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EVIDENCE OF SEQUENTIAL OPENING AND CLOSING OF LUNG UNITS DURING INFLATION–DEFLATION OF EXCISED RAT LUNGS

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Abstract. In this study we propose a descriptive model of the events occurring in an excised lung during an inflation–deflation cycle. The model was developed by observing changes in small pressure–volume loops superimposed on quasistatic pressure volume curves. It was found that the shape of the small loops during lung inflation was a function of the previous end-expiratory pressure. These experimental results could most easily be explained by a model of the lung in which individual lung units open sequentially as the lung is inflated. During sequential recruitment, individual lung units open quickly to a volume determined by the transpulmonary pressure. The units then homogeneously increase and decrease in size according to pressure–volume curves similar to the deflation curve of the entire lung. Once lung units have been recruited, they remain open until the lung has been deflated to end-expiratory pressures below 3–4 cm H_2O. Reducing the end-expiratory pressure to lower values causes additional derecruitment of lung units until a transpulmonary pressure of 0.0 to − 1.0 cm H_2O has been reached.

Lung hysteresis
Lung pressure–volume curves
Recruitment–derecruitment of lung units
Transpulmonary pressure

The contribution of recruitment and derecruitment to the hysteresis of lung pressure–volume curves continues to be a controversial issue. Although many investigators agree that a recruitment–derecruitment mechanism exists in the lung (Bernstein, 1957; Mead *et al.*, 1957; Glaister *et al.*, 1973), its relative contribution to lung hysteresis is still uncertain.

Typically, after initial inflation–deflation cycles from the gas-free state, the inflation curve of an excised lung exhibits a 'knee' on the inflation limb. The 'knee' usually occurs between transpulmonary pressures of + 10 and + 20 cm H_2O for most animal species (Hoppin and Hildebrandt, 1977). Many investigators have suggested that the rapid and nearly complete recruitment of lung units occurs at the 'knee' of the pressure–volume

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(P_L–V_L) curve and is responsible for the rapidly increasing slope of the curve at that point. In contrast, Glaister *et al.* (1973) and Smaldone *et al.* (1983) have suggested that the lung units do not open simultaneously but continue to open sequentially as transpulmonary pressure, P_L, increases beyond the 'knee' pressure.

Recently, Frazer and Khoshnood (1979) have proposed that menisci or bubbles occluding the airways progress toward the alveoli during lung inflation and thus contribute to the sequential opening of lung units. A meniscus moving along a parent airway toward the alveoli must divide when a bifurcation is reached. When the forces acting on a meniscus are analyzed, it can be shown that the two daughter menisci will not necessarily move simultaneously if the total force required to move each meniscus is proportional to the circumference of the airway. If one meniscus is larger than the other, it will move first along that daughter branch until it reaches a second bifurcation. At that time either the larger meniscus will divide or the meniscus in the smaller daughter branch will now move toward its next bifurcation depending upon which takes the least energy. In the intact lung the sequence of movements of menisci in the airway is determined by airway geometry and energy constraints on the surface films.

Once lung units have been opened during lung inflation, they presumably remain open until the lung is deflated. Kleinman (1967) first showed that during lung deflation some airways remain open at zero transpulmonary pressure. Then, Cavagna *et al.* (1967) presented evidence that a pressure difference between the free and trapped spaces did not occur until an end-expiratory pressure of -3 cm H_2O or less had been reached. In a review, Macklem (1971) examined the literature and concluded that most of the experimental evidence was consistent with the conclusion that lung airways remain open during lung deflation until negative transpulmonary pressures are reached.

Later, Glaister *et al.* (1973) using both closing volume measurements and curve fitting techniques to describe the deflation limb of excised lung P_L–V_L curves, concluded that during lung deflation units begin to close at positive transpulmonary pressures. Airway closure appeared to coincide with the inflection point along the pressure–volume curve. The inflection point usually occurred at positive transpulmonary pressures between $+5$ cm H_2O and 0.0 cm H_2O.

