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Experimental Studies on Lung Mechanics, Gas Exchange and Oxygen Delivery under Open Lung Conditions

Mechanical ventilation with decelerating versus constant inspiratory flow

Agneta Markström

Department of Anesthesiology and Intensive Care, Uppsala University Hospital, Uppsala, Sweden

INTRODUCTION

Although artificial ventilation has been in clinical use for more than 40 years, it is known that under certain circumstances such ventilation leads to so-called "respirator lung", i.e. decreased lung compliance and malfunctioning of gas exchange (10,26,29,49,99).

Ventilator-induced lung injury

Since 1960 it is generally agreed that delivery of a pre-set tidal volume is the safest and the most predictable way to support patients with respiratory failure (93,94). The concept of eucapnia, tidal volumes of 12-15 ml/kg and adapted ventilatory rates, is widely accepted. There is still uncertainty, however, regarding the toxic threshold for the inspired oxygen fraction (FIO_2), and whether there is a volume threshold below and above which mechanical ventilation would be risk-free.

The underlying causes of ventilator-induced lung injury seem to be multifactorial. *Pulmonary barotrauma,* defined as presence of extra-alveolar air in locations where it is not normally found, is associated with ventilation at high airway pressure. To prevent this, transpulmonary pressure exceeding 30 cmH_2O should be avoided (68). High airway pressure and excessive cyclic stretching of even normal lung parenchyma has been demonstrated to inflict severe lung damage (92). A tidal volume that overextends the alveoli is unavoidably associated with high airway pressure, but if a "normal" tidal volume can be delivered to a restricted chest cage, this will result in a high alveolar pressure, though without causing lung injury (27,37). Alveolar overdistension is often called "volutrauma", in order to make clear that the damage is directly attributable to the excessive alveolar volume rather than to the alveolar pressure. In short, it has been repeatedly demonstrated (15,27,37) that it is lung overinflation rather than the high pressure *per se*, that should be avoided. Thus, overinflation, especially if prolonged (28), and previous and existing pulmonary injury render the lungs more susceptible to ventilation-induced injury. During artificial ventilation, in the presence of iatrogenic lung injury, parts of the lungs cease to participate normally in gas exchange and we are then often obliged to over-inflate any remaining functioning lung parenchyma. This is known to affect the *pulmonary surfactant system* which, in the normal lung (38), is needed to keep the alveoli open, dry and clean. During cyclic ventilation with large

tidal volume or tidal ventilation with end-expiratory collapse, surfactant molecules are squeezed out of the alveoli and forced into the airways (13,31). This mechanism may explain how loss of surfactant during mechanical ventilation is caused by rhythmic compression (expiration) and decompression (inspiration). If ventilation is below alveolar collapse pressure, surfactant is lost more rapidly. To prevent loss of surfactant, ventilation should be maintained at, or just above, the level of functional residual capacity (FRC) (8,54).

Positive end-expiratory pressure (PEEP) (5) was for many years believed to improve oxygenation through recruitment of lung units, which otherwise were closed at small lung volumes (32,42). Nowadays, it is belived that PEEP also prevents lung injury by reducing high shear forces and also relieves alveolar edema (66).

Ventilation under open lung conditions

According to the experimental animal lung injury model, characterized by highly unstable alveoli in order to mimic acute respiratory failure in the human patient, the basic prerequisite for this thesis was to supply sufficient PEEP to keep the lungs open throughout the ventilatory cycle. Using a successful recruitment procedure together with ventilation with a PEEP level set in order to prevent end-expiratory collapse, various inspiratory patterns were studied. This approach was described by Snyder and Froese (87) and also by Lachmann (45), in relation to our study (54). The critical opening pressure is inversely proportional to alveolar unit size. Progressive recruitment of airspace requires a gradually increasing pressure during inflation, which entails a high peak inspiratory pressure. In order to obtain a certain volume change in larger alveoli, the necessary pressure changes are much smaller than in alveoli which have collapsed or have a smaller volume. From the La Place´s Law it can be concluded that the pressure necessary to keep the alveoli open is lower with good FRC. Therefore, the PEEP necessary to stabilize the end-expiratory volume can be minimized if the lungs are completely opened to the FRC level of a healthy lung (8,54). If we assume that ventilation is to be performed above the end-expiratory collapse pressure (inflection point of the expiratory limb of the pressure/volume loop), then lung recruitment and the concept of resting the lung (avoidance of pressure-volume swings) seems attractive (see Fig1).

Quantal alveolar behavior

Staub´s concept (19,88) of quantal alveolar behavior as a way to explain how individual alveoli behave in pulmonary edema has been used in this thesis. This model states that the individual alveolus fills essentially independently of its neighbors and has a propensity to be either air-filled and expanded, or else completely fluid-filled and collapsed. Intermediate forms are unstable. In this context, collapse is used to describe sudden change to a smaller volume which is accompanied by complete filling with fluid. Sudden transition from an expanded to a collapsed alveolus (or vice versa) does not presuppose fluid flux across the alveolar epithelium. The entire process takes place within the alveolus itself. Accordingly to Staub´s theory, there is essentially no difference between alveolar collapse in pulmonary edema and that in atelectasis. These conditions differ only in terms of alveolar size and the pressures at which collapse and expansion occur. This concept of quantal

alveolar behavior may account for several radiographic manifestations (95-97). To quantify the amount of alveolar fluid, the concept is based on the fact that the greater the amount of fluid is, the larger will be the number of unstable alveoli exhibiting quantal alveolar (98).

