrid modes combining elements from the other categories, with SIMV with PS one example (Putensen, et al. 2002).

Preserving spontaneous breathing efforts during mechanical ventilation offers several potential physiological benefits. Improved gas exchange has resulted from several experimental and clinical studies of the effects of maintained spontaneous breathing (Hörmann, et al. 1997, Putensen, et al. 1995a, b, Sydow, et al. 1994, Valentine, et al. 1991). One mechanism suggested to lead to these benefits is a more favourable distribution of spontaneous ventilation as compared to controlled breaths. During active inspiratory effort, the posterior muscular part of the diaphragm contracts more than does the anterior tendon plate (Froese and Bryan 1974). As the posterior, dependent parts of the lung are well perfused, improvement occurs in the ventilation-perfusion ratio. If diaphragmatic tone is abolished by neuromuscular blockade, the changes are even more pronounced when the diaphragm is moved cranially by the pressure of the intra-abdominal organs (Tokics, et al. 1996). With totally controlled ventilation, posterior and juxtadiaphragmatic lung areas develop atelectasis and consolidation even with normal lungs (Froese and Bryan 1974, Tokics, et al. 1996); and atelectasis formation with ALI is pronounced (Gattinoni, et al. 1986b). If diaphragmatic contractions are maintained, the lung collapse may be counterbalanced. This was shown by Hedenstierna et al in study during which the phrenic nerve was stimulated unilaterally during anaesthesia. Atelectasis size in CT scanning on the stimulated side was almost abolished (Hedenstierna, et al. 1994). It seems that maintained spontaneous breathing can also recruit a previously collapsed lung. One surrogate of this is the improvement of the V/Q ratio, when controlled ventilation is switched to a ventilatory mode, where spontaneous breathing is possible (Wrigge, et al. 2003, Putensen, et al. 1999). The process of recruitment takes time, as shown in a crossover study in ARDS patients by Sydow et al (1994). Decrease in shunting and improvement of oxygenation was observed after several hours when volume-controlled IRV was changed to APRV with unsupported spontaneous breathing (Sydow, et al. 1994). To gain these benefits, only 10 to 30 % of the minute ventilation is necessary, and spontaneous tidal volumes may be as small as 70 to 150 ml (Hörmann, et al. 1997).

Due to cyclic reduction in intrathoracic pressure resulting from spontaneous breathing, partial ventilatory modes have profound effects on the cardiovascular system. During unsupported spontaneous inspiration, venous return is enhanced and filling of the heart is increased. This has been shown to contribute to enhanced cardiac output, which together with improved oxygenation results in increased oxygen delivery; when a moderate amount of spontaneous breathing is maintained, oxygen consumption due to activity of the respiratory muscles is unchanged (Putensen, et al. 1999). In addition, spontaneous breathing has been associated with better renal perfusion when compared to total mechanical control of ventilation (Hering, et al. 2002). In an experimental setting, spontaneous breathing was associated also with improved intestinal blood flow – especially in the mucosal and submucosal layer (Hering, et al. 2003).

Physiological actions of different partial ventilatory modes are not identical. Interaction between ventilator and the patient's effort is a critical issue. In ventilatory modes where each inspiratory effort is assisted, as with PS or ACV, comparable effects on gas exchange and haemodynamics are compared to those in the totally controlled ventilatory mode. Only with a ventilatory mode in which unsupported spontaneous breathing is possible, superimposed on mechanical ventilation, has it been shown that

these benefits can be achieved (Putensen, et al. 1994b, 1997).

Various forms of intermittent mandatory ventilation techniques constitute nowadays the most widely used partial ventilatory mode (Esteban, et al. 2000b). The principle of IMV was introduced to clinical practice by Downs et al (1973). Later, developed synchronisation was presented by Shapiro et al (1976). SIMV was originally presented to facilitate weaning, but it has also been used widely as a primary ventilatory mode. Benefits of SIMV as a weaning mode are controversial, and most studies show that SIMV may have even a tendency to prolong the weaning phase (Butler, et al. 1999). In no studies has SIMV been compared to controlled ventilation or to partial ventilatory modes as a primary ventilatory mode. However, SIMV with PS is the ventilatory mode most commonly used currently, e.g., in the Nordic countries (Karason, et al. 2002), in this survey, particularly pressure-regulated ventilator modes were used for 86 % of the patients.

With a modern ventilator, SIMV is commonly used together with pressure support ventilation. With PS, every inspiratory effort is augmented with a preset pressure, which is maintained until switchover to expiration takes place. This cycling off is governed by inspiratory flow. Usually decay of inspiratory flow down to 25 % of peak inspiratory flow is used as the cycling-off criterion. PS unloads respiratory muscles and reduces the work of breathing, however, with patient-ventilator dyssyncrony commonly observed, which can paradoxically increase the work of breathing. In some studies, PS has improved gas exchange, but most studies show no benefit when compared to controlled ventilation (Cereda, et al. 2000, Dembinski, et al. 2002). PS has been tested in an observational study as a primary mode in ALI/ARDS (Cereda, et al. 2000), but institution of PS was not associated with any significant changes in gas exchange or in haemodynamics.

2.6.4 Airway pressure release ventilation

Airway pressure release ventilation is a partial ventilatory mode which was initially developed to augment alveolar ventilation as an adjunct to spontaneous breathing with continous positive airway pressure (CPAP) (Downs and Stock 1987). The concept is that the patient is breathing spontaneously on CPAP, which is titrated in order to optimise recruitment of alveoli and to increase FRC to a level where oxygenation and the work of breathing are acceptable (Stock, et al. 1987). From this pressure level, a rapid decreases to a lower pressure level (airway pressure release) allows expiratory flow, and re-establishment of higher airway pressure reeinflates the lungs with fresh inspiratory gas (Downs and Stock 1987). The timing of this airway pressure release as well as timing of a higher pressure level can be set separately. Time-setting for airway pressure release is adjusted to ensure enough time for expiratory flow and reduction of lung volume, enabling an adequate tidal volume during re-establishment of higher airway pressure. On the other hand, excessive release time promotes alveolar collapse during lower alveolar pressure. Commonly, the time reserved for airway pressure release is between 0.8 and 2 seconds. If mechanical augmentation is between 8 and 16 times per minute, the time for higher airway pressure is between 2 and 5 seconds. With this type of setting, the patient's spontaneous efforts occur at the higher pressure. Expiratory flow is usually minimal after re-establishment of higher pressure, and tidal volumes of spontaneous inspiratory efforts are usually relatively small. However, as alveoli and conducting airways are filled with inspiratory fresh gas after airway release, this ventilation is not dead space ventilation, and these small tidal volumes augment alveolar ventilation (Hörmann, et al. 1997).

Figure 3 presents airway pressure and flow tracings during APRV.

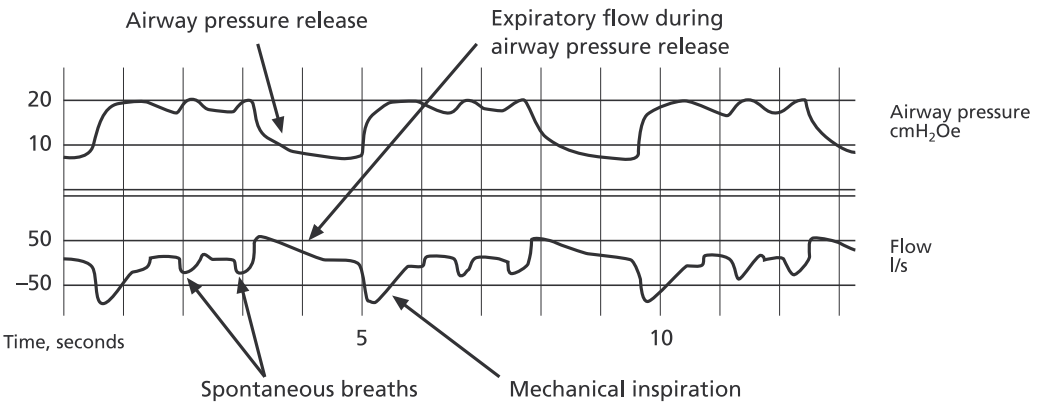
In the original descriptions, APRV was provided by a high-flow CPAP circuit

equipped with a fast-action release valve (Downs and Stock 1987). With airway pressure, the release circuit can be opened to the ambient air or to the CPAP valve with lower pressure threshold. With modern ventilators, APRV can be arranged by a microprocessor-controlled fast-acting expiratory valve and gas source, which can provide an open system enabling spontaneous breathing any time during the respiratory cycle (Hörmann, et al. 1994). With a microprocessor-driven ventilator, various ways have been developed to synchronise airway pressure shifts and spontaneous breathing efforts. The physiological impact of this property is not fully understood (Putensen, et al. 1994a). Considerable confusion is caused by the commercial trade names of various ventilator manufacturers.

Most of the clinical studies investigating physiological variables for APRV as compared to other ventilatory forms have been short-term studies (Cane, et al. 1991, Hörmann, et al. 1997, Putensen 1997, Putensen, et al. 1999, Valentine, et al. 1991). One prospective observational study showed APRV to be a feasible alternative to conventional mechanical ventilation in patients with acute lung injury of mild to moderate severity (Räsänen, et al. 1991). In a crossover setting and with a longer intervention period than in previous trials, Sydow et al (1994) compared APRV to volume-controlled IRV, concluding that APRV was associated with progressive alveolar recruitment over time during the 24-hour intervention period (Sydow, et al. 1994). APRV has also been associated in prospective observational studies with decreased need for sedation and vasoactive drugs (Kaplan, et al. 2001, Sydow, et al. 1994).

Two prospective, non-RCT studies have compared APRV to controlled ventilation. Kiehl et al (1996) showed in severely ill, leukopenic patients that acceptable oxygenation was achieved at lower airway pressures with APRV than with volume-controlled ventilation, but due to small size (n = 20) and high overall mortality, no conclusions as to outcome could be drawn. Putensen´s group investigated multiple trauma patients at risk for ALI in a strictly designed RCT, showing that maintaining spontaneous breathing during APRV requires less sedation and improves cardiopulmonary function, presumably by recruiting nonventilated lung units. They could also show a shorter duration of ventilatory support and ICU stay in the group receiving APRV as a primary ventilatory mode. The control group received ventilation at comparable settings, but they were myorelaxed in order to abolish spontaneous breathing (Putensen, et al. 2001). No randomised, controlled study of ALI/ARDS patients has compared APRV to other ventilatory modes.

Figure 3. Airway pressure and flow tracing during APRV.



