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Factors affecting trapped gas volume in perfused dog lungs

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HUGHES, J. M. B., AND D. Y. ROSENZWEIG. *Factors affecting trapped gas volume in perfused dog lungs.* J. Appl. Physiol. 29(3): 332–339. 1970.—Excised lungs were deflated slowly from submaximal to minimal air volumes, representing changes of transpulmonary pressure (Ptp) from 21 cm H_2O to −6 cm H_2O, respectively. Expulsion of gas ceased at about Ptp −2.5 cm H_2O. At Ptp −6 cm H_2O the volume of trapped gas (VTG) averaged 20% of submaximal volume in freshly perfused preparations. After 4 hr perfusion VTG had increased in 12 lungs from 325 to 678 ml. By using radioactive xenon gas and scanning of the lung we found that the VTG was greater in the more dependent parts of the lung where histological pulmonary edema was most prominent. The infusion of a bronchoconstrictor, histamine, into the pulmonary artery also increased VTG. We suggest that bronchoconstriction of peripheral airways, and peribronchial and intra-airway edema may cause airways to close at higher distending pressures resulting in the trapping of larger volumes of gas.

PV diagrams of lungs; negative transpulmonary pressure; minimal volume; interstitial edema; mechanical properties of lung; bronchoconstriction; airway closure

THE MAXIMAL VOLUME of gas that can be expelled from the lungs by mechanical forces is determined by the compliance of the chest wall, conducting airways, and terminal air spaces. In voluntary maneuvers in young normal subjects the force that can be generated by the respiratory muscles becomes a limiting factor (18). Elderly subjects, on the other hand, appear to be limited by factors within the lung rather than the chest wall and it has been suggested that airway closure occurs (11). In certain circumstances the volume of gas remaining in the lungs after a maximal expiration (residual volume) increases. The increase in residual volume during acute exacerbation of asthma (29) suggests trapping of air by obstruction or closure of airways.

In animals, minimal lung volumes can be studied free from the added complexity of the thoracic cage. Kleinman et al. (16) measured the lung volume in mongrel dogs after the chest had been opened and the lungs allowed to collapse under the influence of their own elastic recoil. At the equivalent of zero transpulmonary pressure the lungs contained on average 202 ml (57% of functional residual capacity). Cavagna et al. (5) showed in open-chested animals that more air could be expelled from the lung as transpulmonary pressure (Ptp) was lowered below zero (by syringe withdrawal) until pleural pressure exceeded airway pressure by 2 cm H_2O. At this point all airways closed, preventing further changes in volume.

The behavior of the isolated perfused lung afforded us an opportunity to investigate some details of airway closure and gas trapping. We had frequently observed that excised dog lungs after being perfused for a short while failed to deflate at low distending pressures. For example, the volume of gas in the lung at zero transpulmonary pressure appeared to us to increase two or three times during the first 2 hr of perfusion. This was surprising because in many other respects—vascular resistance, gas exchange, gain in weight—the preparation had remained very stable. Also, we observed that wedges of tissue removed from the periphery of the lung, without fixation of any kind, remained inflated. In the following study we set out to confirm these impressions and investigate the role of airway closure in determining trapped gas volumes in the isolated lung.

METHODS

Details of the experimental preparation have been described previously (27). Briefly, greyhound dogs were anesthetized with intravenous barbiturate and heparinized. The left lung was excised immediately after the death of the animal by exsanguination. After cannulation of the pulmonary artery, main bronchus, and excised left atrium, the lung was suspended vertically or horizontally in a Lucite box. In the vertical position the weight of the lung was taken by the bronchial cannula; in other experiments the preparation was mounted horizontally with the hilum downward on a perforated plate. The lung was ventilated and perfused with a steady flow of venous blood at 38 C from a mongrel dog to which blood leaving the excised lung was returned. Vascular pressures were measured with saline manometers and blood flow by collecting timed samples in a measuring cylinder. Pulmonary arterial pressure was controlled by varying the input flow pump and venous pressure by raising or lowering the venous reservoir. The lung was weighed on a balance at the beginning and end of the experiment and the weight of the cannulas subtracted. Pieces from the apex, middle, and lower lobes were put into formol saline and processed in a conventional manner using hematoxylin and eosin stains.