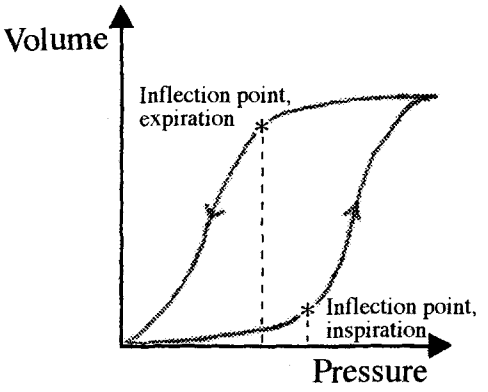

Figure 1.
Pressure/volume loop, the inflection point (P_{infl}) on the inspiratory limb represents the critical pressure necessary to reopen, or recruit, closed peripheral airways and/ or collapsed alveolar units. The inflection point on the expiratory limb represents the end-expiratory collapse pressure.

Quantal alveolar behavior and PEEP

La Place´s law ($P = 2\gamma/r$), where P = pressure to stabilize a bubble/alveolus; γ = surface tension at the air-liquid interface; r = radius of the bubble/alveolus. La Place´s Law states that when the alveolar gas volume falls below a critical value (hypodistension) the elastic retractile forces become overwhelming and alveolar collapse ensues. But as the alveolar gas volume increases, the elastic forces weaken. Thus, the elastic forces strive to maintain an optimal alveolar size. Lung injury may result, or be exacerbated, when the alveolar gas volume either exceeds the limit of distensibility (hyperdistension), or when end-expiratory alveolar collapse occurs. Such collapse will create shear forces during inspiratory re–expansion.

In conjunction with positive pressure ventilation, application of positive airway pressure at end-expiration is known as positive end-expiratory pressure (PEEP) therapy (5). The application of PEEP, in its modern sense, began with a description (3,4) of the adult respiratory distress syndrome (ARDS). PEEP improves oxygenation (30), increases functional residual capacity (79), reduces Qs/Qt and improves lung compliance (90). It has been shown (23) in healthy rat lungs that alveolar diameter increases linearly as PEEP is increased from 0 to 10 cmH_2O; end-expiratory alveolar diameters increased to a greater extent than did end -inspiratory diameters, but this increase in alveolar diameters gradually diminished when PEEP levels exeeded 10 cmH_2O and leveled out at approximately 15 cmH_2O.

Quantal alveolar behavior is also an appropriate model for explaining observations made when positive pressure ventilation with PEEP is instituted. In this context quantal alveolar behavior does not imply that all alveoli collapse simultaneously but rather that individual alveoli collapse in an instantaneous event, and also that each alveolus collapses more or less independently

of its neighbor. It was interesting to note in our experimental model of lung injury, that any radiographic appearance of the lung parenchyma – ranging from completely normal, through ground-glass appearance, to extensive alveolar consolidation with air bronchograms – can be produced simply by modifying the PEEP setting of the ventilator (98).

Ventilation techniques

Mechanical ventilation can be either volume-controlled (constant inspiratory flow) or pressure-controlled (decelerating inspiratory flow). During volume-controlled ventilation the ventilator insufflates the pre-set tidal volume, usually with constant inspiratory flow which produces a linear increase in pressure, culminating when the tidal volume is delivered. This contrasts with pressure-controlled ventilation with decelerating inspiratory flow, where the drive gas pressure generates the flow, initially high but subsequently decelerating and approaching zero. With decelerating flow, the pre-set inspiratory pressure remains constant throughout inspiration. Moreover, with the decelerating inspiratory flow, the major part of the tidal volume will be delivered during early inspiration (see Fig 2).

MATERIAL AND METHODS

Animal population

The pig serves increasingly as an animal model for research. The advantage of using piglets for studies on ventilatory patterns is that the pig has no collateral ventilation. For the experimental studies a total of 64 Swedish Landrace piglets, 10-20 weeks old, of either sex and a mean weight of 26.2 ±2.7 kg were used. The investigations were performed at the Experimental Laboratories of the Department of Anesthesiology and Intensive Care at University Hospital, Uppsala, Sweden. The local ethics committee for animal experimentation reviewed and approved the protocol.

Anesthesia and preparation

Generally the pigs were given pre-anesthetic medication intraperitoneally with pentobarbital (15 mg x kg^{-1}) plus 0.5 mg atropine. A venous line was inserted into a peripheral vessel and 15 min later anesthesia was induced with 500 mg ketamine and 0.5 mg atropine intravenously (12,59,100). In addition, 20 mg morphine was given intravenously before tracheotomy, preparation and introduction of intravascular catheters. Simultaneous with the morphine administration, a 20 mg x kg^{-1}x h ketamine infusion was started and maintained throughout the study. Pancuronium bromide was given as a continuous infusion at 0.26 mg x kg^{-1}x h^{-1}.

