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Discontinuous lung sounds and hysteresis in control and Tween 20-rinsed excised rat lungs

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Abstract

In the past, the relationship between pulmonary hysteresis and a model of the recruitment–derecruitment of lung units has been explored (Cheng, W., DeLong, D.S., Franz, G.N., Petsonk, E.L., Frazer, D.G., 1995, Resp. Physiol. 102, 205–215). The recruitment process is characterized by a sequence of events which represents discrete configurational changes in lung structure. It is assumed that energy released during the opening of lung units is associated with the formation of discontinuous lung sounds. The goal of this study was to record tracheal sounds for lungs inflated from different end-expiratory pressures and to relate the sound power to the normalized hysteresis of individual pressure–volume (PL–VL) loops. PL–VL curves and lung sounds were recorded for control lungs and lungs rinsed with Tween 20 in order to estimate the role of alveolar surfactant on the recruitment–derecruitment process. Results indicate that there may be two populations of lung units, one which is altered by Tween 20 and another which is not. The population not affected by Tween 20 appears to be responsible for producing discrete lung sounds and may represent the opening of larger conducting airways. The second population, possibly within the respiratory zone, is affected by alterations in surface tension and contributes to pulmonary hysteresis, but, apparently, does not contribute significantly to lung sound power measured at the trachea. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

In a recent publication, we examined the contribution of the opening and closing of lung units to lung pressure–volume (PL–VL) hysteresis (Cheng

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et al., 1995). That study tested the predictions of a simple lung model describing the recruitment–derecruitment process by examining the hysteresis of pressure–volume loops as a function of end-expiratory pressure (EEP). The goal of this study was to correlate the production of discontinuous lung sounds, which are potentially indicative of the recruitment–derecruitment process, with the hysteresis of P_L–V_L loops recorded over a wide range of EEPs. Our model of lung expansion assumes that individual lung units open abruptly when their particular opening pressure has been reached during lung inflation. It also assumes that lung units are capable of generating discontinuous, explosive sounds or crackles during the opening process. In the past, it has been widely accepted that crackles are generated by the opening of lung structures which we broadly define in this study as lung units (Forgacs, 1967, 1974, 1978; Nath and Capel, 1974; Ploy-Song-Sang and Schonfeld, 1982; Fredberg and Holford, 1983; Munakata et al., 1986)

Forgacs (1967, 1978) and Forgacs et al. (1971) have argued rather convincingly that crackles result from the rapid equalization of gas pressure between upstream and downstream airway sections following their sudden opening during inspiration. He presented as evidence, the often striking repetitive occurrence of crackles during succeeding inspirations, even when the inspiration followed a cough. These crackles rarely occurred during expiration and were often localized over dependent areas of the lung where gravitational stress predisposes the airways to collapse.

Fredberg and Holford (1983) have conceded that the opening of closed lung units is the mechanism likely to be responsible for the generation of lung crackles, but they suggested that the sudden equalization of pressure may not be required to produce the crackle sound pressure wave. Instead, they proposed that when a closed unit opens, the sudden release of tension in the airway wall, as it approaches a new lower energy state, produces sound energy in the form of a crackle.

There are still some questions as to the size of the region of the lung that opens when a crackle is generated. Munakata et al. (1986) have reported that crackles in normal excised dog lungs are produced by the opening of airways and are not generated by the sudden inflation of individual alveoli.

Even though neither the exact mechanism responsible for generating crackles nor the size of the lung structures from which the sound originates has yet been determined, there appears to be general agreement that crackles originate during the discontinuous opening of small lung structures. As a consequence, the sound energy associated with discontinuous lung sounds has potential not only as an index of when lung units open but also as an indicator of the number of lung units that open. In the past it has been suggested that discontinuous events that occur during lung inflation and deflation could have a significant effect on the hysteresis of lung P_L–V_L curves (Frazer et al., 1985). In an attempt to test this hypothesis, lung sound power was compared with the hysteresis for individual P_L–V_L loops which was computed by a previously described method (Cheng et al., 1995). This analysis was based on the work of Bachofen and Hildebrandt (1971) in which the hysteresis area, H, of lung P_L–V_L curves which formed closed loops were found to be related to the change in transpulmonary pressure (ΔP) and tidal volume (V_T) through the relationship $H = K(V_T)(\Delta P_L)$ where K represents a proportionality constant. Rearrangement of the terms in this expression leads to the hysteresis index (H/V_T) where $(H/V_T) = K(\Delta P_L)$. It should be noted that the lung tissue hysteresivity, η, as described by Fredberg and Stamenovic (1989) is related to K, by the expression $\eta = [(\pi/4K)^2 - 1]^{1/2}$ while the dynamic elastance, Edyn, can be written in terms of K as $Edyn = [1 - (K/\pi)^2]^{1/2} \cdot \Delta P_L/\Delta V_L$.

