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New strategies in mechanical ventilation for acute lung injury

H. Burchardi

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ABSTRACT: In the fluid-filled lungs of early adult respiratory distress syndrome (ARDS) the dependent parts are compressed and atelectatic; whereas, the nondependent areas remain aerated and functional. Ventilating these considerably restricted lungs carries the risk of overinflation and ventilatory-induced lung injury (baro-volutrauma).

The consequences for adjusting mechanical ventilation are: 1) reducing tidal volumes in order to avoid alveolar hyperinflation and excessive alveolar pressures; 2) considering permissive hypercapnia if adequate CO_2 elimination cannot be maintained; 3) keeping open the unstable alveoli by positive end-expiratory pressure (PEEP) (external or intrinsic). However, the large variations in regional lung compliance make it improbable that an optimal external PEEP level beneficial for the whole lung will be found; 4) using intrinsic PEEP in the inverse ratio ventilation (IRV) mode which varies with differences in regional ventilatory kinetics. No clinical study has yet convincingly demonstrated the benefit of IRV compared to conventional ventilation, controlled clinical long-term trials are not yet available; and 5) using superimposed spontaneous breathing which may be considerably more effective in opening up collapsed alveoli, combined with intentional intrinsic PEEP this is achieved in airway pressure release ventilation (APRV).

Other new principles of mechanical ventilation, such as "proportional assist ventilation" or "tracheal gas insufflation" must still be considered as experimental.
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Zentrum Anaesthesiologie, Rettungs- und Intensivmedizin, University Hospital, Göttingen, Germany.

Correspondence: H. Burchardi
Zentrum Anaesthesiologie
Rettungs- und Intensivmedizin
University Hospital
Rob.-Koch-Str. 40
D-37070 Göttingen
Germany

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Mechanical ventilation and ventilatory support techniques have undergone an impressive evolution within the last 10 yrs. This was due to considerable technical development rather than a radical change in our pathophysiological knowledge. Today, a variety of new techniques are available which facilitate new ventilatory strategies. In this review, only strategies for nonobstructive acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) will be presented and discussed. Strategies for chronic obstructive airways diseases (COPD) differ considerably; they will not be mentioned in this connection.

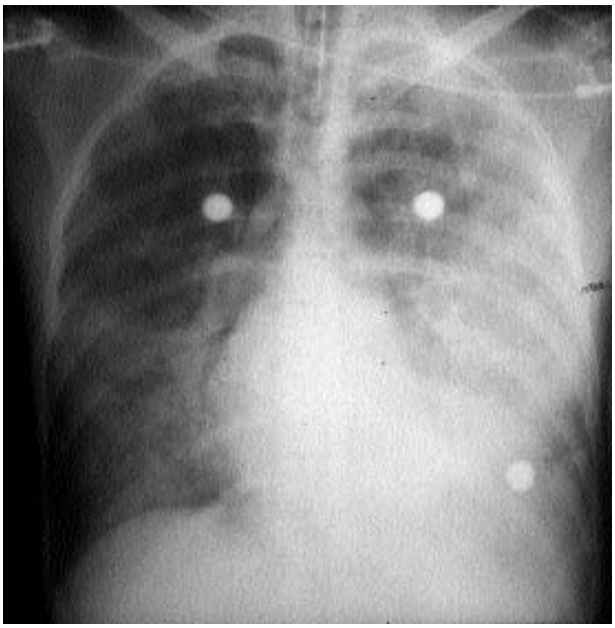
Pathophysiological basis

In ALI and ARDS, (the American-European Consensus Conference on ARDS [1] changed the former expression "adult respiratory distress syndrome" into "acute respiratory distress syndrome", since ARDS is not limited to adults), the hallmark is a critical increase of pulmonary membrane permeability. This can happen by two different pathways: directly by lesion of lung cells; and indirectly as the result of an acute systemic inflammatory reaction (cellular and humoral effects). This results in a bilateral pulmonary interstitial and intra-alveolar (noncardiogenic) oedema.

As a consequence, alveoli are compressed or flooded, and the surface for pulmonary gas exchange is considerably reduced by multiple atelectases. In this way, venous admixture and intrapulmonary shunt perfusion are increased and oxygenation is severely impaired. Pulmonary compliance is significantly reduced.

In general, this oedema was considered to be distributed more or less homogeneously all over both lungs. However, recent analyses of computed tomography (CT) scans [2, 3] reveal a rather inhomogeneous regional distribution (fig. 1). Under the gravitational influence of the fluid-filled lung tissue, alveoli are compressed particularly in the dependent parts, whereas aerated alveoli are found mainly in the nondependent areas. In severe cases, no more than one third of the alveoli may remain patent. Thus, at least in nonfibrotic stages, ARDS lungs are "small" rather than "stiff" lungs. For this condition, GATTINONI coined the term "baby lung". There is now evidence that pulmonary gas exchange function may remain more or less unaltered in the still aerated and ventilated areas of the lungs. In the aerated areas, gas exchange may be maintained if any additional impairment, such as alveolar hyperinflation, can be avoided. Regional alveolar hyperinflation in ARDS patients, such as by high tidal volumes and/or high alveolar pressures, impairs capillary perfusion, which results in an increase of dead space ventilation and ventilation/perfusion mismatching [4].

a)



