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Contribution of opening and closing of lung units to lung hysteresis

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Abstract

The recruitment and derecruitment of lung units is one explanation of the hysteresis observed in an excised lung during inflation and deflation. A simplified model has been proposed in which the recruitment–derecruitment process is a function of end-expiratory pressure (Frazer, D.G., K.C. Weber and G.N. Franz, Respir. Physiol. 61: 277–288, 1985). The object of this study was to test this model with three experimental procedures. During the first set of experiments, progressively larger pressure–volume (PL–VL) loops were recorded with end-expiratory pressure held at either -5 cmH_2O, where all lung units are assumed to be closed, or $+5$ cmH_2O, where all recruited lung units are assumed to be open. In the first case hysteresis is maximal, in the second, minimal. The difference in hysteresis is presumed to arise from the recruitment–derecruitment process. In the second set of experiments, excised lungs are slowly inflated and then deflated at a constant rate while constant-amplitude sinusoidal volume oscillations are superimposed. The end-expiratory pressure of the superimposed loops gradually rose as the lung was inflated and fell as the lung was deflated. Hysteresis was minimal when end-expiratory pressure was above 4 ± 1 cmH_2O even as peak-to-peak loop pressure greatly varied. This supports the notion of an end-expiratory pressure dependent mechanism of recruitment/derecruitment. During the third set of experiments lungs were inflated to either 50%, 75%, or 100% TLC. Volumes of air were then withdrawn and replaced so that the initial volume was restored in sinusoidal fashion as the amplitude of the volume excursions increased. For PL–VL loops with end-expiratory pressures between $+4$ and -2 cmH_2O, pressure amplitudes rose and the hysteresis index (loop area/tidal volume) increased, regardless of the initial lung volume. These results are consistent with the previously described model of Frazer et al. (1985) which assumed that PL–VL curves can be divided into an ‘opening’ region, an ‘open’ region and a ‘closing’ region and that the demarcation of these regions depends on transpulmonary pressure, specifically end-expiratory pressure, and to a much lesser degree on lung volume.

Keywords: Airways, closure; Excised lung, inflation, hysteresis; Lung volume, recruitment, derecruitment; Mechanics of breathing, lung inflation

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1. Introduction

Measurement of the relationship between transpulmonary pressure (PL) and volume (VL) of excised lungs has been used to provide a description of the lungs' mechanical properties. In the static PL–VL characteristic of a normal excised lung, the inflation and deflation curve segments do not follow the same path. The lung volume at any given pressure during deflation is greater than during inflation. Thus, the inflation–deflation curves form the boundary of an enclosed region or 'loop' of finite area; that is, it exhibits hysteresis.

Traditionally, the stretching and compression of the surfactant film at the air–liquid interface in the periphery of the lung has been accepted as the probable explanation for PL–VL hysteresis (Goerke, 1974), but a process of recruitment and derecruitment (or opening and closing) of lung units has also been proposed. Mead et al. (1957) were among the first investigators to suggest that hysteresis associated with pressure–volume curves of air-filled lungs was likely due to the sequential opening and closing of lung units. Later, Macklem (1971) described a mechanism which could explain lung unit closure in terms of the formation of a meniscus or liquid plug forming across the airways as the lung deflates. Subsequently, Glaister et al. (1973) surmised that the closure of lung units and their subsequent reopening could significantly contribute to lung hysteresis. The same investigators proposed that, in excised lungs, derecruitment of lung units could be inferred from differences between actual deflation PL–VL curves and curve-fitted exponential curves. They suggested that deviations of the actual PL–VL curves from the theoretical exponential curves resulted from the derecruitment (closure) of lung units. The points where the lower segments of the actual curves departed from the exponentially fitted curves were thought to represent initial closing of lung units during deflation. By assuming that the ratio of slopes of the actual and hypothetical pressure–volume curves at a given low pressure was proportional to the number of open units, they predicted that unit closure depends on end-expiratory pressure (Davis et al., 1975). Glaister et al. (1973) also proposed that, during lung inflation, lung units reopened as the inflation branch of the PL–VL curve changed from a linear to segment to an exponential. The transition was called the 'knee' of the curve. On inflation deviations, from the exponential curve were taken to manifest reopening of lung units.

Later, additional evidence with regard to airway closure and menisci of liquid plug formation in airways was obtained (Frazer and Weber, 1976; Frazer et al., 1979; Kamm and Schroter, 1989). With more detailed information concerning the closing of lung units, a simple lung model was proposed by Frazer et al. (1981) to explain the effects of the recruitment–derecruitment of lung units on pulmonary hysteresis. Results of subsequent experiments examining the reopening of lung units (Brancazio et al., 1985; Frazer et al., 1986) were consistent with the model. It should be noted that this model has many of the characteristics predicted by Glaister et al. (1973).