In order to explore the role of surface forces at the air–liquid interface of the lung with regard to sequential lung unit inflation–deflation, we measured both P_L–V_L loop hysteresis and the power of lung sounds generated in control lungs and in lungs rinsed with Tween 20. Tween 20 is a nonionic detergent that is often used to replace the normal alveolar surface film and to generate an air–liquid interface having a near constant surface tension of approximately 30 dynes/cm (Radford, 1962). It should be noted that rinsing lungs with Tween 20 alters the configuration of lung microstructure indicating that the lung's peripheral geometry is a function of surface tension (Bachofen et al., 1979).

2. Methods

Lungs were excised from Long Evans hooded male rats weighing between 300 and 350 g. Animals were exsanguinated via the abdominal aorta following intraperitoneal pentobarbital injection (85 mg/kg). The abdominal cavity was opened and a bilateral pneumothorax was obtained by penetrating the sternal area of the diaphragm. Next, the rib cage was sectioned on both sides of the midline, and the heart, lungs, and diaphragm were removed en bloc. The excised lungs were rinsed in saline and placed in a vacuum chamber. The chamber was evacuated with a vacuum pump (Kinney #KC-2) until its internal pressure was reduced to the vapor pressure of H_2O. At that time, the vacuum was released and the chamber pressure was allowed to approach ambient pressure over an approximate 1-min period according to the method of Stengel et al. (1980). This degassing procedure was repeated twice before recording each PL–VL curve using the system shown in Fig. 1. The saline filled plethysmograph was constructed from a solid piece of acrylic. It was designed with a cylindrically shaped body and a cone shaped top, so trapped air or bubbles in the chamber could easily be removed. A removable acrylic base could be fastened to the chamber body with a water tight O-ring seal. During an experiment, a degassed lung was attached to a 15-gauge needle that extended through the base of the plethysmograph so that the trachea was open to the atmosphere. Using this arrangement, a microphone (B&K model #4166) was acoustically coupled to the tracheal cannula to measure tracheal lung sounds. Since the air-filled lung was lighter than saline, it assumed an inverted position as the plethysmograph chamber was filled with saline. Additional ports at the base of the plethysmograph were connected to a pressure transducer, a reference pressure cylinder, and a zero reference tube. These were used to set the zero-transpulmonary pressure reference level.

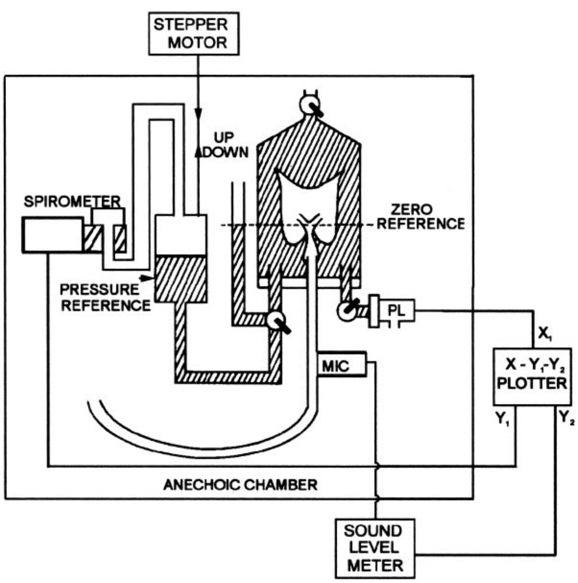

Fig. 1. Configuration of the equipment used to simultaneously measure PL–VL curves and tracheal lung sounds of excised rat lungs. Lungs were inflated–deflated in the liquid filled plethysmograph by lowering–raising the reference pressure chamber.