2.7 The use of prone positioning in ALI

The rationale for treating ALI/ARDS patients in the prone position (PP) rises from several observations. Bryan et al (1974) first suggested that in patients with bilateral lung disease prone positioning could redistribute ventilation to the hypoventilated dorsal part of the lung (Bryan 1974). The clinical benefit for oxygenation has since been described in numerous studies (Douglas, et al. 1977, Gattinoni, et al. 1991, Langer, et al. 1988) which have consistently shown oxygenation to improve markedly in 60 to 70 % of ALI patients when the patient is turned prone (Pelosi, et al. 2002). Clinical studies have also shown that improvement in oxygenation occurs very rapidly and that degree of improvement is unrelated to the extent to which gas exchange is impaired. Improvement can persist is some but not in all patients when they are returned to the supine position. Response to being prone may vary depending on the course of the disease and the underlying aetiology (Messerole, et al. 2002).

Several pathophysiological mechanisms may account for the effects of prone positioning (Messerole, et al. 2002). In the supine position and during controlled ventilation the tendency is for dorsal alveolar collapse and hypoventilation. Lung perfusion has, however, a predilection for dependent lung areas, so decreased regional ventilation results in mismatching of ventilation and perfusion and thus in intrapulmonary shunting. Conversely, the nondependent part of the lung will be better ventilated but less perfused, leading to an increase in alveolar dead space (Pappert, et al. 1994). When the patient is turned prone, pleural pressure is more uniform as a result of the change in diaphragmatic shape (Krayer, et al. 1989) and in postural differences in chest wall mechanics. One claimed physiological phenomenon in the prone position is that the lungs fit into the thorax with less distortion from the heart, mediastinum, and diaphragm (Albert and Hubmayr 2000, Malbouisson, et al. 2000). As ventilation is distributed more uniformly and distribution of perfusion remains fairly intact, ventilation and perfusion more closely match, and oxygenation improves (Mure, et al. 2000). Reversal of dorsal hypoventilation also results in an increase in functional residual capacity and hence in overall recruitment of alveoli (Guerin, et al. 1999). Furthermore, the effects of recruitment manoeuvres are both increased and prolonged (Cakar, et al. 2000, Tugrul, et al. 2003). PP may allow also more efficient drainage of secretions from peripheral airways. By enhancing recruitment and by improving regional ventilation, PP may reduce both overdistension and repeated intratidal collapse of the lung during mechanical ventilation. In an experimental setting, there is evidence that PP may protect the lung from VILI (Broccard, et al. 1997), although, body position has not affected the location of VILI (Nishimura, et al. 2000).

The possible benefit to clinical outcome of a strategy using PP has been tested in one published clinical trial (Gattinoni, et al. 2001b). The two trials available thus far have appeared only as abstracts. An Italian multicenter trial used PP once a day for 6-hour episodes if the PaO_2/FiO_2 ratio dropped below 200 mmHg. In this study, the increase in ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, as measured each morning while patients were supine, was greater in the prone group. The relative risk of death in the prone group vs. the supine group was 0.84 at the end of the 10-day study period, but this difference in mortality was not significant (95 % CI, 0.56 to 1.27). However, in post hoc analysis, those patients in the quartile of the most severely ill showed a reduction in ICU mortality (Gattinoni, et al. 2001b). Hence, inclusion of patients with minor defects in oxygenation might have diluted the effect of PP. All these studies used the controlled mode of ventilation.

2.8 Outcome of ALI/ARDS

In the first reported case series of ARDS, seven of twelve died (Ashbaugh, et al. 1967). The mortality from ARDS/ALI is still high, with mortality in case series havarying from 20 to 89 % (Ullrich, et al. 1999), although mortality seems to be declining (Milberg, et al. 1995). Some case series report even lower mortality rates, but the patient population in those studies has been highly selected (Ullrich, et al. 1999). In recent cohort-based investigations with strict methodology, the reported survival rates have ranged from 34 % (Bersten, et al. 2002) to 42 % (Luhr, et al. 1999). Mortality in the very recent large, randomised, controlled trials have ranged from 25 % (Brower, et al. 2004) to 39.8 % (Anonymous 2000). It is said that this is the concurrent standard to which future trials are to be compared (Levy 2004).

In most cases, deaths of ARDS/ALI patients are not due to respiratory failure. Development of multiple organ dysfunction and its progression to ultimately untreatable multiple organ failure is usually the ultimate cause of death. Interestingly, degree of hypoxemia or other marker for severity of lung injury shows a poor correlation with ARDS mortality (Gould, et al. 1997). In the early phase of lung injury, the increased ratio of dead space ventilation is the only marker of lung function which has shown good correlation with prognosis of ALI/ARDS (Nuckton, et al. 2002). Commonly used prognostic scoring systems include a wide range of clinical variables. Predictive models like APACHE II (Knaus, et al. 1985) and SAPS II (Le Gall, et al. 1995) can be used to describe a patient population and predict mortality in large patient groups also with ALI/ARDS (Knaus, et al. 1991). The value of current scoring systems in estimation of a patient's individual risk of death is low.

Mortality is a very crude measure of outcome, even in conditions with high mortality like ARDS. Mortality in ARDS is attributable to multiple factors including underlying illness, specific treatments, and general supportive therapy. Inclusion of homogenous patient populations in studies testing any new intervention is difficult. For these reasons, surrogate end-points for mortality have been advocated such as, length of mechanical ventilation, ventilator free days, length of ICU-stay and ICU-free days (Schoenfeld, et al. 2002, Vincent 2004).

Pulmonary function in ALI/ARDS survivors has been investigated in several studies (Cooper, et al. 1999, Herridge, et al. 2003, McHugh, et al. 1994) indicating that lung mechanics return to normal within one year, but gas-exchange abnormalities such as decreased diffusion capacity and exercise tolerance persist longer (Cooper, et al. 1999, McHugh, et al. 1994). Abnormalities seen in CT images may even be detectable after one year following the ALI episode (Desai, et al. 1999).

Long-term outcome and quality of life has become an important measure of critical care outcome (Lee and Hudson 2001), but large-scale studies focusing on the quality of life of ARDS/ALI survivors are still few. A Canadian study found that survivors of ARDS have considerable limitations in several physiological functions and a reduced quality of life in several domains of the health survey (Herridge, et al. 2003). Neuropsychological tests may also reveal deficits, especially in ARDS patients who have suffered severe and protracted hypoxemia (Hopkins, et al. 1999). As compared to other critically ill patients, survivors of ARDS show a clinically significant reduction in health-related quality of life that appears to be caused exclusively by ARDS and its sequelae. Reductions were primarily noted in physical functioning and pulmonary function (Davidson, et al. 1999). One year after ICU care, the survivors still have a lower quality of life than an age-matched general population (Pettilä, et al. 2000). Psychological sequalae may also occur, presenting as posttraumatic stress disorder (Schelling, et al. 1998).

3. AIMS OF THE STUDY

The aim of the present study was to evaluate different modalities of treatment for acute lung injury. Partial ventilation modes as a primary treatment strategy throughout the clinical course of ALI and glucocorticosteroid during the late phase of ALI were the primary objectives.

The specific objectives were:

1. To test the hypothesis that in ALI patients, primary use of APRV with maintained unsupported spontaneous ventilation as compared to SIMV with PS
   a. is feasible for ARDS patients (Studies I–III)
   b. increases the number of ventilator-free days (Study II)
   c. improves gas exchange and haemodynamics (Study II)
   d. reduces need for sedative medication (Study II)

2. To investigate the combined effects of APRV and prone positioning on gas exchange as compared to SIMV with PS (Studies I and III)

3. To investigate the effects of APRV as compared to SIMV on lung collapse as measured with lung CT (Study IV)

4. To determine in patients with primary acute lung injury the effects of prolonged methylpredisolone treatment on gas exchange and multiple organ dysfunction (Study V)

4. MATERIAL AND METHODS

4.1 Patients

The 89 study patients were treated in the Intensive Care Unit (ICU), Division of Anesthesia and Intensive Care, Department of Surgery, Helsinki University Hospital. Study I is a report of one severe ARDS patient in whom the feasibility of a combination of prone position and APRV was tested for the first time. Studies II to IV are reports covering one population during the years 1998 to 2000. During the study period, a total of 1584 ICU patients were treated, and from among these 58 ALI patients were included in this study. All of these 58, were subjects of Study II. Study III was a pre-defined subanalysis regarding the effects of prone positionining. All those patients for whom CT scanning could be done twice during the first 7 study days were analysed in Study IV. Study V utilized a retrospective cohort of 31 primary ALI patients during years the 1994 to 1998. Demographic characteristics are presented in Table 7.

4.2 Study design

Study I This report presents the clinical course of one patient with severe ARDS. As a part of the treatment, unsupported spontaneous breathing superimposed on mechanical ventilation with APRV was utilized and used together with PP.

Study II Number of ventilator free-days alive (primary endpoint), length of stay in

Table 7. Demographics of the patients. (Figures are median and interquartile range; for Study V mean ± SD are given).

	Study II (N = 58)		Study III* (N = 33)		Study IV* (N = 23)		Study V (N = 31)	
	APRV	SIMV	APRV	SIMV	APRV	SIMV	Steroid	Control
N	30	28	15	18	13	10	16	15
Gender Female/male	21/9	18/10	4/11	4/14	4/9	1/9	4/12	3/12
Age	50.0 (38.5–60.5)	44.0 (35.5–53.0)	50.0 (37.0–60.0)	46.5 (37.2–55.3)	48.0 (34.0–64.0)	48.0 (40–56)	42.4 ± 2.8	44.9 ± 3.7
APACHE II	15 (12.5–18.0)	14.0 (11.3–17.0)	14.0 (11.0–16.0)	14.0 (13.0–17.3)	14.8 (11.5–18.5)	15.2 (13.8–17.0)	14.4 ± 1.6	14.8 ± 1.6
SOFA (MODS in Study V)	9.0 (7.0–10.5)	8.5 (8.0–9.8)	8.0 (7.0–10.0)	9.0 (7.8–10.0)	9.5 (8.0–10.0)	8.7 (7.0–10.0)	7.5 ± 0.7	8.2 ± 1.0
PaO_2/FiO_2 ratio at inclusion	135 (106–195)	150 (130–187)	123 (100–150)	137 (125–173)	158 (104–213)	165 (140–190)	126 ± 52	107 ± 41
Primary vs secondary ALI	23/7	22/6	10/5	11/7	9/4	9/1	16/0	15/0

