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TRAPPED GAS AND LUNG HYSTERESIS

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Abstract. The amount of gas trapped in excised rat lungs was determined after four inflation-deflation cycles between total lung capacity (TLC) and several end-expiratory volumes or end-expiratory pressures. Lungs ventilated in this way exhibited pressure-volume curves that formed closed loops with varying degrees of hysteresis. The area of these loops was highly correlated with the amount of gas trapped in the lungs. Trapped gas volume and hysteresis increased with deflation to increasingly lower end-expiratory volumes or pressures. The processes responsible for lung hysteresis, however, seem to be primarily dependent upon end-expiratory pressure and only slightly dependent upon end-expiratory volume. A possible explanation of these findings is that menisci, formed in the small airways of the lung during deflation at low lung volumes, are responsible for both the trapped gas and the pressure-volume hysteresis of the lung.

Airway closure
Alveolar trapped gas
Lung hysteresis
Meniscus formation in lungs

Bachofen and Hildebrandt (1971) found that the hysteresis area (A) of lung pressure-volume ($P_L - V_L$) curves forming closed loops could be written in terms of the change in pressure (ΔP), the tidal volume (V_T), and a proportionality constant (K) as $A = KV_T\Delta P$. Their results described first tidal loops along the $P_L - V_L$ 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 A, V_T, and ΔP could be extended to a more general form given by $A = KV_Tf(\Delta P)$. In the more general case it was found that $f(\Delta P)$ was a nonlinear function in that hysteresis area increased at a faster rate as V_T approached vital capacity. One explanation of their finding is that airways open or close at low lung volumes and thus contribute to lung hysteresis. They dismissed this possibility because there was little evidence

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of atelectasis or buckling of airway walls over the pressure ranges in which they recorded their $P_L - V_L$ curves. They did not consider functionally equivalent forms of airway closure such as the formation of menisci across the lumen of airways, however.

Recently, we have described an indirect method for detecting the formation of menisci in airways (Frazer *et al.*, 1979). This method is based on the assumption that the amount of gas trapped in the lung is proportional to the number of menisci formed in the airways during lung deflation. Our study of trapped gas volumes indicates that menisci form in excised lungs at positive transpulmonary pressures and could thus contribute to pulmonary hysteresis. The purpose of this study was to explore the relationship of trapped gas volume and, by implication, meniscus formation to the hysteresis area of pressure–volume loops of excised lungs.

Methods

Long-Evans hooded male rats weighing between 250 and 300 g were anesthetized with sodium pentobarbital (65 mg/kg) injected intraperitoneally. Following a tracheotomy, the animals were ventilated with a positive pressure respirator (Harvard Apparatus, model 665). The abdominal cavity was opened, the diaphragm was penetrated to achieve a bilateral pneumothorax, and the rat was exsanguinated via the abdominal aorta. The rib cage was then sectioned on both sides of the midline, and the heart, lungs, and diaphragm were removed *en bloc*. The excised lungs were vacuum degassed using the method of Stengel *et al.* (1980) and suspended by the trachea in an air-filled, temperature-controlled plethysmograph. Approximately 20 minutes were allowed for temperature equilibration. A series of pressure-volume curves was recorded for each lung as it was ventilated between TLC and constant end-expiratory volumes or constant end-expiratory pressures. The recording system and its accuracy have previously been described in detail (Frazer *et al.*, 1979).

I. CONSTANT END-EXPIRATORY VOLUME $P_L - V_L$ LOOPS

In part I, five different sets of $P_L - V_L$ curves were recorded for each lung at an inflation-deflation rate of 3.82 cc/min. Every set consisted of four inflation-deflation cycles and was characterized by a different end-expiratory volume ($V_L$min). During the first cycle, the lungs were inflated from 0.0 cm H_2O to 30 cm H_2O ($P_L$max) and then deflated to $V_L$min. In cycles 2 and 3, lungs were inflated and deflated between $V_L$min and $P_L$max. The fourth cycle consisted of inflating the lungs from V_L(min) to P_L(max) and then deflating them to -5 cm H_2O. $V_L$min was equal to 75% of total lung capacity for the first set, then 60%, 50%, 40% and 30% TLC for the second, third, fourth, and fifth sets respectively. After each 4-cycle

set was recorded, the ratio Vm/Vmax characterizing the fraction of gas trapped in the lung was determined by dividing Vm, the volume of gas remaining in the lung after the fourth cycle and measured at -5 cm H_2O, by Vmax, the maximum lung volume during the same cycle.

