9. Ventilator settings and gas exchange in respiratory distress syndrome

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Despite great advances in the treatment of acute respiratory failure, many patients do not respond to accepted methods of resuscitation. The great majority of these critically ill patients fall into the category of adult respiratory distress syndrome (ARDS). The name of this syndrome was given by Ashbaugh et al. [1], who based it upon the severe respiratory distress in illness closely resembling the infant RDS (IRDS). Although the pathogenesis varies highly, it is useful to group various categories of patients together if they meet the clinical, physiological and pathological conditions of the RDS, and respond in a similar manner to a given type of treatment [2]. Infant respiratory distress syndrome is closely related to immaturity [73], whereas ARDS develops in conjunction with severe diseases such as trauma, fat embolism, aspiration pneumonitis or virus pneumonitis, acute renal failure or gas intoxication [79].

Both in new-born infants and in adults, the typical clinical findings of the disease are tachypnoea, dyspnoea, cyanosis, hypotension combined with peripheral oedema and a reticulogranular pattern on chest x-ray films with a characteristic air bronchogram. Physiological findings include:

1) Decrease in tidal volume, lung compliance, functional residual capacity, arterial oxygen tension (PaO_2), peripheral and renal blood flow and blood pH.
2) Increase in ventilation, work of breathing, intrapulmonary shunt and $PaCO_2$ tension.

The findings at autopsy include: atelectasis, hyaline membranes, interstitial and intra-alveolar haemorrhage and, in late stages after prolonged artificial ventilation, fibrotic changes with emphysema, decreased surface activity and decreased concentration of surface-active phospholipids [for review see 6, 42, 49, 50, 52, 55, 56, 58, 59, 73, 79].

The mortality of ARDS may be 40%–70% [42, 79]. In infants, it may be as low as about 10% in centres with extensive programmes for neonatal care (for a review see Jonson et al. [25]). Even in such centres, IRDS constitutes a great problem due to the enormous efforts and costs required for the treatment. This disease is, even so, probably the most important of those factors contributing to the mortality in infants under 1000 g in weight. The high mortality rate and the drastic efforts and high costs of treatment required are incentives to find new approaches to combat this critical disease.

The main immediate therapeutic goal in severe ARDS and IRDS consists of attempt-

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ing to overcome hypoxaemia as well as metabolic and respiratory acidosis by means of respiratory therapy, increased inspiratory oxygen concentration and infusion of buffer solution [59]. Some patients, who showed no improvement from this therapeutic regimen, have been treated with extracorporeal membrane oxygenation (ECMO) [83] or with extracorporeal elimination of CO_2 [19] in combination with low-frequency ventilation in a few highly specialized intensive care units.

Although the first of these methods has resulted in clinical failure [29, 42], extracorporeal elimination of CO_2 together with low-frequency ventilation seems more promising [19]. Lung transplantation as a therapeutic measure has no clinical importance at present, due to the immunological problems involved [71].

The aim of respiratory therapy in ARDS is to maintain the gas exchange in the lung by opening and stabilizing closed units with a minimal depression of the heart function and the circulation.

Numerous clinical and experimental studies were performed to investigate the influence of continuous positive airway pressure (CPAP) [21, 25, 68], positive end-expiratory pressure (PEEP) [30, 49, 60, 74], "super"-PEEP [13, 26], inspiratory-expiratory ratio (I/E ratio) [22, 34, 35, 61, 62, 80], frequency [35, 63, 72], inspiratory flow [16], end-expiratory pause (EIP) [18, 28, 35, 67] and intermittent mandatory ventilation (IMV) [14, 15, 38, 81] on the gas exchange of severely damaged lungs.

A significant improvement of the oxygenation could be accomplished by adjusting ventilation in several ways. Up to now it has, however, not been shown that a particular set of data describing the state of the lungs and heart enables making a decision on how respiratory therapy should be performed in an optimal manner.

The failure of respiratory therapy despite a high PEEP and a high inspired oxygen concentration, FIO_2 of 1, in a group of patients with ARDS, the poor results from ECMO and the fact that few intensive care units can perform special, more promising varieties of ECMO give grounds for searching after other methods of respiratory therapy suitable for patients with the most severe respiratory insufficiency.

This chapter discusses and illustrates the rationale behind an approach to open up lung units and to maintain stability by regulation of alveolar pressure. It is based upon prolonged insufflations. These are followed by expirations too short to allow the collapse of terminal lung units. Data from experimental and clinical studies are presented to compare this mode of ventilation with others. For further information about accepted forms of modern respiratory therapy, including their advantages and disadvantages, please see the excellent surveys already published [3, 36, 50, 57, 58, 69, 75].

Experimental mode of ARDS

Deficiency of alveolar surfactants leading to respiratory insufficiency was in the experimental studies produced by bronchial lavage with isotonic saline at body temperature [31, 35]. Variation of the number of lavages enables variation of the severity of functional disturbances. Strict adherence to a certain lavage procedure results in a quite reproducible condition in the lungs.

Severe respiratory insufficiency was defined as being present when arterial oxygen

tension fell below 60 mm Hg during volume-controlled ventilation with an I/E ratio of 1:2 and an FIO_2 of 1. In order to establish this condition in dogs, it was necessary to repeat the lung lavage ten times on the average, with a volume corresponding to the vital capacity (for details see Lachmann et al. [31]).

In this model, we have tested various modes of ventilation, including varying duration of inspiration, different frequencies, the use of post-inspiratory pause, the use of volume- and pressure-controlled ventilation and the application of various degrees of PEEP.

Various breathing patterns were produced by a Servo ventilator 900 B (Siemens-Elema AB, Solna, Sweden). The ventilator was modified to allow an inspiratory time of 80% of the cycle without using the post-inspiratory pause. To produce pressure-controlled ventilation, flow regulation was eliminated by setting the pre-set minute ventilation 3–4 times higher than the ventilation to be achieved. The inspiratory airway pressure will then be equal to the working pressure, which was adjusted to obtain a tidal volume of about 20 ml/kg body weight. At pressure-controlled ventilation, the inspiratory flow pattern decelerated as a die-away exponential curve. After about 0.25 s, the pre-set pressure was attained and only a little gas entered the lungs.

At volume-controlled ventilation, the ventilator produced, as intended, a nearly constant flow during insufflation time. During the pause, pressure changed only slightly, which means that the system did not leak and that only little stress relaxation occurred in the lungs. The minute volume was set to produce a tidal volume of about 20 ml/kg body weight. Pressure in pressure-controlled ventilation and minute volume in volume-controlled ventilation were kept constant in all of the experimental studies. If not otherwise stated, frequency was 40/min. The effects of different

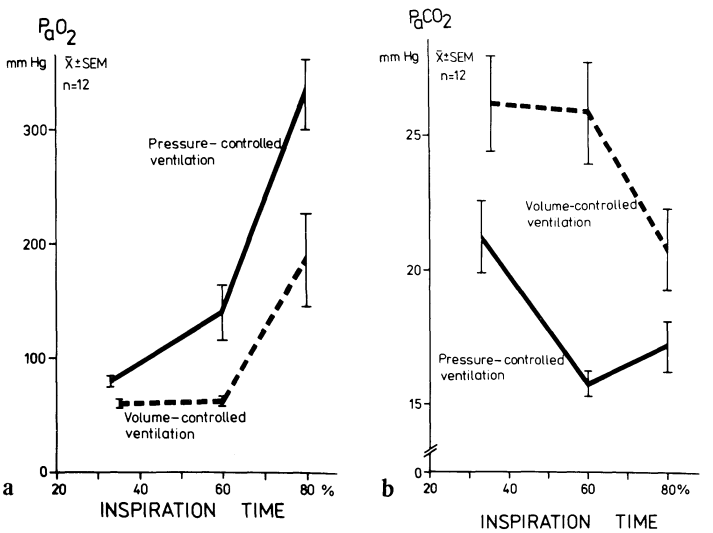

Figure 1. The average PaO_2 (*a*) and $PaCO_2$ (*b*) in relation to inspiration time at pressure- and at volume-controlled ventilation in 12 beagles with severe ARDS; SEM, standard error of the mean. Note that despite hyperventilation, oxygenation was poor when inspiration time was short.

ventilator settings were evaluated by measurements of blood gas and haemodynamic measurements, as well as by morphological studies of lung lesions associated with artificial ventilation in adult rabbits and beagles.

An important property of the model is that the dominant pathogenic factor of RDS – that of surfactant deficiency – is imitated without severe simultaneous damage of the alveolar structures [31]. Major morphological changes can be attributed to ventilation rather than to damage caused by the model itself.

Material

An initial series of experiments were performed on adult rabbits [35]. A large variety of breathing patterns were tested in those animals for the effects of gas exchange and compliance. On the basis of the results obtained in rabbits, several series of adult beagles were studied. In these animals, it was also possible to study haemodynamic data. A pulmonary artery catheter permitted determination of gas concentrations in mixed venous blood and of cardiac output according to the Fick principle. If not otherwise stated, results accounted for in the following text refer to the dogs.

Influence of I/E ratio on gas exchange

The data after lavage are compatible with severe RDS. PaO_2 fell from about 460 mm Hg before lavage to about 55 mm Hg after lavage in the ventilator settings cited above.

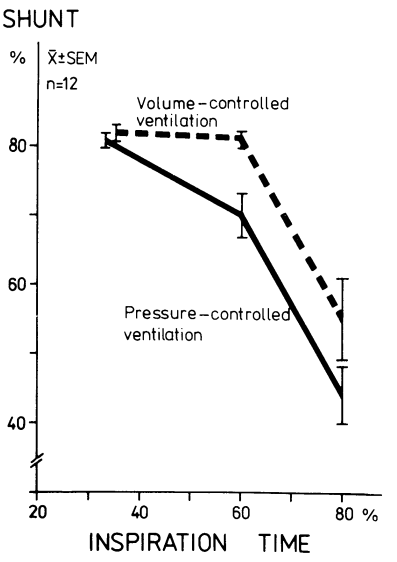

Figure 2. The intrapulmonary shunt was calculated from arterial and mixed venous content of oxygen and related inspiration time at pressure- and volume-controlled ventilation. Same animals as in Figure 1.

After lavage, peak pressure was about 28–30 cm H_2O. Up to this stage, no obvious difference between volume- and pressure-controlled ventilation was observed. When inspiration was prolonged to cover 80% of the cycle, PaO_2 increased. The greatest improvements were found at pressure-controlled ventilation (Fig. 1a). The initial values of arterial CO_2 tension, $PaCO_2$, illustrate that the animals were hyperventilated with 20 ml/kg body weight (BW). The elimination of CO_2 was higher in pressure-controlled ventilation than in volume-controlled ventilation (Fig. 1b).

The increase in arterial oxygenation corresponds to a drastic reduction in intrapulmonary shunt (Fig. 2). Compliance reached a maximum at 60% inspiratory time in pressure-controlled ventilation and improved during volume-controlled ventilation with prolongation of the inspiratory time (Table 1).

Prolongation of inspiratory time to 80% of the cycle led to an increase of mean airway pressure (Fig. 3a) which caused the well-known decrease in cardiac output (Fig. 3b) of about 33% in pressure-controlled ventilation and about 45% in volume-controlled ventilation. A decrease in oxygen transport (Fig. 3c) and systemic pressure as well as an increase in pulmonary artery pressure and pulmonary vascular resistance also occurred (Table 1).

The resulting data show clearly that, also without a PEEP, a significant improvement of gas exchange can be reached by prolongation of the inspiratory time to 80% of the cycle. At an I/E ratio of 4:1, a significantly better oxygenation can be reached in the most severely damaged lungs at pressure-controlled ventilation compared to volume-controlled ventilation (Fig. 1). The negative cardiocirculatory consequences, as well as the reduced oxygen transport, are less influenced by a high I/E ratio at pressure-controlled ventilation than at volume-controlled ventilation.

The influence on compliance is difficult to interpret, as at short expirations the conditions are not static at the end of expiration, particularly not when an improvement of compliance leads to a longer time constant of the respiratory system.

The results presented agree with clinical data of new-born infants with RDS given by Reynolds [61], who showed that massive improvements of the arterial oxygenation without impairment of cardiocirculatory parameters and CO_2 elimination could be obtained by pressure-controlled ventilation and I/E ratios higher than 1:1 (Fig. 4).

Table 1. Mean values ± standard deviations of compliance of the respiratory system, mean blood pressure, ventilation, mean pulmonary artery pressure and pulmonary vascular resistance during pressure- and volume-controlled ventilation as dependent on inspiration time; during volume-controlled ventilation, inspiration comprised 25% insufflation and 10% pause or 50% insufflation and 10% or 30% pause (results from 12 beagles)

	Inspiration time (%)	Compliance (ml/cm H_2O)/kg	Mean blood pressure mm Hg	Ventilation ml/min)/kg	Pulmonary vascular (dyn s)/cm^5	Mean pulmonary artery pressure resistance mm Hg
Pressure -controlled ventilation	33	1.1±0.1	104±21	874±141	292± 80	13.6±3.3
	50	1.4±0.3	95±16	1123±179	374±107	16.3±2.6
	80	1.2±0.1	101±18	776± 39	592±181	20.6±4.3
Volume -controlled ventilation	25–10	1.2±0.2	117±21	–	496±265	19.4±6.5
	50–10	1.3±0.22	103±15	–	590±304	19.8±6.3
	50–30	1.4±0.21	86±24	–	906±335	22.6±5.4

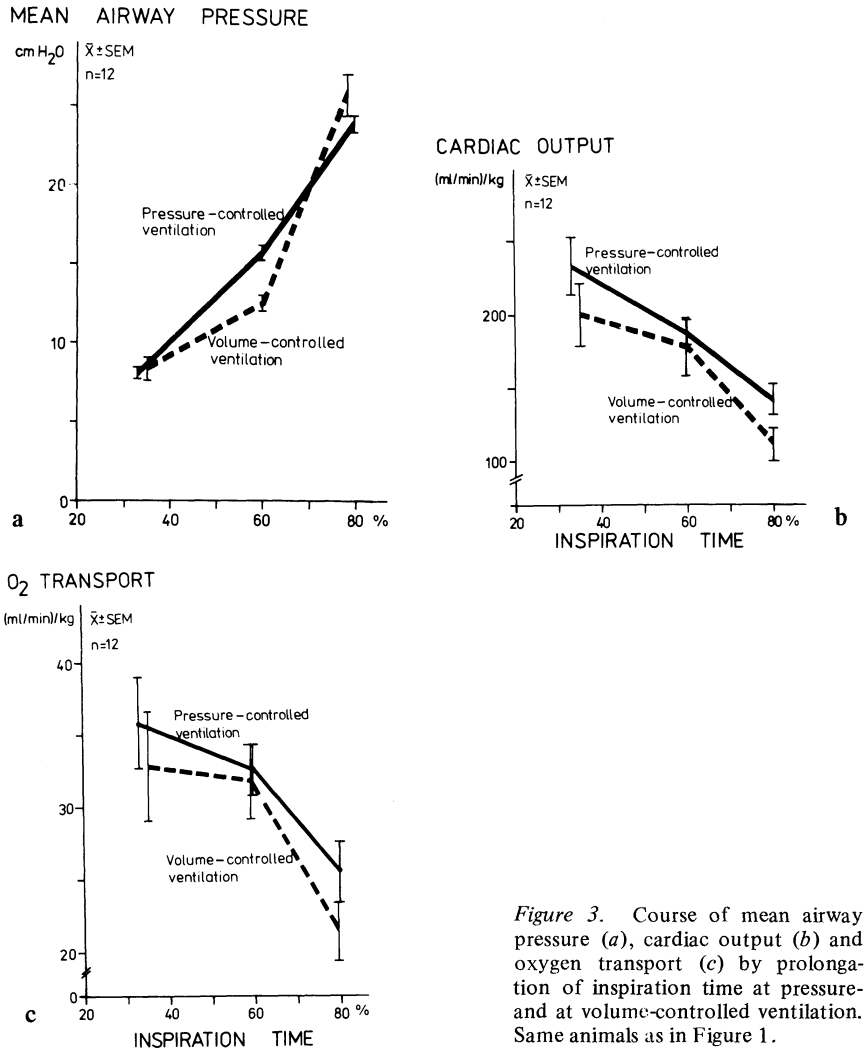

Figure 3. Course of mean airway pressure (*a*), cardiac output (*b*) and oxygen transport (*c*) by prolongation of inspiration time at pressure- and at volume-controlled ventilation. Same animals as in Figure 1.