More recently, after studying the effects of end-expiratory pressure on gas trapping in lungs, Frazer *et al.* (1979a) showed that gas trapping does not occur in lungs inflated–deflated with positive end-expiratory pressures greater than 5 cm H_2O. When excised lungs were deflated to transpulmonary pressures below $+5$ cm H_2O, however, those authors concluded that gas trapping occurred as menisci began to form across the lumina of the small airways. In rat lungs, inflated at rates and pressures similar to those in this study, the number of menisci forming in the lungs (the initial step in airway closure) appears to follow a normal distribution such that 95% of the menisci form between 0.36 and 3.60 cm H_2O, and 50% form at pressures above 1.98 cm H_2O. These values have been shown to vary only slightly between animal species (Frazer *et al.*, 1979b).

It appears that the transpulmonary pressure at which lung units functionally close can be determined by analyzing gas trapping at different end-expiratory pressures (Frazer

et al., 1979a). This being the case it is possible to predict with some certainty how recruitment and derecruitment of lung units affect lung hysteresis. The object of this study was to use a volume perturbation method to detect transitions between pressure ranges where lung units open and close as the lungs are ventilated. To this end, lungs were subjected to small sinusoidal volume perturbations superimposed on slow inflations and deflations.

Methods

Hooded male rats of the Long-Evans strain weighing between 250 and 300 g were anesthetized by intraperitoneal injection of pentobarbital (65 mg/kg). Their lungs were endotracheally intubated, and the animals were sacrificed by exsanguination via the abdominal aorta. The excised lungs were degassed and placed in an air-filled plethysmograph (fig. 1). In this system, lungs were ventilated with a syringe pump (Harvard Apparatus, model 901) and a voltage-controlled pump (KBS, Model 100) consisting of a loud speaker driving a syringe in a feedback system (Khoshnood *et al.*, 1978). The voltage-controlled pump was used to generate small sinusoidal volume variations

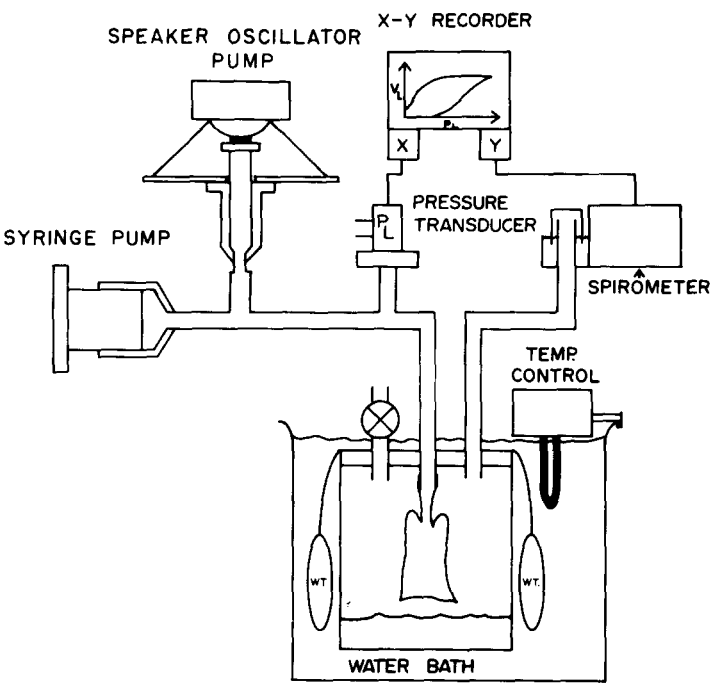

Fig. 1. Schematic diagram of the experimental apparatus used to record pressure–volume curves for excised rat lungs. A voltage-controlled speaker–syringe pump was used to superimpose sinusoidal volume oscillations on slowly varying lung volume changes generated by the syringe pump.

superimposed on the slow inflations (*e.g.*, insert in fig. 3) and deflations generated by the syringe pump. The average inflation–deflation rate was 3.82 ml/min with a sinusoidal small-volume perturbation (10 cycles/min, 0.5 ml peak to peak) superimposed. Transpulmonary pressure was monitored with a capacitance-type transducer (Setra, model 239E), and volume was measured with a minispirometer (Med. Sci., model 118). Pressure and volume were recorded on an X–Y recorder (Gould, model 15).