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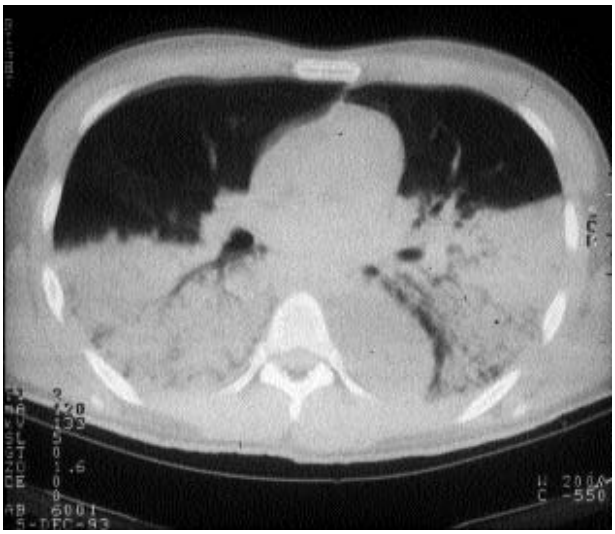

Fig. 1. – Adult respiratory distress syndrome (ARDS) lungs in a 24 year old male with polytrauma, lung contusion and massive aspiration. a) In the chest radiograph diffuse, homogeneous oedema is apparent in both lungs. b) The computed tomography (CT) scan from the same day demonstrates the inhomogeneous distribution: fluid-filled, nonaerated areas are visible in the dependent parts of the lungs, whilst the nondependent parts are aerated.

As long as interstitial fibrosis has not occurred, the compressed or fluid-filled alveoli can potentially be reaerated (= recruited). This has been shown convincingly by CT scan analyses [3] when ARDS patients have been turned from supine to prone position; the formerly compressed dorsal alveoli became reaerated when changing into the nondependent position, whereas, the now dependent ventral alveoli collapsed. However, not only the gravitational effects of heavy, fluid-filled lung tissue cause the extensive atelectasis. In ARDS lungs, surfactant function is also impaired; thus, these alveoli generally tend to collapse.

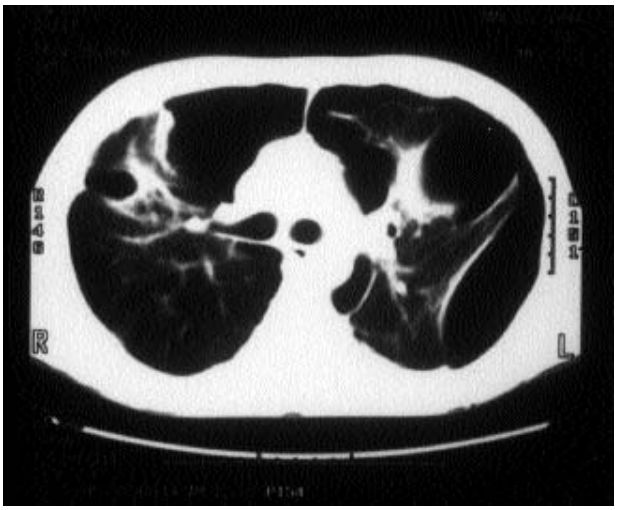

Fig. 2. – Computed tomography of the same patient in figure 1, 6 days after trauma. Severe barotrauma with pneumomediastinum, pneumothoraces and several pulmonary air cysts can be seen.

On the other hand, there is now increasing evidence that mechanical ventilation itself may damage the lungs, if used without considering the special conditions in acute respiratory failure. The mechanisms of this ventilator-induced lung injury [5] are various: regional alveolar overdistension by high airway inflation pressures [6, 7] as well as large volumes (tidal volumes, lung inflation volume) [8–11]; increased shear forces generated by local alveolar overdistension in inhomogeneous lungs, *e.g.* at junctions between mobile (aerated alveoli) and immobile (collapsed or consolidated alveoli) structures [5, 12]; but also repeated opening of collapsed alveoli [13], as well as the lung injury itself (*e.g.* pulmonary inflammation, surfactant deficiency). Alveolar overdistension may cause increased microvascular permeability ("stress failure"), which in itself may induce lung oedema [6, 7, 10, 11]. Alveolar overdistension also increases the risk of barotrauma, which is still a frequent deleterious complication of mechanical ventilation [5, 14–17]. In barotrauma, extra-alveolar air, after rupturing from the alveoli, spreads within the bronchovascular sheaths towards the mediastinum and then enters into different interstitial spaces, and may create pulmonary interstitial emphysema, pulmonary air cysts, pneumomediastinum, pneumothorax, subcutaneous emphysema, pneumoperitoneum, or pneumopericardium (fig. 2).

All these potential risks and adverse effects have considerable consequences for the strategy of mechanical ventilation.

Optimising pulmonary gas exchange during mechanical ventilation

Airway pressure and tidal volume

Recruitment of collapsed alveoli always needs higher pressures than would be necessary to keep them open. The clinical conclusion from this must be that it is important to "open up the lungs and keep them open", as has recently been claimed [18].

A well-established principle for recruitment of collapsed alveoli is to increase lung volume by applying external PEEP. The effect of general external PEEP must be carefully considered. The distribution of additional gas volume induced by any externally applied airway pressure will depend on the individual compliance of regional lung areas, caused not only by the gravitational effects in the oedematous lung but also by the inhomogeneous distribution of the tissue damage. Since regional compliance varies considerably in the different areas of the lungs, it is improbable that a PEEP level which is optimal for the whole lung will be found. Indeed, it often happens that a PEEP level which is suitable for an area with low compliance may be considerably too high for a more compliant area, seriously overdistending the alveoli. Indeed, in ARDS, any increase in lung volume by external PEEP not only reduces intrapulmonary shunt but, equally, also hyperinflates noncompressed lung areas, thereby, potentially converting well-ventilated alveoli into nonperfused dead space [4]. The conclusion from this is that it is necessary to find a compromise which keeps the less compliant alveoli open without overdistending the more compliant areas.