In theoretical, experimental and clinical investigations, other authors have also shown pressure-controlled ventilation with a long inspiration time to be superior to volume-controlled ventilation, especially for ventilation of stiff lungs with a surfactant deficiency [11, 22, 34, 39, 41]. This implies, however, that the widespread support of volume-controlled ventilation using large tidal volumes in patients with severe ARDS, as recommended by numerous authors [3, 37, 50, 59, 75, 77], must be critically questioned.

Influence of post-inspiratory pause on arterial oxygenation

An improvement of oxygenation caused by a high I/E ratio also at volume-controlled

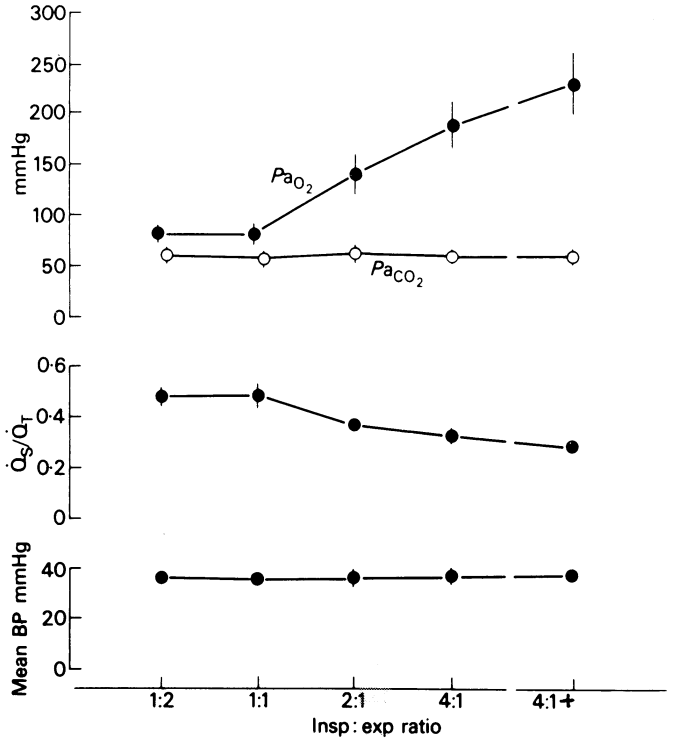

Figure 4. Effect of I/E ratio on arterial blood gas tensions, right-to-left shunt (Q_s/Q_t) and mean arterial blood pressure (BP) in six infants. Respiratory frequency was 30/min. I/E ratio of 4:1+ shows the effect of a 5-cm increment in airway pressure. From Reynolds [61].

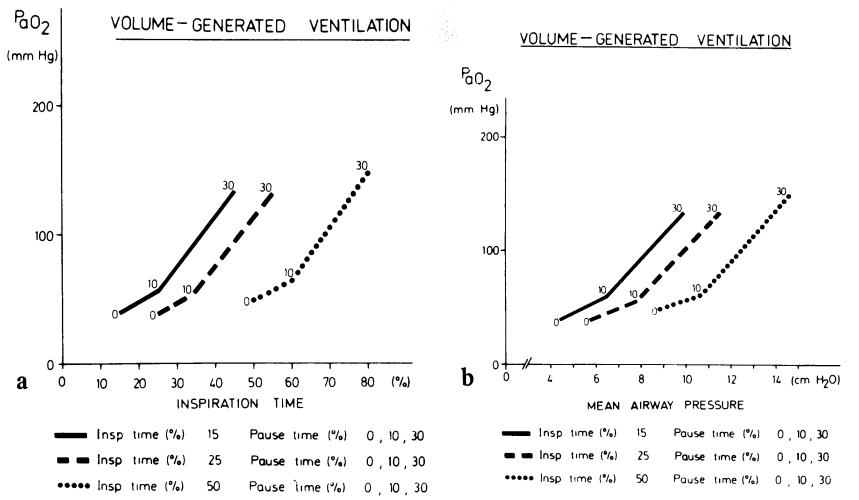

Figure 5. The average PaO_2 related to duration of inspiration (*a*) and mean airway pressure (*b*) during volume-controlled ventilation in two rabbits. At a given total duration of inspiration (*x*-axis), data referring to a short insufflation followed by a long pause showed the best gas exchange. No simple relationship exists between mean airway pressure and PaO_2. From Lachmann et al. [35].

ventilation has been observed in patients with acute respiratory insufficiency [4, 48]. Our experimental results [35] show, however, than an extension of inspiratory time in itself does not lead to a substantial improvement of arterial oxygenation. At a given total inspiratory time, patterns with a long post-inspiratory pause and, hence, a short insufflation lead to very pronounced improvements of the oxygenation (Fig. 5a).

These results are in contrast to the findings of Fuleihan et al. [18], who could not show any improvement of arterial oxygenation from a post-inspiratory pause in patients with acute respiratory failure.

Ventilation patterns with long end-inspiratory pause may be characterized by "an early and sustained insufflation" [35]. The feature *early and sustained insufflation* is particularly pronounced at pressure-controlled ventilation that yields a rapidly decelerating inspiratory flow. This probably explains why pressure-controlled ventilation yields higher PaO_2 than volume-controlled ventilation with constant inspiratory flow at similar I/E ratios (Fig. 1).

Role of mean airway pressure (MAP) on arterial oxygenation

The mean airway pressure has been asserted to be the factor determining the effect of IPPV in RDS [9,10, 22]. The PaO_2 values from the animals in Figure 5a plotted against mean airway pressure (Fig. 5b) give no support for assuming a simple relationship between mean airway pressure and PaO_2 at volume-controlled ventilation.

The data show that, at volume-controlled ventilation, a closer relationship exists

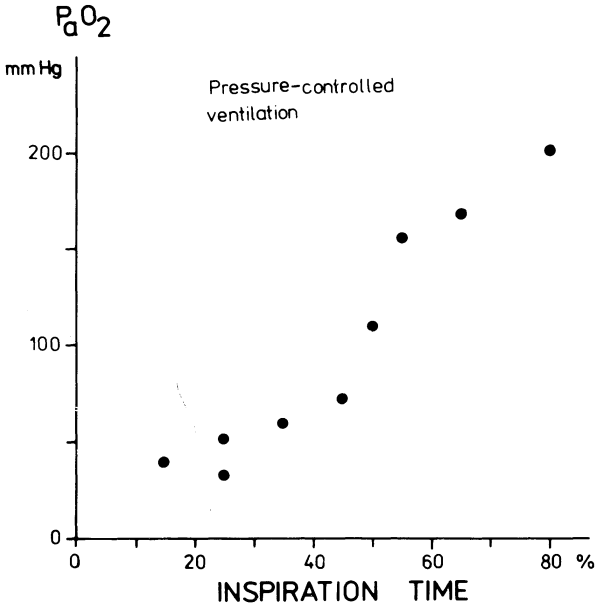

Figure 6. Blood gases from two rabbits (average) ventilated with pressure-controlled ventilation at varying duration of inspiration. From Lachmann et al. [35].

between the degree of oxygenation and post-inspiratory pause, rather than between the degree of oxygenation and mean airway pressure.

At pressure-controlled ventilation, a prolongation of inspiration from 15%–80% of the cycle led to a nearly linear improvement of PaO_2 (Fig. 6). In pressure-controlled ventilation at a constant frequency, a nearly linear relationship between I/E ratio and mean airway pressure exists. The ensuing close relationship between mean airway pressure and the degree of oxygenation at pressure-controlled ventilation [22] must not be regarded as causal. When frequency is changed – and MAP is constant – it is also obvious at pressure-controlled ventilation that there is no direct relationship between MAP and oxygenation (Fig. 7a).

The influence of frequency and inspiration time on gas exchange

During pressure-controlled ventilation, the PaO_2 was highest at frequencies of 30–50/min. The greatest dependency of frequency on PaO_2 was seen at a duration of inspira-

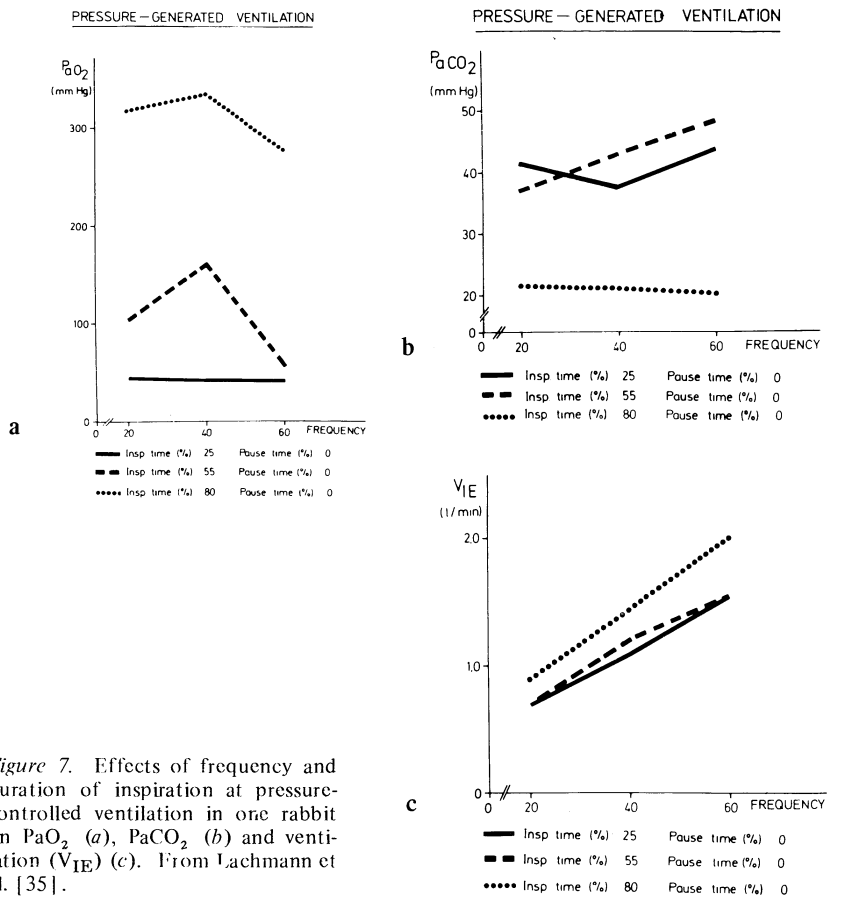

Figure 7. Effects of frequency and duration of inspiration at pressure-controlled ventilation in one rabbit on PaO_2 (*a*), $PaCO_2$ (*b*) and ventilation (V_{IE}) (*c*). From Lachmann et al. [35].

tion just high enough to raise PaO_2 to a level which signifies complete arterial oxygen saturation (Fig. 7a).

The lower PaO_2 observed at the lowest frequencies is interpreted as a tendency towards closure of lung units that occurs when the expiration is of too long duration. The effect of relative duration of inspiration and expiration is thus modified by a dependency of absolute duration of the ventilatory phases. It is noteworthy that there is no simple relationship between tidal volumes and minute ventilation on the one hand, and PaO_2 and $PaCO_2$ on the other. At a given duration of inspiration, some fluctuations in $PaCO_2$ with varying frequency were the opposite of those that could be expected from changes in minute ventilation (Figs. 7b and 7c).

At volume-controlled ventilation, increasing frequencies led to a more and more inadequate gas exchange, even if the beneficial pattern of 50% insufflation and 30% pause was applied (Fig. 8a).

The smaller tidal volumes at higher frequencies were associated with a peak airway pressure of about 23 cm H_2O at 60 breaths per minute compared to 36 cm H_2O at a frequency of 20 (Fig. 8b).

If inspiratory airway pressures were too low, as they were at high frequencies, it was not possible to adequately maintain PaO_2 at any pattern of volume-controlled ventilation. The insufflation must obviously produce an adequate opening pressure in lung units. An efficient ventilation in RDS is thus characterized by early and sustained insufflation at a precisely controlled airway pressure and by a proper frequency. This mode of ventilation is proposed as ideal for treatment of severe RDS.

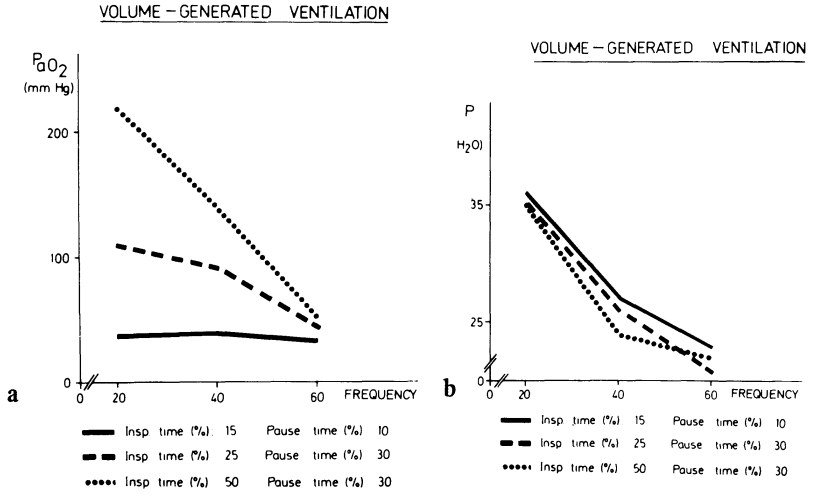

Figure 8. Effects of frequency and characteristics of inspiratory pattern at volume-controlled ventilation on PaO_2 (*a*) and insufflation pressure (P) (*b*) in one rabbit. From Lachmann et al. [35].

Long inspiration time versus PEEP ventilation

On the basis of the favourable results at pressure-controlled ventilation with an inspiratory time of 80%, it must be asked which advantages this ventilation pattern

has over other ventilation patterns that have successfully been clinically applied in connection with PEEP [2, 20, 49, 52, 54, 74, 76].