** Studies III and IV are subgroups of Study II.*

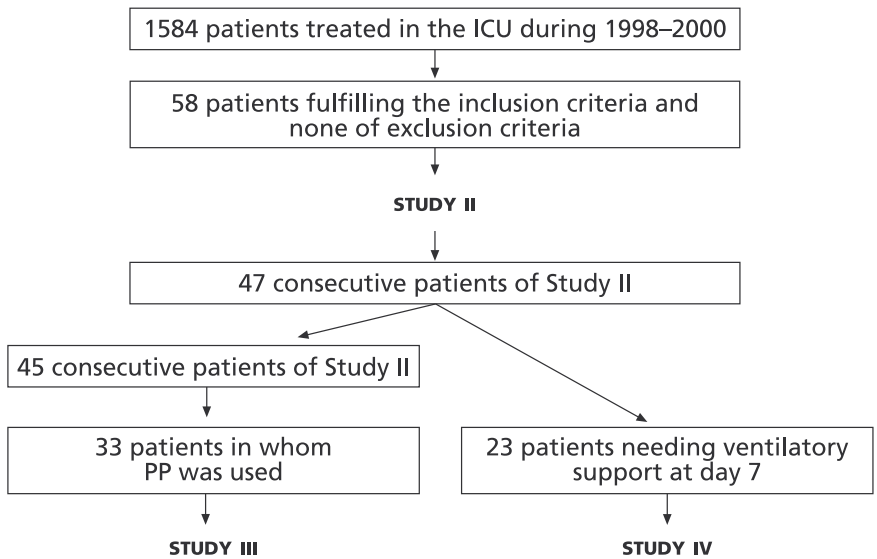
the ICU, mortality, use of sedative medication, gas exchange and haemodynamic data were analysed. In this prospective, open, controlled study, 58 patients fulfilling the AECC criteria for ALI after a structured stabilisation period were enrolled. Exclusion criteria were prior mechanical ventilation for more than 72 hours, chronic pulmonary disorder, neurological cause of respiratory failure, contraindication for permissive hypercapnia, condition in which full life-support was not indicated, or having participated in any interventional trial of septic shock within 30 days. After randomisation, patients received either APRV with maintained unsupported spontaneous breathing or SIMV with pressure support.

STUDY III The effect of ventilatory mode on response to prone positioning was investigated in a prospective, randomised, and open study. Of the 58 patients included in Study II, the first 45 consecutive patients formed the subjects of this study. The prone positioning was part of the general protocol unless contraindicated. For the 33 patients in whom prone positioning was used, the first two periods of prone positioning were analysed. Gas exchange was measured before and at the end of each prone positioning period. Of these patients, 33 were turned prone once and 28 twice. Changes in oxygenation were analysed in response to the first and second prone episodes 5 h and 24 h after randomisation and initiation of SIMV-PC/PS or APRV, respectively.

STUDY IV The CT densitometric technique was used to investigate the extent of lung collapse and gas distribution in the lungs in patients enrolled in Study II. CT scanning was performed before randomisation until 47 patients were included. In the 23 patients who still needed ventilatory support at day 7, a follow-up CT scan was performed. These patients were the subjects of this study. Figure 4 presents flowchart of Studie II~IV.

STUDY V Evaluation of the clinical effects of prolonged methylprednisolone treatment was done by analysis of a retrospective cohort of ARDS patients. The patient records of all those mechanically ventilated during the study period 1994 to 1998 were evaluated. Criteria for inclusion in the study were: mechanical ventilation for acute respiratory

Figure 4. Flowchart of studies comparing airway pressure release ventilation and syncronised intermittent mandatory ventilation.



failure for more than 10 days, and pulmonary, infectious aetiology of ALI. Exclusion criteria were: prior corticosteroid treatment, chronic immunosuppression, respiratory failure due to neurological disturbance, and surgery during the first 10 days in the ICU; 31 patients fullfilled these criteria. Of these, 16 patients had received empiric prolonged methylprednisolone treatment during late phase ALI, and 15 were managed without glucocorticosteroids and served as a control group.

4.3 Methods

4.3.1 Interventions

Studies II–IV Attending physicians were responsible for ventilator management according to a written protocol. In the APRV group, the ventilatory mode was accomplished with a special module (Bivent, Siemens-Elema, Gothenburg, Sweden) attached to the Servo 300 SV ventilator. With this module, the ventilator can be set to a mode in which unsupported, spontaneous breathing is possible throughout the entire ventilatory cycle at two airway pressure levels. Time periods for each pressure level can be set independently. Duration of lower pressure was adjusted to allow expiratory flow to decay to zero. The duration of the higher pressure was adjusted to produce 12 pressure shifts per minute. The target for the patient's spontaneous breathing frequency was 6 to 18 times per minute, with tidal volumes of spontaneous breathing over 10 % of the level of mechanical tidal volumes considered sufficient. Presence of spontaneous breathing was continuously verified from the flow and pressure tracings of the ventilator display. If spontaneous breathing was not achieved, the level of sedation was reduced. If sedation was adequate, the frequency of pressure shifts was decreased. If spontaneous breathing frequency increased to over 20 per minute, sedation was increased and, if needed, mechanical frequency increased.

In the control group, patients were ventilated with the pressure controlled SIMV mode with pressure support. Rate of mandatory time-cycled, pressure-controlled breaths was set initially to 12 per minute. Pressure support of 10 cmH_2O was used for triggered breaths. In pressure-supported breaths, inspiratory pressure was maintained until inspiratory gas flow decreased to 25 % of its peak value. In the SIMV group, triggered breaths were not required. If frequency of triggered breaths increased to over 10 per minute, sedation was increased and, if needed, the rate of mandatory breaths increased. A summary of ventilator strategies following after the randomisation are presented in Table 8.

Study V During the study period, prolonged methylprednisolone treatment was an empiric therapy for patients with unresolved ALI. The decision on prolonged methylprednisolone treatment was based on consultation with a specialist in infectious diseases and individual evaluation of the patient. Patients with consistently high levels of CRP as a sign of sustained inflammation, with progressive respiratory failure despite adequate antimicrobial treatment, and with no evidence of untreated infection were considered candidates for prolonged methylprednisolone treatment. Labile diabetes or gastrointestinal bleeding were contraindications for corticosteroids. Treatment was with intravenous methylprednisolone (Solu-Medrol, Pharmacia & Upjohn, Stockholm, Sweden) initiated at a dose of 80 mg in the morning and 40 mg in the evening in order to simulate circadian variation in the natural hypothalamic-pituitary-adrenal axis. Based on clinical response, the dose was gradually tapered off.

4.3.2 General ventilatory measures

The physiological targets and basis for the main ventilatory settings were as follows: Oxygenation goal PaO_2 8 kPa or more; or target for $PaCO_2$ between 5 and 8 kPa, but higher $PaCO_2$ also allowed, if pH at the same time remained over 7.20.

All patients were ventilated with a Servo 300 SV (Siemens-Elema, Gothenburg, Sweden) ventilator using pressure-controlled ventilatory modes. In order to set inspiratory pressure and PEEP, the following protocol was followed: the pressure-volume (PV) curve of the patient's respiratory system was constructed during the stabilization phase and thereafter according to the judgement of attending clinicians until the weaning phase. PV curves were reconstructed during transient neuromuscular blockade. For the 12 first patients in Study III, the PV curve was obtained by applying variable tidal volumes and measuring static airway pressures, and for the rest of the patients by using the slow-flow inflation method (Lu, et al. 1999). External PEEP was titrated above the lower inflection point (LIP) of the PV curve. If the LIP was undetectable, PEEP was set to 10 cmH_2O. Inspiratory pressure (Pinsp) was set to accomplish a tidal volume between 8 and 10 ml/kg. However, the upper inflection point (UIP), if detected from the PV curve, was never exceeded. Inspiratory pressure was always kept below 35 cmH_2O.

4.3.3 Prone positioning

Indication for prone positioning for both study groups was the same. Oxygenation was assessed twice per day, and a PaO_2/FiO_2 ratio of less than 200 mmHg was a trigger for a change to the prone position. Prone positioning was accomplished in regular ICU beds. The thorax was supported to avoid hyperextension of the neck, but no special equipment was used. The prone periods

Table 8. Summary of ventilatory strategies. (Table 1 from study II).

	APRV-group	SIMV-group
Response to patients effort	Unsupported, spontaneous breathing, required 6 to18 per minute	Pressure support of 10 cmH_2O, not required
Intitial settings		
PEEP	Titrated according PV-curve	Titrated according PV-curve
Pplat allowed	<35 cmH_2O or UIP	<35 cmH_2O or UIP
Tidal volume	Driving pressure titrated to form 8 to10 ml/kg tidal volume	Driving pressure titrated to form 8 to10 ml/kg tidal volume
Set respiratory rate	12 pressure releases/minute	12 SIMV-cycles/minute
Length of inspiratory phase	4 seconds	35 % of the SIMV-cycle
Length of expiratory phase	1 second	65 % of the SIMV-cycle
Measures to achieve oxygenation target (PaO_2 >8 kPa)		
FiO_2 ↑	Increase up to 1.0	Increase up to 1.0
IRV ↑	Not used	IRV ad 2:1
Measures to achieve ventilation target ($PaCO_2$ <8 kPa)		
Spontaneous breathing ↑	Decrease of sedation	Not used
Mandatory ventilation ↑	Shortening of inspiratory time	Increase of the set mandatory rate
Weaning		
Inspiratory pressure ↓	to 20 cmH_2O	to 20 cmH_2O
FiO_2 ↓	to 0.35	to 0.35
	T-piece trials applied with CPAP	T-piece trials applied with CPAP

Definition of abbreviations: PEEP = Positive end expiratory pressure; Pplat = Inspiratory plateu pressure; PV-curve = Pressure-Volume-curve; UIP = Upper inflection point of the PV-curve; FiO_2 = Fraction of inspired oxygen; IRV = Inverse ratio ventilation; CPAP = Continuous positive airway pressure.

lasted approximately 6 h, and the patients were kept supine at least 6 h before the next assessment. In case of critical posture-dependent hypoxemia, the duration of prone positioning was extended.

4.3.4 General care

Excluding the prone-position periods, patients were nursed in a 30% semi-recumbent position. Fentanyl was infused for analgesia, based on clinical subjective assessment of pain. Excessive ventilatory drive was also an indication for increasing the fentanyl dosage. In patients ventilated with APRV, fentanyl dosage was reduced if spontaneous breaths were suppressed. Propofol was infused for sedation based on underlying disease as clinically needed. Muscle relaxants were given only for the measurement of lung mechanics or occasionally for other procedures such as bronchoscopy and tracheostomy. Besides prone position, no other nonventilatory co-interventions (inhaled nitric oxide, almitrine, or extracorporeal membrane oxygenation) for ARDS were used. Prolonged, high-dose methylprednisolone treatment for late-stage fibroproliferative ARDS was used according to a written protocol also for the patients in Studies II to IV.

Other principles of treatment including nutrition, haemodynamic management, renal replacement therapy, or airway management were administered according to the written protocols of the unit.