In some pigs anesthesia was induced with tiletamine 3 mg x kg^{-1}+ zolazepam 3 mg x kg^{-1} and xylazine 2.2 mg x kg^{-1} and atropine 0.04 mg x kg^{-1} intramuscularly, followed 5 min later with induction of ketamine and pancuronium infusion as described above.

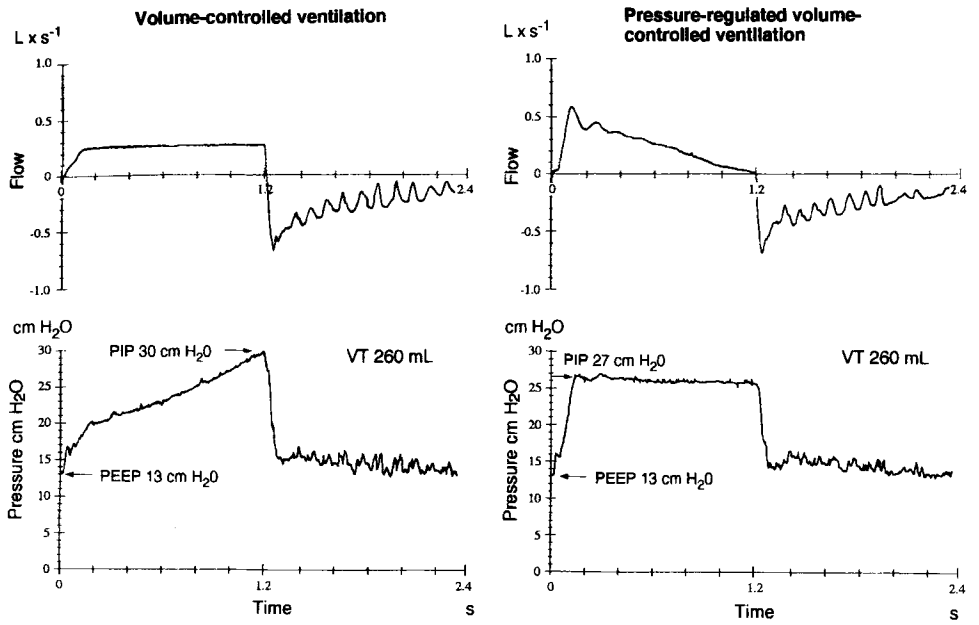

Figure 2. Recordings of inspiratory flow and resulting inspiratory pressure at a ventilatory frequency of 25 bpm, and I:E ratio 1:1, with external PEEP of 13 cmH_2O. Constant inspiratory flow pattern (in the left panel) and decelerating inspiratory flow pattern (in the right panel).

Catheterization and monitoring

Intravascular catheters were placed surgically for measurement of central venous, pulmonary arterial (via the external jugular vein), and aortic pressures (via the carotid artery). The correctness of catheter positioning was confirmed by pressure tracings. Electrocardiogram (ECG), heart rate and all pressures were displayed on a bedside monitor (Siemens Sirecust) and recorded with reference to the mid-thoracic level. Arterial and mixed venous blood gases were measured (ABL 300/OSM III®, Radiometer A/S, Copenhagen, Denmark). Carbon dioxide production was recorded by a metabolic monitor (Datex Deltatrac®, Datex Instrumentation Corp, Helsinki, Finland).

Cardiac output was estimated with a COLD® System (Pulsion Medizintechnik KG, München, Germany). A 4-F fiberoptic catheter with a thermistor was introduced via the femoral artery, and advanced to the descending aorta. The thermistor in the femoral artery catheter connected to the COLD system detects temperature signals in the descending aorta, from which cardiac output is calculated (55). Right ventricular end-diastolic volume was measured according to a previously described technique (53). Extrathermal volume (ETV) and intrathoracic blood volume (ITBV) were measured using the technique of double indicator dilution described in detail elsewhere (53,55). This technique was first developed for measuring ETV. The double indicator consisted of 5 mg of indocyanine green mixed with 10 ml of 5% dextrose in water at a temperature of 5-7^{0}C, and was injected as a bolus into the superior caval vein. The dilution curves for dye and temperature were recorded simultaneously in the descending aorta with the

thermistor-tipped fiberoptic catheter. ETV was calculated as the difference between the volume accessible to the intravascular indicator, indocyanine green, and the extrathermal volume measured by thermodilution. ITBV was calculated as the product of cardiac output and the mean transit time of indocyanine green between the point of injection into the superior caval vein and its detection in the descending aorta at the level of the diaphragm. In our laboratory, triplicate measurements in 9 piglets both pre- and postlavage, gave us a coefficient of variation for cardiac output of 4.0 ±3.5%, and for ITBV and ETV, 6.14 ±2.2% and 5.9 ±3.1%, respectively.

Lung function

Airway pressures were obtained from the digital displays of the ventilator. Before starting the study, the ventilator's pressure and flow transducers had been calibrated with independent devices. Every morning a pre-use functional check was made according to the procedure described in the operating manual for the ventilator. In one of the study, independent measurements of lung mechanics were made by using a Bicore CP-100. There was very good agreement with the airway pressures and lung volumes obtained from the ventilator's digital display and the Bicore equipment.