The investigation on the rabbit model [35] showed that at pressure-controlled ventilation and an I/E ratio of 1:2 in combination with a PEEP of 16 cm H_2O, an oxygenation could be reached similar to that at an I/E ratio of 4:1 with a PEEP of zero. PEEP had in those experiments the disadvantage in comparison with a high I/E ratio that ventilation decreased to less than 50% and $PaCO_2$ increased to very high values (> 90 mm Hg). Also, at volume-controlled ventilation, PaO_2 could effectively be increased with PEEP. The drawback of PEEP was then that very high insufflation pressures were needed. These pressures led to pneumothorax in most cases.

The results in the previous rabbit experiments were confirmed by findings in 12 beagles with severe RDS. In these experiments, we compared a high I/E ratio with PEEP not only in regard to gas exchange and airway pressure, but also to haemodynamics. A PEEP of 5 cm H_2O at volume-controlled ventilation efficiently produced adequate oxygenation if 50% insufflation and 30% pause were used (Fig. 9). At 25% insufflation plus 10% pause, not even a PEEP as high as 15 cm H_2O produced as high PaO_2 as that at 50% insufflation plus 30% pause and a PEEP of 5 cm H_2O did. High values of PEEP were at volume-controlled ventilation associated high peak airway pressures (Fig. 10).

Insufflation pressure at pressure-controlled ventilation was 27–30 cm H_2O. It was kept constant in each animal when PEEP and duration of insufflation were varied. When inspiratory time was 80%, PaO_2 was high even without PEEP (Fig. 9). Further

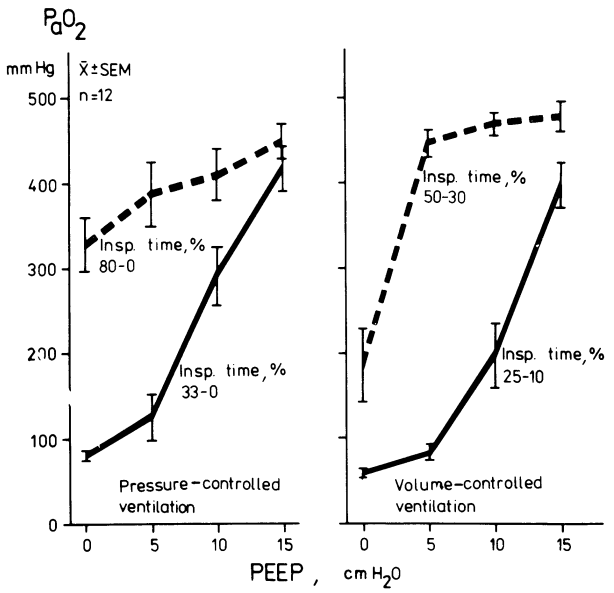

Figure 9. Effects of PEEP and inspiration time at pressure- and at volume-controlled ventilation on PaO_2. Same animals as in Figure 1.

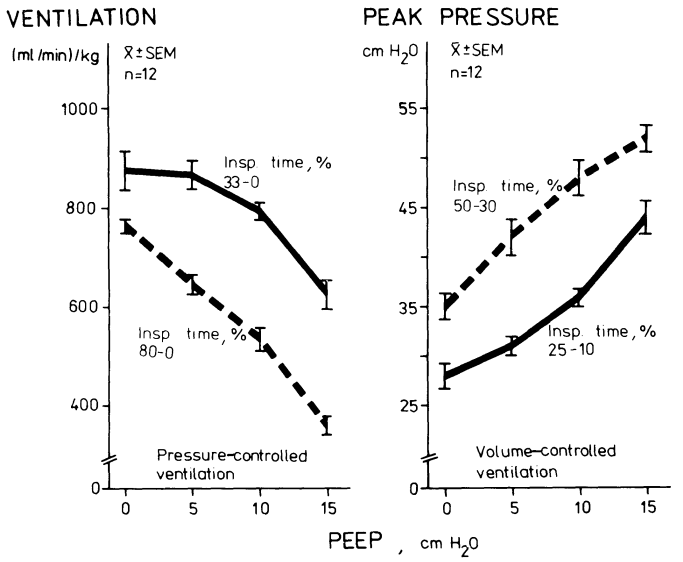

Figure 10. The drawbacks of PEEP at pressure-controlled ventilation and at volume-controlled ventilation are illustrated to the left and right, respectively. At pressure-controlled ventilation, ventilation decreases with PEEP. At volume-controlled ventilation, peak airway pressures increase with PEEP. Same animals as in Figure 1.

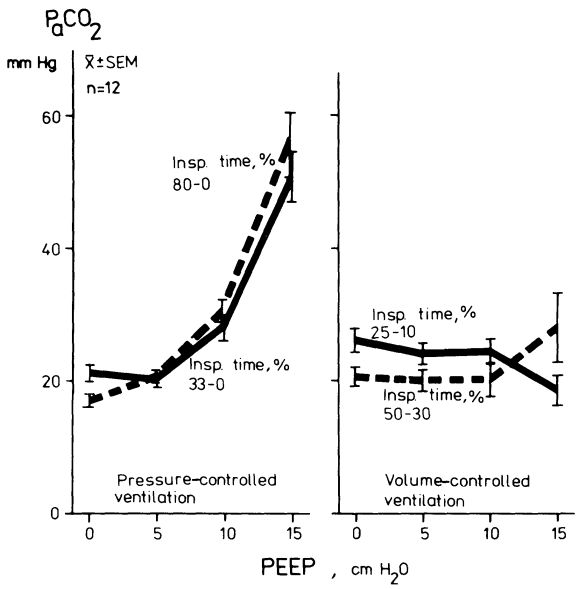

Figure 11. Effects of PEEP and inspiration time at pressure- and at volume-controlled ventilation on $PaCO_2$. Same animals as in Figure 1.

slight increases in PaO_2 were seen when PEEP was present. When PEEP was 10 cm H_2O or higher at pressure-generated ventilation, CO_2 retention was caused by reduced ventilation (Fig. 10). When duration of inspiration was as short as 33%, a higher PEEP was needed to maintain oxygenation. This advantage of PEEP was won at the expense of severe CO_2 retention (Fig. 11) caused by hypoventilation.

Starting from the PaO_2 tension at pressure-controlled ventilation with an I/E ratio of 4:1 and a PEEP of zero, and searching for other ventilation patterns which

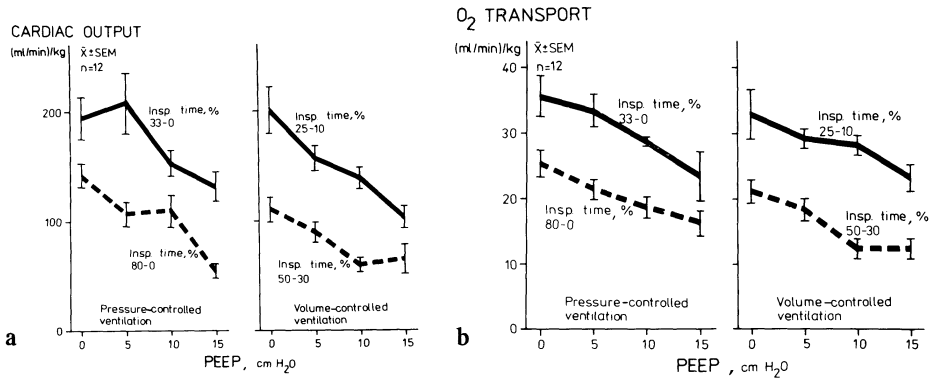

Figure 12. Effects of PEEP and inspiration time at pressure- and at volume-controlled ventilation on cardiac output (*a*) and O_2 transport (*b*). Same 12 dogs as in Figure 1.

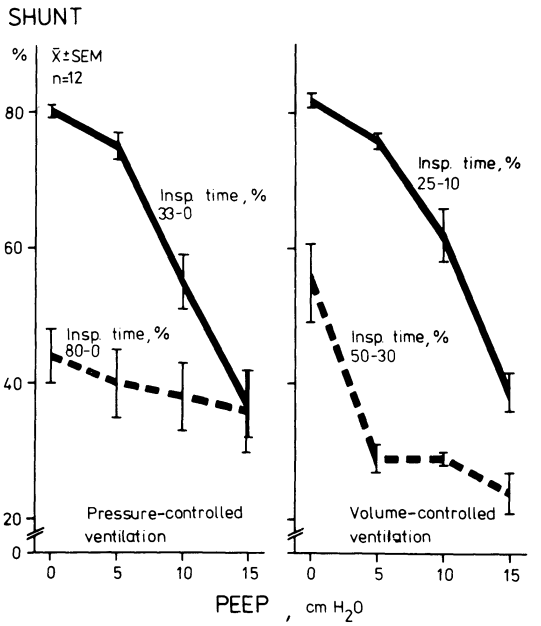

Figure 13. Effects of PEEP and inspiration time at pressure- and at volume-controlled ventilation on intrapulmonary shunt. Same animals as in Figure 1.

produce the same degree of oxygenation (Fig. 9), all such patterns led to a lower cardiac output (Fig. 12a) and a lower oxygen transport (Fig. 12b). The improvement in oxygenation and the decreased intrapulmonary shunt (Fig. 13), from the use of a high I/E ratio and PEEP and at pressure-controlled ventilation, are probably due to prevention of closure of lung units during the expiratory part of the breathing cycle. Of the two manoeuvres, increasing I/E ratio is the more efficient one, probably because the opening pressure of large parts of the lungs is beyond the reach of a practicable PEEP in the severe case of surfactant deficiency [73]. Though the results at pressure-controlled ventilation show that the use of a long inspiratory phase and PEEP acted synergistically to reduce the alveolar-arterial O_2 gradient and to improve PaO_2, the usefulness of PEEP is limited by the reduction of alveolar ventilation (Fig. 10). This has already been shown by Hermann and Reynolds [22], who studied infants with IRDS under artificial ventilation.

Influence of insufflation pressure on lung lesions

Few investigations have been presented on the influence of ventilation on the severe morphological damages which occur at ARDS [43]. Most of the authors believe that these lung damages are caused by the numerous influences that lead to ARDS [6, 7, 40, 66]. Experimental investigations have shown that intermittent positive pressure ventilation (IPPV) can induce lung lesions, including emphysema, interstitial fibrosis and obliterative bronchiolitis with squamous metaplasia that are equivalent to those seen in patients who develop bronchopulmonary dysplasia after ARDS [47] (for a review, see Nilsson [45]). The severity of such lung lesions is clearly correlated to the peak pressure level used during the period of artificial ventilation [78].

These results are in accordance with the studies in adult rabbits with RDS showing that the morphological damages are due to insufflation pressure [35]. We recently studied the influence of insufflation pressure and of the I/E ratio on lung morphology in two groups of beagles with severe ARDS produced by lung lavage. One group of dogs was ventilated between and during lung lavage with an I/E ratio of 1:2 and the other one with 4:1. During the ventilation period of 8 h, ventilation pressure was adjusted so that PaO_2 was 80–130 mm Hg. We applied a PEEP of 5–10 cm H_2O if a peak pressure higher than 40 cm H_2O was necessary, and a PEEP of 15 cm H_2O was used when peak pressure higher than 50 cm H_2O was needed.

In the group of dogs ventilated with an I/E ratio of 4:1, a peak pressure of 20 cm H_2O was sufficient to maintain an adequate gas exchange. In the group of dogs ventilated with an I/E ratio of 1:2, airway pressures twice as high had to be used to produce the same degree of oxygenation (Table 2).

The lungs of the latter dogs were predominantly atelectatic. They had a pronounced degree of desquamation of bronchiolar epithelium and massive intra-alveolar oedema, signs of inflammation and hyaline membranes (Fig. 14a). In the group of dogs ventilated with an I/E ratio of 4:1, the histological findings in the lungs after 8 h of artificial ventilation show well-expanded lungs with discrete signs of intra-alveolar oedema and only a low degree of inflammatory reaction (Fig. 14b).

This means that less damage was caused at pressure-controlled ventilation with 80% inspiration time than at 33%, when airway pressure was adjusted so as to give a

Table 2. Mean values ± standard deviations of peak insufflation pressure, PEEP, FIO_2, PaO_2, $PaCO_2$ and cardiac output as dependent on inspiration time at different time intervals after lung lavage during pressure-controlled ventilation; number of dogs in each group = 5

Time after lung lavage (h)	Inspiration time (%)	Peak pressure cm H_2O	PEEP cm H_2O	FIO_2	PaO_2 mm Hg	$PaCO_2$ mm Hg	Cardiac output (ml/min)/kg
0.5	33	42±3	8±3	1.0±0	137± 74	17.8± 6.5	173±56
	80	19±1	2	0.8±0.2	234±107	41.2±10.3	132±20
3	33	40±5	6±2	1.0±0	89±24	19.9±9.0	98±28
	80	20±2	0	0.7±0.3	124±11	44.2±11.1	114±61
7	33	47±4	8±5	1.0±0	94±14	18.6±4.3	76±28
	80	20±2	0	0.6±0.3	111±30	43.0±5.4	120±53

Table 3. Mean values ± standard deviations of O_2 transport, ventilation, alveolar ventilation, compliance and lung lesions index (LLI) in relation to inspiration time at different time intervals after lung lavage during pressure-controlled ventilation; from the same animals as in Table 2

Time after lung lavage (h)	Inspiration time (%)	O_2 transport (ml/min)/kg	Ventilation (l/min)/kg	Alveolar ventilation (l/min)/kg	Compliance (ml/cm H_2O)/kg	LLI
0.5	33	30.0±11.1	1.49±0.49	1.07±0.47	1.3±0.2	3.3±1.9
	80	25.1± 5.0	0.64±0.11	0.34±0.07	1.2±0.2	15.2±3.4
3	33	20.0± 4.2	1.39±0.47	0.99±0.44	1.2±0.3	2.2±0.6
	80	24.0±11.7	0.57±0.08	0.30±0.08	1.1±0.2	13.0±5.2
7	33	18.0± 5.0	1.54±0.44	1.09±0.42	1.2±0.3	2.2±0.4
	80	23.5± 7.2	0.62±0.13	0.31±0.08	1.0±0.2	11.7±6.2

similar PaO_2. This is probably not only due to a lesser degree of trauma because of lower peak pressures, but also to the fact that prolongation of inspiration results in more stable and even expansion of various lung units. The shear forces accompanying non-homogeneous expansion of lungs can be considerable [23]. Such forces may well be a major reason for structural damage, especially to the bronchiolar epithelium, as is typical for RDS, and they may form the basis for the formation of hyaline membranes [44–46, 78]. Potentially damaging shear forces will appear in the zone between open and closed compartments within the lungs and may be particularly important when closure and opening of lung units occur during each breathing cycle [24]. The ventilatory support at RDS should thus subtly open up closed units and keep them stable, but should avoid local or general hyperinflation.

Because high peak pressure and high FIO_2 during artificial ventilation lead to functional and morphological changes in the lung [43, 47, 58, 78], we propose using a so-called lung lesion index (LLI) [PaO_2 (FIO_2 × peak pressure)] containing these two risk factors.