The recruitment–derecruitment model makes the following assumptions which are consistent with the experimental evidence: (1) For deflations and reinflations from approximately TLC to 50% TLC, hysteresis is minimal, all lung units are open, and neither derecruitment nor recruitment occurs. This constitutes the 'open' region or zone of the PL–VL curve (Fig. 1). It should be noted that this model assumes that the minimal hysteresis of PL–VL loops recorded

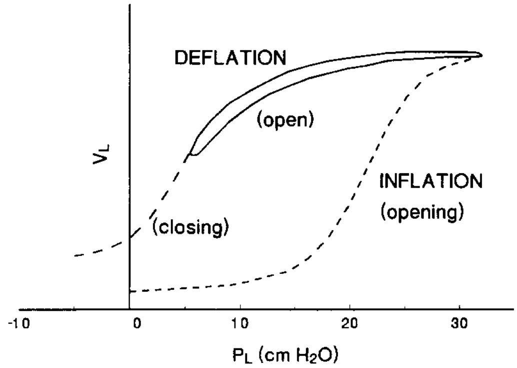

Fig. 1. The pressure–volume curve for open lung units is illustrated by the solid curve ('open' segment) which exhibits only a modest amount of hysteresis associated with the expansion and contraction of open lung units. When the end-expiratory pressure falls below the 'critical closing pressure' of a particular lung unit, that lung unit closes ('closing' segment). To reopen a closed unit, pulmonary pressure must rise to the 'opening pressure' of the lung unit during inflation ('opening' segment). The result is increased hysteresis.

within the 'open' zone is a function of the mechanical properties of the air–liquid interface and lung tissue. As a result, the recruitment–derecruitment model is not mutally exclusive with respect to other models which attribute PL–VL hysteresis to the intrinsic propeties of alveolar surfactant. (2) For deflations with end-expiratory pressures below a certain level (approximately +4 cmH_2O for excised rat lungs), airways begin to close in the so-called 'closing' region (Fig. 1). Closing pressures are distributed normally with a mean of about 2 cmH_2O (s.d. = ±1 cmH_2O). At −5 cmH_2O all lung units are closed. (3) Inflation, from a state of complete or partial closure, produces increasing recruitment in the 'opening' region (Fig. 1). This occurs as the opening pressures of individual units are being reached.

If the basic assumptions of the recruitment–derecruitment model are correct, the area of the hysteresis loop should then be (1) minimal for deflations and reinflations between TLC and end-expiratory pressures (EEPs) equal to or greater than $+4 \pm 1$ cmH_2O, (2) increasing for deflations with EEPs $< +4 \pm 1$ cmH_2O, which in normal lungs correspond to volumes slightly smaller than 50% TLC, as lung units close (derecruitment) in a pressure-dependent manner during deflation and reopen (recruitment) during reinflation, and (3) maximal for inflations from a state of maximal lung unit derecruitment at negative end-expiratory pressures to a state of complete recruitment to TLC and subsequent deflation to complete derecruitment.

In the past, Bachofen and Hildebrandt (1971) described a method for analyzing pulmonary hysteresis by relating the hysteresis area, H, of lung PL–VL curves forming closed loops with the change in pulmonary pressure ΔP, and the tidal volume (VT), through the relationship $H = K(V_T)(\Delta P)$ where K is a proportionality constant. They rearranged terms to produce the hysteresis index: $H/V_T = K(\Delta P_L)$, the same index used in this study. Fredberg and Stamenovic (1989) showed that lung tissue hysteresivity, η, is related to K, by the expression $\eta = [(\pi/4K)^2 - 1]^{1/2}$. In a similar manner, the dynamic elastance of the lung, Edyn, can be written as a function of K as: $Edyn = [1 - (4K/\pi)^2]^{1/2} \Delta P_L / \Delta V_L$.

In this study, three different sets of experiments were performed using a volume perturbation method in which PL–VL loops were recorded as the lung was ventilated under a variety of conditions. The objective of the first two sets of experiments was to show that a normalized measure of hysteresis, namely the hysteresis index, H/VT (loop area/tidal volume), increases for loops having low end-expiratory pressures because of the increased energy loss related to the closure and reopening of lung units. The objective of the third experiment was to show that the recruitment–derecruitment process depends primarily on end-expiratory pressure and not on initial lung volume.

In the first set of experiments, sinusoidal volume perturbations of increasing amplitude were applied to excised lungs while the end-expiratory pressure was maintained at either −5 or +5 cmH_2O. Pressure–volume curves with an end-expiratory pressure of −5 cmH_2O, according to Fig. 1, form loops for which all open lung units should close during deflation ('closing' zone) and then reopen on subsequent inflation ('opening' zone). In this case, loop area should increase as larger and larger inflations from the maximally closed state produce increasing recruitment. Loops with an end-expiratory pressure of +5 cmH_2O, according to Fig. 1, represent pressure–volume curves recorded in the 'open' zone where neither derecruitment nor recruitment occur. Here, hysteresis should be minimal.

During the second set of experiments, a sinusoidal volume perturbation of constant amplitude was superimposed on slow inflations and deflations of constant rate. The end-expiratory pressure varied for individual loops in these experiments so that, according to Fig. 1, three states could be observed: (1) all open lung units remain open during a perturbation cycle (minimal loop area expected); or (2) a fraction of the open lung units closes during the downswing of the volume perturbation and then reopens during the upswing (increasing loop area); the rest of the lung units are open throughout and contribute little hysteresis; or (3) all lung units are closed at the end of the downswing of the volume perturbation; the subsequent upswing of the perturbation opens (recruits) all units for which the opening pressure is exceeded (maximum loop area for the particular volume increment).