As each 4-cycle set was recorded, three individual $P_L - V_L$ loops were formed. The first loop consisted of the deflation limb of cycle 1 and the inflation limb of cycle 2, the second loop was generated by the deflation limb of cycle 2 and the inflation limb of cycle 3, and the third loop was formed by the deflation limb of cycle 3 and the inflation limb of cycle 4. The hysteresis area, H, of each of the three loops was measured with a Manual Optical Image Analyzing System (Technics, MOP/AM 01) and normalized with respect to the product $P_{L}max \times TLC$, *i.e.* divided by the maximum possible hysteresis area per cycle, Hmax, to yield the hysteresis index H/Hmax.

II. CONSTANT END-EXPIRATORY PRESSURE $P_L - V_L$ LOOPS

In part II of the study four sets of $P_L - V_L$ curves were again recorded for all lungs. The lungs were ventilated in a manner similar to that in part I except they were deflated to constant end-expiratory pressures ($P_{L}min$) instead of constant end-expiratory volumes. $P_{L}min$ was $+6$ cm H_2O for the first set and was reduced to $+4$, $+3$, and $+2$ cm H_2O, respectively, for the second, third, and fourth sets. After each set was recorded, Vm/Vmax and H/Hmax were determined in the same manner as described in part I.

Results

I. CONSTANT END-EXPIRATORY VOLUME $P_L - V_L$ LOOPS

Typical 4-cycle $P_L - V_L$ curve sets of an excised lung ventilated between TLC and five different end-expiratory volumes, $V_{L}min$, are shown in fig. 1. Note that the curves of this particular lung are shown to indicate that lungs could not always be deflated to 30% TLC during the third cycle because of the accumulation of trapped gas (fig. 1E). The average values (N = 6) of Vm/Vmax, the index of trapped gas derived from the fourth cycle of each set of curves, are plotted against the corresponding values of $V_{L}min$ in fig. 2A. It can be seen that as end-expiratory lung volume was decreased below 50% TLC, values of Vm/Vmax increased greatly.

Average values (N = 6) of H/Hmax for the first recorded $P_L - V_L$ loop of each curve are plotted against $V_{L}min$ in fig. 2B. It can be seen that hysteresis, like trapped gas, increased significantly as lung volume was decreased below 50% TLC. The correlation coefficient, r, for the measures of trapped gas and hysteresis,