In animals which could be ventilated with lower insufflation pressure, the index

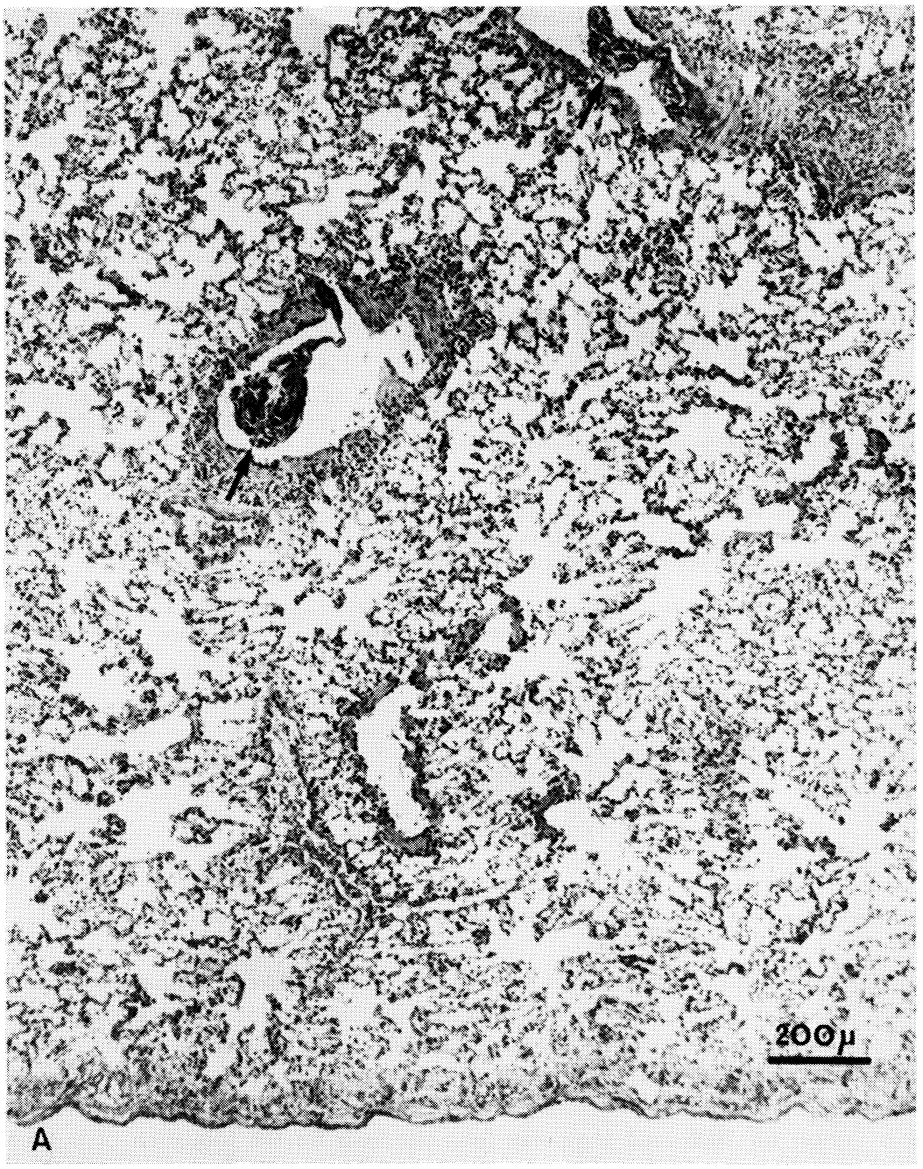

Figure 14a. Typical histological lung section from a dog ventilated with high insufflation pressure (44 cm H_2O) and I/E ratio of 1:2 for 8 h after lung lavage. There is widespread atelectasis, prominent desquamation of bronchiolar epithelium (arrows), oedema, inflammation and hyaline membranes.

was always higher than 10, whereas in the other group it never exceeded 4 within 8 h after lung lavage (Table 3). To keep the morphological and functional changes of the lung as small as possible during artificial ventilation, the index should be higher than 4.

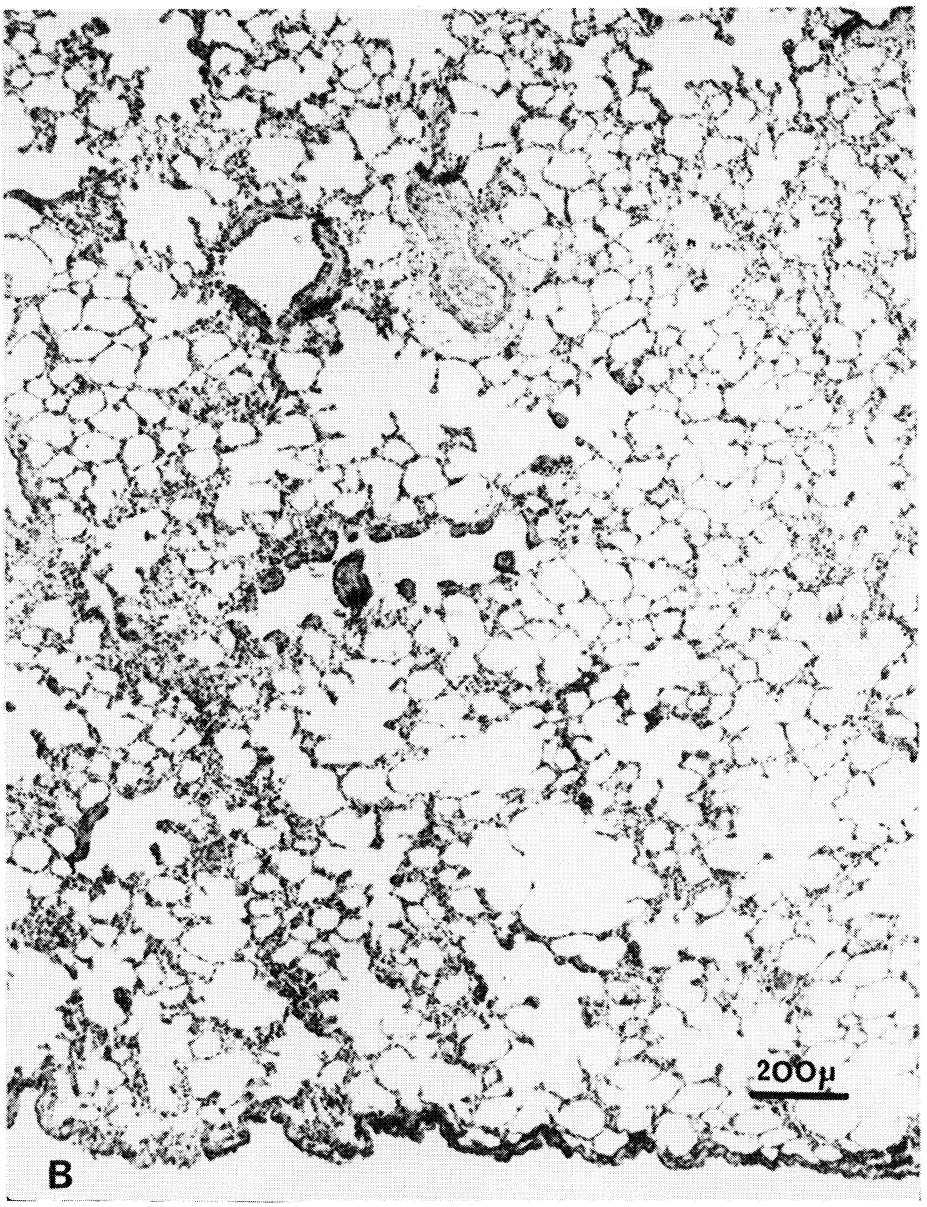

Figure 14b. Lung section from a dog ventilated with low insufflation pressure (20 cm H_2O) and prolonged inspiration phase 8 h after lung lavage. Nearly normally aerated lung parenchyma with only minor intra-alveolar oedema and slight inflammatory reaction. Hematoxylin-eosin, x 50.

First results by pressure-controlled ventilation with an I/E ratio of 4:1 in ARDS patients

Six patients who could not be sufficiently ventilated by common ventilation patterns, including PEEP and a FIO_2 of 1, were exposed to pressure-controlled ventilation with

decelerating flow and an I/E ratio of 4:1. Three of them had such severe damage to the lung parenchyma with gas leakage that PEEP pressure higher than 4–8 cm H_2O could not be administered. In two patients, PEEP higher than 12–16 cm H_2O had no influence on oxygenation. In one patient with myocardial re-infarction, a PEEP higher than 8 cm H_2O led to acute cardiac failure. Before the special ventilation pattern was started, all of the patients were ventilated with volume-controlled ventilation with an I/E ratio of 1:2 or 1:1. An FIO_2 of 1 had been used for an average of 72 h.

When the pattern of ventilation was changed to pressure-controlled ventilation with

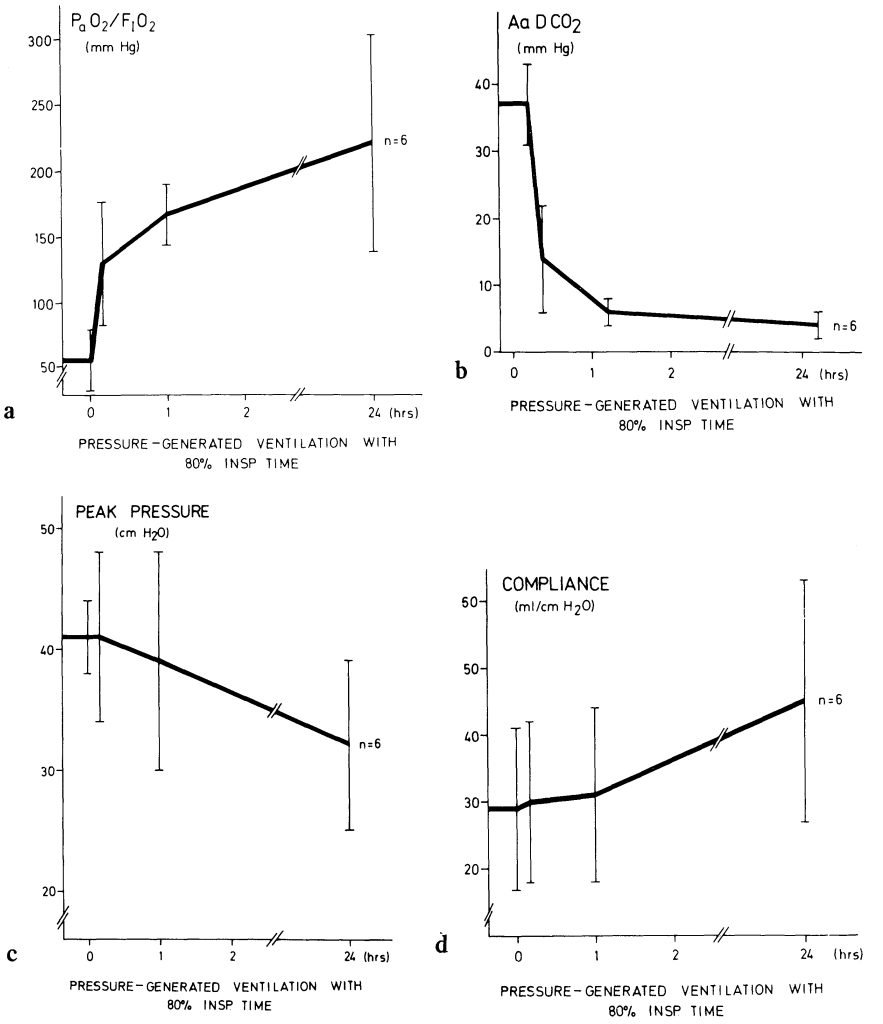

Figure 15. Course of the quotient PaO_2/FIO_2 (*a*), arterial–end-expiratory CO_2 gradient ($AaDCO_2$) (*b*), peak airway pressure (*c*) and compliance (*d*) in six patients with most severe ARDS after a change of ventilator therapy from volume-controlled ventilation with I/E ratio of 1:2 or 1:1 to pressure-controlled ventilation with an I/E ratio of 4:1.

an I/E ratio of 4:1, a significant increase in PaO_2 from an average of 55 mm Hg to 130 mm Hg was observed in 10 min. One hour later, PaO_2 has increased to about 170 mm Hg (Fig. 15a). Despite lowering of the ventilation pressure (Fig. 15c), the arterial oxygenation further increased during the following 23 h. FIO_2 could simultaneously be reduced from 1 to 0.65. The arterial–end-expiratory CO_2 gradient was about 40 mm Hg before starting the special ventilation. Normalization to 4 mm Hg could be observed within 24 h (Fig. 15b). The thorax-lung compliance improved very little within the first hour, but showed a significant improvement after 24 h (Fig. 15d).

The drastic improvement of the gas exchange and general status of the patient after application of pressure-controlled ventilation with an I/E ratio of 4:1 is further demonstrated in three out of six patients who had very severe respiratory insufficiency.

Case reports

Case 1

A 35-year-old man had a traffic accident and very severe trauma of the thorax and lungs, combined with shock. He was admitted to the intensive care unit, ICU. During volume-controlled ventilation, the chest x-ray showed only a few ventilated lung areas (Fig. 16a). Minute ventilation was 14 ℓ of pure oxygen. PEEP higher than 8 cm H_2O could not be applied because of the large lung parenchyma defects. Arterial oxygen tension was between 30 and 40 mm Hg, and $PaCO_2$ varied between 75 and 91 mm Hg under these conditions. After 10 min of pressure-controlled ventilation with an I/E ratio of 4:1 and a lower peak pressure than before, PaO_2 had increased to a value twice as high as earlier, and $PaCO_2$ was only 46 mm Hg. Arterial oxygenation, CO_2 elimination and compliance improved despite further lowering of peak pressure (Fig. 17). After three days with this breathing pattern, the arterial–end-expiratory Co_2 gradient was nearly zero, indicating that substantial disturbances of ventilation perfusion and of diffusion no longer existed. Chest x-ray after four days was nearly normal (Fig. 16b).

Case 2

A 54-year-old woman suffering from myocardial re-infarction had massive lung congestion (Fig. 18a). She was treated with volume-generated ventilation with pure oxygen and a PEEP of 4 cm H_2O. Gas exchange deteriorated. Severe hypoxaemia and respiratory acidosis contributed to cardiocirculatory shock. After implementation of pressure-controlled ventilation with an I/E ratio of 4:1, oxygenation improved very quickly (Fig. 19a).