4.3.5 Data collection

Studies II–IV During the study period our unit used an automatic patient data management system (CareVue, Hewlett-Packart, Boston, MA, USA). All physiological variables displayed from the multichannel patient monitors (DatexCS 3, Datex-Ohmed, Helsinki, Finland) are stored in the database at a 5-minute sampling frequency. Variables were extracted from the patient data management system's database. A sampling frequency for continuous variables was every second hour during the first 3 days and every 4 hours during days 3 to 7. Median values for physiological parameters represent values of each time period.

Study V Two investigators collected data from patient records. Demographical data, blood, and bronchoalveolar lavage (BAL) culture findings, length of mechanical ventilation, length of ICU stay, development of nosocomial infections, and 30-day mortality figures were collected. On admission, severity of illness was evaluated by the Acute Physiology and Chronic Health Evaluation (APACHE II), Multiple Organ Dysfunction Score (MODS), PaO_2/FiO_2 ratio, and Lung Injury Score (LIS). When steroid therapy was started, the following data were recorded: MODS, PaO_2/FiO_2 ratio, and serum C-reactive protein (S-CRP) concentration. The same data were collected 3 and 7 days thereafter. The corresponding data were collected for control patients on days 10, 13, and 17 after admission.

4.4 Outcome measures

4.4.1 Ventilator-free days, length of stay and mortality

Ventilator-free days (VFD), the main outcome variable for Study II, was defined as a number of days alive without mechanical ventilation between inclusion in the study and day 28. If a patient died before day 28 and had not been weaned, VFD was 0. Extubation or decanylation for 24 h was considered as a day without mechanical ventilation. Use of VFD allows a smaller sample size and has been advocated as a good surrogate measure for mortality in interventional trials of critical illness (Schoenfeld, et al. 2002).

Length of ICU stay was calculated as whole days from admission to discharge or to death of the patient. Mortality data was checked from hospital records, and one year outcome by telephoning to patients who, according hospital records, were still alive.

4.4.2 Assessment of organ failures

Demographical data was collected during the first 24 hours after admission to ICU. Severity of illness was assessed by using APACHE II score (Knaus, et al. 1985). Assessment of organ failures was by Multiple Organ Dysfunction Score (MODS) (Study V) (Marshall, et al. 1995) and SOFA-score (Vincent, et al. 1996) (Studies II to IV). Severity of lung injury was assessed by Lung Injury Score (Murray, et al. 1988). Evaluation of chest x-rays was performed by a radiologist blinded to the randomisation.

4.4.3 Physiological variables

Haemodynamic measurements were performed based on the information from arterial cannulae and pulmonary artery catheters. Side-stream spirometry (MCOVX, Datex-Ohmeda, Helsinki, Finland) integrated into a patient monitor (CS/3, Datex-Ohmeda, Finland, Helsinki) served for monitoring of ventilatory variables: minute ventilation (MV), tidal volume (TV), fraction of inspired oxygen (FiO_2), end-tidal CO_2 ($ETCO_2$), PEEP, and Pinsp. Arterial blood gases were determined by use of standard blood gas electrodes. All measurements were made under stable conditions.

4.4.4 Computer tomography and analysis

CT examinations were performed during transient neuromuscular blockade (rocuronium bromide; Esmeron, Organon Teknika) to prevent any breathing efforts during scanning. CT scanning was performed during manual end expiratory breathhold at 10 cmH_2O of PEEP. Apnoea was verified by monitoring airway pressure during the CT acquisition.

CT was performed with a commercial spiral one-detector device (Somatom Plus 4 Power, Siemens, Erlangen, Germany), scanning from the apex of the lung below the diaphragm with a continuous spiral technique. Tube voltage was 120 kV and current was 171 mA, with a pitch of 1, slice thickness of 10 mm. All CT data were stored on optical discs enabling off-line analysis.

Quantitative analysis of the CT images was performed by a radiologist blinded to the modes of ventilation. Window widths of 1600 Hounsfield units (HU) and a level of –700 HU sereved for the assessment. Two CT sections were selected at two levels (lung hilum 3 cm below the carina and basal lung areas 3 cm above the diaphragm). The lung region-of-interest (ROI) was manually delineated along the inside of the ribs and the inner boundary of the mediastinum. Total areas and areas of different CT attenuation were analysed by the commercial Siemens CT workstation. CT attenuation values between –1000 and –512 were considered normally aerated, values between –512 and –100 HU poorly aerated, and those between –100 and +100 as nonaerated or consolidated. The proportion of each CT attenuation value range of the total lung area at each level measured was calculated, and also mean CT density at each measured level. Changes in HU values measured at both time-points (days 1 and 7) were assessed.

4.5 Statistical methods

Studies II–IV The patients were randomised by a concealed allocation approach with sealed envelopes provided by an independent statistician. The primary endpoint of Study II was number ventilator-free days, defined as number of days the patient is breathing without assistance from randomisation to day 28. Prestudy calculations of ventilator-free days with ALI/ARDS patients in our department revealed mean 10.2 days with SD 2.9. According routine methods (power of 80 % and p-value less than 0.05) sample size calculations yielded a sample size of 40 patients per group to detect a 15 % difference in ventilator-free days between study groups, and thus the targeted sample size was set at 80 patients.

Outcome measures and continuous physiological variables are presented as mean and standard error of mean. For com-

parisons, the Fisher Exact test and Mann-Whitney test were used when appropriate. Multiple logistic regression analysis served to test the independent effect of APRV, of age and of APACHE II score, each as a determinant of outcome. A p-value less than 0.05 was considered to indicate statistical significance. Statistical tests were performed with SPSS 11.1 (SPSS Inc, Chicago IL, USA) and with SigmaPlot.

For Studies III and V, post hoc analysis was made in order to evaluate the possibility of too small a sample size. For that purpose, the 95 % confidence interval was calculated for a difference in the means of main outcome variables (ventilator-free days in Study II and decrease of nonaerated lung in Study IV) between the groups (Gardner 1988).

Study V The convenience sample covering past 5 years was set. All data were expressed as means with standard deviation. Continuous non-paired variables were tested with the Mann-Whitney independent rank sum test and categorical data with the Fisher exact test (2-tail). A probability level of less than 0.05 was considered significant. Statistical tests were performed with BMDP 1.1 version for Windows (BMDP Statistical Software Inc., Los Angeles, CA, USA)

4.6 Ethical aspects

For the case report in Study I, consent was obtained from patients´ next of kin. Approvals for Studies II to IV were provided by the Ethics Committee of the University of Helsinki Central Hospital, the Division of Anaesthesia and Intensive Care Medicine. Informed oral and written consent was obtained from the next of kin. Because Study V was retrospective, the Ethics Committee waived the need for informed consent.

5. RESULTS

5.1 Feasibility of APRV and PP in severe ARDS

APRV and extended PP episodes were combined for one patient with severe ARDS. A 14-year old patient, after severe skin injury and septic shock, developed multiple organ dysfunction, including severe ARDS. Ventilatory strategy consisted of lung-protective ventilation, permissive hypercapnia and prone positioning. Due to high ventilatory drive and difficulties in adapting to the ventilator, the ventilation mode was changed to APRV, allowing the patient's unrestricted spontaneous and unsupported breathing superimposed on mechanical ventilation. After application of APRV, dramatic improvement in oxygenation occurred. The patient eventually recovered and after 25 days of mechanical ventilation could be extubated. Combination of APRV and PP was thus feasible, and this experience generated the hypothesis that this combination may have beneficial, synergistic effects.

5.2 Impact of ventilatory mode on respirator free days and mortality

For comparative studies between APRV and SIMV, a total of 58 patients were enrolled and randomised. Demographical data at inclusion are presented in Table 7. No differences in any demographical or prognostic parameters were detected between groups. The median length (± SEM) of mechanical ventilation prior to the start of the randomised ventilatory strategy was 39.1 (±2.3) hours in the whole study population with no difference between groups. Delays were caused by referral of the patient from another hospital, obtaining the consent, and diagnostic procedures during the stabilization phase.

The primary outcome measure was number of ventilator-free days after randomisation. An interim analysis, performed after analysis of two-thirds of the estimated 80 patients, revealed that the APRV strategy would achieve no significant difference within the planned frame of the study. Therefore, the study was terminated as futile.

Numbers of ventilator-free days were comparable: in the APRV group 13.4 (± 1.7) and in the SIMV group 12.2 (± 1.5) ($p = 0.83$). Numbers of ICU-free days out of 28 days were also similar: 11.9 (± 1.7) in the APRV group and 10.7 (± 1.4) in SIMV group. The difference in means for respirator-free days was 1.2 days with a 95 % confidence interval between –3.4 and 5.7 days.

Mortality at day 28 was 5 of 30 (17 %) in the APRV group and 5 of 28 (18 %) in the SIMV group ($p = 0.91$). Mortality at one year was 21 % in all patients: 17 % (5 of 30) and 25 % (7 of 28) ($p = 0.43$). Survival curves and proportion of patients breathing without ventilator are presented in Figure 5. Development of organ failure was assessed by counting the change in SOFA score between randomisation and day 7. The SOFA score decreased by 2.8 (± 0.8) in the APRV group and by 1.7 (± 0.2) in the SIMV group. The LIS score decreased during the first 7 days 0.8 (± 0.1) points in the APRV group and 0.6 (± 0.2) points in the SIMV group.

5.3 Impact of ventilatory mode on gas exchange, haemodynamics, and sedation

Ventilatory variables during stabilisation and the first 7 days after randomisation are presented in Figures 7 and 8. During the stabilization phase, PaO_2/FiO_2 ratio in the SIMV group (21.9 ± 1.4 kPa) and in the APRV

group (20.0 ± 1.4 kPa) were comparable (p = 0.213). Changes in PaO_2/FiO_2 ratio after randomisation were comparable, as well (Figure 6). Tidal volume per body weight during the first week was 9.38 (± 0.16) ml/kg in the whole population and with no differences between groups or with time. In both study groups, moderate hypercapnia developed during the first study day, and $PaCO_2$ returned towards normal after 4 days. In both groups, arterial pH remained within the normal range during the study. Inspiratory pressure was significantly lower in the APRV group (25.9 ± 0.6 vs. 28.6 ± 0.7 cmH_2O) during the first week (p = 0.007). Externally applied PEEP did not differ during the first week; 11.2 ± 0.3 cmH_2O in the APRV group and 11.9 ± 0.3 cmH_2O in the SIMV group (p = 0.08). (Figure 7).

Haemodynamic data are summarized in Table 9. Each patient had an indwelling pulmonary catheter during the first 3 days. Pulmonary artery wedge pressures and cardiac indexes between groups were comparable during the first week, as was the number of patients receiving cathecholamines ;. at study entry 96 % of the patients in the APRV group and 93 % of patients in the SIMV group received cathecholamines. At day 7, nine patients of the 24 patients alive in the APRV group and 12 of 24 in the SIMV group were recieving vasoactive medication.