For morphological reasons (counterbalancing the superimposed lung weight), however, total PEEP may hypothetically not exceed much more than 15 cmH_2O. We believe that "super PEEP" levels (*e.g.* >25 cmH_2O), as proposed formerly [19], offer no further benefit and may even be harmful (*e.g.* impaired haemodynamics, barotrauma). Recently, high levels of PEEP (up to 27 cmH_2O) have again been recommended, based on a retrospective study [20]; but an incidence of 17% of barotrauma, as these investigators found while using high-level PEEP, does not encourage its reintroduction.

Transalveolar pressure (*i.e.* alveolar-pleural pressure difference) should be kept within the range that normal lung tissue is designed for at maximal lung capacity. This generally corresponds to a maximum airway plateau pressure of about 35–40 cmH_2O. When using volume-controlled modes, the pressure excursion depends on the relationship of the actual tidal volume (V_T) to the capacity (and compliance) of the aerated lung volume. Thus, in an ARDS patient with "baby lungs", the conclusion must be that it is necessary to reduce V_T considerably in order to avoid high inflation pressures and alveolar overdistension. The level of V_T depends on the actual situation; it is misleading to recommend V_T by $mL \cdot kg^{-1}$. Indeed, high V_T (12–15 $mL \cdot kg^{-1}$), as formerly proposed, will certainly overdistend the ventilated alveoli.

Likewise, V_T has to be adapted to the preset PEEP level: with higher PEEP levels in restricted lungs, V_T must be reduced considerably in order not to get into the flatter part of pressure-volume curve, which indicates overdistension. This would only aggravate gas exchange mismatching by increasing dead space ventilation and make ventilation less effective. Restriction of the ventilatory excursion may be even more important in inhomogeneous lungs, in order to reduce local tissue stress forces [12]. In this report, it is recommended that smaller V_T and a higher level of PEEP be used in these lungs.

Thus, there is now an increasing acceptance of the recommendation to restrict V_T in ventilated ARDS lungs. To a certain degree, minute ventilation (V'_E) can be compensated by increasing respiratory frequency (f_R). However, there is no further benefit from an f_R above 25 $breaths \cdot min^{-1}$. V'_E then has to be reduced, accepting inadequate CO_2 removal ("permissive hypercapnia") (see below).

Permissive hypercapnia

A notable breakthrough in ventilatory strategy was the understanding that "normal values" may not always be the most important aim in ventilatory support, especially if the cost is increased risk of barotrauma and lung injury. If excessive airway pressures must be strictly avoided, the level of total ventilation has to be questioned. We have to consider that alveolar ventilation can be reduced by 50% if arterial carbon dioxide tension (P_{a,CO_2}) is allowed to increase from 5.3 to 10.7 kPa (40 to 80 mmHg) [21]. The principle of reducing V_T in order to avoid excessive airway pressure was first applied by DARIOLI and PERRET [22] for mechanical ventilation in severe status asthmaticus. Limiting the peak airway pressure to 50 cmH_2O they were able to reduce mortality to zero. HICKLING *et al*. [23] were first to demonstrate that also in ARDS patients permissive hypercapnia was well-tolerated. They showed that mortality could be considerably decreased when peak airway pressures were reduced by decreasing total ventilation and limiting peak inspiratory pressures to 40 cmH_2O. This study has been questioned because of its retrospective design. Meanwhile, the authors have published a prospective study, which presents similar results [24]. It has to be noted that, in these studies, partial ventilatory support (synchronized intermittent mandatory ventilation (SIMV)) was used. Today, permissive hypercapnia is used in many competent intensive care units when ventilation becomes critical in severe ARDS, and it was also recommended by a consensus conference on mechanical ventilation [25, 26].

Acute hypercapnia causes increased sympathetic activity, cardiac output and pulmonary vascular resistance, alters bronchomotor tone, dilates cerebral vessels, and influences central nervous functions. However, the gradual elevation of P_{a,CO_2} is often remarkably well-tolerated, and chronic hypercapnia is known to have only few clinically relevant side-effects [27]. Thus, permissive hypercapnia may be quite acceptable if the real contraindications, such as coexisting head injury and the risk of cerebral oedema, recent cerebrovascular accident, and significant cardiovascular dysfunction, are taken into account. Nevertheless, controlled clinical studies to balance the risks and benefits of this strategy are still missing.

Variation of the inspiration:expiration (I:E) ratio

The aim of keeping collapsible alveoli open can be achieved either by external PEEP or by intrinsic PEEP ($PEEP_i$, auto-PEEP) [28, 29]. The total PEEP applied, *i.e.* the sum of external and $PEEP_i$, should at least be kept at a level sufficient to prevent recollapse of the alveoli at risk. $PEEP_i$ occurs when regional or total expiration remains incomplete within the expiratory time available. This is a dynamic phenomenon, which depends on the actual conditions for ventilation. Thus, $PEEP_i$

can be caused either by high tidal volumes, short expiratory time, or by high ventilatory time constants, or a combination of these. As the time constant (τ) is equal to resistance (R) × compliance (C), high time constants are caused by high airway resistance and/or compliance, which may occur on a regional basis (*e.g.* slow compartments), as well as for the whole respiratory system (including the ventilator system, *e.g.* caused by narrow tubes, slow PEEP valves *etc.*). There may often be a broad spectrum of different $PEEP_i$ within the lungs, which we are not able to discriminate.