Four different PL–VL curve sets each were recorded for six lungs. Each curve set consisted of 4 inflation–deflation cycles. For the first cycle (fig. 2), lungs were inflated slowly at 3.82 ml/min from a transpulmonary pressure of 0.0 cm H_2O to a maximum transpulmonary pressure of + 30 cm H_2O (PLmax). The corresponding maximum volume of the lungs at PLmax during the first cycle was designated VLmax. The lungs were then deflated at the same rate from PLmax to – 5 cm H_2O. During the second cycle the speaker pump added small oscillations, and the lungs were reinflated to one half their maximum volume (VLmax/2) and then deflated to a predetermined minimum transpulmonary pressure (PLmin). The lungs were then inflated a third time from PLmin to VLmax and deflated back to PLmin again with small oscillations superimposed. Following a fourth inflation to VLmax, the speaker pump was turned off, and the lungs

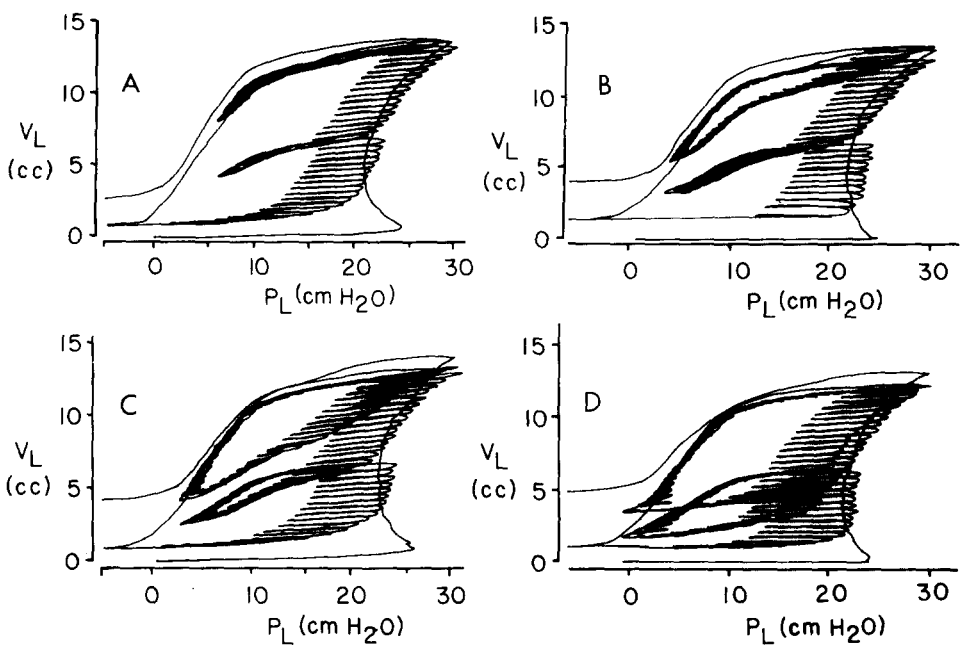

Fig. 2. Four representative sets of PL–VL curves recorded for a typical rat lung. In each set, the first cycle was an inflation–deflation at 3.82 ml/min between 0.0 and + 30 cm H_2O. During the second cycle a sinusoidal volume signal was superimposed on the PL–VL curve as the lung was inflated to VLmax/2 and then deflated to an end-expiratory pressure (PLmin). This was repeated during the third cycle with the inflation ending at VLmax. Deflation proceeded without oscillation. PLmin was (A) + 6 cm H_2O, (B) + 3 cm H_2O, (C) + 2 cm H_2O, and (D) 0.0 cm H_2O.