The third set of experiments was designed to examine the assumption that lung unit closure and reopening depend on end-expiratory pressure and not on end-expiratory volume. Lungs were initially inflated to 1/2 TLC, or 3/4 TLC, or TLC. PL–VL loops were then recorded as increasing volumes of air were withdrawn and replaced in the lungs. This was continued until lung units closed at low end-expiratory pressures and subsequently reopened. The results were compared for PL–VL loops recorded at the three different initial lung volumes.

2. Methods

Long Evans hooded male rats weighing between 300 and 350 g were anesthetized by intraperitoneal injection of pentobarbital (65 mg/kg). Their tracheas were intubated, and the animals were sacrificed by exsanguination via the abdominal aorta. The lungs were excised, degassed in a vacuum chamber after the method of Stengel et al. (1980), and then attached by the trachea to a cannula extending through the top of the plethysmograph as shown in Fig. 2. The cannula was connected, in parallel, to a syringe pump (Harvard Apparatus, Model 901) and electronically controlled pump (Khoshnood et al., 1978). The syringe pump inflated and deflated the lung slowly and at a constant rate (3.82 cc/min). The electronically controlled pump superimposed sinusoidal volume changes under control of a function generator (Hewlett Packard, Model 3310A). Transpulmonary pressure, PL, was measured at the trachea (Fig. 2) with a pressure transducer (Setra, Model 239E), and lung volume was determined by measuring the volume of gas displaced from the plethysmograph with a spirometer (Med. Science, Model 118). Pressure–volume curves were recorded simultaneously on an X–Y plotter (Seltec VP-6432S) and a digital computer with an ISAAC (Cyborg, Model 91) digital sampling system at a rate of 50 Hz per channel.

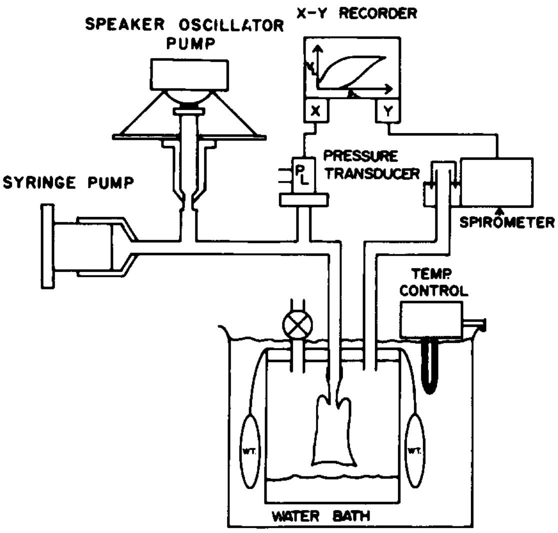

Fig. 2. The schematic diagram of the airfilled plethysmographic system used to record PL–VL curves of excised rat lungs. The plethysmograph was heated to 27°C to increase temperature stability.

During the initial set of experiments, degassed lungs ($N = 4$) were placed in the air-filled plethysmograph, inflated from 0 to 30 cmH_2O, and then deflated to -5 cmH_2O at a rate of 3.82 cc/min. During the second inflation cycle, a sinusoidal volume perturbation of variable amplitude (Vp) was used to ventilate the lung and generate a series of PL–VL loops. Each loop had a constant end-expiratory pressure (EEP) of -5 cmH_2O while maximum loop pressure (PL_{max}) was gradually increased from $+6$ to $+30$ cmH_2O. A second series of PL–VL loops was recorded in a similar manner except that during the first cycle the lungs were inflated from the degassed state to $+30$ cmH_2O and deflated to an EEP of $+5$ cmH_2O. Sinusoidal volume perturbations were again used to inflate and deflate the lungs while the EEP was held at $+5$ cmH_2O and PL_{max} was gradually increased from $+8$ cmH_2O to $+30$ cmH_2O. Tidal volume (VT), hysteresis area (H), hysteresis index (H/VT) and pressure change (ΔPL) were calculated, and the hysteresis index (H/VT) was plotted as a function of ΔPL for each PL–VL loop. Loop area (H) was calculated from the digitized PL–VL curves with a third order integration algorithm.

At the beginning of the second set of experiments, degassed lungs were slowly inflated (3.82 cc/min) to TLC, which was defined as the volume of the lung at 30 cmH_2O and then deflated to an EEP of -5 cmH_2O. During the second cycle, the lungs were inflated and deflated at the same slow rate but with a sinusoidal volume perturbation superimposed. The perturbation had a peak-to-peak magnitude, 2Vp, of 3 cc and a frequency of 10 cycles/min. The resulting pressure–volume curve, recorded during a slow underlying inflation, consisted of a series of PL–VL loops with different EEP values. A second series of PL–VL loops was recorded by slowly deflating the lungs from TLC to -5 cmH_2O with the same constant-volume perturbation superimposed.

Once the PL–VL loops were recorded, they were individually analyzed by measuring or computing the following parameters: (1) end-expiratory pressure (EEP), (2) maximum loop transpulmonary pressure ($\text{PL}_{\max}$), (3) end-expiratory volume (EEV), (4) peak-to-peak difference in transpulmonary pressure (ΔPL), (5) tidal volume (VT), (6) loop or hysteresis area (H), and (7) hysteresis index (H/VT). In order to analyze the results, ΔPL was plotted as a function of the loop EEP, and the hysteresis index was plotted against ΔPL for the same loop.