Use of sedatives (propofol) and analgesics (fentanyl) is presented in Figure 8. Dosages of analgosedatives between the groups were comparable. Prone positioning was part of the protocol as an adjunctive treatment, applied in a similar fashion in both groups. During the first week, patients in the APRV group spent 30.5 (± 5.1) hours in the prone position and those in the SIMV group 30.3 (± 4.5) hours (p = 0.11).

5.4 Impact of ventilatory mode on response to prone positioning

After 45 patients were enrolled in the study, a predetermined subanalysis compared the combined effects of prone positioning and ventilatory mode. The 33 of these 45 patients, turned prone after the start of the randomised ventilation strategy were included in the analysis. For these 33, the first and second prone episodes were analysed, comprising 61 episodes (27 episodes in the APRV group and 34 episodes in the SIMV group). Demographic factors, degree of oxygenation impairment, severity of illness, haemodynamic profile, period of prior me-

Figure 5. Survival and ventilator free days. (Figure 4 from Study II).

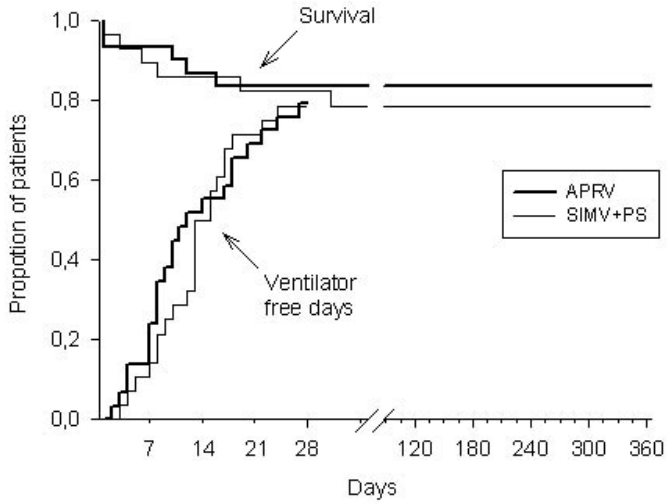


Figure 6. PaO_2/FiO_2 ratio during the first 7 days. (Figure 2 from Study II).

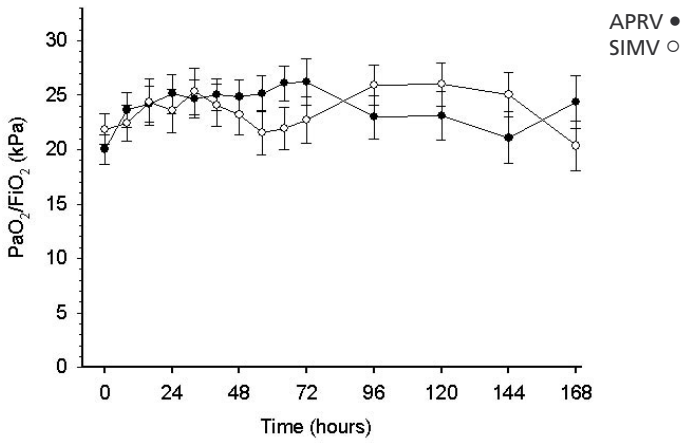


Figure 7. Inspiratory pressure (Pplat) and PEEP during first seven days.
* = significant differece between the groups. (Figure 1 from study II).

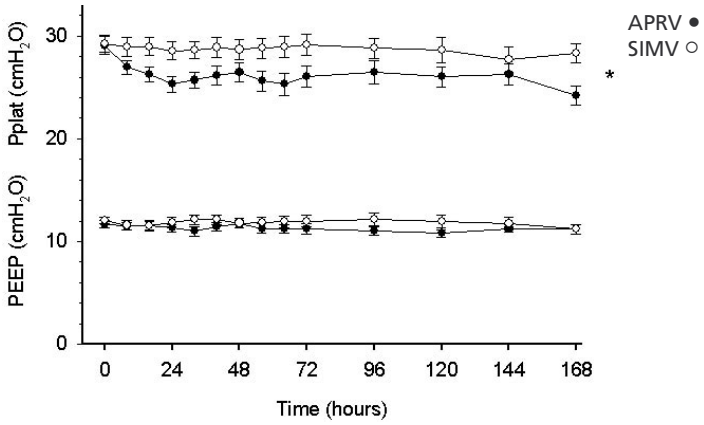
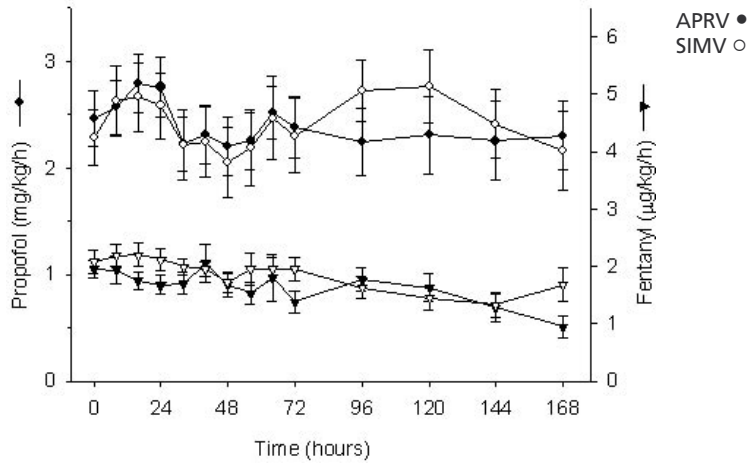


Figure 8. Consumption of propofol and fentanyl during the first 7 days.
(Figure 3 from Study II).



chanical ventilation, and type of lung injury were in both groups comparable (Table 7).

The interval from randomisation to the first prone episode was 5.0 h (median) for all patients, with no differences between the groups. Interval to the second prone episode was 24.9 h (median). Comparison of ventilatory parameters (minute ventilation, inspiratory pressure, and tidal volume) and dosage of sedatives revealed no significant differences between groups.

The median (interquartile range) of the PaO_2/FIO_2 ratio during the stabilization phase was 137 (125–173) mmHg in the SIMV group and 123 (100–150) mmHg in the APRV group (p = 0.38). However, after 5 h (median) of ventilation in the randomised ventilatory mode immediately before the first prone episode, the PaO_2/FIO_2 ratio was significantly (p = 0.02) higher in the APRV group (Figure 9). At the end of the first prone episode, the PaO_2/FIO_2 ratio was significantly higher in prone position than in the supine in both groups. A trend occurred towards better oxygenation in the APRV group after the first prone episode, but this difference was not statistically significant (p = 0.06). The response to prone positioning in both groups was similar; medians for increase in PaO_2/FiO_2 ratio were 75.0 (9.0–125.0 mmHg) in the APRV group and 39.5 (17.75–77.5 mmHg) in the SIMV group (p = 0.49). This was 44 % in the APRV group and 43 % in the SIMV group respectively (p = 0.49).

For three patients in the APRV group and two in the SIMV-PC/PS group, the PaO_2/FIO_2 ratio improved and was maintained over 200 mmHg. Thereafter, prone positioning was no longer indicated, according to the protocol. Those patients who were turned prone again (16 in the SIMV group and 12 in the APRV group), showed no difference in PaO_2/FiO_2 ratio before the second prone episode: 134 (98.3–175) in the APRV group and 130 (61.0–161.8) in the SIMV. At the end of the second prone episode the PaO_2/FIO_2 ratio was significantly better (p = 0.01) in the APRV-group compared to the SIMV group (Figure 10). During the second prone episode, the improvement of oxygenation (change of PaO_2/FIO_2) was also better in

Table 9. Main haemodynamic variables at inclusion and at days 1, 3, 5, and 7.

Variable		n	APRV group	n	SIMV group	p-value
Mean arterial pressure, mmHg	Inclusion	30	75 (1.65)	28	74 (2.59)	0.75
	Day1	30	76 (1.79)	28	75 (1.62)	0.99
	Day3	28	83 (2.53)	27	79 (1.87)	0.44
	Day 5	25	85 (3.10)	26	83 (2.28)	0.69
	Day 7	24	86 (2.65)	24	84 (2.71)	0.52
Pulmonary occulusion pressure, mmHg	Inclusion	30	14.8 (0.34)	28	15.1 (0.46)	0.64
	Day1	30	14.3 (0.36)	28	14.6 (0.44)	0.43
	Day3	27	14.2 (0.55)	26	14.3 (0.39)	0.41
	Day 5	23	13.8 (0.50)	26	14.1 (0.55)	0.39
	Day 7	21	13.1 (0.61)	21	12.9 (0.49)	0.83
Cardiac index, L/min/m^2	Inclusion	30	4.3 (0.19)	28	4.3 (0.15)	0.88
	Day1	30	4.6 (0.20)	28	4.3 (0.16)	0.29
	Day3	27	4.5 (0.20)	26	4.5 (0.18)	0.90
	Day 5	23	4.3 (0.15)	26	4.5 (0.18)	0.24
	Day 7	21	4.4 (0.20)	21	4.5 (0.18)	0.98

Values are mean and SEM. Variables analyzed by Mann-Whitney Rank sum test.

the APRV group (p = 0.02). Stepwise forward logistic multiple regression analysis comprising demographic variables (age, sex, APACHE II and SOFA day 1), type of ALI, supine PaO_2/FIO_2 ratio, duration and time-delay to prone positioning, and type of ventilatory mode revealed that APRV was an independent predictor (p = 0.02) of oxygenation index in the prone position.

In post-hoc analysis, the proportion of patients showing improvement in oxygenation in response to prone positioning (at least 20 % improvement in PaO_2/FIO_2 ratio) was similar between groups: 74 % in the APRV group and 80 % in the SIMV-PC/PS group. In these responders, the improvement in the PaO_2/FIO_2 ratio was significantly (p = 0.001) larger in the APRV group: (mean ± standard deviation) 104.0 ± 50.7 mmHg versus 66.9 ± 38.2 mmHg, with all prone episodes analysed.

5.5 Impact of ventilatory mode on quantitative CT-scanning

In 47 patients, 23 were alive and on a ventilator at day 7. All these 23 were eligible for analysis. No differences appeared in clinical characteristics between groups at inclusion and at the first CT scan.

A trend (p = 0.09) appeared toward lower lung density in the APRV group (–335 ± 34 HU) than in the SIMV group (–436 ± 43 HU) at the carinal level. At diaphragmatic level, mean CT densities were similar at baseline: –305 ± 38 HU in the APRV group and –406 ± 36 HU in the SIMV group (p = 0.24). At day 7, mean CT densities showed

Figure 9. First episode of prone positioning. (Figure 1 from Study III).