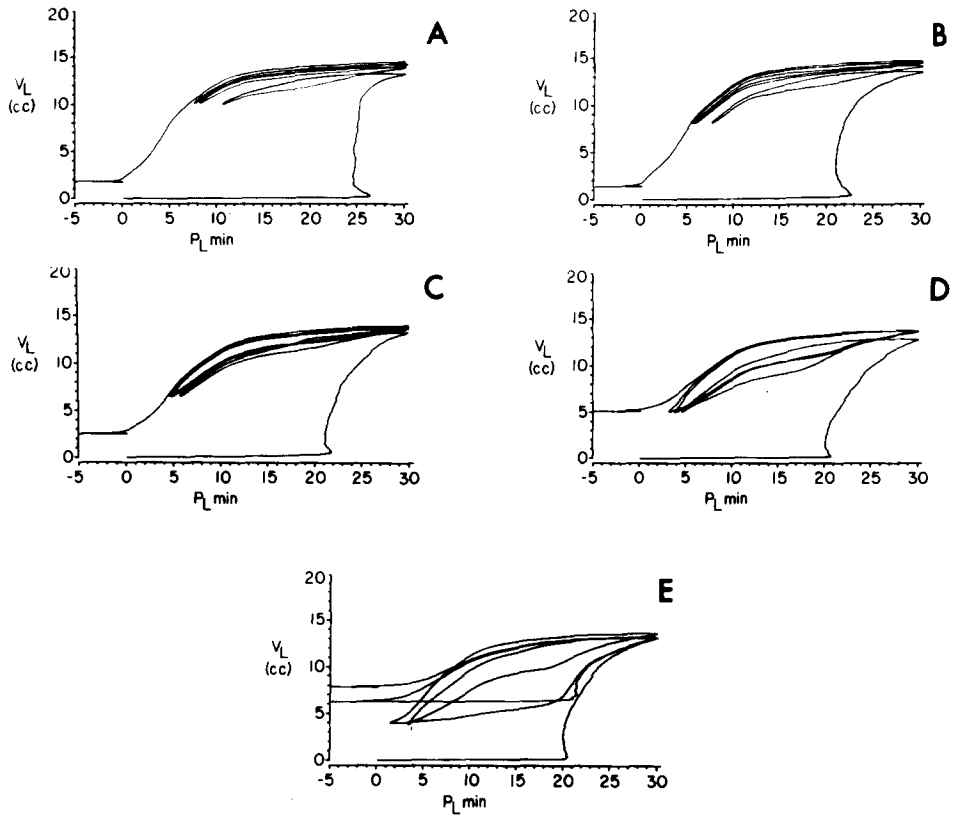

Fig. 1. Sets of pressure–volume curves for typical rat lung ventilation at 3.82 cc/min for four inflation-deflation cycles as the end-expiratory volume was held at (A) 75%, (B) 60%, (C) 50%, (D) 40%, and (E) 30% TLC. This particular lung could not be deflated to 30% TLC during cycle 3 (E).

Vm/Vmax and H/Hmax, was 0.933 for the third constant end-expiratory volume loop. Because of shape differences of loops for a given VLmin, the relative increases (+) or decreases (−) in hysteresis area (ΔH/Hmax) between the first loop and the second and third loops are plotted in figs. 2C and 2D, respectively. These figures illustrate that hysteresis for the second and third PL − VL loops increased greatly. The change in hysteresis during the third cycle at 30% TLC may be underestimated because it was not always possible to deflate the lungs to 30% TLC during cycle 3 (see fig. 1E). The average minimum values of transpulmonary pressure, PLmin, for cycles 1, 2, and 3 in the constant end-expiratory volume loop study are shown in fig. 3. The distribution of airway closures with respect to PLmin previously found by Frazer *et al.* (1979) is superimposed on these curves. It can be seen that airway closure becomes significant as lungs are ventilated between TLC and end-expiratory volumes below 50% TLC.