During the third set of experiments, rat lungs were degassed, then inflated–deflated in the air-filled plethysmograph for one cycle between -5 and $+30$ cmH_2O. Lung volume at $+30$ cmH_2O was designated as TLC. In the second cycle, lungs were reinflated to either 1/2 TLC, 3/4 TLC or TLC and allowed to stress-adapt for 2 min. At that time a sinusoidal volume perturbation (10 cycles/min) of variable amplitude, Vp, was applied to the lung by withdrawing and replacing a volume of gas with the electronically controlled pump. As Vp was gradually increased, PL–VL loops were generated and recorded on the X–Y recorder operated as a strip chart recorder and on the digital computer using the ISAAC system. In these experiments ΔPL, VT, and H were recorded or calculated for all loops; ΔPL was plotted against time; and the hysteresis index, H/VT, was plotted as a function of the EEP.

3. Results

During the first set of experiments, two groups of PL–VL loops were recorded. One set was recorded with end-expiratory pressure at -5 cmH_2O. The second set was recorded over the 'open' region ($+5$ to $+30$ cmH_2O during lung deflation, see Fig. 1). These results are shown in Fig. 3A and B. In Fig. 4, the hysteresis index, H/VT, is shown as a function of ΔPL for each PL–VL loop in the manner of Bachofen and Hildebrandt (1971) and Horie and Hildebrandt (1973). It should be noted that when K is constant, plots of H/VT (Fig. 4) form straight lines of slope K. The slope of the upper hysteresis index curves in Fig. 4 represents K for the 'opening' region, while the slope of the lower curves represents K for the 'open' region for the same lungs. The difference in slope between the upper and lower curves increases as ΔPL increases. Presumably, the difference in the slope of the hysteresis index curves at the same ΔPL reflects the contribution of the recruitment–derecruitment process to total PL–VL loop hysteresis. This linear relationship is similar to

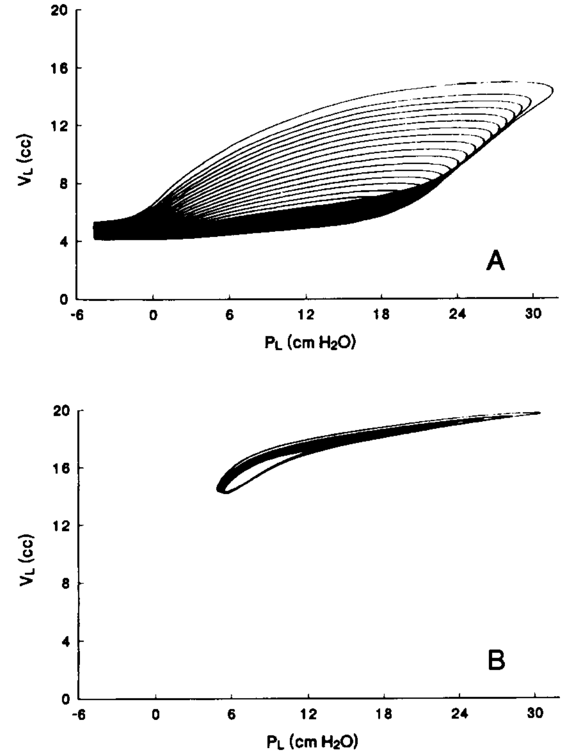

Fig. 3. (A) A lung was inflated and deflated for one cycle between -5 and $+30$ cm H_2O (not shown). Then, a series of sinusoidal volume perturbations of increasing amplitude was used to generate a series of PL–VL loops having an EEP of -5 cm H_2O. Loops were formed until a $\text{PL}_{\max}$ of $+30$ cm H_2O was reached. (B) On the first cycle the lung was inflated from the degassed state to $+30$ cm H_2O and then deflated to a positive transpulmonary pressure of $+5$ cm H_2O (not shown). A series of PL–VL loops with a constant EEP of $+5$ cm H_2O was recorded as the amplitude of a sinusoidal volume perturbation increased. Loops were recorded until a value of $\text{PL}_{\max}$ of $+30$ cm H_2O was reached.

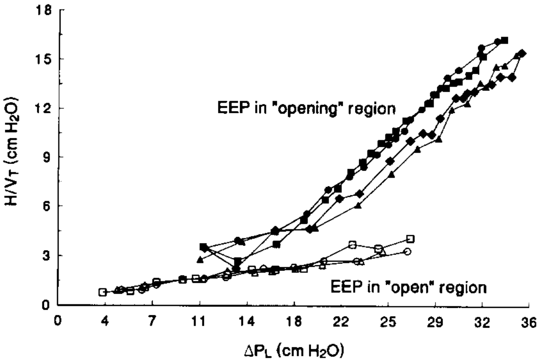

Fig. 4. The hysteresis index, i.e., hysteresis area/tidal volume (H/VT), for PL–VL loops depicted in Fig. 3. The upper set of curves corresponds to recordings in Fig. 3A. The lower set of curves corresponds to recordings in Fig. 3B.