The static chest-lung compliance (CLT) was calculated according to the formula

$$CLT = \text{Tidal volume} \times (\text{end-inspiratory pressure} - \text{end-expiratory pressure})^{-1},$$

but with appropriate modifications to make allowance for the compressible volume (77,83).

When the end-inspiratory occlusion pressure (PAW_{endin}) and the total PEEP were measured, the hold function of the ventilator was applied for 5 s before the equilibrium values were noted. During the hold procedure, the ventilator measures the pressure in the respiratory limb where there is no on-going flow, i.e. end-expiratory hold pressure is measured from the inspiratory limb and end-inspiratory pressure from the expiratory limb.

For measurements of functional residual capacity (FRC), serial dead space (SDS) and alveolar mixing efficiency, the SF_6 tracer gas wash-in-wash-out method was used (47,48). Measurements of SF_6 were made with a rapidly responding infrared analyser (Siemens-Elema, Sweden). During washout, SF_6 flow was calculated by a computer every 10 msec from signals of expiratory flow and SF_6 concentration. The total volume of washed-out SF_6 is obtained by integration. FRC is calculated as the volume of SF_6 washed-out, divided by the alveolar concentration at the end of wash-in. These measurements were carried out twice at each ventilatory setting and the second-measured value of the two observations was used. In our laboratory the coefficient of variation for three sequential measurements in 9 animals for FRC, across a broad range of tidal volumes and different flow conditions, was 1 ±0.08%.

Lavage procedure

In these investigations we used the lavage model originally described by Lachmann and coworkers (44). Pulmonary surfactant was removed by a series of 10 instillations of 0.9% saline at a temperature of 37° C, each of 1-1.5 liter volume. In previous studies (54,72,85) this lavage model by our group has been described in greater detail. It has the advantage of simplicity, and

remain stable for about 3 h which makes it suitable for studies on short-term effects of ventilatory patterns. The lavage procedure causes a mono-organ failure but does not induce a generalized hypoxic injury, which would lead to a multi-organ failure. The model is very reproducible, probably by virtue of the highly standardized lavage procedure and the standardized anesthesia procedure (12). Lavage induces a two, threefold increase in extrathermal volume. The shunt fraction increased from 9 ±2% before, to 35 ±6.5% immediately after lavage during zero PEEP ventilation. Compliance decreased from 31 ±8 to 13 ±4 ml/cmH_2O after lavage. Different ventilatory patterns were sequentially applied in each animal, thereby reducing the number of animals needed.

Recruitment procedure and inflection point (P_{infl})

Immediately after lavage, the surfactant-deficient lung was recruited with a ventilatory setting at an inspiration/expiration ratio (I:E ratio) of 1:1, FIO_2 of 1.0, and the external PEEP set to produce a peak inspiratory pressure (PIP) of 50 cmH_2O for 5 min. After this initial procedure, the external PEEP was re-set to zero, after which the inflection point (P_{infl}) was determined.

To assess pulmonary mechanics during induced respiratory failure the pressure/volume curve (PV loop) was determined. On the inflation limb of the PV loop, an inflection point can be observed representing an abrupt change in pulmonary compliance, i.e. recruitment phenomena occur (50,67).

Pressure-volume loop (PV loop)

The static pressure-volume loop (PV loop) was generated using volume control with a constant inspiratory flow of 0.15 l x s^{-1} and a tidal volume of 1200 ml and FIO_2 1.0. The inflection point on the inspiratory limb of the PV loop was determined by observing a separate PC monitor. The projection on the airway pressure axis of the vertex of the lower curved section was designated the inflection point pressure.

Thermo-dye-dilution

To measure thoracic intravascular and extravascular fluid volumes, the thermo-dye-dilution technique was used. A fiberoptic thermistor was advanced via the right femoral artery into the descending aorta. Indocyanine green (intravascular marker)10 mg was mixed with iced-cold (5-7^{0}C) glucose 5% (thermal intra- and extravascular marker) and 10 ml was injected by hand within 1-2 s into the superior vena cava. The dilution curves for dye and temperature were recorded simultaneously in the descending aorta with the thermistor-tipped fiberoptic catheter. The dye and the thermal curves recorded in the femoral artery were used to calculate cardiac output (CO), intrathoracic blood volume (ITBV) and extrathermalvolume (extravascular lung water) ETV. ITBV was calculated as a product of mean transit time (MTT) and CO.