The zero-pressure reference was chosen at the level of the first airway bifurcation by adjusting the level of the saline solution in the reference tube and then closing the reference tube valve (Fig. 1). The lungs were inflated and deflated by moving the pressure reference cylinder down and up with a winding mechanism powered by a stepper motor. As the reference cylinder was lowered below the zero-pressure reference level, the pressure within the saline filled plethysmograph at the level of the first bifurcation became negative with respect to atmospheric pressure (tracheal pressure), and the lung inflated as air entered the lung through the tracheal cannula. This fluid displaced from the plethysmograph reference cylinder entered the reference chamber, and its volume was determined with the spirometer. Plethysmograph pressure with respect to the reference pressure and spirometer volume were digitized and recorded by computer at a rate of 20 Hz.

2.1. Effect of end-expiratory pressure on tracheal lung sounds

Non-invasive tracheal lung sound measurements were used in this study to estimate the recruitment of lung units. Excised lungs were inflated and deflated in a saline-filled plethysmograph that was placed inside an anechoic chamber while the stepper motor was mounted outside the chamber. The inside walls of the anechoic chamber were covered with wedge shaped, sound-absorbing material to absorb incident sound energy. Lungs were initially inflated from the degassed state to 30 cm H_2O (PL_{max}) and then deflated to −5 cm H_2O. During the second inflation–deflation cycle, the lungs were inflated from −5 cm H_2O to PL_{max}. Then 11 consecutive PL–VL loops were recorded as the lungs were deflated and inflated from PL_{max} to 11 successively lower values of EEP as transpulmonary pressure was changed at either a rate of either 8 or 48 cm H_2O/min. The ventilation rate was controlled by adjusting the speed of the stepper motor that raised and lowered the pressure reference cylinder. Values of EEP were decreased in 1 cm H_2O steps from +5 cm H_2O for the first loop to −5 cm H_2O for loop 11. Lung sounds were measured during lung inflation for each of the 11 PL–VL loops with the microphone acoustically coupled to the trachea cannula as described by Frazer et al. (1986). Sound signals were analyzed with a sound level meter (B&K #2218) which calculated the average sound power, LEQ, in decibels using the following relationship:

$$\mathrm{LEQ} = 10\log\left[1/\mathrm{T}\int_0^{\mathrm{T}} \mathrm{P}^2(\mathrm{t})/\mathrm{P}_o^2\,\mathrm{dt}\right]$$

In this expression, P(t) is the instantaneous sound pressure measured at the microphone, P_o is the sound pressure reference and T is the total time taken to inflate the lung starting from zero time. Lung volume and instantaneous sound pressure during lung inflation were recorded simultaneously as a function of PL on an X-Y_1-Y_2 recorder.

2.2. Effect of end-expiratory pressure on lungs rinsed with Tween 20

Both the surface properties of the lung and the recruitment–derecruitment of lung units can contribute to PL–VL hysteresis, and it is likely that they may not be independent of each other. In the final experiment, the effect of displacing the normal surface film on the process of recruitment–derecruitment was examined. After excised lungs were degassed and rinsed with 0.5% Tween 20, they were degassed a second time and placed in a saline filled plethysmograph that was enclosed in the anechoic chamber. The lungs were initially inflated to 30 cm H_2O (PL_{max}) and held at that pressure during a 4 min equilibration period. Next, the lungs were deflated and inflated between PL_{max} and a series of EEPs ranging from +20 to −5 cm H_2O to form a series of consecutive PL–VL loops. Tracheal lung sound power during lung inflation (LEQ), lung volume changes (VT), and hysteresis area (H) were determined, and values of LEQ and H/VT were plotted versus EEP for each loop. The ratio H/VT has been defined by Bachofen and Hildebrandt (1971) as the hysteresis index of a PL–VL loop. In these experiments the excised lungs were inflated–deflated as PL was changed at a rate of 15 cm H_2O/min.