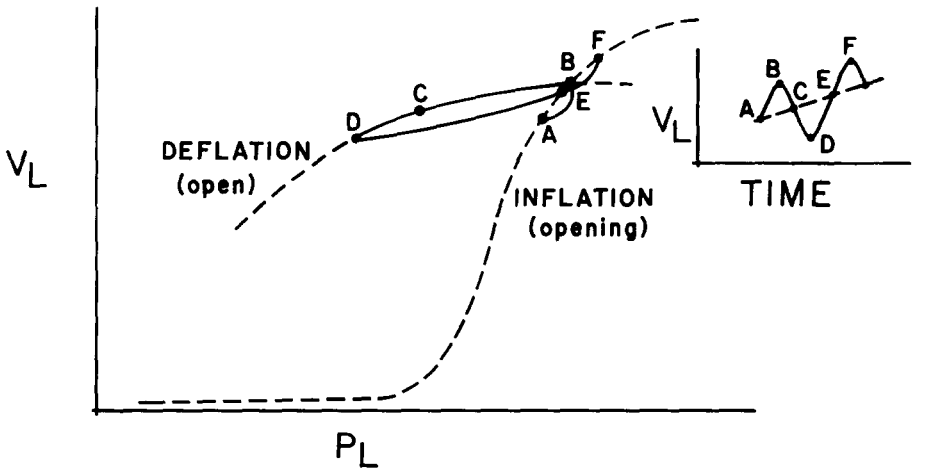

Fig. 3. Inflation with a single sinusoidal volume oscillation superimposed on a slowly increasing volume signal. The recorded loop (points A–F) results from switching from the opening of lung units along the inflation ('opening') curve to the homogeneous contraction and re-expansion of the units along the deflation ('open') curve. See text.

were deflated to -5 cm H_2O. In this study PLmax was always 30 cm H_2O, but PLmin was reduced in order (fig. 2A) from $+6$ for the first curve set to $+3$, $+2$ and $+0.0$ cm H_2O for the second through the fourth curve sets (fig. 2B–D), respectively. Lungs were degassed between curve sets, using the method of Stengel *et al.* (1980), to insure that they always had the same volume history.

For linear or piecewise linear PL–VL characteristics, the incremental compliances computed for slow inflation–deflation curves at a given operating point (quasistatic compliance, QSC) would be the same as those computed for perturbation cycles at the same point (perturbation compliance, PC). In the nonlinear region of typical PL–VL curves, these compliances could, of course, differ depending upon the type of non-linearity. Our experiments are designed to exploit such differences in order to discern the recruitment and derecruitment of lung units during incremental inflation and deflation. Computations of these compliances can be illustrated with the aid of fig. 3. For a complete perturbation cycle (points A to E), the quasistatic compliance, QSC, is approximately $[V_L(B) - V_L(A)]/[P_L(B) - P_L(A)]$ for the 'opening' curve and the perturbation compliance, PC, is taken as the chord ratio $PC = \Delta V_L/\Delta P_L = [V_L(B) - V_L(D)]/[P_L(B) - P_L(D)]$ for the 'open' curve.

The amplitude ($\Delta V_L/2$) of the volume perturbations used in this study was nearly constant although there were small differences at points along the PL–VL curve due to the compressibility of the gas. Hence, the PC compliance was approximately inversely proportional to the change in pressure, ΔP_L, during a volume perturbation.

Results

Figure 2 shows PL–VL curve sets for a typical excised rat lung. In the figure, small sinusoidal volume perturbations are superimposed on slow volume changes beginning with the second cycle. During inflation, PC and QSC are initially very similar but as inflation continues beyond the 'knee' of the curve, QSC increases rapidly while PC remains small. This clearly indicates a nonlinear process. The differences between PC and QSC during inflation persisted to TLC.