A lung water computer determined the mean transit time for thermal indicator and for dye indicator. The cold indicator diffuses and is convected into the extravascular compartment, depending on time, heat conductivity, heat capacity and vascular surface area, whereas the dye

indicator binds rapidly to plasma proteins (52). The dye indicator is confirned to the intravascular compartment during one passage through the heart, pulmonary vessels and aorta. Two distribution volumes can be calculated

$$ITBV_{MTT}=Q_{dye} \times MTT_{dye} \quad (1)$$

$$TTV_{MTT} = Q_T \times MTT_T \quad (2)$$

In equation 1, $ITBV_{MTT}$ is the intrathoracic blood volume (=intravascular volume from the point of injection of the indicator until its detection in the descending aorta) and Q_{dye} and MTT_{dye} represent the flow and the mean transit time for the dye-indicator, respectively (69,89)

In equation 2, for the thermal indicator, a total thermal distribution volume TTV_{MTT} is obtained by means of the thermodilution flow (Q_T) and the mean transit time of the thermal indicator (MTT_T). TTV_{MTT} represents the sum of $ITBV_{MTT}$ and the extravascular heat-exchangeable volume. Thus, extravascular thermal volume ($EVTV_{MTT}$) is defined as the difference between

TTV_{MTT} and $ITBV_{MTT}$

$$EVTV_{MTT} = TTV_{MTT} - ITBV_{MTT} \quad (3)$$

If perfusion of the pulmonary vessels is not significantly impaired, EVTVMTT is regarded as a reliable estimate of extravascular lung water (EVLW). Using the dilution curve decay approach (73), the pulmonary thermal decay volume (PTV_{DT}) is calculated as

$$PTV_{DT} = Q_T \times \pi_T \quad (4)$$

where π_T is the exponential decay time for the thermal indicator, measured in the descending aorta. Likewise, PBV_{DT} is obtained for the dye indicator as

$$PBV_{DT} = Q \times \pi_{dye} \quad (5)$$

where PBV_{DT} constitutes the pulmonary blood volume (PBV) and π_{dye} represents the exponential decay time for dye indicator, measured fiberoptically. This method is based on two assumptions: (i) that for a single mixing chamber with complete mixing of the indicator and constant fluid flow, the dilution curves decay exponentially with time π, and (ii) that for a number of different serial mixing chambers constituting different mixing volumes but identical chamber flow, the decay of the dilution curve is determined predominantly by the largest chamber (69).

Thus, $EVTV_{DT}$ is calculated as

$$EVTV_{DT} = PTV_{DT} - PBV_{DT} \quad (6)$$

Computed tomography (CT)

Chest CT scans were performed with a Somatom HiQ (Siemens AG, Erlangen, Germany) with a 512 x 512 matrix, 150 kV, 133mA, a 2 sec exposure time and 4 mm collimation. For attenuation measurements the entire right lung was chosen as region of interest (ROI) and the mean attenuation was calculated: -1000 Hounsfield units (HU) correspond to air and 0 HU corresponds to water. As the scans were close to the diaphragm in order to cover an area containing the largest possible number of lung parenchyma, it was often necessary to shift the

table position about 20 mm cranially, as the volume of the lung decreased with gradual collapse. When lung collapse was extensive, both right and left lung were chosen *en bloc* as ROI, though at full lung expansion the computational capacity of the CT scanner did not permit the use of both lungs together as a single ROI. Particular care was taken to include only lung parenchyma in the ROI, i.e. excluding soft tissue and pleural effusion, though some vessels within the lung parenchyma, especially peripheral ones, were unavoidably included. Scans were evaluated visually for signs of alveolar edema, interstitial edema, and pleural effusion.

Experimental procedure

Following anesthesia and preparation, the animals were laid prone. Lavage was performed followed by a recruitment procedure. Pinfl was then determined, followed by a second recruitment procedure. The animals were then randomized to different studies (56,64,65,98). A PEEP level corresponded to 75% of Pinfl was used (56,65), and this was called *ventilation with open lung.*

Statistical analysis

Values presented are either values for individual animals, or mean ±SEM, and linear regression analysis was applied to study relationships between FRC and attenuation. In all studies, ventilatory volumes and derived parameters were converted to BTPS conditions. Indexed values were related either to body mass or to body surface area (BSA).Values were expressed as means ±1 standard deviation (SD). A standard statistics package was used (Statview)™. Differences between the ventilatory settings were evaluated with a t-test for all paired differences within each variable. Differences between the ventilatory settings were evaluated with a one-way analysis of variance for factorial measures for all paired comparisons within each variable, using Scheffe´s F-test. If a significant difference was detected, a post hoc test was performed to determine the significances in the analysis of variance. Statistical significance was declared at
$p \leq 0.05$ (=*) and $p \leq 0.01$(=**) and $p \leq 0.001$(=***).

RESULTS

In the following, results from the five studies comprising this thesis are presented.

With decreasing PEEP, functional residual capacity (FRC) and PaO_2 decreased and the lung became progressively more dense, as reflected by the radiological attenuation. To avoid hypoxic damage, FIO_2 was maintained at 1.0 throughout the study, and under low PEEP conditions, arterial gas samples were taken after 4 min. Lung FRC was related directly to its radiological attenuation ($R^2 = 0.83$: $p \leq 0.01$). Irrespective of the degree of lung injury, the attenuation at full recruitment varied only slightly between the animals. In contrast, at low levels of PEEP there was considerable variation in attenuation, related to the degree of lung injury. From the pressure/attenuation loop it was observed that the attenuation on the down slope for identical end-expiratory pressures, always had a higher value than that of expansion. Thus, the pressure at which collapse takes place differs from that of expansion of the lung.