The lung was connected to a 2-liter bell spirometer on which volume changes were recorded at ATPS. Pleural pressure was changed by altering the pressure in the Lucite box. Box pressure was measured in centimeters of water on a

water manometer. The lung was inflated nearly maximally by lowering the pressure in the box to −24 cm H_2O and then ventilated tidally for 3–4 breaths from 10 to 5 cm H_2O transpulmonary pressure (Ptp). The lung was next slowly inflated from Ptp 5 to 21 cm H_2O and transpulmonary pressure and volume changes were recorded at intervals as the lung was deflated to a negative Ptp of 6 cm H_2O and reinflated to Ptp 21 cm H_2O. The time taken was 3–5 min. In four experiments electrical signals from the spirometer and from a transducer (measuring box pressure) were displayed continuously on an *X-Y* plotter.

Measurement of Lung Volume

Absolute lung volumes were measured by the gas-dilution technique using radioactive xenon gas as the indicator. At Ptp 5 cm H_2O the lung was connected to a small rubber bag containing a measured volume (about 800 ml) of xenon 133 in air in a concentration of approximately 5 mc/liter. The bag was enclosed within a bottle to which the spirometer was attached to measure volume changes. The lung ventilated to and from the bag for 2–3 min until equilibration occurred.

The concentration of xenon 133 in the bag was continuously monitored by a scintillation counter placed beside a short length of glass tubing leading from the bag and shielded with lead; the initial and final count rates were recorded.

Basic assumptions in the gas-dilution technique are, first, complete mixing between the indicator gas and all intrapulmonary gas and, second, negligible diffusion of the indicator into pulmonary tissue or fluid, or into the blood. Our criterion of complete mixing was an equal inspired and expired level of radioactivity in the glass tubing leading from the lung. We found the equilibration generally occurred within the first minute of the 2- to 3-min ventilation period. Xenon gas is relatively insoluble in water or plasma; the ratio of the amount in solution to the amount in air being about 0.09 (17). Calculations from the data in Tables 1 and 2 show that xenon dissolved in tissue would only account on average for 1.2% of the xenon in the lung at an end-expiratory (Ptp 5 cm H_2O) volume of 1,000 ml, and for only 1.45% in the "late" measurements when lung weight had increased. We have not corrected for this small error. Removal of tissue xenon by blood flow during the equilibration period was discounted because of the low blood flows.

Measurement of Regional Volumes

After equilibration with xenon 133 the lung was inflated to Ptp 21 cm H_2O and scanned with a pair of scintillation counters from bottom to top at a speed of approximately 0.25 cm/sec. Under equilibrium conditions the count rate at any level is proportional to the lung volume in the counting field. The lung was deflated to Ptp −6 cm H_2O, disconnected from the bag containing radioactive gas, and reinflated with air from the spirometer to the same volume at which the previous scan (at equilibration) was made. A further scan of the lung was performed to record the amount of radioactivity remaining. By relating this to the previous scan we were able to calculate the distribution of residual radioactivity at Ptp −6 cm H_2O as a percentage of that at Ptp 21 cm H_2O. Since no more air could be expelled from the lung even though Ptp was lowered below −6 cm H_2O, the residual radioactivity chiefly reflects gas trapped within the lung. Untrapped airway gas probably contributes 1–3% of the lung volume (12) the exact amount depending on the airway caliber at Ptp −6 cm H_2O and the site of airway closure. Xenon 133 in the bronchial cannula at Ptp − 6 cm H_2O was also reinspired; this volume was only 15 ml (2–4% of the volume at Ptp − 6 cm H_2O) and has been neglected.