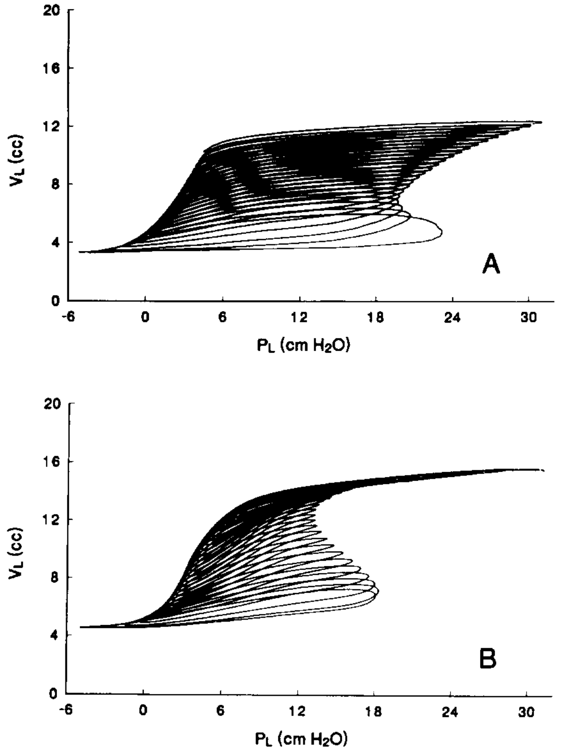

Fig. 5. (A) A representative set of 'inflation' PL–VL loops recorded for a typical rat lung as the lung was inflated from -5 cm H_2O to 30 cm H_2O with sinusoidal volume perturbations (10 cycles/min) of constant amplitude (3 cc peak-to-peak) superimposed on a slow constant rate inflation (3.82 cc/min). (B) A representative set of 'deflation' PL–VL loops. In this case, the lung was deflated from 30 cm H_2O to -5 cm H_2O with the same sinusoidal volume perturbations superimposed on a slow constant-rate deflation (3.82 cc/min).

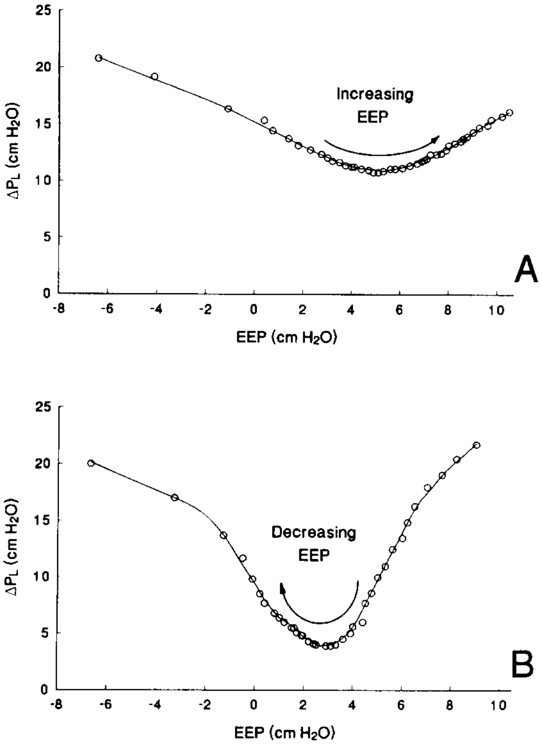

Fig. 6. (A) The relationship between peak-to-peak loop pressure, ΔPL, and end-expiratory pressure, EEP, for 'inflation' loops shown in Fig. 5A. (B) The relationship between peak to peak loop pressure, ΔPL, and end-expiratory pressure, EEP, for 'deflation' loops shown in Fig. 5B.

that described previously for cat lungs by Horie and Hildebrandt (1973). The plots of the hysteresis index against ΔPL for an end-expiratory pressure of -5 cmH_2O appear to resemble sigmoidal segments, changing from low slopes (or lower values of K) at the 'knee' at low ΔPL to higher slopes (or higher values of K) as ΔPL increases.

Representative PL–VL loops produced by sinusoidal volume perturbations (3 cc peak-to-peak) superimposed on a slow constant-rate inflation rate are shown in Fig. 5A for the second set of experiments. Fig. 5B shows PL–VL loops recorded under similar conditions during slow deflation. The magnitude of the peak-to-peak pressure change, ΔPL, is plotted as a function of the loop EEP in Fig. 6A for inflation and Fig. 6B for deflation. For this lung, the pressure change, ΔPL, reached a minimum at an end-expiratory pressure of about $+5$ cmH_2O during inflation and at about +3 cmH_2O during deflation. In general, during the slow underlying inflation, the hysteresis index and the pressure change are initially high because end-expiratory loop volume is below 50% TLC, and the end-expiratory loop pressure is less than 4 ± 1 cmH_2O (upper limb in Fig. 7A). As slow inflation progresses, end-expiratory loop volume is above 50% TLC, end-expiratory loop pressure exceeds 4 ± 1 cmH_2O, and the hysteresis index barely increases as ΔPL rises (lower limb in Fig. 7A). During slow deflation, ΔPL starts out high while the hysteresis index starts at a low level and decreases slightly as long as end-expiratory loop volume stays above 50% TLC and end-expiratory loop pressure remains above 4 ± 1 cmH_2O (lower limb in Fig. 7B). As end-expiratory loop volume is reduced to values below 50% TLC and end-expiratory loop pressures falls below 4 ± 1 cmH_2O, the hysteresis index rises with increasing ΔPL (upper limb in Fig. 7B). In the course of the third set of experiments, when sinusoidal volume perturbations of gradually increasing amplitude were imposed on the lung at TLC, 3/4 TLC or 1/2 TLC, transpulmonary pressure oscillations were observed as shown in Fig. 8A,B,C. The envelopes of the PL vs. time plots show that (1) PL_{max} remained constant for EEP $> 4 \pm 1$ cmH_2O, (2) PL_{max} increased for EEP values decreasing from +4 to −2 cmH_2O, and (3)