With FIO_2 1.0 and ventilation with zero PEEP, lavage reduced PaO_2 from 76 ±4 prelavage to 7 ±2 kPa postlavage and extravascular lung water increased from 5 ±1 to 19 ±3 ml/kg. Compliance was reduced from 26 ±4 to 11 ±2 ml/cmH_2O and FRC from 674 ±167 to 180 ±43 ml. The inflection point was determined at 23 cmH_2O, corresponding to 100% P_{infl}. In a previous study (83) in the same lung model, this PEEP was found to impair hemodynamics, which is why during ventilation at the reference setting and I:E ratio 1:1, external PEEP was reduced to 75% of P_{infl} in each animal.

During prolonged inspiration, intrinsic PEEP increased, and external PEEP had to be reduced in order to maintain mean airway pressure in one study, and to keep total PEEP constant in another study. With mean airway pressure constant, peak and end-inspiratory pressures displayed identical values, while with extended inspiration they decreased from 32 to 29 cmH_2O. Arterial oxygen tension (PaO_2) was unchanged following increased inspiration, although cardiac index (CI), stroke index (SI) and right ventricular ejection fraction (EF) decreased at I:E ratio 2.3:1 with an attendant decrease in the oxygen delivery index (DO2I).

Due to the shortened expiratory time and hence increased intrinsic PEEP, airway pressures increased when total PEEP was kept constan. A minor increase in PaO_2 was seen when I:E was increased from reference setting to I:E 1.5:1, but no further improvement ensued. With I:E ratio 2.3:1, stroke index and EF decreased, but cardiac index and oxygen delivery index did not decrease until I:E 4:1. In both studies with prolonged inspiration, CO_2 elimination increased at I:E ratio 2.3:1 and above.

For all levels of PEEP, with decelerating inspiratory flow, peak inspiratory pressure (PIP) was lower and mean airway pressure higher than that obtaining with constant inspiratory flow. However, no differences in end-inspiratory pressure were seen. At PEEP 13 and 9 cmH_2O the smallest inspiratory pressure amplitude, PIP – total PEEP (Δp) was seen with both inspiratory flows. Notably, compliance values were highest only at 13 cmH_2O with both flow patterns, though not significantly so. Differences in PaO_2 between the flow pattern when ventilation was under, at, or above inflection point were not seen. For all levels of PEEP, $PaCO_2$ was lower with the decelerating inspiratory flow, i.e. increased alveolar ventilation.

Decelerating inspiratory flow produced lower $PaCO_2$ and less serial dead space (SDS) than did constant flow. With constant inspiratory flow, 12 bpm, and an end-inspiratory pause of 25%, an increase in FRC was seen and a decrease in SDS. Despite this, no improvement in CO_2 elimination was evident compared with constant flow without a pause, or vis-à-vis decelerating inspiratory flow. From the integrated tidal volume traces it was evident that decelerating inspiratory flow delivered the tidal volume early. Hemodynamics, oxygen delivery and mixed venous oxygen saturation did not differ between the decelerating and constant inspiratory flow patterns.

Discussion

The major findings were that the decelerating inspiratory flow was no better than constant flow for alveolar recruitment or oxygenation of the blood, but it did increase carbon dioxide elimination, i.e. improved alveolar ventilation. The main aspects to be considered in this discussion are:

aspects of the open lung concept;
enhanced CO_2 elimination with the decelerating inspiratory flow;
clinical implications of decelerating inspiratory flow.

To analyse the radiological observations and their relationship to airway pressure in our lung model with unstable alveoli, the principle of quantal alveolar behavior has been found useful (98). Application of PEEP redistributes tidal ventilation from less dependent (upper) regions to the more dependent (lower) regions of the lung (33). The response to PEEP titration varies not only with the type of lung pathology but also within the lungs. As stated by Gattinoni et al. (34), due to gravity the alveoli in the dependent parts of the lung have a greater propensity to collapse than in the non-dependent parts. Hence the non-dependent alveoli are the more recruitable, while dependent ones may be difficult, even impossible to recruit (35).

Stepwise sequential deflation from full expansion, followed by stepwise inflation produces a pressure attenuation loop, which implies that the attenuation of the lung is related not only to the preset PEEP, but also to its immediately preceding structural status (98). For identical end-expiratory pressures levels, the attenuation on the down slope was invariably greater than that on the up slope. Thus, the pressure at which collapse takes places during inflation differs from that of expansion. This pressure difference has the important consequence that a collapsed alveolus will not expand and fill with air again until a pressure exceeding that of alveolar collapse is applied (18,82). Conversely, once an alveolus has expanded it will not collapse until collapse pressure is reached (see Fig 3).

In order to prevent lung injury due to high shear forces between open and closed lung units, the PEEP necessary to stabilize end-expiratory volume can be minimized if the lungs are complete opened to FRC equivalent to that of a healthy lung (64,85,98). Thus, PEEP has to exceed the critical collapse pressure, otherwise (see Fig 3) already recruited alveoli would undergo end-expiratory collapse.