In severe acute respiratory failure, there is usually a certain spectrum of slower and faster alveolar compartments [30, 31]. Fast compartments may be able to expire completely, even within a very limited expiratory time. However, as they may concurrently tend to collapse (*e.g.* because of impaired surfactant function) this must be prevented by external PEEP. On the other hand, there is evidence that external PEEP (above 10 cmH_2O) itself may increase the expiratory resistance and time-constant inequalities of the respiratory system [32, 33].

Therefore, in lungs with a larger variety of different time constants, a combination of external PEEP (to "open up and keep open" the fast compartments) and a well-adapted $PEEP_i$ (to "keep open" slower compartments) could be an appropriate method of adapting mean airway pressure, and thereby improving ventilatory distribution [34, 35, 36]. By shortening the expiratory time, $PEEP_i$ can be deliberately manipulated: this is the special effect of the "inverse ratio ventilation" (IRV) mode, whereby slower alveolar compartments may be kept open by an "individual" intrinsic PEEP; thus, using regional air-trapping as prevention from alveolar collapse.

The concept of a prolonged inspiratory phase and a shortened expiration was first proposed by REYNOLDS [37] for improving pulmonary gas exchange in neonates with hyaline membrane disease. IRV has since also been proposed for ARDS lungs [38–42]. The possible advantages in lungs with considerable ventilation/perfusion mismatching are: 1) the prolonged inspiration ensures a more homogeneous ventilation and keeps collapsible alveoli open for a longer period of time; and 2) during the short expiration slower compartments will not exhale completely, they remain distended by $PEEP_i$ (regional or "individual" trapped volume) which is, indeed, intended.

It is evident that mainly the slower compartments will profit from this $PEEP_i$. In ARDS lungs, there is generally a preponderance of fast compartments. Nevertheless, there is evidence that regional airway and tissue resistances may also be elevated [31]. Increased resistance in the lung periphery is difficult to measure directly. However, this can be deduced from ventilatory inhomogeneities [30, 33, 43, 44], which may be caused by variations in time constants.

In all modes using inverse I:E ratio, it is absolutely essential to take the actual $PEEP_i$ into account [45]. It must to be remembered that increasing V_T also carries the risk of increased $PEEP_i$ because more time is required to return to functional residual capacity (FRC). The problem is that $PEEP_i$ is not clinically evident. A remaining terminal flow at the end of the expiration indicates that a certain $PEEP_i$ exists but it does not quantify the amount. In pressure-controlled ventilation, a decrease in V_T when expiration is further shortened also indicates an increase of $PEEP_i$. Direct measurements can be performed by an additional occlusion manoeuvre, which provides an average value of $PEEP_i$. This can be achieved by means of simple equipment (a rapid occlusion valve and a differential pressure transducer). Some ventilators are equipped with an end-expiratory hold; $PEEP_i$ is then easy to determine.

Formerly, inverse ratio ventilation was performed with a volume-controlled mode (VC-IRV). However, for more than 10 yrs it has been argued that inverse ratio ventilation performed with the pressure-controlled mode (PC-IRV) may be more beneficial [46]. In principal, there may be good theoretical reasons for this: in extremely restrictive ARDS lungs, airway pressure must be strictly limited, if not, even minimal deteriorations may produce a critical increase in airway pressure. The pressure-controlled mode ensures that alveolar pressures everywhere within the inhomogeneous lung never exceed the targeted value. Nevertheless, pressure limitation could also be achieved in a volume-controlled mode by setting the maximal inspiratory switch at a narrow pressure limit.

An even more relevant argument for the PC-IRV mode may be that inspiratory pressure always remains constant, and apparently closed airways often require moderately high and sustained pressures to open. The inspiratory pressure remains constant, not only during the whole period of inspiration, but also when lung compliance finally improves by alveolar recruitment. Additional V_T will then be applied. In contrast, in the VC-IRV mode, airway pressure decreases in the case of improved compliance, which diminishes the chance of further alveolar recruitment unless the preset V_T is manually readjusted.

The possible advantage of pressure-controlled ventilation itself (with normal I:E ratio) compared to the volume-controlled mode was recently demonstrated by RAPPAPORT *et al.* [34]. In the PC-IRV mode, mean airway pressure is relatively higher than in VC-IRV under comparable settings. Since mean airway pressure is the key determinant of gas exchange [35, 36], pulmonary oxygenation may profit from this. On the other hand, this may also interfere with pulmonary circulation and, thereby, the benefit from PV-IRV in oxygen transport may be lost, if not counterbalanced by volume and/or vasoactive drug therapy.

Up to now, clinical studies have not convincingly demonstrated the superiority of PC-IRV. In 31 ARDS patients [47], pulmonary gas exchange improved during PC-IRV, however, the volume-controlled ventilation (not in IRV mode) was only compared retrospectively. More recent studies on PC-IRV in ARDS patients [48–51] revealed inconsistent results in comparison with conventional ventilation. In an experimental study [52], comparing five different ventilatory modes in pigs with surfactant depletion, ventilatory volumes and peak airway pressures were lowest in the PC-IRV mode; however, higher mean airway pressures impaired pulmonary circulation and oxygen transport. On the other hand, in a study in 12 ARDS patients haemodynamics improved under PC-IRV, as demonstrated by transoesophageal echocardiography [53]. This demonstrates that haemodynamics and oxygen transport function must always be taken into account

and should be an essential criterion when assessing the net advantage of a certain mode of mechanical ventilation. With this in mind, the benefits of PC-IRV still need to be proved.