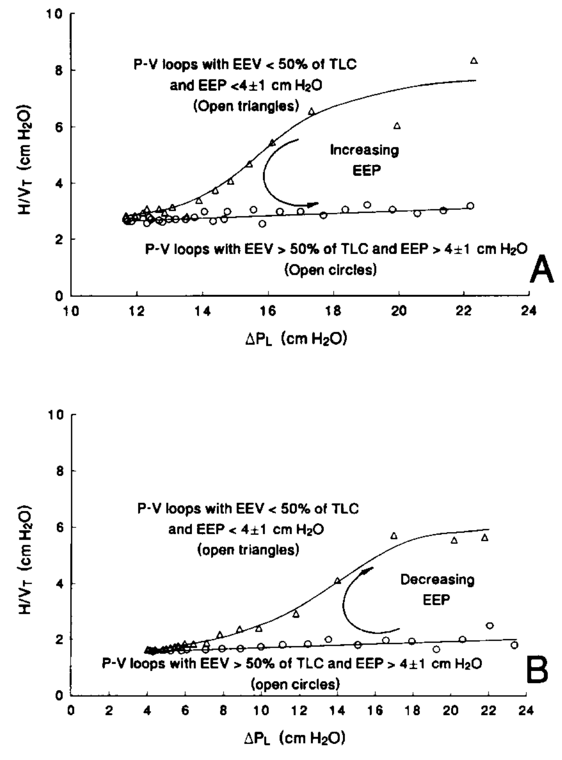

Fig. 7. (A) The hysteresis index, H/VT, as a function of peak-to-peak loop pressure, ΔPL, for the 'inflation' PL–VL loops shown in Fig. 5A. (B) The hysteresis index, H/VT, as a function of peak-to-peak loop pressure, ΔP, for the 'deflation' PL–VL loops shown in Fig. 5B.

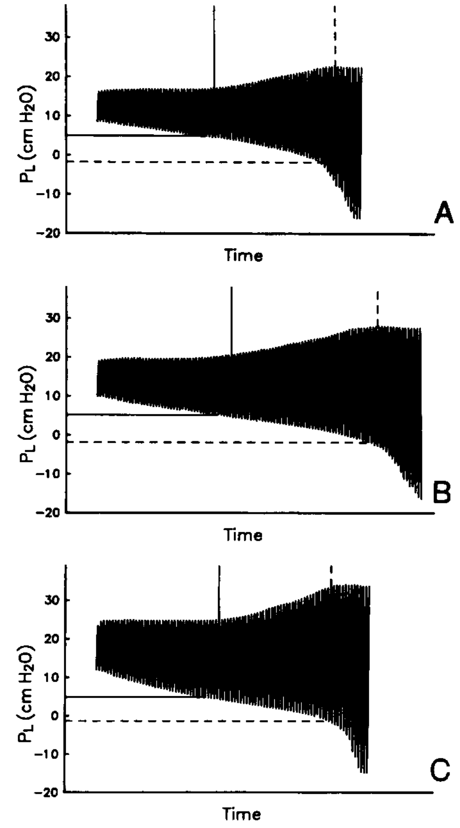

Fig. 8. (A) Transpulmonary pressure (PL) oscillations recorded as a result of applying volume perturbations (10 cycles/min) of gradually increasing amplitude from and back to a lung volume held at 1/2 TLC. (B) A similar curve as in (A) but with the initial and final lung volume held at 3/4 TLC; (C) a similar curve as in (A) with the initial and final lung volume held at TLC. The solid lines in panels A, B and C indicate the EEP during lung deflation at which peak loop pressure begins to increase and the dashed line shows the EEP at which peak loop pressure reached a maximum. The pressure range between the solid and dashed lines represents the region in which lung unit closure presumably occurs.

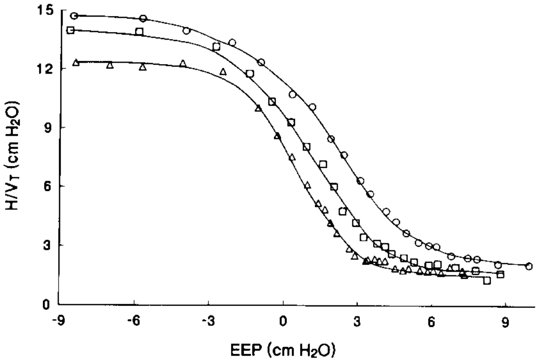

Fig. 9. The hysteresis index, H/VT as a function of EEP for the PL–VL loops shown in Fig. 8A, B and C. The open circles, open squares and open triangles represent volume oscillations beginning at TLC, 3/4 TLC and 1/2 TLC respectively.