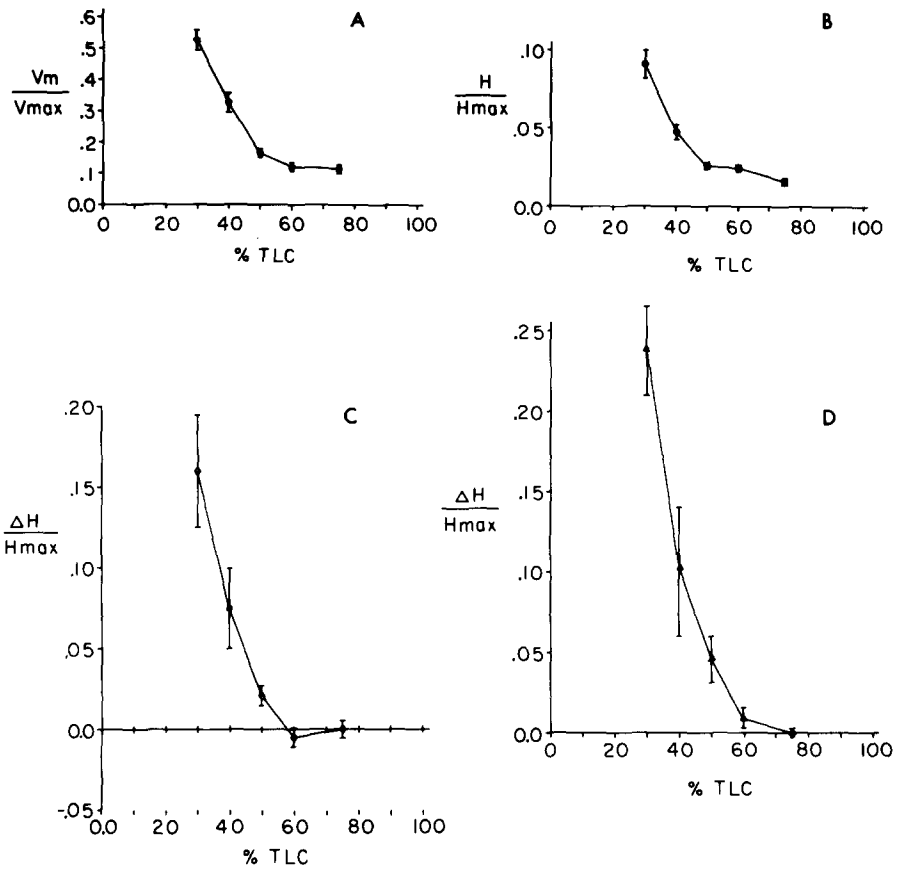

Fig. 2. (A) The normalized mean minimum volume of the lung, Vm/Vmax ± SEM (N = 6), plotted as a function of end-expiratory volume, % TLC, following 4 inflation-deflation cycles at a rate of 3.82 cc/min. (B) The normalized mean hysteresis area, Hmax ± SEM, enclosed during the first PL – VL loop plotted as a function of end-expiratory volume when the lungs were ventilated between TLC and 5 different end-expiratory volumes. (C) The normalized mean difference in hysteresis area, ΔH/Hmax ± SEM, between the first and second PL – VL loops plotted as a function of lung volume, % TLC. (D) The normalized mean difference in hysteresis area, ΔH/Hmax ± SEM, between the first and third PL – VL loops plotted as a function of lung volume.

II. CONSTANT END-EXPIRATORY PRESSURE PL – VL LOOPS

Typical sets of PL – VL curves have previously been shown for excised rat lungs ventilated for four cycles with constant end-expiratory pressures (Frazer *et al.* 1979). The average value (N = 6) of Vm/Vmax for each curve in this study is shown as a function of PL(min) in fig. 4A. The value of H/Hmax for the first PL – VL loop at each end-expiratory pressure is given in fig. 4B. Here, H/Hmax increased sharply when the lungs were deflated to pressures below 4 cm H_2O. The correlation coefficient, r, for the measures of trapped gas and hysteresis, Vm/Vmax and

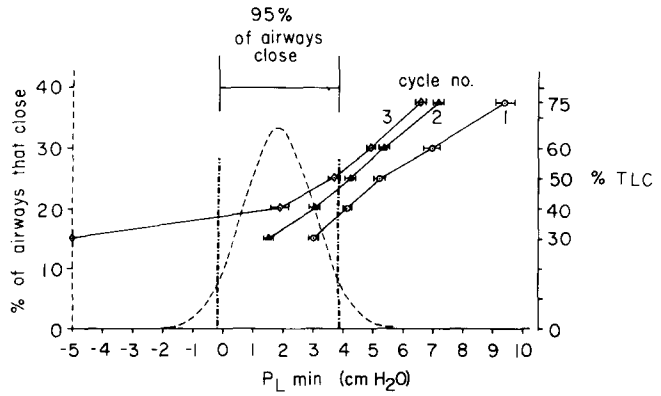

Fig. 3. The solid lines show the mean minimum transpulmonary pressure ± SEM (N = 6) for $P_L - V_L$ loops 1, 2, and 3 as the lungs were deflated to five different end-expiratory volumes expressed as % TLC on the right ordinate. The dashed curve shows the relative number of airways closing at each transpulmonary pressure (see fig. 5, Frazer *et al.*, 1979). The two noncontinuous vertical lines indicate the range of transpulmonary pressures over which 95% of the airways close.