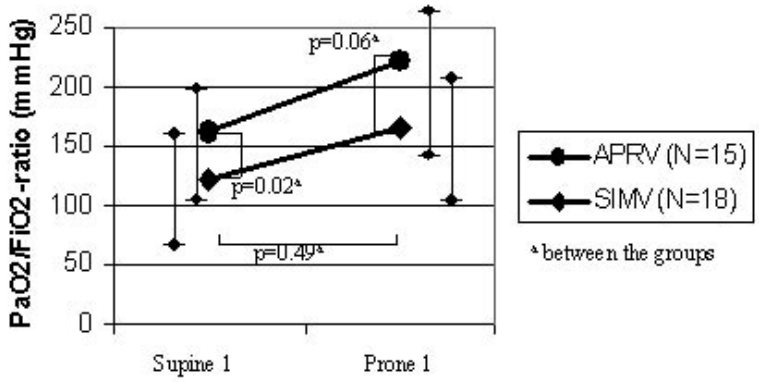
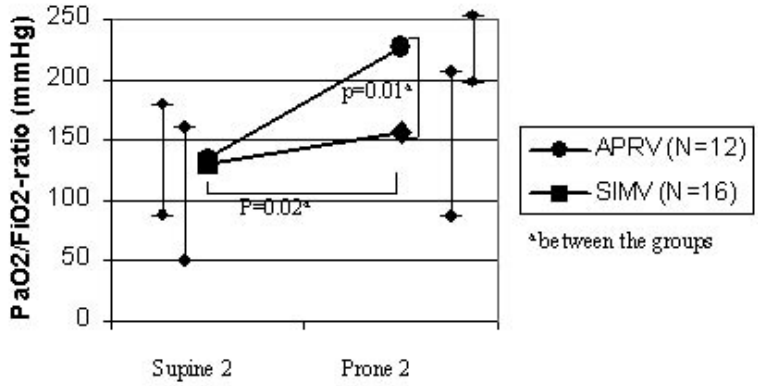


Figure 10. The second episode of prone positioning. (Figure 3 in Study III).



no significant differences: –378 ± 47 in the APRV group and –470 ± 49 in the SIMV group (p = 0.3). (Figure 11)

The amount of consolidated lung at diaphragmatic level in the first CT was comparable in both groups: 36 % ± 5.9 % in the APRV group and 24 % ± 3.2 in the SIMV group (p = 0.23). At the diaghragmatic level on day 7 the amount of consolidated lung showed no significant difference (24 % ± 5.3 % and 17 % ± 4.6 %; p = 0.74). In the first CT scanning, the amount of normally aerated lung was higher in SIMV group (50.9 % ± 6.6 %) than in APRV group (33.4 % ± 4.8 %) at carinal level (p = 0.04). At day 7, the amount of normally aerated lung at carinal level was similar: 40 % ± 6.7 % and 59 % ± 8.9 %; (p = 0.08). At the diaphragmatic level the amount of normally aerated lung was similar on day 1 (30 % ± 5.1 % and 45 % ± 5.6 %; p = 0.13) and on day 7 (38 % ± 7.4 % and 54 % ± 7.5 %; (p = 0.26). Individual CT scan data

Figure 11. Mean (± SEM) CT number at carinal and diaphragmatic at day 1 and day 7. (Figure 2 from Study IV).

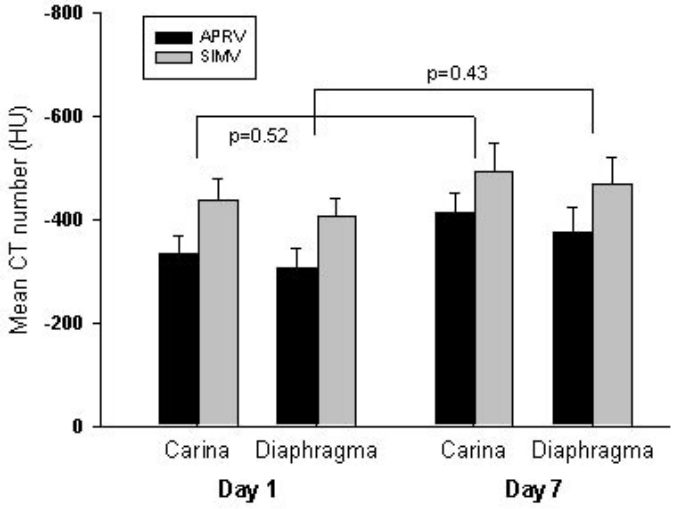
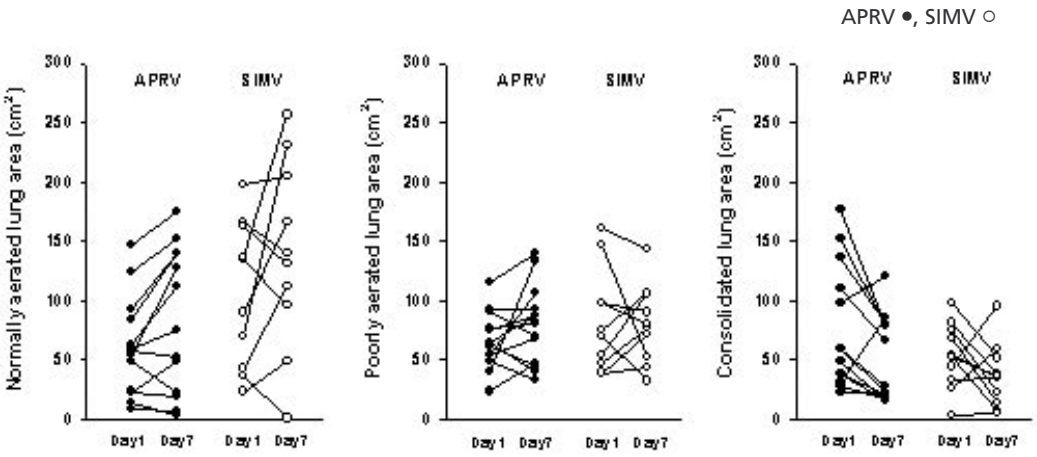


Figure 12. Individual data on the absolute areas of normally aerated (–512 to –1000 HU), poorly aerated (–100 to –512 HU), and non-aerated (–100 to +100 HU) lung at diaphragmatic level at days 1 and 7. (Figure 3 from Study IV).



at the diaphragmatic level during day 1 and day 7 are presented in Figure 12.

Change between first and the second CT scanning at day 7 at diaphragmatic level was the primary outcome variable. Changes in proportion of atelectatic/consolidated lung area in the diaphragmatic CT section in both groups were similar. The decrease in the extent of nonaerated lung was 12.1 ± 4.3 % in the APRV group and 7.2 ± 5.7 % in the SIMV group (p = 0.65). The absolute difference of means was 4.9 % with a 95 % confidence interval from –9.0 to 19.0 %.

For extent of poorly aerated lung, an increase was observed of 4.1 ± 4.4 % in the APRV group and a decrease of 2.8 ± 4.7 in the SIMV group, a difference not significant (p = 0.48). The amount of normally aerated lung increased 8.0 ± 4.0 % and 9.3 ± 7.7 % (p = 0.88).

Figure 13. Mean daily dose of methylprednisolone (Figure 1 from Study V).

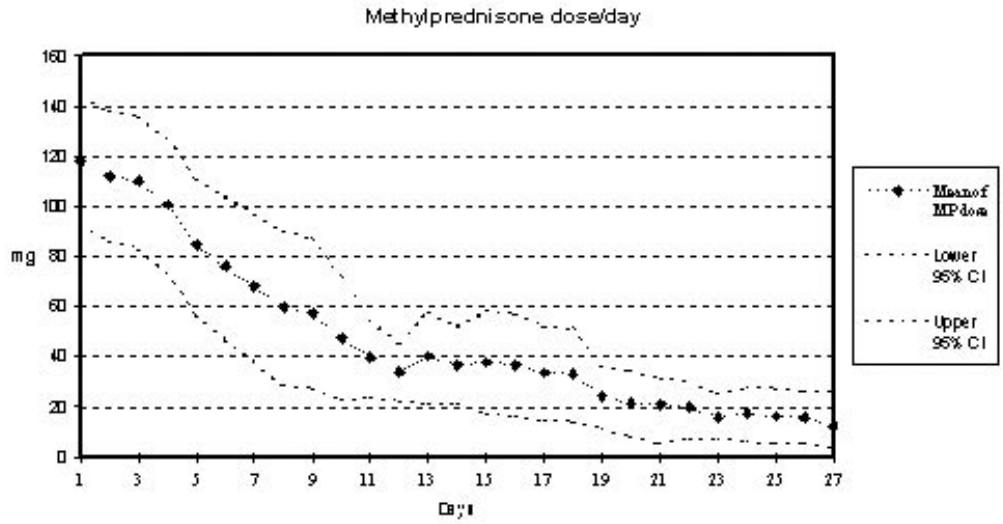


Table 10. Response to steroid therapy. (Table 4 from Study V).

	Steroid therapy (n = 16)	Control patients (n = 15)	P value
MODS at inclusion	6.6 (2.6)	6.3 (3.3)	0.71
Change in 3 days after inclusion	–2.0 (0.4)	–0.4 (0.6)	0.15
PaO_2/FiO_2 at inclusion	136.9 (48.7)	160.4 (55.0)	0.15
Change in 3 days after inclusion	60.0 (12.9)	–6.0 (7.6)	0.004
CRP at inclusion, mg/ml	170.3 (47.9)	131.0 (50)	0.03
Change in 3 days after inclusion	–130.7 (9.1)	–19.2 (10.1)	<0.001
Length of mechanical ventilation, days	20.5 (2.3)	20.1 (2.7)	0.70
Length of ICU stay, days	20.9 (2.2)	20.8 (2.8)	0.63
30-day mortality	19 % (3/16)	20 % (3/15)	0.82

5.6 Prolonged methylprednisolone treatment in primary ALI

Demographic data and aetiology of ALI were presented in Table 7 in Methods. On admission, at the start of methylprednisolone treatment, and on day 10, the groups were comparable, and all patients fulfilled the criteria for ALI. The mean (standard deviation) start of steroid treatment was on ICU-day 9.7 (0.7). Mean dose of methylprednisolone per day with 95 % confidence interval and tapering schedule is in Figure 13.

Changes in certain variables as a response to methylpredinolosolone therapy is presented in Table 10. The PaO_2/FiO_2 ratio improved within 3 days after the start of methylprednisolone treatment compared with the ratios of the control patients. Significant decreases occurred in MODS and CRP. In the length of mechanical ventilation, in length of ICU stay, and in 30-day mortality, no significant differences appeared.

Infectious complications were similar between groups. Frequency of nosocomial infections was not significantly higher in the steroid group. Autopsies of nonsurvivors (three in each group) revealed no clinically undetected nosocomial infections. No other steroid-related complications; i.e., gastrointestinal bleeding or therapy-resistant hyperglycaemia, occurred.