Alveolar recruitment

Alveolar recruitment refers to an increase in FRC secondary to inflation of previously collapsed alveoli (43,60). On the pressure/volume curve the appearance of an inflection point (Pinfl) is thought to represent the critical pressure necessary to reopen, or recruit, closed peripheral airways and/ or collapsed alveolar units (7,67,80).

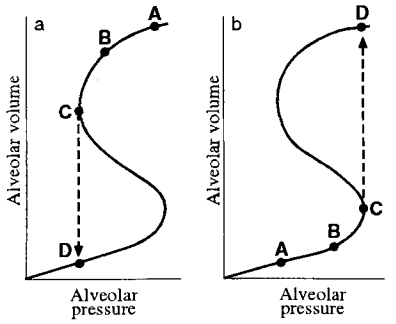

Figure 3a. Schematic drawing illustrating the proposed alveolar non-collapse and collapse mechanism and its relation to alveloar pressure. A) Air-filled alveolus; B) alveolus still air-filled; C) end-expiratory collapse pressure has been reach; D) alveolar fluid and collapse of alveolus. Note that the intra-alveolar pressure is identical at point C and D.
Figure 3b. A). Alveolar fluid with alveolar collapse; B) pressure increases without recruitment, alveolar collapse still occur; C) alveolar recruitment, the critical level of intra-alveolar pressure has been reach; D) air-filled alveolus. Note that points C and D are at identical pressures.

In the lavage model of lung injury the ability to produce a PV loop with an inflection point increases with increasing extravascular lung water. In other words, the greater the amount of intrapulmonary fluid (reflected as extra thermal volume), the larger the number of unstable alveoli that will exhibit quantal alveolar behavior. As mentioned earlier, the pressure at which alveolar collapse occurs differs from that of expansion.

The inflection point pressure was invariably quite high (23-24 cmH_2O); and this we called Pinfl of 100% (85). But as ventilation with PEEP set at this level impaired hemodynamics, PEEP level was reduced to 75% of the Pinfl value. Even this level of PEEP impaired hemodynamics slightly. This is further illustrated (64), where a PEEP level of 22 cmH_2O corresponded to Pinfl 100%. When PEEP was gradually reduced to a level corresponding to about Pinfl 60% (13 cmH_2O), PaO_2, compliance and oxygen delivery increased with both inspiratory flow patterns. This then indicates that the lung was open at PEEP levels at or above 13 cmH_2O. A applicable approach to identify the minimum level of PEEP needed to prevent end-expiratory collapse could be to find the lowest inspiratory pressure amplitude (Δp = peak inspiratory pressure – total PEEP) for delivery of the tidal volume. As seen, PEEP levels of 9 and 13 cmH_2O yielded the lowest inspiratory pressure amplitude, though at 13 cmH_2O, compliance, PaO_2 and oxygen delivery increased.

Ventilation techniques

Several studies (1,2,6,39,40) have shown that the decelerating inspiratory flow gives a better gas exchange than does constant flow. The theoretical advantages (41) underlying this are related to the effects of the rate of rise in alveolar pressure, the associated rise in mean airway pressure (76), the

effects upon alveolar residence time for gas exchange and on the intrapulmonary distribution of tidal ventilation. We therefore hypothesized that a ventilatory pattern with the major part of the tidal volume delivered early could avoid end-expiratory collapse at a lower end - expiratory pressure (PEEP) than would constant flow. Thereby pressure-controlled ventilation with decelerating inspratory flow could potentially aid recruitment due to the flow pattern itself.

Both inspiratory flow patterns showed an increase in PaO_2 at and above PEEP set at 13 cmH_2O. However, no differences in PaO_2 were seen between the decelerating and constant inspiratory flow patterns, despite higher mean airway pressure with the decelerating flow. Peak inspiratory pressure was lower with the decelerating inspiratory flow, and it is generally agreed that end-inspiratory pressure more reliably reflects alveolar pressure (86). With constant tidal volume and the same set external PEEP, no differences were seen in end-inspiratory pressure between the flow patterns. FRC was unchanged, and the hypothesis of inspiratory flow-dependent recruitment with the decelerating inspiratory flow was not supported.

In order to reduce ventilation-related lung injury, pressure-controlled ventilation with prolonged inspiratory time (PC-IRV) has also been used (11,16,36,46,61,91). Several studies have shown reduced airway pressures (2,6,51) and increased PaO_2 (1,2,6), believed to be due to the short expiratory time and intrinsic PEEP with PC-IRV. In contrast to several other studies (11,16,36,46,61,91) which used decelerating inspiratory flow with increased inspiratory time to recruit collapsed alveoli, we ventilated the lungs with sufficient PEEP to prevent end-expiratory collapse already with the reference mode (I:E ratio of 1:1). To elucidate the underlying mechanism of increased inspiration/expiration ratio, mean airway pressure (MPAW) was maintained constant in the first study (56), and total PEEP was kept constant in the second study (65). Several investigations (9,14,62,70,75,91) have shown increased CO_2 elimination with inverse ratio ventilation. This was also seen in ours studies of IRV.