PL_{max} remained constant for EEP values less than -2 cmH$_2$O. The family of plots of the hysteresis index, H/VT, as a function of EEP is shown in Fig. 9. Over the end-expiratory pressure range between $+4$ and -2 ± 1 H$_2$O, the hysteresis index increases as end-expiratory pressure falls for all three initial volumes. The similarity of these curves, except for shifts due to the change in initial volume, suggests strong dependence on pressure rather than volume.

4. Discussion

In recent analyses of lung hysteresis (Fredberg and Stamenovic, 1989; Ludwig et al., 1990), there has been renewed interest in the work of Hildebrandt and coworkers (Bachofen and Hildebrandt, 1971; Horie and Hildebrandt, 1973; Nagao et al., 1979) who studied the normalized hysteresis (K) of lung pressure–volume (PL–VL) loops. Normalized hysteresis was defined as the total loop area (H) divided by the maximum possible hysteresis for the loop; i.e., $K = [H/(\Delta PL_{max})(\Delta VL_{max})]$ where ΔPL_{max} and ΔVL_{max} represent the maximum pressure and volume changes for that loop. It should be noted that Glaister et al. (1973) recognized the relevance of the work of Bachofen and Hildebrandt (1971) which showed that at high lung volumes K was virtually the same for air and saline inflation. In addition, Glaister et al. (1973) also noted that Bachofen and Hildebrandt (1971) and Horie and Hildebrandt (1973) purposely made comparisons of only small tidal volumes and end-deflation levels above 50% TLC. At lower lung volumes where lung unit closure has been shown to occur, K in saline-filled lungs remained constant, but K increased in air-filled lungs as the end-deflation volume was progressively reduced.

The results of Bachofen and Hildebrandt (1971) described first tidal loops along the PL–VL deflation curve beginning at TLC. Later, Horie and Hildebrandt (1973) noted that first loops tended to exhibit more hysteresis than loops of later cycles. They showed that if one avoided first cycles, the relationship between H, VT and ΔP could be extended to a more general form as $H = K(VT)f(\Delta PL)$. In this case, the term $f(\Delta PL)$ was a nonlinear function since hysteresis area (H) increased at a faster rate as VT approached the vital capacity.

It is known that K represents the net work done during a PL–VL cycle, compared to the maximum possible work that could be done. Fredberg and Stamenovic (1989) have noted that K may be composed of several components which result from: the kinetics of crossbridges which are formed in the tissue structure, the kinetics of the surface film and the associated surface to volume hysteresis, and the kinetics of the lung unit recruitment–derecruitment process. The purpose of our study was to attempt to define the contribution of lung unit recruitment–derecruitment to lung PL–VL hysteresis. It can be predicted that in air, when part or all of the cycle pressure range is reduced below the closing pressure, non-recoverable work would be required during inflation to reopen closed units.

The results of the present study can be interpreted in terms of the model previously described by Frazer et al. (1985) and illustrated in Fig. 1. The model assumes that the PL–VL curve of an excised lung can be divided into three zones: an 'opening' zone, an 'open' zone, and a 'closing' zone. An important characteristic of the model is that the zones are separated by boundaries which depend on transpulmonary pressure rather than lung volume. During inflation, lung units are recruited as their particular opening pressure is reached in the 'opening' zone. Upon deflation, all recruited lung units will stay open ('open' zone) until their particular closing pressure is reached in the 'closing' zone. With the range for lung unit closing pressures previously determined by gas trapping and tracheal lung sound measurements (Frazer et al., 1981,1985, Cheng and Frazer, 1985; Cheng et al., 1986), the recruitment–derecruitment model can be used to predict the effect of airway closure as more and more closed units are recruited. The contribution of the recruitment–derecruitment appears to vary from a minimum of zero for small loops to a maximum of about two-thirds of the total PL–VL hysteresis for large loops. It also should be pointed out that PL–VL loops with increasing end-expiratory pressures in the 'closing' zone are associated with a decreasing fraction of lung units that close during lung deflation. Hence, the hysteresis index for loops in which only a fraction of lung units close and reopen should fall between the boundaries defined by the 'open' and 'opening' curves in Fig. 4.

In the second set of experiments, PL–VL loops were recorded during inflation and deflation so that the end-expiratory pressure for the volume perturbations increased as the lung was inflated and decreased as the lung was deflated. Typical sets of PL–VL curves recorded during slow lung inflation and deflation are shown in Fig. 5A and B, respectively. For inflation loops, end-expiratory pressure of the loops increases from a point in the 'closing' zone where all the lung units are closed, upward through the 'closing' zone where only a fraction of the lung units close to the 'open' zone in which none of the lung units close during the deflationary swing of the volume oscillation. For deflation loops, end-expiratory pressure gradually moves from the 'open' region (corresponding to little hysteresis) to the 'closing' region with a concomitant increase in hysteresis. The results of these experiments demonstrate that loop end-expiratory pressure has a large effect on the area and shape of PL–VL loops recorded during lung inflation. This again is evidence for a pressure-dependent recruitment–derecruitment process.