To evaluate a more homogenous patient group, a subanalysis was conducted involving patients with microbiologically confirmed pneumococcal pneumonia. In 18 patients who were mechanically ventilated for more than 10 days, a positive blood or BAL culture for Streptococcus pneumonie was identified. Among these patients prolonged methylprednisolone therapy was given to 11, with the remaining 7 serving as controls. In the methylprednisolone group, significant improvement was detectable in oxygenation and in reduction inmultiorgan failure scores.

6. DISCUSSION

6.1 Maintanence of spontaneous breathing during mechanical ventilation

This comparative trial between APRV and SIMV has been the first randomised and controlled trial comparing two partial ventilatory modes in patients fulfilling the criteria of ALI or ARDS. The goal in this investigation was to assess the potential benefits of a ventilator strategy which employs specifically unsupported spontaneous breathing superimposed on mechanical ventilation.

The hypothesis for the potential benefits of APRV was based on several experimental and clinical studies in which APRV has been associated with improved ventilation-perfusion matching, decreased shunting, and hence, better arterial oxygenation (Downs and Stock 1987, Putensen, et al. 1994b, Räsänen, et al. 1991, Stock, et al. 1987, Wrigge, et al. 2003). Due to the cyclic reduction in intrathoracic pressure resulting from spontaneous breathing, venous return is enhanced, and filling of the heart is also enhanced, which increases cardiac output. Improved oxygenation and cardiac output results in increased oxygen delivery (Putensen, et al. 1999, Wrigge, et al. 2003). These beneficial changes occur even if the spontaneous minute ventilation is only a very small fraction of the total minute ventilation and occurs without a significant increase in oxygen consumption due to the activity of respiratory muscles (Hörmann, et al. 1997).

Most of these studies have compared APRV to a strategy in which the ventilator either passively ventilates the subject or does the majority of the work of breathing, even if the patient initiates some or even most of the breaths. In contrast to the present prospective long-term study, Putensen and co-workers (1999), in a crossover setting compared APRV with spontaneous breathing, to PS and to controlled ventilation. When equal pressure limits or minute ventilation were used, they found that PS ventilation did not differ from controlled ventilation in its effects on gas exchange, haemodynamics, oxygen delivery, or oxygen consumption; beneficial effects in these variables were seen only with APRV with unsupported spontaneous breathing maintained.

In the present study, the level of pressure support in the SIMV group was much lower (10 cmH_2O) than was inspiratory pressure for controlled insufflations. Thus, spontaneous breathing with a relatively low level of PS may have been associated with the same physiological benefits as was the unsupported spontaneous breathing with APRV, because small inspiratory support compensated for the resistance of the intubation tube. The difference between the groups may thus have been so small that no possible benefit from unsupported breaths could be demonstrated.

In some studies, APRV improved oxygenation during early phases of ALI (Hörmann, et al. 1997, Putensen, et al. 2001). In a prospective and crossover study, APRV has improved gas exchange and reduced the venous admixture in ARDS patients when compared to inverse ratio volume-controlled ventilation, an effect observed after 8 hours (Sydow, et al. 1994). In a recent study, Wrigge and coworkers showed in a pig model with x-ray computer-assisted tomography that end-expiratory lung volume increased after 4 hours of spontaneous breathing as compared with ventilation with equal airway pressure without spontaneous breathing. This recruitment was seen as a larger amount of normally aerated lung in depen-

dent lung regions (Wrigge, et al. 2003). In the present study, improvement in PaO_2/FiO_2 ratios in the APRV group, albeit not significant, was evident after 24 hours, but no differences appeared after the fourth day.

APRV has been compared to totally controlled ventilatory support in one prospective, randomised clinical trial by Putensen and co-workers (2001). In that trial, the study population was multiple trauma patients at risk for ARDS. In the treatment group, APRV was employed very early (6 hours) after the start of ventilatory support (Putensen, et al. 2001). The present study comprised confirmed ARDS patients and the delay to start of the ventilatory treatment under study was much longer (mean 39 hours). Alveolar collapse, the hallmark of severe ARDS, develops early in the disease process. Once dependent collapse and consolidation have developed, they are often very resistant to measures to recruit alveoli (Negri, et al. 2002). The type of lung injury may also have had an impact. In the Putensen study, patients had a secondary or indirect type of lung injury. Some studies have shown that a lung with secondary injury is more easily recruitable than a lung with direct or primary injury, the type of injury of most of our patients (Lim, et al. 2003a, Pelosi 2000). Another major difference between the present study and the Putensen study was the non-ventilatory management of the control group. Our sedation policy was the same in both groups, and long-term muscle paralysis was used in neither group. Both of these factors could per se could impact outcome variables such as length of mechanical ventilation, length of ICU stay, and even mortality. In analgosedation, no differences appeared, which could be explained by the fact that the control group also had the possibility of triggering the ventilator, and this was not suppressed with sedation.

Several limitations of this study should be addressed. Either the ventilator used or our spirometry technique was unable to measure accurately the amount of spontaneous ventilation. Measuring spontaneous breathing precisely during partial ventilatory support is difficult and requires measurement of oesophageal pressure, not feasible in a long-term clinical trial. However, meticulous care was taken that patients in the APRV group maintained spontaneous breathing, and this was verified by the flow and pressure tracings of the ventilator. Due to variability in inspiratory pressures and in inspiratory times because of the use of pressure support in the SIMV group, it was impossible to compare accurately the mean airway pressures between the study groups. We thus cannot rule out the possibility that mean airway pressures might have differed between groups.

The use of prone position as part of the protocol is another confounding factor, although the protocol and the actual use of PP in both groups were similar. Mean tidal volume per body weight was larger than that used for the treatment group in the ARDSnet study. Plateau pressures in both groups in our trial were, however, well below the 35 cmH_2O recommended by the consensus conference in 1993 (Slutsky 1994). Recently, criticism towards the use of very low tidal volumes has also appeared (Eichacker, et al. 2002). Very low tidal volumes may be harmful, especially in patients without severely impaired lung compliance (Gattinoni, et al. 2003).

Sample size in this APRV vs. SIMV study was based on a power analysis with the assumption of a decrease in ventilator-free days of 15 % with APRV. However, the study was terminated for futility on the basis of an interim analysis, when only two-thirds of the estimated 80 patients were included. The decision to terminate was also based on slow recruitment of patients and on the need to change several general principles of care. The difference in ventilator-free days between the groups was 9 % (1.2 days) in favour of APRV, which is not statistically significant. However, to evaluate the possibility of too small sample size, the 95 % confidence interval for the difference in ventilator-free days between the groups was calculated (Gardner 1988),

and analysis showed that the upper limit of the confidence interval was 5.7 days, i.e., a 43 % increase in ventilator-free days with APRV over that with SIMV with PS. This indicates that the possibility of a clinically significant difference between ventilatory modes cannot be definitely excluded and that the study lacked the power to answer the hypothesis posed.

This study also lacked the power to evaluate mortality between groups. However, the one-year mortality in our study, 21 % for the whole material, is below the range of recently published mortality rates (from 31 to 70 %) in clinical trials and case series with ARDS patients (Estenssoro, et al. 2002, Milberg, et al. 1995, Valta, et al. 1999). The inclusion criteria were those of AECC for ALI. However, the criteria were confirmed after the standardised stabilisation phase including ventilatory management with PEEP guided by a PV curve. During this phase, fluid homeostasis and haemodynamics were optimised as guided by PAC. Thus, patients fulfilling AECC ALI criteria after this period truly represent patients with severe lung injury. After this stabilisation phase, most patients with a paO_2/FiO_2 ratio over 200 mmHg could be considered for weaning and they were excluded from the study. Only a few patients with ALI criteria were included and most had a more severe type of oxygenation failure, i.e. , ARDS.

6.2 Prone positioning in ALI

Allowing spontaneous breathing during mechanical ventilation had an additive effect on the improvement in oxygenation in response to prone positioning. Improvement in gas exchange in the APRV group occurred over time and was significant 24 h after the shift from totally controlled mechanical ventilation. In accordance with several other investigations, in this study PP improved oxygenation in approximately 70 to 80 % of the patients with ARDS or ALI (Messerole, et al. 2002).

Achievement and maintenance of maximal aeration of the lung may be an important tool for reduction in lung injury related to mechanical ventilation (Lachmann 1992). PP has been shown to induce alveolar recruitment (Guerin, et al. 1999) and in animal experiments to reduce VILI (Broccard, et al. 2000). However, in the only prospective study addressing effects of PP on survival, benefit occurred only in the patient group with severe hypoxemia (Gattinoni, et al. 2001b). In Gattinoni´s study, PP was used only once per day, and the mode of mechanical ventilation was controlled ventilation (Gattinoni, et al. 2001b).

Prone position has been proposed to change the effect of abdominal mass on the dorsal lung (Froese and Bryan 1974). By this mechanism, PP reduces transdiaphragmatic pressure on the dorsal part of the diaphragm. Reduced pressure creates better working conditions for the diaphragm and enhanced movement of the diaphragm during spontaneous breathing, and redistributes ventilation towards dorsobasal lung areas. Thus, PP and spontaneous breathing may thus show synergistic effects on recruitment of juxtadiaphragmatic areas. However, this theory of the effects of PP on intra-abdominal pressure and regional ventilation in the basal lung area has been challenged (Colmenero-Ruiz, et al. 2001), and neither intra-abdominal pressure nor lung mechanics during prone positioning was measured in the present study. Another issue concerning the effects of PP is the effect of PEEP. Turning a patient prone has been shown to induce changes especially in chest wall compliance (Pelosi, et al. 1998). Thus, in the prone position, optimal PEEP, as well as the effects of spontaneous breathing may differ.

The time period between onset of ARDS and the beginning of prone positioning has varied considerably (Chatte, et al. 1997, Douglas, et al. 1977, Gattinoni, et al. 2001b, Langer, et al. 1988). In the present study, the effect of prone positioning was employed relatively early (27–35 h) after ALI onset in order to study a patient population in which time-related physiological conditions were as homogenous as possible. Time-related

factors related to PP have been proposed to explain the variance in response (Lamm, et al. 1994). Similarly, type of ALI may correlate with response to PP (Pelosi 2000). A marked oxygenation response occurs significantly more often in a patient with indirect lung injury (Lim, et al. 2001). In the present study, most patients had primary ALI, and type of lung injury was not an independent determinant of change in oxygenation.

6.3 CT scanning in ALI

Lung recruitment as assessed with CT scanning densitometry was similar after 7 days with APRV and with the other partial ventilatory mode, i.e., SIMV with pressure support.