When I:E ratios of 2:1, or above, was used, both studies (56,65) showed impaired hemodynamics, though arterial oxygenation tension remained unaffected. During IRV, the effects of shortened expiratory time lead to increased intrinsic PEEP ($PEEP_i$). This, in combination with constant inspiratory pressure, increased mean airway pressure considerably. It is well known that mean airway pressure is closely related to the cardiovascular effects of mechanical ventilation (22,25,78). The effect of a given mean airway pressure will vary with such factors as compliance of lung and the chest wall, vascular filling and cardiac competence. Both studies, showed a reduction in cardiac index and stroke index with I:E ratio 2.1:1. The conclusion drawn from those results is that, if the lung is ventilated with sufficient total PEEP to prevent end-expiratory collapse, IRV will not provide any additional advantage. In order to prevent lung injury due to high shear forces between open and closed lung units, ventilation which result in the smallest possible pressure amplitude (peak inspiratory pressure-total PEEP=Δp) should be used. Judging by the results of both studies of IRV, the smallest Δp is achieved with I:E ratios of 1:1 and 1.5:1.

Alveolar ventilation

Several studies (17,20,21,71,74) have tried to explain the finding of increased CO_2 elimination and reduced dead-space to tidal volume with decelerating inspiratory flow. Watson et al. (94) believed that with insufflation of a duration of more than 1 second, intrapulmonary gas distribution would not be affected by the inspiratory flow pattern, but it is important to realize that this study was with normal lungs and the sample size was small. Baker et al. (6) hypothesized that the combination of changes in mean airway pressure and improved intrapulmonary gas distribution would account for longer diffusion time, and explaines the improved gas exchange effect seen with the decelerating flow, which both Mang (61) and Boros (11) supported. Rappaport (81) and Lessard (51) incorporated an end-inspiratory pause which is believed to increase intrapulmonary gas mixing and alveolar diffusion time (24), and thereby incresed CO_2 elimination.

Decelerating inspiratory flow yielded lower $PaCO_2$ than constant for all levels of PEEP (63). The increased efficiency of carbon dioxide elimination with decelerating inspiratory flow, might well be linked to the early delivery of tidal volume. In one of the study, we used integrated tidal volume traces, and seen from this it was evident that the decelerating flow delivered the tidal volume early. With pressure-controlled ventilation and 24 breaths per minute (bpm), tidal volume was delivered during the first 60%, and with 12 bpm during the first 40% of the inspiratory cycle. Early delivery of the tidal volume, with pressure-controlled ventilation and its constant inspiratory pressure, allows more time for even distribution of the inspired tidal volume.

In all our studies, decelerating inspiratory flow showed increased CO_2 elimination. The tidal volume will be better distributed due to the sustained pressure, and by delivering the tidal volume early, the diffusiontime will be longer. By ventilating the surfactant - deficient lungs above alveolar collapse pressure, this thesis showed that differences in inspiratory flow pattern could be detected even when there was no severe ventilation-perfusion mis-match. This might then mean that a decelerating inspiratory flow is of advantage even for ventilation of normal lungs.

Ventilatory management

We suggest that, in order to optimally support ventilation , and in order to avoid iatrogenic lung injury, the following ought to be observed: (1) maintain all lung units open with the smallest feasible pressure amplitude, (2) maintain normovolemia, in order to avoid hemodynamic impairment, (3) in view of the viscoelastic properties of the lungs, perform recruitment procedures intermittently during mechanical ventilation (57).

When ventilation is maintained under open lung conditions, no categorical, statement can be made regarding the superiority of either flow pattern over the other. In this thesis we could show that decelerating inspiratory flow allowed more efficient alveolar ventilation, than did constant flow, although it failed to reduce airway pressure.

Nevertheless, decelerating inspiratory flow is beneficial in the clinical setting, by virtue of its ability to reduce the likelihood of an inadvertently uncontrolled increase in alveolar pressure (63,84). The resulting improved alveolar ventilation may even reduce ventilatory volumes in both healthy and diseased lungs. There is no guarantee that results from animals studies are relevant to

patients with acute respiratory failure. Consequently, a definitive clinical study on the relative effects of constant versus decelerating inspiratory flow needs to be undertaken.

CONCLUSIONS

1. To analyse radiological observations and their relationship to airway pressure in our lung model with unstable alveoli, the principle of quantal alveolar behavior has proved useful.

2. Ventilation with decelerating inspiratory flow revealed lower peak inspiratory pressure and higher mean airway pressure than did constant inspiratory flow, but no differences in end-inspiratory pressure were seen.

3. Decelerating inspiratory flow delivers the bulk of the tidal volume during early inspiration under sustained constant inspiratory pressure. This reduces serial dead space and improves alveolar ventilation, but decelerating inspiratory flow was found to be no better than constant flow for alveolar recruitment or oxygenation of the blood.

4. When the lung is ventilated with sufficient total PEEP to prevent end-expiratory collapse, an increased I:E ratio will impair hemodynamics and provide no additional advantage.

5. Open lung conditions are not only attributable to arterial oxygen tension; hemodynamics is influenced by the ventilatory pattern and must also be taken into account if oxygen delivery is to be optimal.

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Correspondence to:
Agneta Markström, MD., PhD.
Departement of Anesthesiology and Intensive Care
Uppsala University Hospital
Uppsala, Sweden