A further observation, which seems to be important, is that the positive effect of recruiting collapsed alveoli by IRV appears to take considerable time; according to our own clinical experience, the positive effect of IRV on gas exchange may take several hours. The recruitment process caused by the long-lasting inspiratory pressure seems to open the alveoli "one by one". This has also been observed by others [38, 47, 54, 55], and may be the reason why positive effects of IRV could not be assured by studies with shorter observation periods [48, 49–51]. Thus, pulmonary gas exchange should be monitored for a sufficient period of time (*i.e.* several hours) waiting for the expected positive effects of IRV. Unfortunately, the few long-term studies mentioned above are either retrospective and noncontrolled [38, 47], or have considered only a small number of patients [54, 55]. The main reason for this might be the difficulties of performing such long-term studies under stable conditions in intensive care medicine.

It is obvious that the concept of IRV is strictly counterindicated in obstructive lung diseases (acute bronchial asthma, COPD) because of the risk of a further deterioration of the already increased lung volume.

Supplementary spontaneous breathing efforts

There is a general tendency in modern ventilation strategies to incorporate spontaneous breathing efforts, even if clearly insufficient. For this purpose, various ventilatory support modes ("ventilatory assist") have been developed. This concept may offer considerable advantages. Even a small additional contribution by spontaneous breathing reduces the amount of mechanical ventilation and reduces peak airway pressures, thereby, offering a less "invasive" mode of mechanical ventilation. By this means, venous return and pulmonary circulation may also be less affected and oxygen delivery may improve as a consequence of increased cardiac output. Likewise, the inhibitory effects of mechanical ventilation on renal function are less in ventilatory assist modes [56, 57]. However, we must take into account that, with spontaneous inspiratory effort, intrathoracic pressure becomes negative and transpulmonary pressure difference will increase. Thus, the risk of barotrauma, which is partly determined by the transpulmonary pressure difference and the corresponding lung volume, may not directly profit from supplementary spontaneous breathing.

The most remarkable effect of maintained, partially spontaneous breathing appears to be the improved recruitment of atelectatic and collapsed alveoli. HEDENSTIERNA *et al*. [58] were able to show that contracting the diaphragm by phrenic nerve stimulation reduces the size of the atelectasis (measured by computed tomography) occurring during halothane anaesthesia in the dependent lung regions. In general, spontaneous breathing seems to be more efficient. JOUSELA *et al*. [59] measured diaphragmatic movement using ultrasound during spontaneous breathing and mechanical ventilation in men; during mechanical ventilation a relatively larger tidal volume was required to produce a movement of the same magnitude as during spontaneous breathing.

Furthermore, when supplementary spontaneous breathing is possible, sedation of the ventilated patients can be kept at a much lower level. In our own experience [60], it could be demonstrated that during partial ventilatory support (namely biphasic positive airway pressure (BiPAP), see below) sedation could be kept at a much lower level. This may be potentially beneficial even in critically ill patients. Some of these benefits may be: 1) less interaction with other organ functions, *e.g*. haemodynamics, gastrointestinal motility; 2) accumulation of sedatives can be avoided; 3) analgesics are easier to adapt to the actual individual needs; 4) interference by acute complications are easier to recognize (*e.g*. cerebral function disturbances); and 5) patients are easier to mobilize, and active coughing may improve clearance from bronchial secretions.

Deep sedation and neuromuscular blocking can lead to prolonged muscle weakness and protracted immobilization [61, 62]. Therefore, spontaneous breathing should be incorporated into the ventilation mode whenever possible, even if insufficient. In our own experience, this seems to be possible more often than normally supposed, even in severe respiratory failure. Muscle relaxation is unnecessary and undesirable. Today, the concept of analgo-sedation in mechanical ventilation should be not to adapt the patient to the ventilator but to adapt the ventilator to the patient. This is indeed possible with the highly sensitive demand valves of the new generation ventilators.

There are many studies which demonstrate the benefits of these ventilatory assist techniques [63–66]. These modes (namely pressure support ventilation (PSV)) have been widely used (at least in Europe) for many years, for COPD as well as for ARDS patients. However, there have also been reports showing their limitations, mainly due to maladaptation and desynchronization between the patients instantaneous efforts and the ventilatory consequences [67, 68]. Several reasons could be determined [68]: 1) inspiratory response delay caused by the inspiratory triggering mechanisms and the demand flow characteristics of the ventilator; 2) a mismatch between the patient's completion of the inspiratory effort and the ventilator's criterion for terminating pressure support; and 3) expiratory flow limitation due to the resistance from the patient's airways, endotracheal tube, and expiratory valve. In COPD patients with high respiratory drive, in particular, the individual adaptation of the ventilatory support may be difficult and repeated readaptation is often necessary.

Some of these difficulties can perhaps be avoided with the following new, different mode of ventilatory assistance.

Proportional assist ventilation (PAV). PAV [69, 70] is a different approach to ventilatory support, in which the ventilator amplifies the patients instantaneous effort whilst leaving him complete control over the breathing pattern, such as tidal volume, inspiratory and expiratory duration, and flow. The pressure delivered from the ventilator increases in proportion to the patient's effort. With this method, the total pressure applied, tidal volume and flow will be altered accordingly, if the patient

increases or decreases his effort. Thus, the system operates by positive feedback (*i.e.* mechanical unloading); this is analogous to the operation of power steering in motor vehicles.