As the lung was deflated from either VLmax/2 or VLmax to a PLmin of 6 cm H_2O, changes in ΔPL decreased, QSC increased, and PC was similar to QSC (fig. 2A). Upon reinflation the PL–VL curve closely followed the deflation curve. There was very little hysteresis and PC was again similar to QSC.

After deflation to a PLmin of + 3 cm H_2O (a transpulmonary pressure below which menisci begin to form in the airways), the reinflation curve begins to deviate from the deflation curve (fig. 2B). This deviation becomes more dramatic as PLmin is lowered to + 2 and 0.0 cm H_2O, respectively (fig. 2C, D). The minor loops that are formed between PLmin and either VLmax/2 or VLmax exhibit increasing degrees of hysteresis as PLmin is decreased. Except for deviations for pressures below + 3 cm H_2O due to gas trapping, there is little change in the overall shape of the deflation curves in the four panels of fig. 2 as PLmin is lowered from + 6 to 0.0 cm H_2O. Also in fig. 2, the deflation curves from VLmax/2 and VLmax are approximately scaled replicas of each other. The hysteresis developed over the entire range of PLmin arises from the change in shape of the reinflation curves which tend to look more and more like the second-cycle inflation curve with the typical 'knee' as PLmin is decreased. Once the 'knee' pressure has been exceeded, QSC increases rapidly without a similar change in PC. The larger the degree of hysteresis, the larger the divergence between QSC and PC on reinflation.

Discussion

A model of lung hysteresis. Large differences between incremental (PC) and quasistatic compliance (QSC) along a given portion of a PL–VL curve can be interpreted as an indication that a nonlinear mechanical process is occurring in the lungs. This can result from at least two possible mechanisms. The first mechanism is related to the nonlinear properties of the lung material itself and includes both tissue and surface components. Hildebrandt (1970) has developed a viscoelastic model of the uniformly expanding lung based on this assumption. He concluded that approximately 2/3 of lung hysteresis could be explained by a linear viscoelastic mechanism and the remaining hysteresis arose from rate-independent plastic strain. It is also possible, however, that the nonlinearity evident during lung inflation results from the sequential opening of lung units having less severe nonlinear tissue properties. Such a model has been used by other investigators to describe static PL–VL curves of lungs (Mead *et al.*, 1957; Glaister *et al.*, 1973).