The oscillatory peak-to-peak change in transpulmonary pressure of individual PL–VL loops during lung inflation, ΔPL, is initially high (Fig. 6A), then decreases to a minimum, and gradually increases once again as end-expiratory pressure rises during slow inflation. A minimum also appears for slow deflations as end-expiratory pressures move from positive to negative levels (Fig. 6B). It should be noted that a reduction in PL is normally not seen along static PL–VL curves during the second inflation–deflation cycle. At high lung volumes, the increase of peak-to-peak pressure, ΔPL, can be attributed to the decrease in lung compliance as all lung units are open and expanded. At low lung volumes, closure of open lung units (derecruitment) reduces lung compliance. During lung inflation (Fig. 7A), hysteresis index and ΔPL are initially high and then decrease as ΔPL decreases, but once the EEP is greater than about +4 cmH$_2$O, the hysteresis index barely increases as ΔPL rises once again. Fig. 7B shows that, during lung deflation, the hysteresis index is initially low and remains low while ΔPL decreases from a high level to a minimum when an EEP of +4 cmH$_2$O is reached. Then, both the hysteresis index and ΔPL increase significantly as EEP falls more and more below +4 cmH$_2$O. The double-valued functions in Fig. 7A and B demonstrate that hysteresis does not uniquely depend on ΔPL, but rather hysteresis depends primarily on end-expiratory pressure.

In the third series of experiments, the lung was inflated to TLC, 3/4 TLC and 1/2 TLC, then following a stress relaxation period, transpulmonary pressure excursions were measured as increasing volumes of air were withdrawn then replaced in a sinusoidal manner. It was reasoned that by withdrawing and replacing the same volume of gas, PL would decrease from PL$_{max}$ to the EEP and then return to the original value of PL$_{max}$. Fig. 8A, B and C show the results of that experiment. As the amplitude of the volume perturbations was gradually increased, the envelope of the oscillatory changes in PL showed that, regardless of the initial lung volume, PL$_{max}$ remained constant as predicted for EEPs greater than 4 ± 1 cmH$_2$O; that PL$_{max}$ gradually increased for loops with EEPs between −2 and 4 ± 1 cmH$_2$O; and that PL$_{max}$ remained nearly constant for EEPs less than −2 cmH$_2$O. A likely explanation for these findings is that when the lung is deflated to end-expiratory pressures below 4 ± 1 cmH$_2$O, lung unit derecruitment begins to take place, and additional energy is required to return to the original lung volume. The requirement for additional energy is manifested by an increase in PL$_{max}$. When the EEP finally reaches −2 cmH$_2$O, a further reduction in the EEP no longer has an effect on $P_{L_{max}}$ since no additional lung units are available for derecruitment.

As previously stated, PL–VL hysteresis results from the dissipation of energy during an inflation–deflation cycle. Since additional energy must be supplied to reopen lung units closed during deflation, one would expect that such recruitment of lung units would increase in PL–VL hysteresis. Fig. 9 shows that the hysteresis index, H/VT, increases as end-expiratory pressure decreases from 4 ± 1 cmH_2O to -2 cmH_2O or less. In summary, the results from the third set of experiments suggest that the degree of lung unit derecruitment depends principally upon end-expiratory pressure and not the end-expiratory lung volume.

The mechanism responsible for the minimum values of $P_{L_{max}}$ and ΔPL of PL–VL loops for which the EEP is between -2 and 4 cmH_2O is not known. There are, however, several possible explanations. The minimum values could result either from the physical properties of the alveolar surface film at low lung volumes or from an irreversible mechanical process such as the opening and closing of lung units. If the process responsible for this behavior were chiefly due to the area-surface tension relationship of alveolar surfactant, it should be volume dependent. And if the process involved mechanical events such as the opening and closing of lung units, it would be pressure dependent. Since the magnitude of the pressure changes in the PL–VL loops recorded in this study depend on end-expiratory pressure, it seems most likely that the mechanical events associated with lung unit closure account for the minimum values of $P_{L_{max}}$. This conclusion is also supported by a plot of the hysteresis index, H/VT, against the peak-to-peak pressure, ΔPL, as in Fig. 7A and B. These figures show that the hysteresis index is a double-valued function of ΔPL: for a given value of ΔPL, the hysteresis index, H/VT, is higher for EEPs below 4 ± 1 cmH_2O than for EEPs above 4 ± 1 cmH_2O.

Several investigators (Klingel and Staub, 1970; Daly et al., 1975; Ardila et al., 1979) have reported that the lung expands nearly uniformly between 50 and 100% TLC; but below 50% TLC, where PL–VL loop hysteresis begins to increase rapidly, the lungs exhibit nonuniform expansion. One explanation is that uniform expansion occurs above 50% TLC because all the lung units which have been opened upon inflation remain open during deflation, whereas nonuniform expansion results from the pressure-dependent recruitment of lung units that begins to occur when the end-expiratory volumes are less than 50% TLC.

The results from this study support the view that the recruitment and derecruitment of lung units is an end-expiratory pressure dependent and sequential event as proposed by Glaister et al. (1973) and Frazer et al. (1979). The events occurring during an inflation–deflation cycle can now be summarized as follows: When an excised lung is deflated to an end expiratory pressure of 4 ± 1 cmH_2O or lower, lung units are sequentially closed (derecruited), and additional energy must be supplied during subsequent inflation to reopen the closed units. The increased energy that is required to open (recruit) these units results in increased energy dissipation that is reflected as an increase in PL–VL hysteresis.

Finally, the physiological significance of the findings in this study should be addressed. Since transpulmonary pressure is likely to assume values of $+4$ cmH_2O or less in the lower regions of the thorax at FRC, our results would indicate that lung units would begin to close near or slightly below FRC in a normal rat.

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