Potential advantages can be assumed from this new concept: more comfort for the patient, less fighting against the machine and less need for sedation. Furthermore, preservation and enhancement of the patient's own control mechanisms and, thereby, better adaptation to the patients ventilatory needs. However, these advantages are still hypothetical. At present, there have been no clinical or physiological studies on PAV in ARDS patients. Of course, this technique depends on an active central respiratory drive. Patients with a potentially critical central depression of the respiratory drive have to be excluded. Furthermore, there may be a tendency to pressure "runaway" in case of airway leakage or inadequate settings.

This new concept is promising but not yet commercially available. Further studies are needed to prove its clinical applicability and its special indications. Perhaps, this mode will be indicated preferably for COPD patients.

Airway pressure release ventilation (APRV). In 1987, DOWNS and co-workers [71] introduced a new mode of ventilation which allows spontaneous breathing on a preset continuous positive airway pressure (CPAP) level and which is interrupted by short (1–1.5 s) releases of the pressure niveau for further expiration. The principle of reducing rather than increasing lung volume distinguishes this technique from other modes of ventilatory support. It maintains a moderately high airway pressure (about 20–30 cmH_2O) for most of the time; thereby, keeping the alveoli open. Furthermore, during the short expiratory release, slow compartments remain expanded by PEEPi which in fact resembles the effects of the IRV mode. An essential advantage, however, is the preservation of spontaneous breathing. The benefits from this concept may be: less barotrauma; reduction in circulatory compromise; and a better matching of pulmonary ventilation and perfusion.

In a multicentre study [72], APRV proved effective in 50 patients with and without mild-to-moderate respiratory failure. Compared to conventional ventilation with equal mean airway pressures, the maximum pressures were significantly lower at APRV, whilst oxygenation improved. APRV was considered useful in mild-to-moderate nonobstructive respiratory failure.

In our view, APRV offers several essential preconditions, which seem potentially advantageous even for ventilation of severe ARDS lungs: 1) a nearly continuous airway pressure level, favourable in keeping the alveoli open; 2) a short expiratory time, which favours ventilation in the fast compartments; 3) preservation of spontaneous breathing, which reduces the "invasiveness" of mechanical ventilation and avoids the need for muscle relaxation and deep sedation; 4) a minimal deviation from an individually adapted "optimal" lung volume (*i.e.* level of mean airway pressure), which may reduce the risk of barotrauma (or volutrauma); and 5) a "pressure-controlled" spontaneous breathing, which makes it possible to maintain relatively low airway pressures and, thereby, improves the conditions for pulmonary circulation and oxygen delivery.

An interesting new method of applying APRV is offered by the BiPAP mode, which facilitates a synchronized pressure release ventilation.

Biphasic positive airway pressure (BIPAP). BIPAP [73] is a pressure-controlled ventilation, during which unrestricted spontaneous breathing is possible in each phase of the respiratory cycle. This mode, which was developed for mechanical ventilation in intensive care medicine, should not be confounded with "BiPAP" which is a mode for home ventilation of COPD patients and for treatment of obstructive sleep apnoea syndrome. At the present time, BIPAP is produced by the EVITA ventilator (Dräger Werke, Lübeck, Germany): the circuit switches between a high and a low airway pressure level in an adjustable time sequence. At both pressure levels, the patient can breathe spontaneously in a CPAP system. This spontaneous breathing is further supported by the