In this study, we propose a model of lung hysteresis based upon the sequential

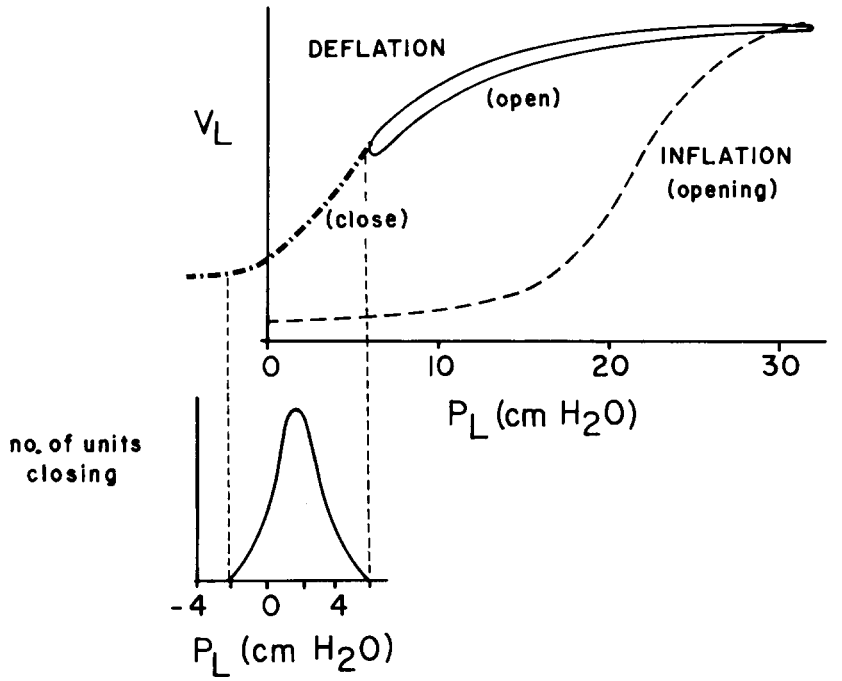

Fig. 4. The pressure–volume curve for open lung units is illustrated by the solid curve ('open') in which very little hysteresis is exhibited by the expansion and contraction of open lung units. When the lung is deflated to transpulmonary pressures below +4 cm H_2O, however, the lung units begin to close following a normal probability distribution. For those units to be reopened the lung must be reinflated to transpulmonary pressures above +4 cm H_2O along the dashed 'opening' curve.

opening and closing of elementary lung units in order to interpret our results. Our model rests on the assumption that a typical lung PL–VL curve (fig. 4) can be divided into three distinct regions: (1) an 'open' region, in which neither derecruitment nor recruitment takes place, (2) an 'opening' region characterized by recruitment, and (3) a 'closing' region associated with derecruitment. In the open region between TLC and 50% TLC there is evidence that there is very little airway closure (Frazer *et al.*, 1979a; Cavagna *et al.*, 1967), and PL–VL curves recorded in this region exhibit much less hysteresis than lungs ventilated between TLC and minimum lung volume (Cavagna *et al.*, 1967; Glaister *et al.*, 1980; Frazer and Franz, 1981). In the analysis that follows, it will be assumed that the normal pressure–volume relationship for individual open lung units (PL–Vu) is approximately a scaled replica of the deflation curve of the whole lung and exhibits only a small amount of quasistatic hysteresis.

If total lung volume, VL, in region 1 ('open'; fig. 4) is composed of the sum of individual volumes of open units, Vu_i, the following relationship must be true:

$$VL = \Sigma Vu_i. \quad (1)$$

If it is assumed that the pressure volume–relationship of each open unit is approximately

the same, *i.e.* Vu_i (P_L) = Vu(P_L), then eq. (1) reduces to:

$$V_L(P_L) = [No]Vu(P_L). \quad (2)$$

Thus the deflation curve in region 1 ('open' region) can be considered as the scaled replica of the P_L–V_L curve of a 'typical' lung unit where No is the number of open units. Since No is constant in region 1 there is neither recruitment nor derecruitment and differentiation of eq. (2) with respect to transpulmonary pressure gives the total lung compliance as:

$$\partial V_L/\partial P_L = [No]\partial Vu/\partial P_L \quad (3)$$

Thus, under these conditions, lung compliance is proportional to the compliance of a single lung unit when the lungs are deflated from any initial volume. This theoretical result fits the experimental observation made on the deflation curve of fig. 2A: (a) PC and QSC are approximately the same (there is no effect of recruitment on QSC), and (b) the curves for deflation from $V_L$max and $V_L$max/2 are approximately scaled replicas of each other.

During lung inflation, in region 2 ('opening' region), the lungs can expand either by the homogeneous expansion of units already open or by the recruitment of additional lung units. With recruitment, No would not remain constant in region 2; therefore, the compliance of the opening lung computed from differentiation of eq. (2) would be:

$$\partial V_L/\partial P_L = [No]\partial Vu/\partial P_L + [Vu]\partial No/\partial P_L. \quad (4)$$