3. Results

The instantaneous sound pressure level and lung volume, recorded as a function of tracheal pressure on an X-Y_1-Y_2 recorder, are shown in Fig. 2. The acoustical sound power (LEQ ± SEM), measured at the trachea during lung inflation, following lung deflation to a decreasing sequence of end-expiratory pressures is shown in Fig. 3A. These results illustrate that the average sound power level resulting from the summation of all the discontinuous lung sounds during lung inflation increased as end-expiratory pressure decreased. Fig. 3B shows that the hysteresis index, H/VT, of the same PL–VL loops increased similarly as the EEP decreased. When values of H/VT, along the continuous curve in Fig. 3A were plotted versus values of LEQ, along the

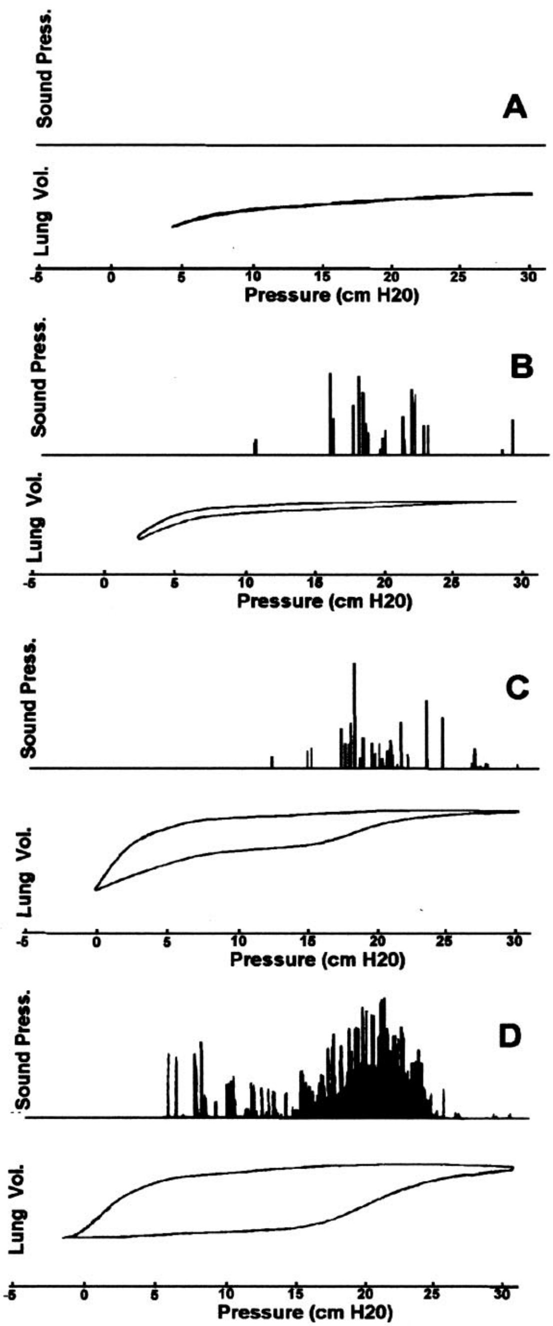

Fig. 2. Representative PL–VL loops and tracheal sound pressure recorded during lung inflation with an end-expiratory loop pressure (EEP) of: (A) +4 cm H_2O; (B) +2 cm H_2O; (C) 0 cm H_2O; and (D) −2 cm H_2O.