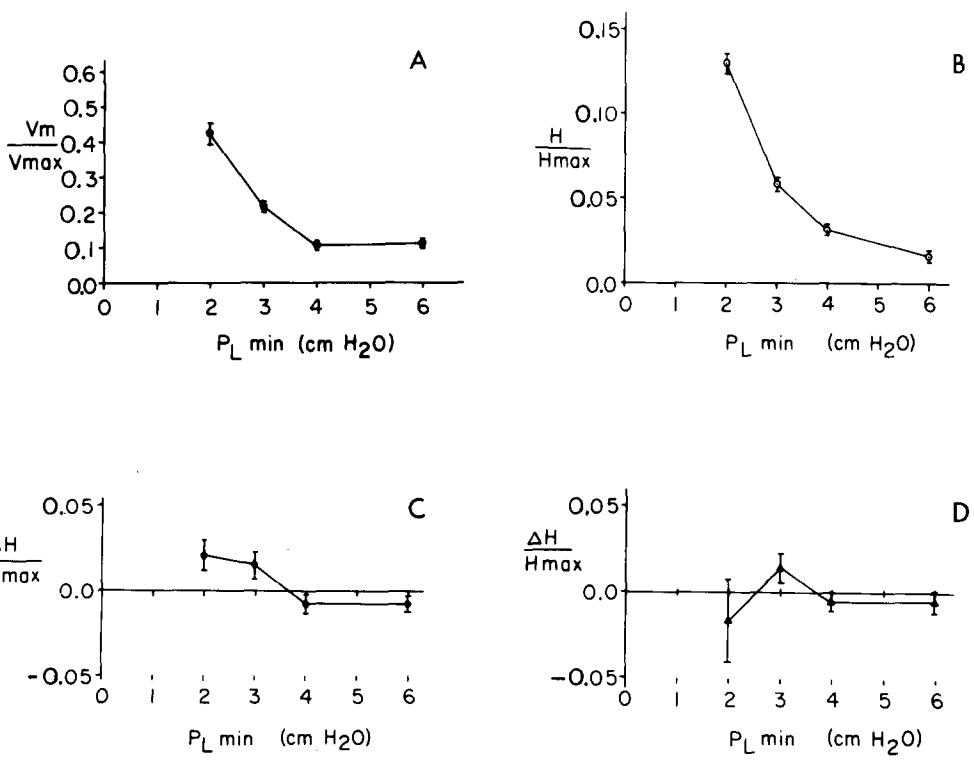

Fig. 4. The normalized mean volume of the lung, Vm/Vmax ± SEM (N = 6), plotted as a function of end-expiratory pressure, PLmin, following four inflation–deflation cycles at a rate of 3.82 cc/min. (B) The normalized mean hysteresis area, H/Hmax ± SEM, enclosed by the first $P_L - V_L$ loop plotted as a function of end-expiratory pressure. (C) The normalized mean difference in hysteresis area, ΔH/Hmax ± SEM, between the first and second $P_L - V_L$ loops plotted as a function of end-expiratory pressure. (D) The normalized mean difference in hysteresis area, ΔH/Hmax ± SEM, between the first and third $P_L - V_L$ loops plotted as a function of end-expiratory pressure.

H/Hmax, was 0.936 for the third constant end-expiratory pressure loop. These results, too, indicate that hysteresis is highly correlated with the amount of trapped gas in the lungs. Although there are shape differences, the hysteresis area of the first, second and third $P_L - V_L$ loops remained nearly identical when the end-expiratory pressure was held constant, so the values of $\Delta H/Hmax$, the relative change in hysteresis area between the first cycle and the second and third cycles, respectively, were very small (figs. 4C,D).

Discussion

This study shows that $P_L - V_L$ curves recorded for excised lungs exhibit very little hysteresis or gas trapping when the lungs are deflated from TLC to lung volumes above 50% TLC. At end-expiratory volumes below 50% TLC, however, hysteresis area and trapped gas volume increases are significant, approximately parallel, and highly correlated.

It is interesting to note that other investigators (Klingele and Staub, 1970; Daly *et al.*, 1975) have found that lungs expand nearly uniformly between 50% and 100% TLC, but below 50% TLC, where gas trapping and hysteresis begin to increase rapidly the lungs showed nonuniform expansion. Their findings, together with ours imply, therefore, that the processes contributing to gas trapping and lung hysteresis may also be associated with some form of nonuniform expansion.

In part I of this study, lungs were ventilated over nearly constant volume intervals resulting in the formation of three consecutive $P_L - V_L$ loops. The hysteresis areas enclosed by these loops were not constant but increased with each successive loop (figs. 2C,D). Pressure-volume curves showed that the end-expiratory pressure, P_{Lmin}, decreased (ΔP increased) slightly for each additional cycle, indicating a possible association between P_{Lmin} and the amount of hysteresis. In part II of the study, the lungs were ventilated over a constant pressure range, again forming three consecutive $P_L - V_L$ loops. In this case, however, the hysteresis area remained nearly constant (figs. 4C,D), while end-expiratory lung volume tended to increase (V_T decreased) as the three loops were recorded. It appears, therefore, that at low lung volumes the process responsible for pulmonary hysteresis is much more a function of end-expiratory pressure changes than end-expiratory volume changes. These results are consistent with those of Horie and Hildebrandt (1973) who showed that the pressure term $f(\Delta P)$ in their hysteresis area equation increased rapidly as the end-expiratory lung volume was decreased.