Recruitment refers to the opening of previously closed alveoli. Quantitative CT analysis has been used to investigate this phenomenon in various experimental and clinical settings (Gattinoni, et al. 2001a) (Rouby, et al. 2003a). However, the interpretation that change from consolidation to normal aeration as measured with CT densitometric is due to recruitment has been recently challenged (Hubmayr 2002). It has been proposed that change in CT density in one region of interest (ROI) can be due to change in alveolar size, i.e., alveolar distension, or it can be due to change in amount of tissue and interstitial fluid or due to alveolar flooding (Hubmayr 2002). At present however, the only clinically available method for the measurement of regional air content of the lung is the CT densitometry.

Several technical and analytical factors influence the CT findings of this study. Only two sections of the lung were measured. Investigation with CT using more sections or whole lung scanning have shown that analysis based on only a few slices may underestimate changes in lung aeration (Malbouisson, et al. 2001a, Puybasset, et al. 2000). In volumetric studies, decrease in FRC has been greatest in the lower lobes (Puybasset, et al. 2000, Rouby, et al. 2003a). Because the effect of spontaneous breathing is most likely to occur in juxtadiaphragmatic slices, the choice of primary endpoint, change in nonaerated lung in the basal sections, is justified.

Volumetric studies have revealed that massive loss of aeration is homogeneously distributed, with a slight predominance in the upper lobes. On the other hand, increase in tissue volume is heterogeneously distributed. In severe ALI, the lower lobes are essentially nonaerated, while the upper lobes may remain normally aerated. Two opposite radiologic presentations, corresponding to different lung morphologies, may occur. In patients with focal computed tomographic attenuations, the lower lobes are entirely atelectatic. In patients with diffuse computed tomographic attenuations, lung volume is preserved in the upper lobes and reduced in the lower lobes, although the loss of aeration is equally distributed between upper and lower lobes. When a positive intrathoracic pressure is applied to patients with focal acute respiratory distress syndrome, poorly aerated and nonaerated lung regions are recruited, whereas lung regions normally aerated at zero end-expiratory pressure tend to be rapidly overinflated, increasing the risk for ventilator-induced lung injury (Puybasset, et al. 2000, Rouby, et al. 2003a). Ventilatory mode or position change may produce similar physiological consequences. In this study, no categorisation based on CT morphology was performed.

Respiratory settings during the CT scanning may also have influenced measurement of gas distribution. We investigated lungs at expirium during transient relaxation given immediately before the scanning. Reduced muscle tone induced by neuromuscular blockade can have effects on lung volume (Froese 1989). Relaxation of the diaphragm could have caused compression by the abdominal contents in basal lung areas and closure of alveolar units. Cephalic movement of the diaphragm could have abolished the possible reopening achieved by spontaneous breathing (Hedenstierna, et al. 1989). Very rapid dynamic or multidetector CT scanning would have enabled

evaluation without neuromuscular blocking drugs and thus would have been the method of choice (Markstaller, et al. 2003). However, this technology was unavailable at the time of this investigation.

6.4 Prolonged methylpredisolone in the late-phase of ALI

Prolonged methylprednisolone treatment started after 10 days of mechanical ventilation was associated with improved oxygenation and decrease in C-reactive protein concentration within 3 days after the start of treatment in patients with late-phase primary ALI. These findings agree with earlier findings regarding effects of glucocorticosteroids in the late or unresolving phase of acute lung injury (Biffl, et al. 1995, Hooper and Kearl 1990, Keel, et al. 1998, Meduri, et al. 1998a). Such studies with heterogenous groups of ALI patients have consistently shown improvement in lung function and reduction in associated organ failures.

Optimal timing for the start of corticosteroid treatment is a critical issue. Earlier studies have investigated the potential of high-dose steroids to control the initial inflammatory response in sepsis, i.e., in patients at risk for ARDS, or in patients with ARDS in an early phase of the disease process (Cronin, et al. 1995, Lefering and Neugebauer 1995). These studies have failed to show any benefit from this early or prophylactic immunomodulation (Cronin, et al. 1995, Lefering and Neugebauer 1995). The pathophysiological basis of late steroid therapy does, however, differ. The goal is to prevent or alleviate the exaggerated and sustained host defence response which prevents effective restoration of lung anatomy and function. A protracted inflammatory response leads to proliferation of myofibroblasts and to collagen deposition in the lung parenchyma. Lung fibrosis and alveolar obliteration in the lungs lead to deterioration of oxygenation and of lung mechanics (Luce 2002).

Mechanisms regulating development of this fibroproliferative process are complex. As a measure of inflammatory response and fibroproliferation in ARDS, various proinflammatory mediators have been investigated (Goodman, et al. 1996). Levels of interleukin-6 have been found to be increased in patients with a tendency to develop unresolving ALI. Clinical signs of fibroproliferation correlate with levels of procollagen types I and III aminoterminal propeptides. Steroid therapy is associated with reduced levels of these markers (Meduri, et al. 1998b).

CRP also correlates well with the intensity of systemic inflammatory response and can serve as a measure of the effect of corticosteroid treatment. Because CRP has a special function against pneumococcal infections via binding to pneumococcal C-polysaccharide, following CRP levels may offer special attraction for the treatment of pneumococcal ALI. In patients with late ARDS, glucocorticoid treatment reduces levels of several proinflammatory mediators and markers of fibroproliferation, suggesting that premature discontinuation of steroids can induce a rebound effect and an increase in production of cytokines (Headley, et al. 1997, Meduri, et al. 1995b). Early discontinuation of steroid therapy in late ARDS has been associated with deterioration in the clinical status. In the present study, methylprednisolone was continued at a high dose of 80 to 125 mg/day until a clear response was achieved in inflammatory parameters.

Before institution of corticosteroid therapy, diagnostic survey has been recommended for untreated infections (Meduri 1996). In the present investigation, steroids were considered only after comprehensive antimicrobial therapy which was based on culture results or broad-spectrum empirical therapy. Detection of occult infection or development of nosocomial infection was through regular urine culture, and through displaced intravenous catheters, brochoalveolar lavage, and tracheal suction. Based on high degree of clinical suspicion, thoracic and abdominal CT-scans were performed.

6.5 Clinical implications and future perspectives

In evidence-based medicine, several treatments applied to critically ill patients in ICUs lack even grade-B evidence (Dellinger, et al. 2004). This is also still the case with most of the treatments applied in ALI/ARDS. A particular problem in research on the critically ill patient is the low signal-to-noise ratio. Impact of ventilatory treatment on mortality is most likely rather small. Thus, several aspects of care and the failure to standardise them may easily obscure this effect. Development of algorithms to standardise care, e.g., fluid therapy, treatment of any underlying disorder, and several other aspects of care, is very difficult.

Nevertheless, over the years, the outcome for ALI/ARDS has improved (Milberg, et al. 1995), and our understanding of the pathophysiological mechanisms involved has increased enormously. However, major gaps still exist. ALI/ARDS is a very complicated and multifactorial process, and several aspects of treatment are very difficult to investigate in the frame of a randomised and controlled trial. Considering, for instance, the fast-evolving possibilities of modern ventilator technology, it is probable that the outcome benefit of most of these features will not be investigated in a randomised controlled setting. For this reason it is very important to discover reliable surrogates of morbity and mortality in ALI/ARDS. Studies with reasonable surrogate endpoints and physiological measures will continue to be important before any new technology is employed in critical care.

Epidemiological data on the clinical course of ALI are still scarce, and incidence and risk factors of fibroproliferative late-stage ALI poorly known. Employment of lung-protective ventilation may have an influence on incidence, as will other supportive therapies. The pathogenetic pathways of the transition from acute alveoli-endothelial injury to the late proliferative phase may vary depending on initial cause of lung injury. Indirect (secondary or extrapulmonary) and direct (primary or pulmonary) insults may lead to differing pathophysiological types of ALI (Pelosi 2000). Due to the complex pathogenesis of ALI, especially studies concerning effects of immunomodulative therapy should focus on a homogenous group of patients. This poses a logistical challenge when patients with comparable underlying conditions and during the same phase of the disease process must be included in the study. With a relatively rare condition such as late-stage ARDS, this can be very difficult even with large-scale multicenter trials.

Despite the lack of large-scale prospective randomised trials, steroids are nowadays widely used in late phase ALI/ARDS. The ARDS network consortium has been conducting a trial testing the effects of methylprednisolone in a heterogeneous group of patients with late phase ARDS (Anonymous 2004).

The effects of ventilatory treatment should also be investigated in a homogenous patient group. Data from CT scanning studies suggest that lung morphology may have implications for selection of ventilatory settings (Rouby, et al. 2003b). Development of on-line monitoring of lung mechanics and bed-side tools to investigate more precisely regional ventilation may help in selecting individual settings for each patient which will cause the least mechanical stress on injured lungs (Hedenstierna 2004, Stenqvist 2003).

APRV offers physiological benefits demonstrated in several trials discussed here. Although the results of this investigation concerning primary outcome measures did not differ from those of current practice, some clinical implications can drawn. APRV is a very flexible ventilatory mode. Without changing ventilatory mode, the amount of mechanical support can be adjusted from almost total mechanical support (total support is not APRV by definition) to CPAP with the total work of breathing done by the patient. Logistically, continuous monitoring of the weaning protocol is simple and may offer advantages in

everyday clinical practice. APRV is suitable for most ALI patients. Benefits in renal and gut perfusion should be tested in a patient population in which these issues could have special implication for the outcome. Sedation consumption did not differ in this study, a finding that should be investigated further with a strict sedation policy and precise monitoring of sedation.

The best evidence for supportive treatment of ALI/ARDS are the data from the ARDSnet trial (Anonymous 2000). This investigation has raised several questions concerning ethics and the planning of studies with the critically ill (Miller 2004, Steinbrook 2003). Very important is the management of the control group: Treatment of the control group should represent current routine practice. Otherwise positive results of a trial may be interpreted as a harmful effect imposed upon the control group, as has been the case with the ARDSnet study (Eichacker, et al. 2002). In the future, selection of treatment options for the control group must be even more carefully justified and truly represent the current gold standard.

7. CONCLUSIONS

On the basis of these studies the following conclusions can be drawn:

1. In ALI patients, primary use of APRV with maintained unsupported spontaneous ventilation as compared to SIMV with PS
    a. is feasible and potentially beneficial in severe ALI.
    b. does not increase the number of ventilator-free days.
    c. does not improve variables of gas exchange and haemodynamics.
    d. does not reduce sedative use.

2. Prone positioning and allowing spontaneous breathing during APRV have advantageous synergistic effects on gas exchange.

3. The effects of APRV with spontaneous breathing and SIMV with pressure support on lung aeration, as measured by CT after 7 days of mechanical ventilation, do not differ significantly.

4. In patients with primary ALI, prolonged methylprednisolone therapy, begun 10 days after the start of mechanical ventilation, improves gas exchange and is associated with a decrease in multiple organ dysfunction.

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