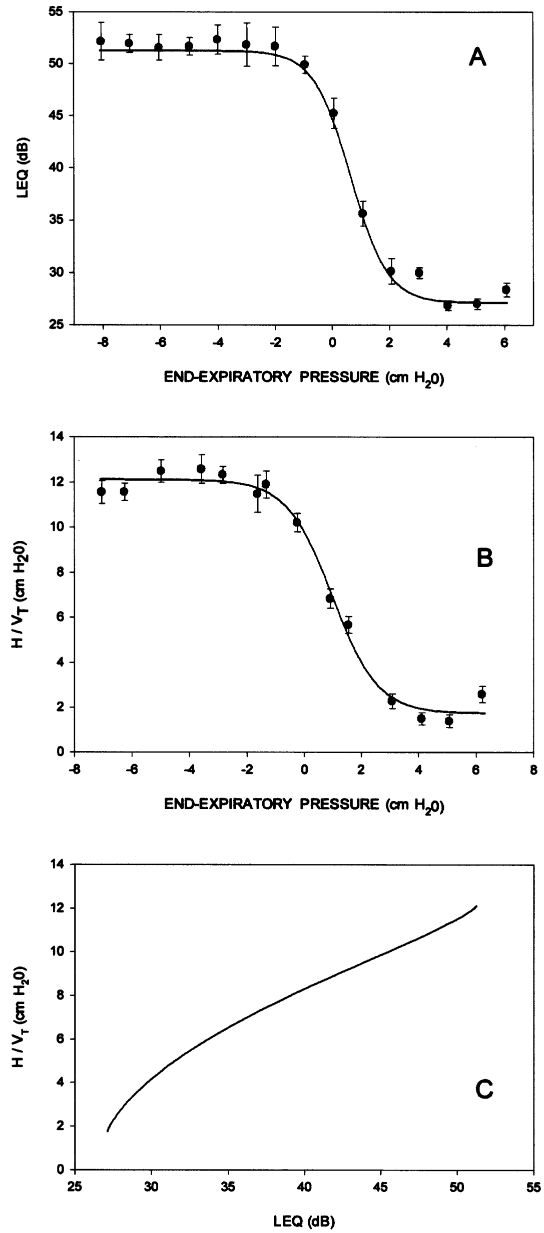

Fig. 3. (A) The tracheal sound pressure power (LEQ ± SEM) recorded during the inflation portion of a P–V loop as a function of loop end-expiratory pressure (EEP). (B) The hysteresis index (H/VT ± SEM) per loop, plotted as a function of the loop end-expiratory pressure (EEP). Loops in A and B were recorded as lung transpulmonary pressure increased and decreased at a rate of 8 cm H_2O/min. (C) Values of H/VT from the continuous curve shown in Fig. 3A plotted versus values of LEQ along the continuous curve in Fig. 3B for equal values of EEP.

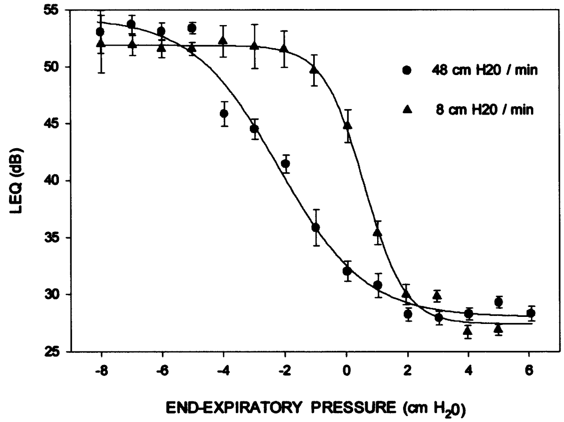

Fig. 4. Sound power (LEQ ± SEM) as a function of end-expiratory pressure for PL–VL loops recorded at inflation rates of 8 (▲, $N=6$) and 48 cm H_2O/min (●, $N=6$).

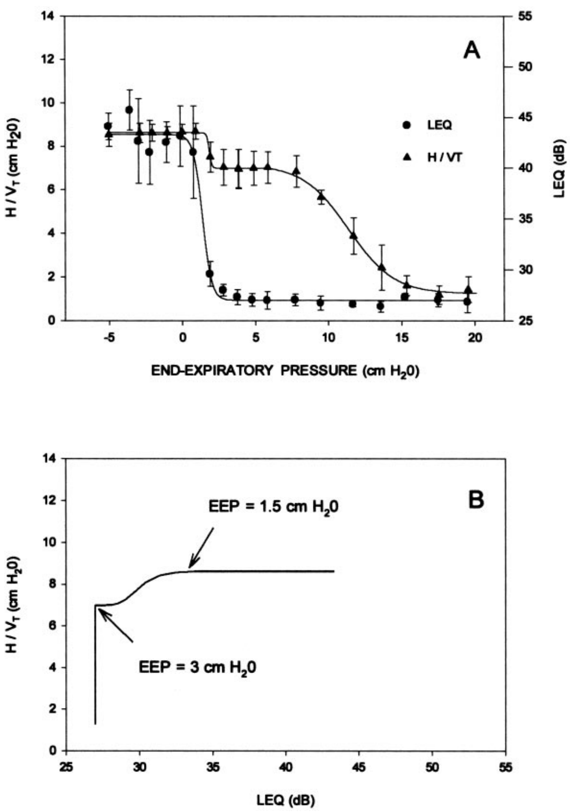

Fig. 5. (A) Normalized hysteresis (H/VT ± SEM, ▲) and the average sound power (LEQ ± SEM, ●) per PL–VL loop as a function of end-expiratory pressure (EEP) for lungs rinsed with Tween 20 ($N=6$). (B) Values of H/VT and LEQ for the same EEP values taken from the continuous curves in Fig. 5A.

continuous curve in Fig. 3B at equal values of EEP, the curve in Fig. 3C was obtained. It can be seen that there is nearly a linear relationship between H/VT and LEQ for control lungs over the entire EEP range.