Two recent reviews (Macklem, 1978; Goerke, 1974) have stated that most of the evidence thus far supports the viewpoint that pressure-volume hysteresis arises primarily from the surface tension-lung area ($\gamma - A_L$) relationship of the lung. Macklem (1978) further concluded that although alveolar recruitment may have an effect on the area (A_L)-volume (V_L) relationship of the lung, it does not contribute to lung hysteresis. This implies that there is no geometric area-volume

hysteresis as the lung is inflated and deflated and that each value of AL must correspond to a unique value of VL. Since AL can be expressed as a function of VL, AL = f(VL), the (γ – AL) relationship presumably responsible for lung hysteresis could also be written as a (γ – f(VL)) relationship. It would follow, then, that the hysteresis area resulting from a changing surface tension should also be a function of lung volume, and thus be related to end-expiratory volume. Conversely, the hysteresis area should remain constant when the lung is ventilated to form constant volume PL – VL loops. Our experimental results show, however, that hysteresis area does vary considerably when lungs are ventilated under constant end-expiratory volume conditions (figs. 2C,D) but remains nearly constant when the lungs are deflated to constant end-expiratory pressures (figs. 4C,D). This means that either the (γ – AL) relationship for the lung varies as a function of the end-expiratory pressure for a given inflation–deflation cycle or another pressure-dependent mechanism is responsible for lung hysteresis. The parallelism of the indices for gas trapping (Vm/Vmax) and hysteresis (H/Hmax) evident in figs. 4A and 4B, the pressure (PLmin) dependence, and the high correlation between the two indices suggest common mechanisms for the two phenomena. Because we consider meniscus formation a major mechanism for gas trapping, under the given experimental conditions, we also favor the notion that meniscus formation in small airways may be a major contributor to hysteresis.

It has been shown previously that the excised lungs of many mammals, including the rat, accumulate trapped gas as they are inflated and deflated at a slow, continuous rate (Faridy and Permutt, 1971; Frazer and Weber, 1976; Hutcheon *et al.*, 1978; Frazer *et al.*, 1979). Gas trapping has also been observed *in vivo* in the dog (Sergysels *et al.*, 1977) and in the rat (Morgan and Frazer, 1980).

We have examined several properties of the gas trapping process in the lung and have found that most gas is trapped in the lung during inflation (Frazer and Weber, 1976), that there is trapped gas in the lung at maximum lung volume (Frazer and Weber, 1979), and that gas trapping can occur at positive transpulmonary pressures (Frazer *et al.*, 1979).

Since foam has been observed exuding from the trachea of lungs containing trapped gas, it has been suggested that bubbles or menisci are somehow responsible for the trapped gas (Pattle, 1958; Radford, 1964; Faridy and Permutt, 1971; Frazer and Weber, 1976; Sergysels *et al.*, 1977; Lai-Fook *et al.*, 1978). From experiments with several gases and gas mixtures we have concluded that gas must diffuse across a liquid barrier to enter the trapped gas space (Frazer and Weber, 1980).

All these properties of the gas trapping mechanism are consistent with a model of the gas trapping process (Frazer and Khoshnood, 1979) in which menisci form across the airways of the lung at positive end-expiratory pressures as the lungs are deflated. These menisci have been observed by Macklem *et al.* (1969) and Scarpelli (1978) and have been indirectly detected by Frazer *et al.* (1979).

The experiments of Cavagna *et al.* (1967) and Hughes and Rosenzweig (1970)

showed that airways do not physically collapse until transpulmonary pressure becomes negative (Macklem, 1971). Thus it is likely that airway closure is related to two separately occurring events as lungs are deflated. These two events are the formation of menisci across the airways at positive transpulmonary pressures followed by the mechanical buckling of the airway wall at negative transpulmonary pressures. Under the experimental conditions ($P_{L}min > 0$) of our study, we consider hysteresis to be mainly a consequence of airway closure by meniscus formation rather than airway collapse.

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