It was then considered alarming that central venous pressure increased to about 20 mm Hg and mean pulmonary artery pressure to more than 35 mm Hg. An I/E ratio of 1:2 was therefore re-initiated. Indices of shock worsened and arterial blood gases deteriorated again dramatically. It was then determined that the only possibility

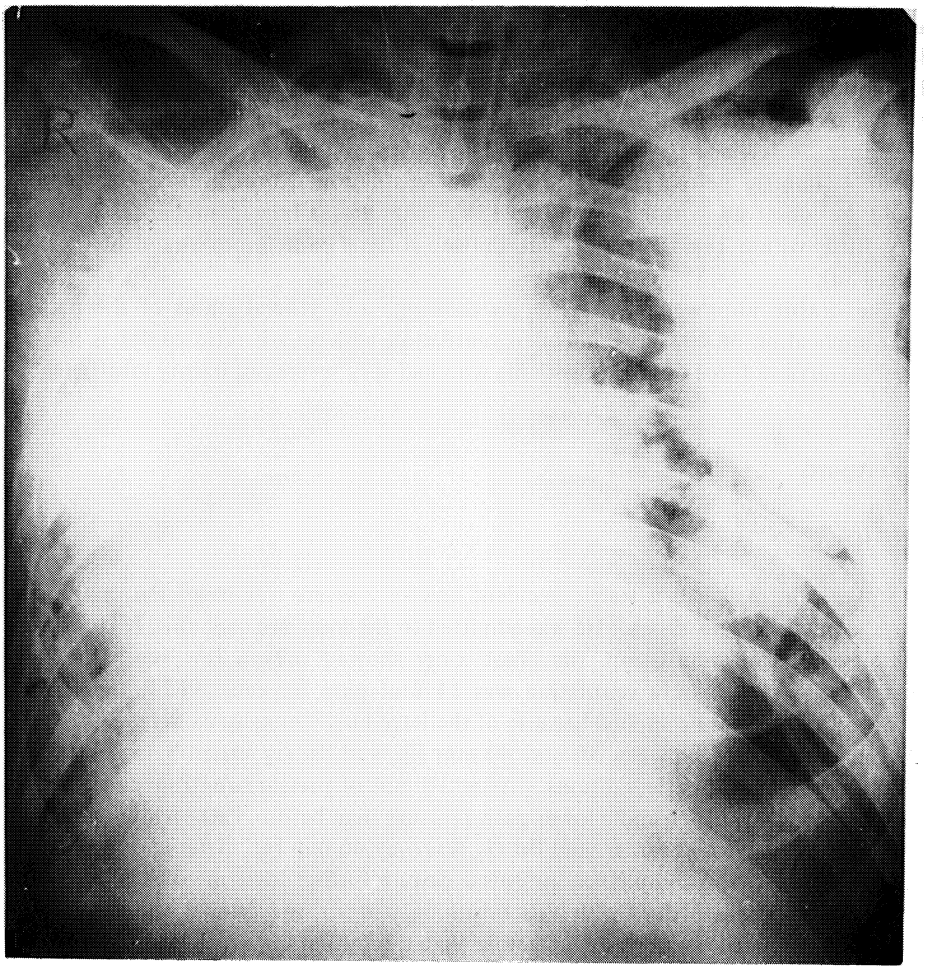

Figure 16a. Chest x-ray of a 35-year-old man 10 h after blunt trauma of the thorax; artificial ventilation with an I/E ratio of 1:2.

was to apply an I/E ratio of 4:1 and accept high central venous and pulmonary artery pressures. Arterial oxygenation increased with about 100 mm Hg in 30 min, systemic blood pressure improved and signs of circulatory shock ceased. Within the next 24 h, further improvement of gas-exchange and circulatory parameters occurred (Fig. 19). Inspiratory time could be reduced to 70% and on the second day to 60%. The functional improvement of the lung corresponded to changes of chest x-ray (Fig. 18b). The patient could be transferred to the medical clinic in good condition a fortnight later.

Case 3

A 30-year-old woman with post-operative complications was admitted to the ICU. She

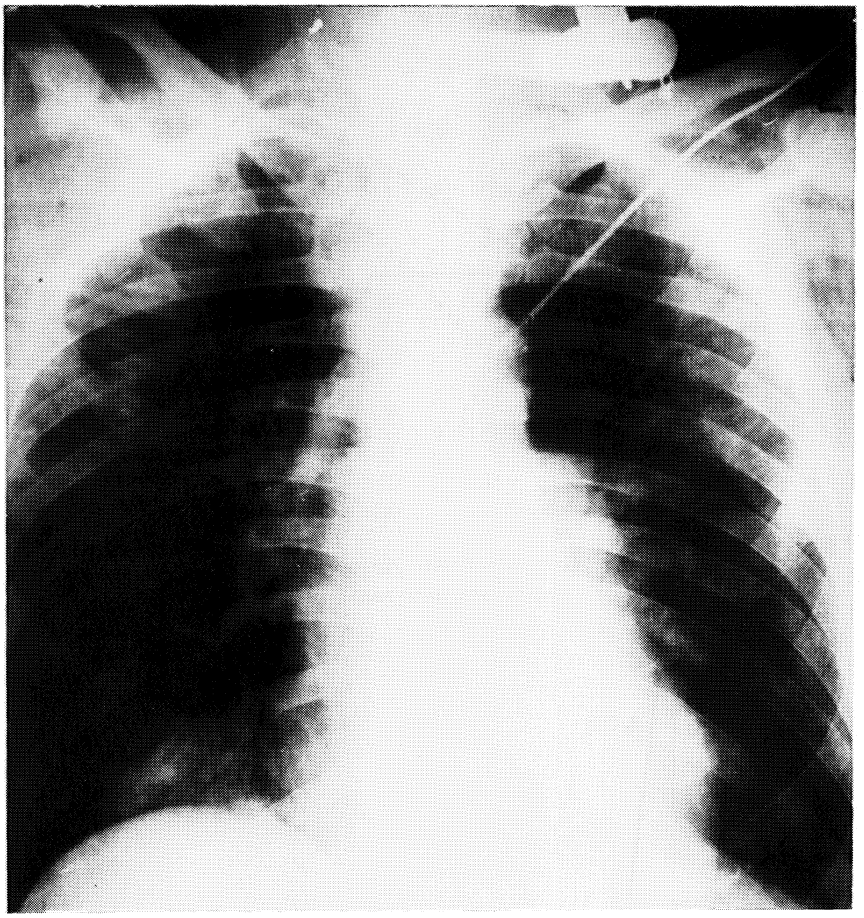

Figure 16b. Chest x-ray of the same patient after four days of pressure-controlled ventilation with an I/E ratio of 4 :1.

had severe bilateral pneumonia and had already been ventilated for about two weeks. She had developed a septicaemia and got a pneumothorax which was treated with thoracic drainage (Fig. 20a). Ventilation was volume-controlled with a minute volume of 12 ℓ of pure oxygen. PEEP was 4–8 cm H_2O and the I/E ratio 1:2. Peak pressure during inspiration increased to about 50 cm H_2O. The lengthening of inspiration time during pressure-controlled ventilation was performed step by step in this patient. Only application of an I/E ratio of 4:1 led to an improvement of oxygenation and CO_2 elimination (Fig. 21). The improvement of the chest x-ray also indicated successful aeration of the lungs (Fig. 20b). The patient was ventilated about five days without any further functional improvements. She then died from septicaemia, but not due to respiratory insufficiency. Septic metastases were found in the brain and in the kidneys. The right side of the heart showed no changes due to artificial ventilation.

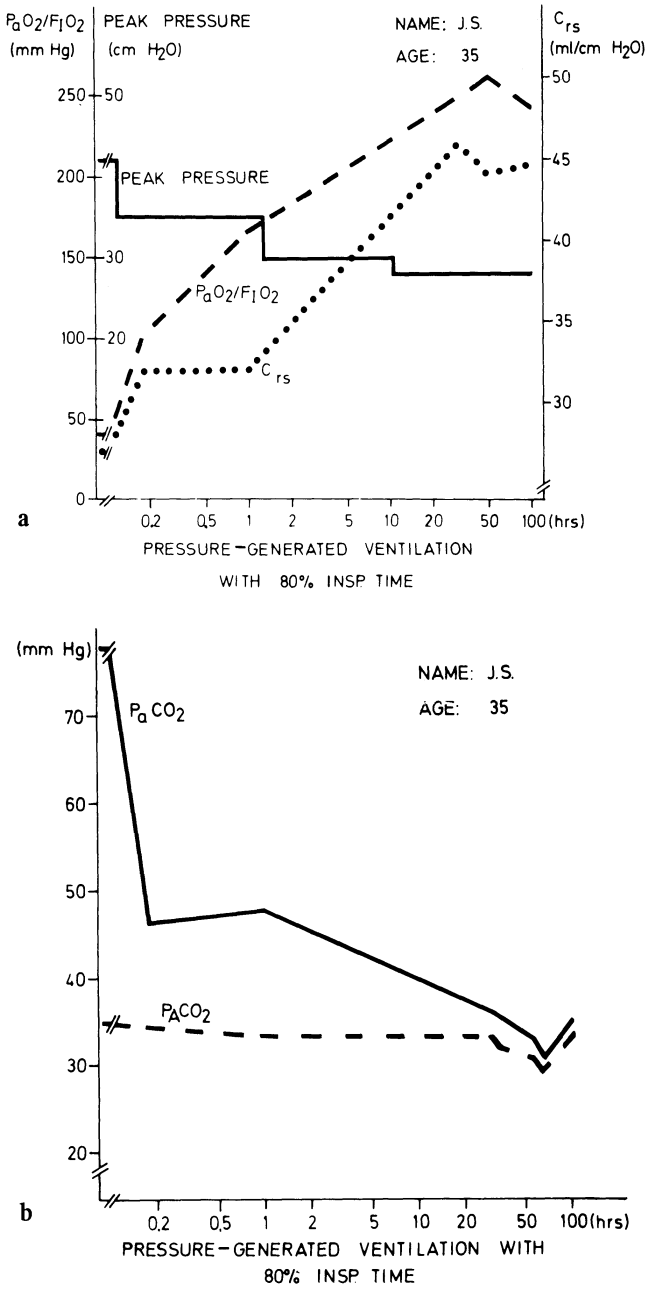

Figure 17. Evaluation of peak insufflation pressure, compliance and PaO_2/FIO_2 (*a*) and at end-expiratory $PACO_2$ and $PaCO_2$ (*b*) at pressure-controlled ventilation with an I/E ratio of 4:1 in the same patient as in Figure 16. Note the logarithmic time scale. Ventilator setting before starting pressure-controlled ventilation: minute volume = 14 ℓ; peak pressure = 42 cm H_2O; PEEP = 8–10 cm H_2O; FIO_2 = 1.

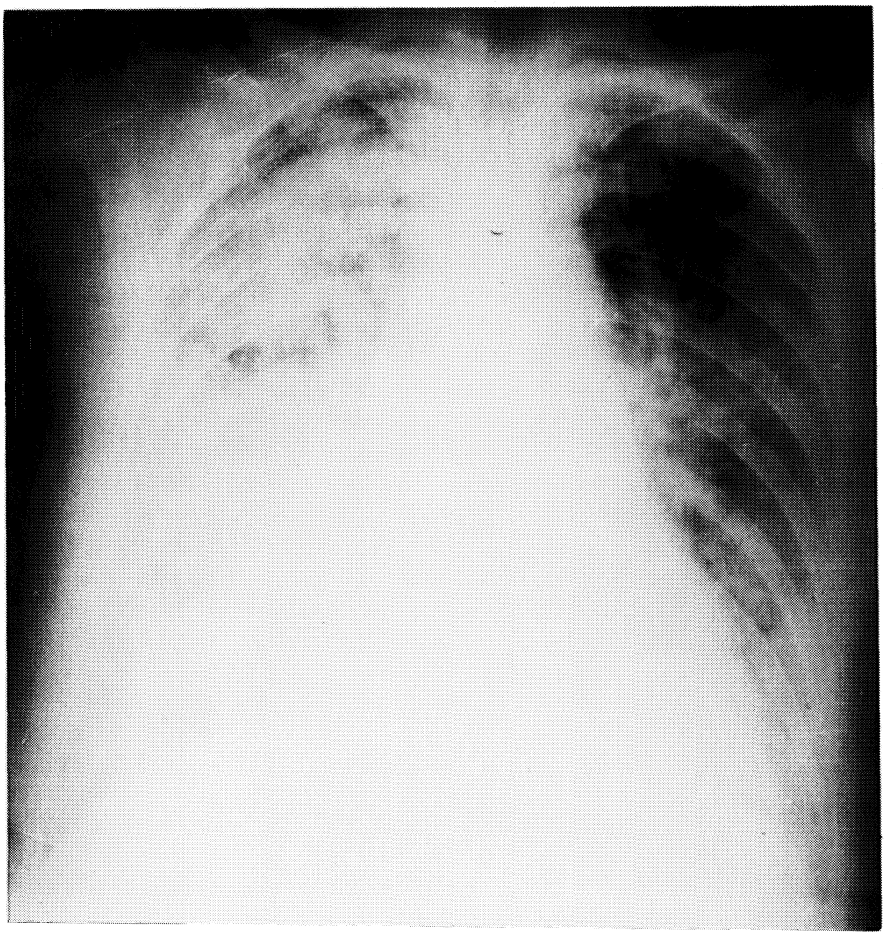

Figure 18a. Chest x-ray of a 54-year-old woman with myocardial re-infarction and massive lung congestion during volume-controlled ventilation with an I/E ratio of 1:2.

Pressure-controlled ventilation with long inspiration time

Considering the impressive experimental and clinical results by application of pressure-controlled ventilation with a high I/E ratio in acute severe respiratory failure, it seems that this form of ventilation therapy is superior to others. For an optimal ventilation, this ventilation pattern requires (Fig. 22):

1) One must overcome a critical opening pressure during inspiration.
2) This opening pressure must be maintained for a sufficiently long period of time.
3) During expiration, no critical time that would allow closure of lung units should pass.

The critical opening pressure is necessary to overcome forces related to surface tension,

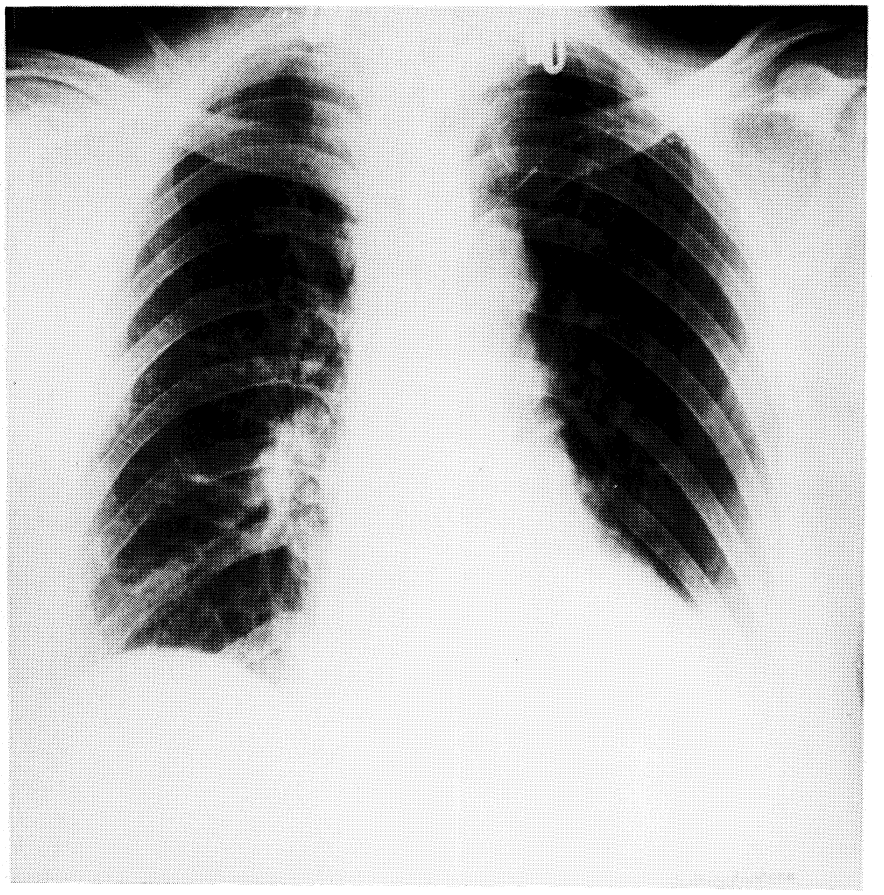

Figure 18b. Chest radiograph of the same patient after four days of pressure-controlled ventilation.

e.g. adhesive forces of collapsed alveoli and terminal bronchioli, and capillary forces in the small fluid-filled airways, so that air can reach the alveoli. The height of the critical opening pressure is a function of the content of surface-active phospholipids in the lungs of patients with ARDS. A varying content of surface-active material in different lung areas could also explain the apparent paradox that a large shunt can exist even with high PEEP and with a pressure which exceeds critical opening pressure. Some lung units then have a strong tendency to collapse when expiration is too long and/or when the counterpressure induced by PEEP is not high enough to prevent collapses in these regions.