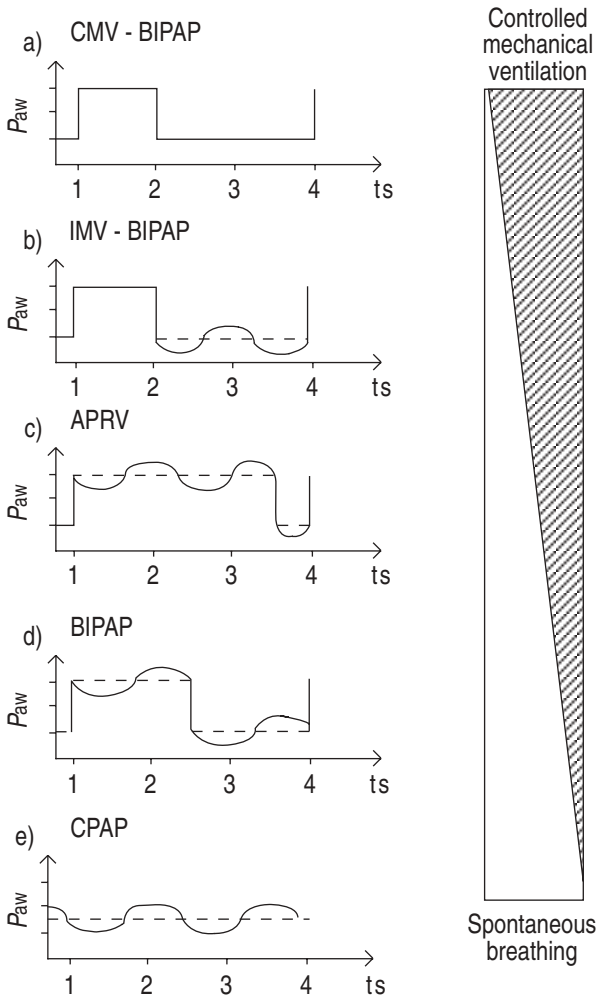

Fig. 3. – Modes of total and partial ventilatory support covered by biphasic positive airway pressure (BIPAP). a) CMV-BIPAP: pressure controlled ventilation without any spontaneous breathing. b) IMV-BIPAP: spontaneous breathing only during the lower CPAP level (similar to intermittent mandatory ventilation (IMV)). c) APRV: spontaneous breathing only during the upper CPAP level, short release to a lower level (equal to airway pressure release ventilation (APRV)); inverse I:E ratio. d) Genuine BIPAP: spontaneous breathing during both CPAP levels. e) CPAP: continuous positive airway pressure (CPAP) without any change of the pressure level. CMV: continuous mandatory ventilation; IMV: intermittent mandatory ventilation; I:E: inspiratory/expiratory ratio. (From HÖRMANN *et al.* [74], with permission).

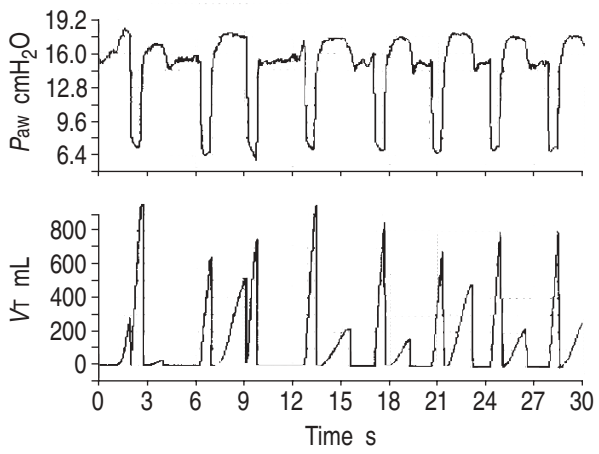

Fig. 4. – Airway pressure release ventilation (APRV) realized with BIPAP (Dräger EVITA ventilator). Note the short release time (1 s); spontaneous breathing only during the upper CPAP level. P_{aw}: airway pressure; V_T: tidal volume; BIPAP: biphasic positive airway pressure; CPAP: continuous positive airway pressure.

volume displacement caused by the differences in CPAP levels. If there is no spontaneous breathing effort, this mechanical volume displacement is taken as a pressure-controlled mechanical ventilation. The duration of both pressure levels can be separately adjusted, which makes it possible to achieve a broad variation in ventilatory frequency as well as in I:E ratio (fig. 3). BIPAP has also been presented as "intermittent mandatory pressure release ventilation" (IMPRV) [75], which is produced by the CESAR ventilator (TAEMA, Air liquide, France).

As BIPAP allows rather short expiratory times (down to 0.5 s), this method can easily be used in an APRV mode (fig. 4). In our experience, BIPAP-APRV seems to be particularly effective for ventilating ARDS lungs [76].

In 18 patients with moderate-to-severe acute respiratory failure alveolar to arterial difference in oxygen tension ($P_{(A\text{-}a),O_2}$) >40 kPa (>300 mmHg) during conventional volume-controlled mechanical ventilation, with inspiratory oxygen fraction (F_{I,O_2})=1.0, PEEP=5 cmH$_2$O, I:E=1:2) two different modes of ventilation were compared, each applied for a period of 24 h: 1) conventional volume-controlled ventilation in inverse ratio mode (VC-IRV) with V_T=8–12 mL·kg^{-1}, I:E=2:1 to 3:1, PEEP= 5 cmH$_2$O, f_R 10–15 breaths·min^{-1}; 2) Biphasic positive airway pressure in airway pressure release mode (BIPAP-APRV) with a high CPAP level=15–30 cmH$_2$O for 2–4 s, a pressure release to 5 cmH$_2$O for 0.5–0.7 s. The individual sequence of both ventilation modes were randomized. During the study, the settings of each ventilation mode (F_{I,O_2}, minute volume or frequency) were adapted to individual clinical needs. With VC-IRV there was no relevant change of either airway pressures, $P_{(A\text{-}a),O_2}/F_{I,O_2}$ ratio or venous admixture during the 24 h period. During BIPAP-APRV, however, $P_{(A\text{-}a),O_2}/F_{I,O_2}$ ratio and venous admixture improved significantly after 8 h and then improved further (fig. 5). Despite initially similar levels, mean airway pressures could be reduced significantly during the 24 h of BIPAP-APRV, indicating progressive alveolar recruitment. Even oxygen delivery increased slightly (but nonsignificantly) because of a higher cardiac output (perhaps because of the lower sedation level possible).