The effect of two different ventilation rates ($\Delta P/\Delta t$) on average sound power recorded during inflation for each loop (LEQ) as a function of end-expiratory pressure Fig. 4. (EEP) is shown in Fig. 4. It can be seen that the average sound power as a function of EEP is shifted to the left toward lower values and changes over a broader range of EEPs as the ventilation rate was increased from 8 to 48 cm H_2O/min.

In a second set of experiments, pressure–volume (PL–VL) loops with EEPs ranging between + 20 and − 5 cm H_2O were recorded for both control and Tween 20-rinsed lungs. The relationships between both LEQ, measured during lung inflation, and H/VT for Tween 20-rinsed lungs are shown in Fig. 5A. When values of H/VT and LEQ, at identical EEP values, were plotted for the continuous curves in Fig. 5A, the resulting curve in Fig. 5B was obtained. In this case, there is only a small range of EEP values, between + 1.5 and + 3.0 cm H_2O, where changes in LEQ were proportional to changes in H/VT. LEQ and H/VT were not correlated outside this range of EEPs. Fig. 6 demonstrates differences between H/VT as a function of EEP for control and Tween 20-rinsed lungs. The results illustrated in Fig. 5 and Fig. 6 along with Fig. 3 reveal the following: (1) In control lungs, the normalized hysteresis per loop (H/VT) and sound power (LEQ) rise as the EEP is lowered (Fig. 3). LEQ begins to increase at approximately + 3 cm H_2O with a maximum negative slope at near + 0.7 cm H_2O (Fig. 3A), while H/VT begins to increase at an EEP of approximately + 3 cm H_2O with a maximum negative slope at near + 1 cm H_2O (Fig. 3B). (2) The hysteresis index, H/VT, of Tween 20-rinsed lungs forms a reverse double sigmoid shaped curve (Fig. 5A). As the EEP is lowered, the curve gradually rises, beginning at + 16 cm H_2O, and reaching a maximum negative slope near + 12 cm H_2O. The curve rises again in the vicinity of + 3 cm H_2O and reaches a maximum negative slope at + 1.8 cm H_2O. The LEQ relationship, however, remains low until 3 cm H_2O is reached and then rises in a manner similar to control lungs. (3) The hysteresis index, H/VT, for Tween 20-rinsed lungs is higher than that for control lungs at high EEPs (between 15 and +1cm H_2O) and less for EEPs below 0 cm H_2O (Fig. 6).

4. Discussion

Tracheal lung sound measurements were used in this study to explore the effects of lung unit recruitment–derecruitment on pulmonary hysteresis. Despite the fact that the stethoscope has been used for more than a century and a half, the connection between discontinuous lung sounds and lung unit opening has been difficult to prove. This is due, in part, to the subjectivity of the interpretation of stethoscopic auscultation (Wooten et al., 1978; Thacker and Kraman, 1982; Murphy et al., 1984).

In this study, lung sound power in the form of discontinuous sounds or crackles was measured using a microphone acoustically coupled to the trachea of excised lungs as they were inflated/deflated in a saline-filled plethysmograph. The instantaneous sound pressure levels were measured at the trachea during lung inflation following lung deflation to a specific end-expiratory