A sufficiently long application of the critical opening pressure is necessary to ventilate all alveoli despite different retraction forces in the airways. An intrapulmonary pressure that balances closing pressure must be maintained for most of the respiratory cycle. Even a slightly lower pressure will lead to collapse of lung units and to an increase of the intrapulmonary shunt. This was illustrated in 12 dogs with ARDS

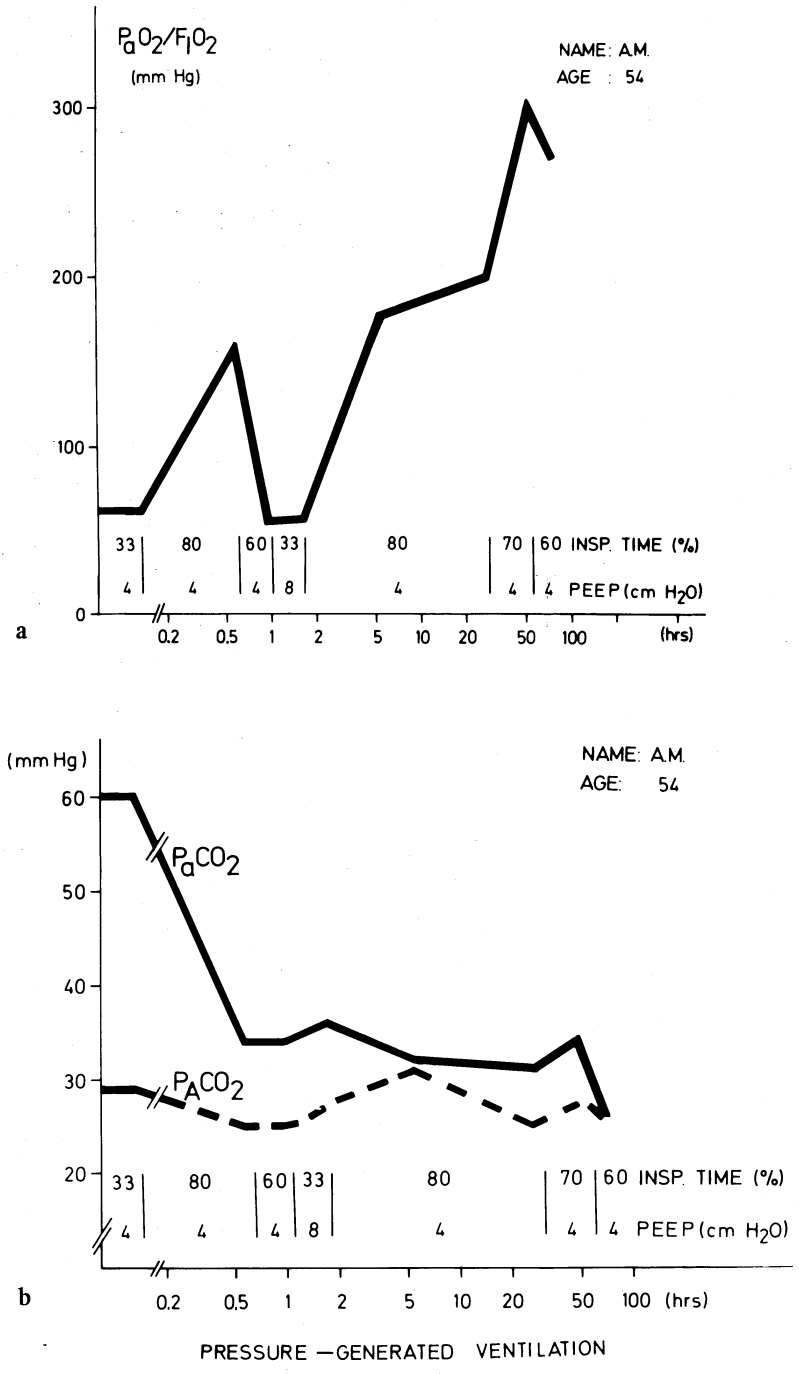

Figure 19. Course of the PaO_2/FIO_2 (*a*) and of $PACO_2$ and $PaCO_2$ (*b*) from the same patient as in Figure 18 after initiation of pressure-controlled ventilation. Note the logarithmic time scale.

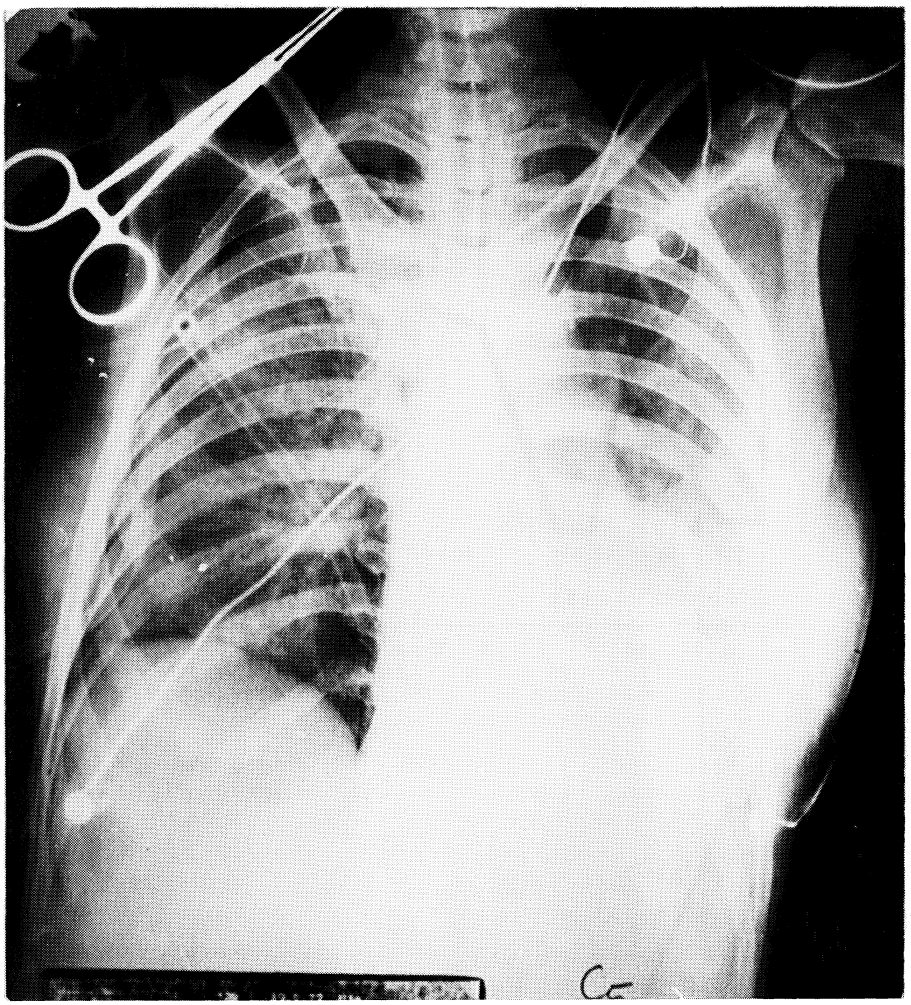

Figure 20a. Chest radiograph of a 30-year-old woman with bilateral pneumonia and bronchopulmonary fistulae after 14 days of volume-controlled ventilation with an I/E ratio of 1:2.

ventilated with pressure-generated ventilation. Each dog was ventilated with two patterns at two frequencies with only a slight difference. In one pattern, the controlled pressure was applied during the whole inspiratory phase. In the other, insufflation was followed by a pause during which both inspiratory and expiratory lines of the ventilator were shut. Such a pause allows some stress relaxation to occur – particularly at low frequencies when each phase is longer. Although the airway pressure never fell more than 3 cm H_2O during the pause, this fall was sufficient to cause a pronounced drop of PaO_2 at the lower frequency (Fig. 23). This reflects a delicate balance between closing and opening forces acting within the terminal lung units with surfactant deficiency.

The expiration should ideally be interrupted as soon as the expiratory flow has

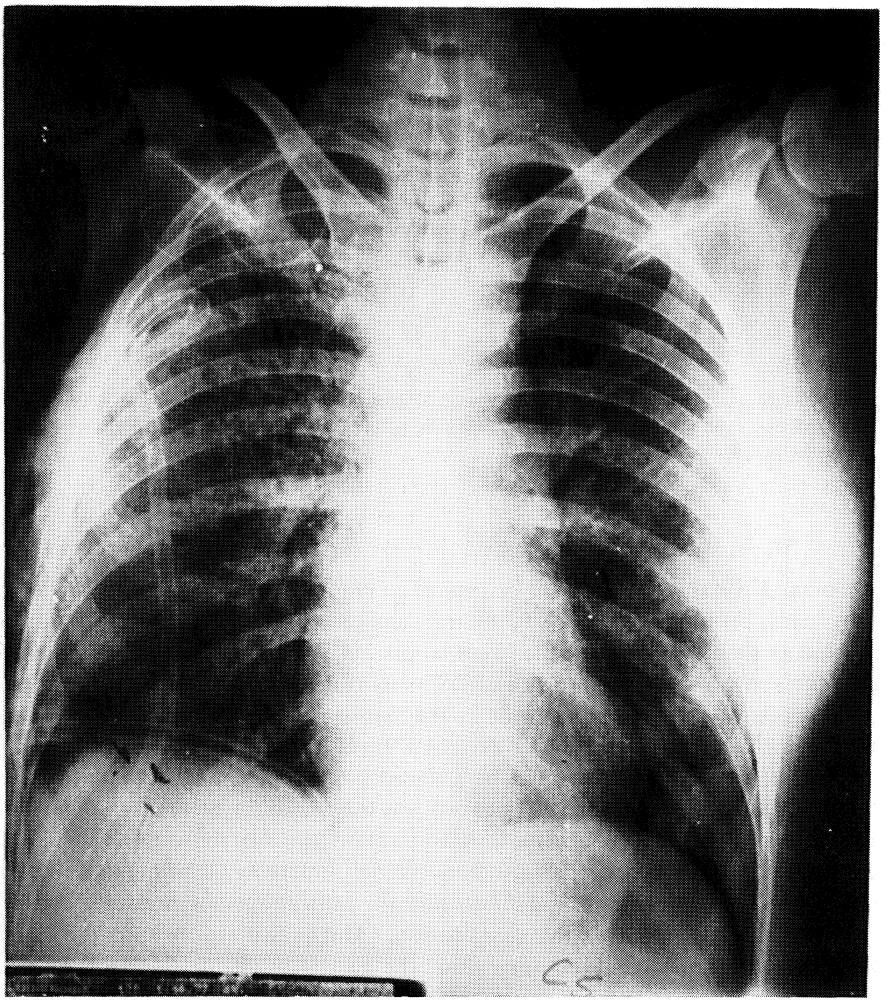

Figure 20b. Chest radiograph from the same patient after four days of pressure-controlled ventilation.

fallen to low values. Monitoring of expiratory flow at the airway opening may be valuable in this regard. It is, however, possible that some units have collapsed even before the total flow has ceased. It may be so that PEEP has a value as an adjuvant to the high I/E ratio at severe RDS, particularly when very short pulmonary time constants warrant higher frequencies than 20/min.

Indications for pressure-controlled ventilation with an I/E ratio of 4:1

The most important clinical consideration here is that in therapy of the most severe forms of respiratory distress syndrome, pressure-controlled ventilation with decelerating

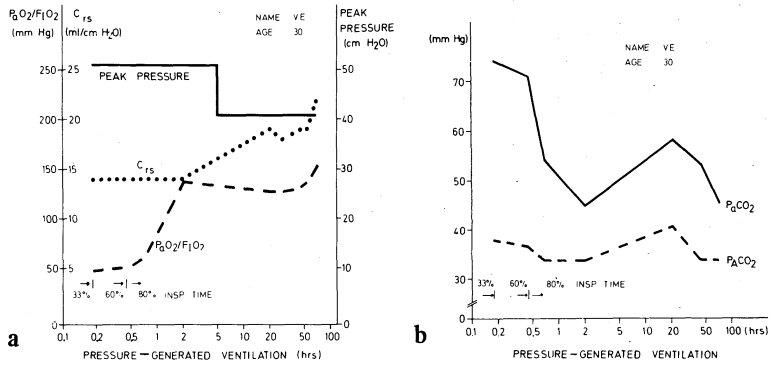

Figure 21. Course of PaO_2/FIO_2 peak airway pressure, and compliance (*a*) and of $PaCO_2$ and $PACO_2$ (*b*) from the same patient as in Figure 20 during pressure-controlled ventilation. Note the logarithmic time scale.

flow and an I/E ratio of 4:1 should be applied to improve gas exchange. This ventilator setting leads, furthermore, to less structural damage and less marked cardiorespiratory impairments then volume-controlled ventilation and PEEP. We therefore propose the use of the above ventilator pattern in RDS patients if the PaO_2/FIO_2 is below 80 mm Hg and peak pressure at volume-controlled ventilation with an I/E ratio of 1:1 is higher than 35 cm H_2O, and if PEEP exceeds 8 cm H_2O.

When the necessary PEEP cannot be attained in some patients due to grave defects in the lung parenchyma leading to excessive gas leakage to the pleural space, pressure-controlled ventilation with a very long inspiration time is the only possibility of maintaining the gas exchange. Very frequent or, preferably, continuous control of the arterial blood gases must be done to find the critical opening pressure that leads to a sudden improvement of the oxygenation. This pressure differs in each case of RDS. By monitoring the expiratory flow, the special frequency must be found at which this flow has not quite fallen to zero at the end of expiration. If this frequency is higher than 20/min, a PEEP of 5–10 cm H_2O should be applied.

When a clear improvement of gas exchange has occurred, the intensity of treatment is lowered by first reducing the inspiratory pressure. Pressure constitutes the most important aetiologic factor in severe lung damage, in our opinion. FIO_2 is reduced later on.

Inspiratory time should be shortened when the airway pressure is to an undue degree transmitted to the capillary bed. This situation is recognized when there has been a considerable improvement of the compliance, increased mean pulmonary artery pressure and a decrease of the pressure gradient between airways and oesophagus.

Our present knowledge and experience give no grounds for proposing any other form of therapy in intermediate stages of ARDS than those accounted for in the literature. Certain evidence found in the following text gives, however, hypothetical support for assuming that patients in danger of developing severe RDS may benefit from ventilation with a prolonged inspiration in order to prevent further deterioration.