The benefit of superimposed spontaneous breathing

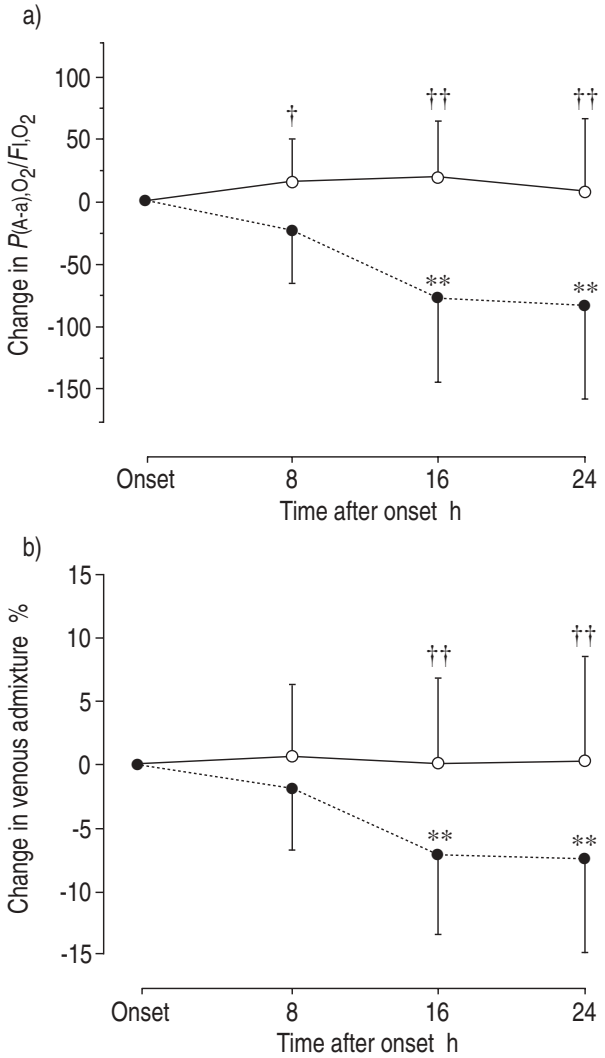

Fig. 5. – Effects of long-term application of volume-controlled inverse ratio ventilation (VC-IRV) and BIPAP in airway pressure release setting (APRV) in patients with acute lung injury. a) Change in ratio of alveolar to arterial oxygen pressure difference to inspiratory oxygen fraction $P_{(A\text{-}a),O_2}/F_{I,O_2}$). b) Change in venous admixture. The beneficial effect of APRV upon oxygenation begins only after 8 h. —○—: VC-IRV; —●—: APRV. **: p<0.005 compared to value at onset; †,††: p<0.05, p<0.01 compared between VC-IRV and APRV. (From SYDOW *et al*. [76], with permission).

during BIPAP was recently also demonstrated by PUTENSEN *et al*. [77] in dogs with oleic acid-induced lung injury: spontaneous breathing during BIPAP (only 10% of the minute volume) significantly improved oxygenation, cardiac output and oxygen delivery (compared to BIPAP without spontaneous breathing), whereas oxygen consumption and total minute ventilation remained unchanged. This demonstrates that even minimal spontaneous breathing superimposed on mechanical ventilation contributes to improved ventilation/perfusion (V'_A/Q') distribution and increased systemic blood flow.

The main advantages of BIPAP with superimposed spontaneous breathing in acute respiratory failure could be: 1) less invasiveness of mechanical ventilation (by partial supplementary spontaneous breathing); 2) less impairment of pulmonary circulation (and, thereby, possibly) improved oxygen delivery; and 3) a more effective recruitment during continuous application.

Tracheal gas insufflation (TGI)

One interesting alternative to bring about a reduction in dead space and to make mechanical ventilation more effective is tracheal gas insufflation (TGI). Phasic TGI as an adjunct to mechanical ventilation is delivered selectively during inspiration or expiration [78, 79]. Phasic TGI during the expiratory period augments alveolar ventilation by flushing CO_2 from the tracheal and apparatus dead space (V_D/V_T). From animal experiments it could be shown that TGI significantly reduced P_{a,CO_2} and V_D/V_T without raising tidal volume or maximal airway pressure. However, the ventilatory benefit appears often to be modest in lungs with large alveolar dead space. Moreover, the risk of mucosal damage, secretion retention and barotrauma have not yet been fully investigated. Thus, the optimal usage and the long-term safety remain to be determined.

Strategies of ventilatory support seem to develop continually. Indeed, from some of these new concepts further benefit for patients with acute lung injury is expected (table 1). Others, such as liquid ventilation [80], are still experimental. A recent consensus conference [25] concluded that there are no convincing data that any ventilatory support mode is superior to others for ARDS patients. Certainly, careful studies comparing the different modes in well-defined clinical conditions are needed in order to achieve a more thorough understanding and to discriminate useful applications. However, it may be difficult to prove superiority of any mode by measuring outcome if respiratory failure is only one (and not the most essential!) reason for fatal outcome in multiple organ failure. Thus, evidence of improved physiological parameters may also indicate promising new strategies in mechanical ventilation.

Nevertheless, it seems apparent that the way in which mechanical ventilation is used and how closely ventilation is adapted to the individual patient's needs differ considerably, and this obviously has the most decisive influence on success in restoring physiological function in acute respiratory distress syndrome lungs.

Table 1. – General statements for the strategy of mechanical ventilation in ARDS

1. Alveolar overdistension appears to be a key factor of ventilator-induced lung injury. When possible, plateau pressure should be limited to a maximum of 35 cmH_2O.
2. To minimize the risk of alveolar overdistension, it may be necessary to reduce ventilation and to permit hypercapnia.
3. The clinical benefit of inverse ratio ventilation has not yet been proved. Most observations cease too early, improvement in oxygenation may happen after hours.
4. The underlying pathophysiology of the disease states varies with time. Thus, close observation and monitoring is mandatory; ventilatory settings have to be readjusted promptly whenever necessary.
5. Minimizing the invasiveness of mechanical ventilation by supplementary spontaneous breathing may be advantageous (*e.g.* by ventilatory assist, APRV). Some possible benefits may be: 1) lower sedation levels are tolerated; 2) less impairment of haemodynamics; and 3) more effective alveolar recruitment.

ARDS: acute respiratory distress syndrome; APRV: airway pressure release ventilation.

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