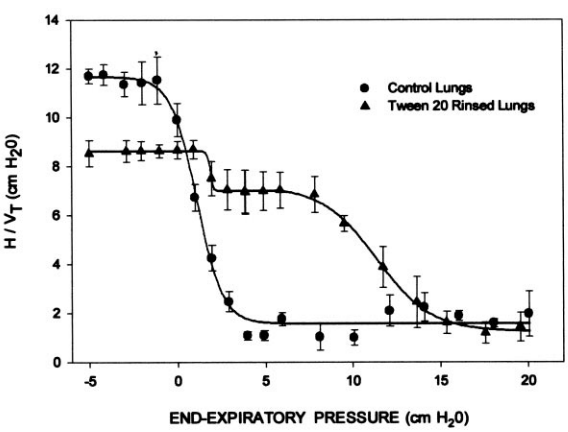

Fig. 6. Comparison of the normalized hysteresis (H/VT ± SEM) as a function of end-expiratory pressure (EEP) for individual P–V loops for control (●, $N=6$) and Tween 20-rinsed lungs (▲, $N=6$).

pressure. The corresponding PL–VL curves are shown in Fig. 2A, B, C, and D. By recording a specified series of PL–VL curves with different end-expiratory pressures, it was possible to find the relationship between energy dissipated in peripheral regions as sound power and end-expiratory pressure.

Results showed that sound power recorded at the trachea increased as end-expiratory pressure decreased. It is evident that the envelope of the total sound pressure recorded during lung inflation changes as a function of end-expiratory pressure (Fig. 2). The highest intensity of sound pressure occurred slightly beyond the 'knee' of the inflation limb and appeared to correspond to the steepest slope of the PL–VL relationship. Sound pressures recorded between the 'knee' of the inflation limb and TLC indicate that lung units continued to be recruited until lung volume reached a maximum value which is consistent with a model previously used to describe pulmonary hysteresis (Frazer et al., 1985). Although not shown, there was no detectable sound power recorded at the trachea while the lung was deflated during any PL–VL cycle until transpulmonary pressure was below 0.0 cm H_2O.

The average acoustical power (LEQ) generated during each inflation–deflation cycle was plotted versus end-expiratory pressure in Fig. 3A. This figure indicates that the average sound power level, resulting from the summation of all the discontinuous lung sounds for individual PL–VL loops, increased as end-expiratory pressure decreased. Fig. 3B shows that normalized loop hysteresis (H/VT) also increased as end-expiratory pressure decreased. Fig. 3C shows a nearly linear relationship between H/VT and LEQ which supports the hypothesis that PL–VL hysteresis and tracheal lung sound power may be associated with the same mechanical process. According to the recruitment–derecruitment model, a likely explanation of the results in Fig. 3A, 3B and 3C is that as end-expiratory pressure is lowered, the number of lung units closing rises, and the increased energy required to re-open them increases PL–VL hysteresis.

The effect of ventilation rate ($\Delta P/\Delta t$) on the production of lung crackles measured at the trachea is illustrated in Fig. 4. The curve of the average sound power as a function of end-expiratory pressure is shifted to lower EEPs when the ventilation rate is increased. In other words, the higher the ventilation rate, the lower the derecruitment pressure and the more the airways tend to remain open. These results suggest that over the measured range of ventilation rates, the process of lung derecruitment is time-dependent in the rat. The most likely explanation of this observation is that the lung behaves as a viscoelastic structure so that lung unit closure becomes a function of time.

The aim of the second part of this study was to determine how changing the air–liquid interface of the lung affects the recruitment–derecruitment of lung units. Normally, surfactant is present at the air–liquid interface of the lung (Pattle, 1955; Clements, 1957). This material greatly enhances the mechanical stability of the alveoli, as Clements et al. (1958) have described. Radford (1962) demonstrated that rinsing the lung with Tween 20 displaces the normal surfactant–air interface in the alveolus and replaces it with an interface characterized by a constant surface tension of approximately 30 dynes/cm.

Results show that the maximum average sound power (LEQ) was greater in control lungs than in Tween 20-rinsed lungs. When tracheal lung sound power was plotted as a function of end-expiratory pressure (EEP), however, both control and Tween 20-rinsed lungs exhibited curves of similar shape (Figs 3 and 5A). In each case, LEQ remained nearly constant until the EEP reached + 3 cm H_2O, then it increased and reached a maximum slope near + 0.7 cm H_2O.

In contrast, there were marked differences in the hysteresis index, H/VT, for PL–VL loops of control and Tween 20-rinsed lungs as EEP decreased (Fig. 6). In control lungs, the index H/VT for individual PL–VL loops has a small slope and remains low as the EEP is reduced until approximately + 3 cm H_2O is reached. At that point, H/VT begins to increase with maximum slope near + 1 cm H_2O and then reaches a plateau for negative values of EEP.