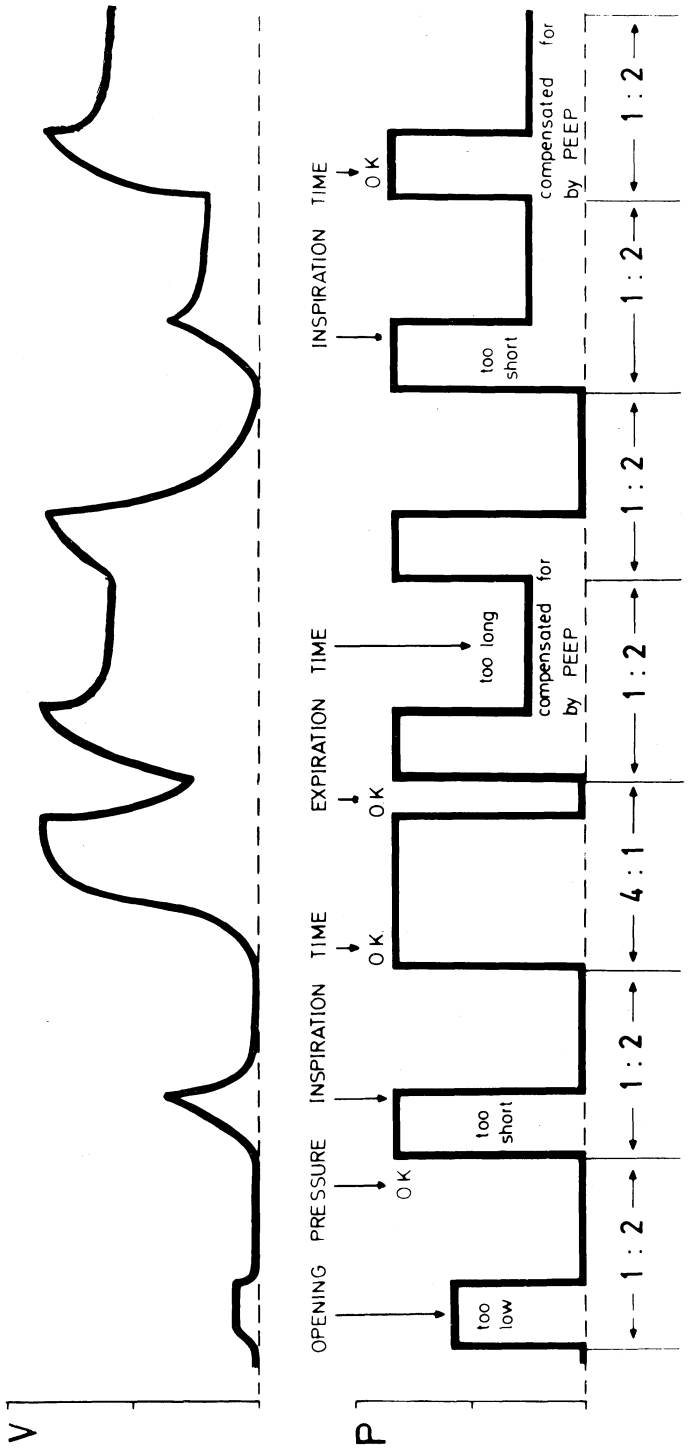

Figure 22. Schematic diagram showing tidal volume (V) during pressure-generated ventilation of surfactant-deficient lungs, in relation to variations in insufflation pressure (P), PEEP, and I/E ratio. Alveolar collapse can be prevented, and arterial oxygenation improved, by application of high I/E ratio or PEEP. Treatment with high PEEP, however, implies a reduction of tidal volume and a consequent risk of respiratory acidosis. From Lachmann [33].

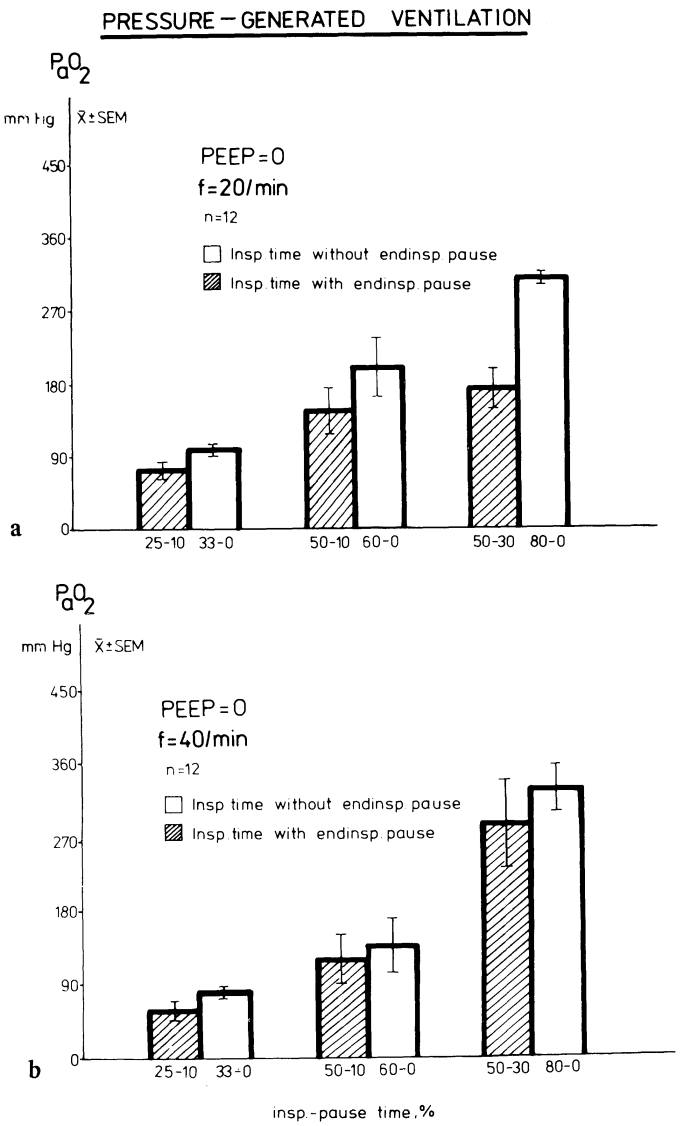

Figure 23. Mean values and standard errors of mean PaO_2 during pressure-controlled ventilation with a frequency of 20 (*a*) and of 40 (*b*) per minute dependent on inspiratory time and post-inspiratory pause in 12 beagles. Note the high difference of 150 mm Hg in PaO_2 between inspiration time of 50% and pause time of 30% in contrast to 80% inspiration time without pause at a frequency of 20/min (*a*). During pause time, intrapulmonary pressure fell only by 2–3 cm H_2O.

High-frequency ventilation in the treatment of ARDS

It is not possible to ascertain at present what importance, if any, very high frequencies can have in the treatment of the most severe forms of ARDS. Striking evidence has

been presented as to its effectiveness for improving the gas exchange in healthy or only slightly damaged lungs [8, 27, 70]. Similar benefit for the ventilation of ARDS patients has not been documented in the literature. Preliminary, as yet unpublished studies that we have carried out with an oscillation technique (frequencies from 5 to 20 Hz) confirm the results of other centres in regard to healthy lungs. Positive results were not, however, obtained in advanced stages of ARDS, in which adequate oxygenation requires a CPAP higher than 20 cm H_2O to sufficiently eliminate CO_2 with this technique.

Prophylaxis of ARDS by early ventilator therapy

Several authors [6, 82] have reported that patients first thought to be in danger of developing ARDS have not done so if they were at an early stage ventilated with IPPV and PEEP. These measures thus seem indicated for all cases of polytrauma.

The clinical results obtained by Wolff [82] are very impressive. In 250 cases of polytrauma, only seven succumbed from respiratory insufficiency caused by ARDS. Consequent application of ventilation has shown that ARDS can in some cases be prevented. This form of therapy probably prevents the start of the vicious circle of permeability disturbance of the alveolor-capillary membrane, surfactant inactivation, surfactant wash-out into the bloodstream, decrease of functional residual capacity and compliance, inhibition of the production of new surfactants by hypoxia and acidosis, etc. It can thus be assumed to prevent damage of the surfactant system, which plays such an important role in the pathogenesis of ARDS [5, 12, 33, 51, 53, 58].

This hypothesis was tested in a series of dogs after inducing a surfactant deficiency by bronchial lavage. The dogs were divided into two groups. One group was ventilated prior to lavage with an I/E ratio of 4:1 and the other group with an I/E ratio of 1:2. Both groups received pressure-controlled ventilation using FIO_2 of 1. Ventilation pressure was increased when arterial oxygenation fell below 70 mm Hg after lung lavage.

The group ventilated with an I/E ratio of 4:1 showed only a small decrease of oxygen tension that was dependent on the number of lavages given (Fig. 24a). Other cardiocirculatory parameters that were studied also showed only slight deterioration due to the number of lavages given.

The animals with an I/E ratio of 1:2 had decreased arterial oxygenation of about 300 mm Hg already at the first lavage. The ventilation pressure (Fig. 24b) had to be raised after each lavage in order to prevent excessive hypoxaemia. Lung lavages in this group also led to a higher decrease in compliance, cardiac output and oxygen transport.

It can be assumed that the progress of functional lung impairment due to disturbances in the surfactant system can be compensated for by use of the ventilation pattern described above, which gives the lung a chance to maintain its normal function.

These findings and earlier clinical results [6, 82] have convinced us that there are strong indications for artificial ventilation with PEEP or with a long inspiratory time in patients with acute respiratory failure following severe trauma, extensive shock,

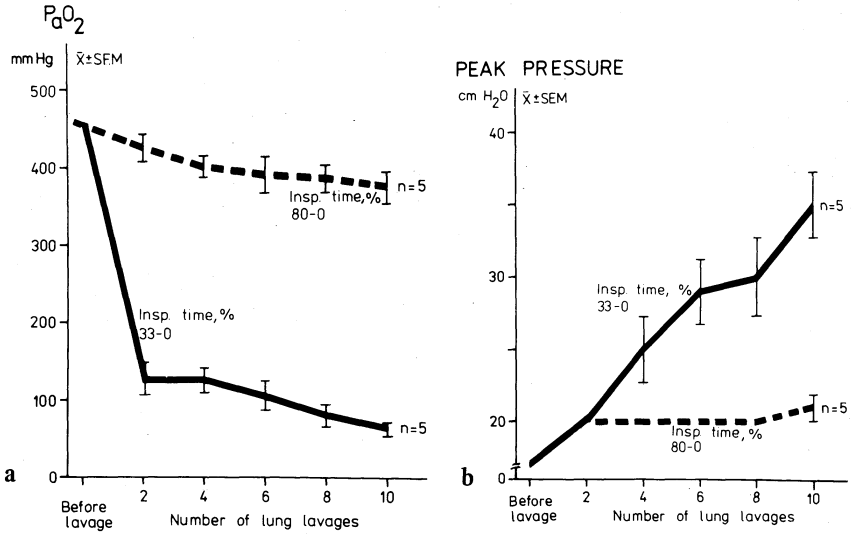

Figure 24. Course of PaO_2 (*a*) and peak insufflation pressure (*b*) at pressure-controlled ventilation in relation to the number of lung lavages at different durations of inspiration.

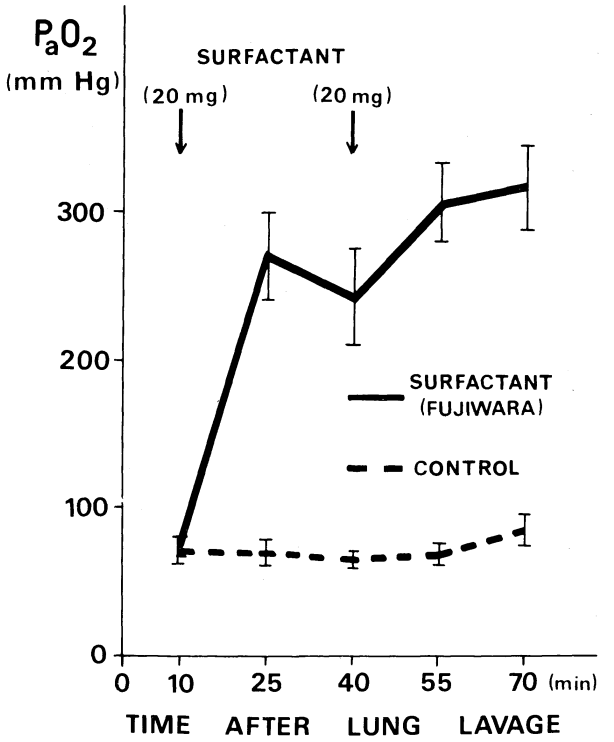

Figure 25. Behavior of PaO_2 in adult guinea pigs with severe RDS after tracheal instillation of surfactant in comparison to controls. Animals were ventilated under pressure control with pure oxygen, an I/E ratio of 1:1, a frequency 20/min, an insufflation pressure 28 cm H_2O, and a PEEP of 5 cm H_2O. From Lachmann et al. [32].

burns, etc., especially during the latent period and even when functional lung parameters at this early stage do not seem to require artificial ventilation. CPAP may be a rational alternative at an early stage of RDS.

Since the progressive formation of atelectasis in RDS is believed to be due to altered surfactant function, another feasible approach to prophylaxis and therapy in RDS might be the introduction of surfactant into the lungs. Extensive experimental investigations in immature new-born animals have shown that tracheal instillation of surfactant improves lung compliance, gas exchange, enhances aeration of the alveolar compartment, prevents the development of lesions of bronchiolar epithelium and enables ventilation of the lungs with an insufflation pressure and ventilator settings normally used for ventilating healthy lungs (for a review see Robertson [64, 65]).

These experimental findings have been confirmed by the first clinical results in new-born infants [17]. It was therefore attempted to improve gas exchange even in full-grown animals with severe respiratory insufficiency by tracheal instillation of surface-active phospholipids [32]. The instillation of surfactant produced a striking improvement in oxygenation in comparison with the controls (Fig. 25). This was confirmed at autopsy – the lungs of the controls were liver-like in appearance, but the lungs of the animals given surfactant were well aerated. These finding support the hypothesis that the surfactant system is an important factor in the pathogenesis of RDS. The authors therefore draw the conclusion that surfactant instillation can be of value for the treatment of ARDS.