The term, $[No]\partial Vu/\partial P_L$, represents the total compliance of the units previously opened while $[Vu]\partial No/\partial P_L$ represents the contribution to the compliance made by the recruitment of additional lung units. As has been noted previously, we have assumed that there is very little hysteresis in the P_L–Vu curve of open units so that the average unit compliance $\partial Vu/\partial P_L$ in region 2 is approximately the same as in region 1. According to eq. (4), the difference between the quasistatic compliance for the same No during inflation and deflation equals $[Vu]\partial No/\partial P_L$ which is the 'effective' compliance resulting from the opening of additional units. This is shown graphically in fig. 3 where the superposition of sinusoidal volume perturbations has been illustrated. With the perturbation cycle beginning at point A, additional lung units are recruited until point B is reached. The deflation from point B to D follows the region 1 ('open') curve intersecting with the region 2 ('opening') curve at B. The total compliance, $[No]\partial Vu/\partial P_L$, of the open units (eq. (3)) is represented by the slope of the region 1 ('open') curve at point B while the difference between $\partial V_L/\partial P_L$ of the region 2 ('opening') curve (fig. 3) and $[No]\partial Vu/\partial P_L$ represents the effective compliance contributed by the opening of additional lung units. The slopes at point B for the region 1 and 2 curves can be approximated by the chord ratios used to estimate PC and QSC as stated in the Methods section. The larger the difference in slope between the two curves at the intersection point B, the larger the contribution of recruitment.

At low transpulmonary pressures during deflation, the number of lung units, No, does

not stay constant because lung units close (derecruitment). In this case differentiating eq. (2) again gives eq. (4), but $\partial No/\partial P_L$ is now negative so that the slope (compliance) of the lung deflation curve is reduced at low transpulmonary pressures due to the closure of lung units.

The effect of oscillations superimposed on quasistatic P_L–V_L curves. During lung inflation sinusoidal volume perturbations superimposed on a steadily increasing volume expansion cause transitions such as the intersection at point B of fig. 3 between the 'opening' and 'open' regions of the lung P_L–V_L curve. During lung deflation at low transpulmonary pressure the perturbations initiate transitions between the 'open' and 'closing' regions (fig. 4). Figure 2 shows that during lung inflation beyond the 'knee' (cycle 1) the quasistatic compliance of the P_L–V_L curve, QSC, is large while the dynamic compliance during a single sinusoidal perturbation, PC, at the same volume is quite small.

The transitions which occur during a single sinusoidal perturbation, PC, can easily account for the differences between PC and QSC. For instance, fig. 3 shows the possible transitions as the lung is inflated. As lung volume increases during the initial portion of a sinusoidal perturbation, the P_L–V_L curve follows the 'opening' curve and lung volume increases, in part, with recruitment from point A to point B. The slight loop in the curve is primarily due to the dynamic effects of airflow in the airways and the viscoelastic properties of lung surface and tissue. With the perturbation frequency held constant, the influence of the dynamic effects on the PC measurements are minimized. During the deflation portion of the oscillation, the lung deflates uniformly along the path B–C–D. During this time transpulmonary pressure falls considerably, and lung volume decreases along the 'open' curve. Volume changes occur without derecruitment because closing pressures are not reached. When lung volume increases once again, the path D–E–F is followed as the open alveoli expand uniformly until the 'opening' curve is reached (point E). From this point on, additional units open with the perturbation cycle along the path from E to F. Thus, when the effective compliance of the lung is calculated during one perturbation cycle as the lung is inflated, PC is very small compared to QSC of the lung at the same volume. The low PC results from the transition between the 'opening' and the 'open' regions of the P_L–V_L curve.

Now consider the lung during deflation from $V_L max/2$ or $V_L max$. Initially, lung volume decreases without derecruitment; hence, the compliance of the lung during one oscillation is just slightly less than the static compliance of the lung during deflation at a slow constant rate. As the lungs are deflated still further (fig. 2B–D), the closing or derecruitment region of the P_L–V_L curve is reached (fig. 4). We believe that in this pressure range menisci begin to form across airways (Frazer *et al.*, 1979a). In the transition zone between the 'open' and 'closing' regions, the dynamic compliance of the lung during small volume oscillations, PC, gradually decreases from a value approximately equal to the slope of the static 'open' curve (QSC) to a compliance near zero. This decrease in compliance may be due to the formation of menisci in the very small airways of the lungs at low lung volumes. The movement of menisci formed in the

airways would require additional energy that must be supplied by an increase in transpulmonary pressure difference, $P_L(B) - P_L(A)$ (fig. 3) and would cause a decreased perturbation compliance.