The index H/VT for PL–VL loops recorded for Tween 20-rinsed lungs, on the other hand, forms a bimodal cumulative distribution function with respect to decreasing EEP. In this case, as the EEP is reduced, H/VT initially begins to rise at + 16 cm H_2O and reaches a maximum rate of change near + 12 cm H_2O. One way to interpret the initial rise in the hysteresis index at higher EEPs is that it represents the energy losses as a result of the premature closing and reopening of small lung units whose closing pressure was increased to higher EEPs when the lung was rinsed with Tween 20. Of course, there are other possible explanations. Fredberg and Stamenovic (1989) have suggested that in addition to the recruitment–derecruitment of lung units, the kinetics of cross bridges which are formed in the tissue structure and the kinetics of the alveolar surface film could also play a significant role in altering the hysteresis index of individual PL–VL loops.

As the EEP is reduced further, for Tween 20-rinsed lungs, a second increase in the hysteresis index, H/VT, is observed beginning at an EEP of + 3 cm H_2O and reaching a maximum rate of change near + 1 cm H_2O. The second rise in hysteresis, with respect to EEP, coincides with the increase in tracheal sound power and is responsible for the small range of the linear relations shown in Fig. 5B. A comparison with the results for control lungs suggests that the second increase in hysteresis along with the generation of lung sounds is much less influenced by rinsing the lungs with Tween 20 and may not depend much on the surface tension of the air–liquid interface. It seems likely that most lung sound power and the second component of hysteresis are generated by a population of larger lung structures such as the large airways, as previously described by Munakata et al. (1986).

It has been known for many years (Radford, 1962) that rinsing lungs with Tween 20 reduces the hysteresis of PL–VL curves recorded between + 30 and 0 cm H_2O. This study shows, however, that the normalized hysteresis index for Tween 20-rinsed lungs normally exceeds the hysteresis index of PL–VL loops of control lungs ventilated over the same pressure range as long as end-expiratory pressure is above + 1 cm H_2O. Surprisingly, only at end-expiratory pressures below + 1 cm H_2O does the hysteresis index of control lungs exceed that of lungs rinsed with Tween 20.

In the past it has been suggested that the overall hysteresis of PL–VL curves is reduced in Tween 20-rinsed lungs as a consequence of changing the surface tension-area characteristics of the alveolar air–liquid interface (Macklem, 1971). A possible alternative explanation is based on a model of the recruitment–derecruitment of lung units whose closing pressure is a function of surface tension. This hypothesis assumes that rinsing the lung with Tween 20 causes a surface tension-dependent population of lung units to close prematurely at higher end-expiratory pressures. Closing pressures move toward higher end-expiratory pressures and approach the range of the distribution of opening pressures. Radford (1962) observed this phenomena in his original comparison of control and Tween 20-rinsed lungs. The redistribution of closing pressures in Tween 20-rinsed lungs may thus reduce the geometric hysteresis caused by the sequential opening and closing of lung units. This would reduce PL–VL hysteresis for complete inflation–deflation cycles between +30 and 0 cm H_2O. In contrast, the PL–VL hysteresis of individual PL–VL loops ending at higher end-expiratory pressures would increase because additional energy would be dissipated by the derecruitment–recruitment process. In control lungs there would be little derecruitment for these same EEPs and, hence, less hysteresis.

In summary, this study provides support for the following statements:

1. In normal rat lungs, both the sound power generated by discontinuous lung sounds measured at the trachea and the degree of PL–VL loop hysteresis appear to be similarly related to end-expiratory pressure.
2. There appear to be at least two distinct populations of lung units contributing to pulmonary hysteresis. The behavior of one population is surface tension dependent and, therefore, altered by rinsing the lung with Tween 20. The behavior of the other is not altered by Tween 20, presumably because it is not surface tension dependent.
3. Discontinuous lung sounds seem to be generated by the population of lung units not altered by rinsing with Tween 20 (surface tension independent). This population consists most likely of larger airways of the lung's conducting zone.
4. The large population of lung units altered by rinsing with Tween 20 (surface tension dependent) probably represents small structures within the respiratory zone where the radii of curvature are small and surface forces predominate.

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