References

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE: Acute respiratory distress in adults. Lancet 2:319–323, 1967.
2. Ashbaugh DG, Petty TL, Bigelow DB, Harris TM: Continuous positive-pressure breathing (CPPB) in adult respiratory distress syndrome. J Thorac Cardiovasc Surg 57:31–41, 1969.
3. Ashbaugh DG: Acute respiratory failure after surgery or trauma. In: Petty TL (ed) Respiratory care, 2nd edn. Philadelphia: Lea and Febiger, 1974, pp 190–204.
4. Baum M, Benzer H, Mutz N, Pauser G, Tonczar L: Inversed ratio ventilation (IRV). Die Rolle des Atemzeitverhältnisses in der Beatmung beim ARDS. Anaesthetist 29:592–596, 1980.
5. Benzer H, Coraim F, Mutz N, Geyer A, Pauser G: Probleme der "Respiratorischen" Beatmung bei der Schocklunge. In: Mayrhofer-Krammel O, Schlag G, Stoeckel H (eds) Acute respiratory failure Stuttgart: Georg-Thieme-Verlag, 1979, pp 263–270.
6. Blaisdell FW, Lewis FR Jr: Respiratory distress syndrome of shock and trauma: post-traumatic respiratory failure. In: Ebert PA (ed) Major problems in clinical surgery. Philadelphia: WB Saunders, 1977, pp 28–132.
7. Bleyl U: Die Histophysiologie und Histopathologie der terminalen Lungenstrombahn bei akutem Lungenversagen. In: Ahnefeld FW, Bergmann H, Burri C, Dick W, Halmagyi M, Hossli G, Rugheimer E (eds) Akutes Lungenversagen. Berlin: Springer-Verlag, 1979, pp 1–13.
8. Bohn DJ, Miyasaka K, Marchak BE, Thompson WK, Froese AB, Bryan AC: Ventilation by high-frequency oscillation. J Appl Physiol (Respir Environ Exerc Physiol) 48:710–716, 1980.
9. Boros SJ, Matalon SV, Ewald R, Leonard AS, Hunt CE: The effect of independent variations in inspiratory-expiratory ratio and end-expiratory pressure during mechanical ventilation in hyaline membrane disease: the significance of mean airway pressure. J Pediatr 91:794–798, 1977.
10. Boros SJ: Variations in inspiratory: expiratory ratio and airway pressure wave form during mechanical ventilation: the significance of mean airway pressure. J Pediatr 94:114–117, 1979.
11. Burchardi H: Verteilungsstörungen bei Langzeitbeatmung. In: Wiemers K, Scholler KL (eds) Lungenveränderungen bei Langzeitbeatmung. International symposium, Freiburg, 1971. Stuttgart: Georg-Thieme-Verlag, 1973, pp 100–105.

12. Büsing CM, Bleyl U, Rüfer R: Correlation between plasma proteins and surfactants. In: Wichert PV (ed) Progress in respiration research. Clinical importance of surfactant defects. Basel: S Karger, 1981, pp 224–233.
13. Douglas MME, Downs JB: Pulmonary function following severe acute respiratory failure and high levels of positive end-expiratory pressure. Chest 71:18–23, 1977.
14. Downs JB, Klein EF Jr, Desautels D, Modell JH, Kirby RR: Intermittent mandatory ventilation: a new approach to weaning patients from mechanical ventilators. Chest 64:331–335, 1973.
15. Downs JB. Douglas ME, Sanfelippo PM, Stanford W, Hodges MR: Ventilatory pattern, intrapleural pressure and cardiac output. Anesth Analg 56:88–94, 1977.
16. Fairley HB, Blenkarn GD: Effect of pulmonary gas exchange of variations in inspiratory flow rate during intermittent positive pressure ventilation. Br J Anaesth 38:320–328, 1966.
17. Fujiwara T, Chida S, Watabe Y, Maeta H, Morita T, Abe T: Artificial surfactant therapy in hyaline membrane disease. Lancet 1:55–59, 1980.
18. Fuleihan SF, Wilson RS, Pontoppidan H: Effect of mechanical ventilation with end-inspiratory pause on blood-gas exchange. Anesth Analg 55:122–130, 1976.
19. Gattinoui L, Pesenti A, Rossi GP, Vesconi S, Fox U, Kolobow T, Agostini A, Pelizzola A, Langer M, Uziel L, Longoni F, Damia G: Treatment of acute respiratory failure with low-frequency positive-pressure ventilation and extracorporeal removal of CO_2. Lancet 2:292–294, 1980.
20. Gilston A: The effects of PEEP on arterial oxygenation: an examination of some possible mechanisms. Intensive Care Med 3:267–271, 1977.
21. Gregory GA, Kitterman JA, Phibbs RH, Tooley WH, Hamilton WK: Treatment of the idiopathic respiratory distress syndrome with continuous positive airway pressure. N Engl J Med 284:1333–1340, 1971.
22. Herman S, Reynolds EOR: Methods for improving oxygenation in infants mechanically ventilated for severe hyaline membrane disease. Arch Dis Child 48:612–617, 1973.
23. Hughes JMB, Hoppin FG, Mead J: Effect of lung inflation on bronchial length and diameter in excised lungs. J Appl Physiol 32:25–35, 1972.
24. Jonson B: Positive airway pressure – some physical and biological effects. This book, ch 8.
25. Jonson B, Ahlström H, Lindroth M, Svenningsen NW: Continuous positive airway pressure: modes of action in relation to clinical applications. Pediatr Clin North Am 27:687–699, 1980.
26. Kirby RR, Downs JB, Civetta JM, Modell JH, Dannemiller FJ, Klein EF, Hodges M: High level positive end-expiratory pressure (PEEP) in acute respiratory insufficiency. Chest 67: 156–163, 1975.
27. Klain M, Smith RB: High frequency percutaneous transtracheal jet ventilation. Crit Care Med 5:280–287, 1977.
28. Knelson JH, Howatt WF, DeMuth GR: Effect of respiratory pattern on alveolar gas exchange. J Appl Physiol 29:328–331, 1970.
29. Kolobow T, Solca M, Gattioni L, Pesenti A: Adult respiratory distress syndrome (ARDS): why did ECMO fail? Int J Artificial Organs 4:58–59, 1981.
30. Kumar A, Falke KJ, Geffin B, Aldredge CF, Laver MB, Lowenstein E, Pontoppidan H: Continuous positive-pressure ventilation in acute respiratory failure. Effects on hemodynamics and lung function. N Engl J Med 283:1430–1436, 1970.
31. Lachmann B, Robertson B, Vogel J: In vivo lung lavage as an experimental model of the respiratory distress syndrome. Acta Anaesthesiol Scand 24:231–236, 1980.
32. Lachmann B, Fujiwara T, Chida S, Morita T, Konishi M, Nakamura K, Maeta H: Improved gas exchange after tracheal instillation of surfactant in the experimental adult respiratory distress syndrome [abstr]. Crit Care Med 9:158, 1981.
33. Lachmann B: The role of lung surfactant in etiology, pathogenesis and therapy of acute respiratory distress syndrome in newborn infants and adults. Eur J Respir Dis [Suppl 113] 62:123–125, 1981.
34. Lachmann B, Grossmann G, Freyse J, Robertson B: Lung-thorax compliance in the artificially ventilated premature rabbit neonate in relation to variations in inspiration/expiration ratio. Pediatr Res 15:833–838, 1981.
35. Lachmann B, Jonson B, Lindroth M, Robertson B: Modes of artificial ventilation in severe respiratory distress syndrome. Lung function and morphology studied in rabbits after washout of alveolar surfactant. Crit Care Med (in press).
36. Lamy M: Management of ventilatory supports in adult respiratory distress syndrome (ARDS). In: Mayrhofer-Krammel O, Schlag G, Stoeckel H (eds) Acute respiratory failure. Stuttgart: Georg-Thieme-Verlag, 1979, pp 245–255.

37. Lawin P, Scherer R: Beatmung. In: Lawin P (ed) Praxis der Intensivbehandlung, 4. Aufl. Stuttgart: Georg-Thieme-Verlag, 1981, pp 16.1–16.39.
38. Luce JM, Pierson DJ, Hudson LD: Intermittent mandatory ventilation. Chest 79:678–685, 1981.
39. Manginello FP, Grassi AE, Schechner S, Krauss AN, Auld PAM: Evaluation of methods of assisted ventilation in hyaline membrane disease. Arch Dis Child 53:878–881, 1978.
40. Mittermayer Ch, Riede UN, McEwan JR: Pathologisch-anatomische Untersuchungen der Schocklunge. II. Spätschäden und Irreversibilität. In: Mayrhofer-Krammel O, Schlag G, Stoeckel H (eds) Acute respiratory failure. Stuttgart: Georg-Thieme-Verlag, 1979, pp 163–170.
41. Modell HI, Cheney FW: Effects of inspiratory flow pattern on gas exchange in normal and abnormal lungs. J Appl Physiol (Respir Environ Exerc Physiol) 46:1103–1107, 1979.
42. Murray JF: Mechanism of acute respiratory failure, conference report. Am Rev Respir Dis 115:1071–1078, 1977.
43. Nash G, Blennerhassett JB, Pontoppidan H: Pulmonary lesions associated with oxygen therapy and artificial ventilation. N Engl J Med 276:368–374, 1967.
44. Nilsson R, Grossmann G, Robertson B: Bronchiolar epithelial lesions induced in the premature rabbit neonate by short periods of artificial ventilation. Acta Pathol Microbiol Scand [A] 88:359–367, 1980.
45. Nilsson R: Artificial ventilation in the newborn rabbit. MD thesis, Karolinska Institute, Stockholm, Sweden, 1980.
46. Nilsson R, Grossmann G, Robertson B: Pathogenesis of neonatal lung lesions induced by artificial ventilation: evidence against the role of barotrauma. Respiration 40:218–225, 1980.
47. Northway WH, Rosan RC, Porter DY: Pulmonary disease following respirator therapy of hyaline-membrane disease. N Engl J Med 276:357–367, 1967.
48. Osswald PM, Hartung HJ, Klose R, Spier R: Die Wirkung von verlängerter Inspirationszeit und PEEP auf die Compliance und den Gasaustausch bei der mechanischen Ventilation. Anaesthetist 30:71–76, 1981.
49. Petty TL, Ashbaugh DG: The adult respiratory distress syndrome clinical features, factors influencing prognosis and principles of management. Chest 60:233–239, 1971.
50. Petty TL, Ashbaugh DG: The adult respiratory distress syndrome. In: Petty TL (ed) Respiratory care, 2nd edn. Philadelphia: Lea and Febiger, 1974, pp 205–222.
51. Petty TL, Reiss OK, Paul GW, Silvers GW, Elkins ND: Characteristics of pulmonary surfactant in adult respiratory distress syndrome associated with trauma and shock. Am Rev Respir Dis 115:531–536, 1977.
52. Petty TL, Newman JH: Adult respiratory distress syndrome. West J Med 128:399–407, 1978.
53. Petty TL, Silvers GW, Paul GW, Stanford RE: Abnormalities in lung elastic properties and surfactant function in adult respiratory distress syndrome. Chest 75:571–574, 1979.
54. Petty TL: Why (not) try PEEP? Crit Care Med 9:67–68, 1981.
55. Pontoppidan H, Geffin B, Lowenstein E: Acute respiratory failure. Part I. N Engl J Med 287:690–698, 1972.
56. Pontoppidan H, Geffin B, Lowenstein E: Acute respiratory failure. Part II. N Engl J Med 287:743–752, 1972.
57. Pontoppidan H, Geffin B, Lowenstein E: Acute respiratory failure in the adult. Part III. N Engl J Med 287:799–806, 1972.
58. Pontoppidan H, Geffin B, Lowenstein E: Acute respiratory failure in the adult. Boston: Little Brown and Co, 1973, pp 1–89.
59. Pontoppidan H, Wilson RS, Rie MA, Schneider RC: Respiratory intensive care. Anesthesiology 47:96–116, 1977.
60. Qvist J, Pontoppidan H, Wilson RS, Lowenstein E, Laver MB: Hemodynamic responses to mechanical ventilation with PEEP; the effect of hypervolemia. Anesthesiology 42:45–55, 1975.
61. Reynolds EOR: Effect of alterations in mechanical ventilator settings on pulmonary gas exchange in hyaline membrane disease. Arch Dis Child 46:152–159, 1971.
62. Reynolds EOR: Pressure waveform and ventilator settings for mechanical ventilation in severe hyaline membrane disease. Int Anesthesiol Clin 12:259–280, 1974.
63. Reynolds EOR, Taghizadeh A: Improved prognosis of infants mechanically ventilated for hyaline membrane disease. Arch Dis Child 49:505–515, 1974.
64. Robertson B: Surfactant substitution: experimental models and clinical applications. Lung 158:57–68, 1980.
65. Robertson B: Review of experimental hyaline membrane disease. Diagn Histopathol 4:49–60, 1981.

66. Safar P, Grenvik A, Smith J: Progressive pulmonary consolidation: review of cases and pathogenesis. J Trauma 12:955–967, 1972.
67. Schlimgen R: Die Bedeutung des endinspiratorischen Beatmungsplateaus von Respiratoren. Prakt Anaesth 12:505–510, 1977.
68. Shah DM, Newell JC, Dutton RE, Powers SR: Continuous positive airway pressure versus positive end-expiratory pressure in respiratory distress syndrome. J Thorac Cardiovasc Surg 74:557–562, 1977.
69. Shapiro BA: Airway pressure therapy for acute restrictive pulmonary pathology. In: Critical care, vol 2. State of the art. The Society of Critical Care Medicine, 1981, pp II C 1–53.
70. Sjöstrand U: High-frequency positive-pressure ventilation (HVPPV): a review. Crit Care Med 8:345–364, 1980.
71. Skoskiewicz MJ: Role of pulmonary transplantation in patients with acute respiratory failure. In: Zapol WM, Quist J (eds) Artificial lungs for acute respiratory failure. Washington: Hemisphere Publishing Corporation: distributed by Academic Press, 1976, pp 483–488.
72. Smith PC, Daily WJR: Mechanical ventilation of newborn infants, II. Effects of independent variation of rate and pressure on arterial oxygenation of infants with RDS. Anesthesiology 37:498–502, 1972.
73. Strang LB: Neonatal respiration – physiological and clinical studies. Oxford: Blackwell Scientific, 1977, pp 181–249.
74. Suter PM, Fairley HB, Isenberg MD: Optimum end-expiratory airway pressure in patients with acute pulmonary failure. N Engl J Med 292:284–289, 1975.
75. Suter P: Individuell adaptierter Einsatz verschiedener Beatmungsmethoden zur Therapie des akuten Lungenversagens. In: Ahnefeld FW, Bergmann H, Burri C, Dick W, Halmagyi M, Hossli G, Rügheimer E (eds) Akutes Lungenversagen. Berlin: Springer-Verlag, 1979, pp 113–119.
76. Suter PM: "Optimal" regulation of mechanical ventilation. Anaesthetist 29:163–164, 1980.
77. Suter PM: Respirator-Therapie. In: Peter K (ed) Akute respiratorische Insuffizienz. Berlin: Springer-Verlag, 1980, pp 94–97.
78. Taghizadeh A, Reynolds EOR: Pathogenesis of bronchopulmonary dysplasia following hyaline membrane disease. Am J Pathol 82:241–264, 1976.
79. Task Force Report on Problems Research Approaches Needs: The lung program. National Heart and Lung Institute, October 1972. Panel X: Respiratory distress syndrome. Washington: DHEW Publication no. (NIH) 73-432, pp 165–180.
80. Tyler DC, Cheyney FW: Comparison of positive end-expiratory pressure and inspiratory positive pressure plateau in ventilation of rabbits with experimental pulmonary edema. Anesth Analg 58:288–292, 1979.
81. Weinstein ME, Rice CL, Peters RM, Virgilio RW: Hemodynamic and respiratory response to varying gradients between end-expiratory pressure and end-inspiratory pressure in patients breathing on continuous positive airway pressure. J Trauma 18:231–235, 1978.
82. Wolff G: Was ist die akute respiratorische Insuffizienz? In: Peter K (ed) Akute respiratorische Insuffizienz. Berlin: Springer-Verlag, 1980, pp 21–59.
83. Zapol WM, Snider M, Hill JD: Extracorporeal membrane oxygenation in severe acute respiratory failure. JAMA 242:2193–2196, 1979.