Interpretation of the experimental results. Consider fig. 2A. As the lungs were inflated during cycle 2 to $V_L max/2$, PC was much lower than QSC because of the transitions between the 'open' and 'opening' curves. When the lungs were deflated from $V_L max/2$ to + 6 cm H_2O along an 'open' curve, PC is approximately equal to QSC. It can be assumed that few if any lung units closed as the lungs were deflated to + 6 cm H_2O (Frazer *et al.*, 1979a), and the inflation curve from + 6 cm H_2O to $V_L max/2$ retraces the deflation curve. There is very little hysteresis evident in the minor P_L–V_L loop between $V_L max/2$ and + 6 cm H_2O. As inflation proceeds at volumes above $V_L max/2$ following the first minor loop, QSC again exceeds PC, and inflation follows the 'opening' curve determined by the recruitment of additional lung units and the uniform increase in size of units already 'open'. The second minor P_L–V_L loop recorded between $V_L max$ and + 6 cm H_2O is similar to the first loop.

In fig. 2B, $P_L min$ was equal to + 3 cm H_2O. At this pressure airway derecruitment begins (Frazer *et al.*, 1979a). The results were still similar to those described in fig. 2A, but, because of some derecruitment, reinflation follows a slightly different 'opening' curve. The reinflation to $V_L max$ also shows evidence of recruitment as QSC progressively exceeds PC.

Figure 2C shows the results of reducing $P_L min$ to + 2 cm H_2O. The inflation curve during the second cycle of $V_L max/2$ is as that in fig. 2A. During deflation from $V_L max/2$ to + 2 cm H_2O, PC initially approximates QSC as in fig. 2A; but PC becomes significantly less than QSC as lung transpulmonary pressure approaches + 2 cm H_2O. We interpret this to mean that during the deflation part of the perturbation, airway closure or derecruitment exceeds that present without perturbations because the oscillatory pressure minimum is less than the static $P_L min$. On reinflation, therefore, an 'open' curve corresponding to a smaller number of open lung units should be followed. In fact, upon reinflation to $V_L max/2$, a minor loop exhibiting hysteresis develops as the inflation curve drops below the deflation curve. As before, PC initially approximates QSC during reinflation. On further inflation toward $V_L max/2$, PC becomes significantly less than QSC as the pressure range for recruitment is reached. A similar analysis can be made for the second minor loop between $V_L max$ and + 2 cm H_2O in fig. 2C. In this case the hysteresis arising from derecruitment and subsequent recruitment is more pronounced because deflation begins with a maximum number of open units.

In fig. 2D the sequence of events occurring during the minor loops was the same except that many more lung units were closed as the lung deflated to a $P_L min$ of 0.0 cm H_2O. With this more dramatic derecruitment, subsequent reinflation shows a more pronounced recruitment effect. Accordingly, the difference between PC and QSC and the degree of corresponding hysteresis is enhanced.

The events occurring during a minor P_L–V_L loop can now be summarized in terms of the previously described model as follows: During deflation, the curve follows the

'open' curve for a given number of open lung units (PC is approximately equal to QSC) until menisci begin to form in the airways at low transpulmonary pressures (PC decreases). Upon reinflation (PC again approaches QSC) the loop follows the 'open' curve of the lung units that have remained open. If a large number of lung units close as the lung is deflated to PLmin, hysteresis will become obvious as the reinflation curve falls significantly below the deflation curve. As the reinflation pressure reaches the range for recruitment, the lung units that closed on deflation reopen again along an 'opening' curve. This is illustrated by the fact that PC assumes values much lower than QSC along the 'opening' curve above the 'knee' of that curve.

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