Counting conditions. The pair of scintillation counters scanning the lung had multiholed focused collimators whose 50% response was 0.75 cm from the center of the counting field. In the scans after the inhalation and rebreathing of radioactive gas 1,000–2,500 counts/sec were available over most regions of the lung. The time constant of the counting and recording equipment was 1.0 sec. The scanning speed was 0.2–0.5 cm/sec. The count rate recorded by the scintillation detector monitoring radioactivity in the tubing connecting the lung and the bag usually exceeded 10^4 counts/sec. The counts from the front and back counters over the lung were summed and passed to rate meters to be displayed on a pen recorder. Additionally, a scaler-timer chain accumulated the counts and time during each centimeter of distance traversed by the counters; the information was fed sequentially into a data logger with a punch tape output (Elliot-Automation Ltd., Boreham Wood, England) and later analyzed by computer (15).

Bronchoconstriction

The effect of drugs such as histamine and serotonin on the percentage of regional residual radioactivity was studied by infusing them at a constant rate into the pulmonary artery immediately after the equilibration scan. The lung was deflated and ventilated for 1.5–2.5 min until pulmonary arterial pressure had become constant. The lung was then inflated to Ptp 21 cm H_2O and deflated to Ptp − 6 cm H_2O as previously described.

RESULTS

Twenty-four isolated lungs were examined. The initial weight ranged from 111 to 168 g with an average of 134 g. Lungs were perfused for approximately 4 hr and showed an average gain in weight of 38% (range 1–180%). Nineteen lungs were suspended in the vertical position and five horizontally. At Ptp 10 cm H_2O the initial average pulmonary arterial pressure referred to the hilum of the lung was 0.1 cm saline in the vertical preparations (average height of the lung 33 cm; distance from hilum to bottom of lower lobe 19 cm); flow was 145 ml/min throughout the experiment. After approximately 3 hr perfusion the increase in pulmonary arterial pressure averaged 1.5 cm H_2O. In horizontal lungs (average maximal height 8 cm; hilum 4 cm above the bottom of the lung) average pulmonary arterial pressure was 8.0 cm saline; flow was 160 ml/min. The level of the venous reservoir was below the bottom of the lung in both situations. The reasons for the apparent difference in vascular resistance between the vertical and horizontal lungs are complex and depend upon the amount of lung perfused and the relations in a gravity field between pulmonary arterial, alveolar, and venous pressures; for a

discussion of this subject the reader is referred to the paper by West and Dollery (26).

Measurements of submaximal and minimal gas volumes before and after about 4 hr perfusion were obtained in 12 lungs; the results and the changes in lung weight are shown in Table 1. The submaximal volume (V_{submax}) refers to the volume of gas in the lungs at Ptp 21 cm H_2O. The gas capacity of the lung can be increased by about 5% if Ptp is raised further. However, our experience is that high distending pressures accelerate the formation of edema and we avoid them where possible. The decrease in V_{submax} after 3–4 hr perfusion was small averaging 6% or 100 ml. The volume of trapped gas (VTG) on the other hand more than doubled; the increase (353 ml) was highly significant ($P > 0.01$). As a proportion of V_{submax}, VTG increased from 20 to 44%. Similar changes occurred for the lung volume at zero transpulmonary pressure (V_0) which increased from 30 to 48% of V_{submax}; the absolute values were 494 ml (SEM ± 57) initially, and 749 ml (SEM ± 61) for the late measurement of V_0. Absolute lung volumes were measured in only one of the horizontal lungs; but the changes were similar to lungs in the vertical position.

TABLE 1. *Isolated lung weights and submaximal and minimal gas volumes at beginning and end of 4-hr perfusion*

Exp No.	Wt, g	Wt Gain, %	V_{submax},* liters ATPS		VTG,† ml ATPS	
			Early	Late	Early	Late
4	150	78	1.76	1.66	510	790
6	144	30	2.35	2.10	250	925
7	124	6	1.60	1.39	180	310
8	132	1	1.70	1.39	290	390
9	152	32	1.60	1.47	150	755
11	134	8	1.25	0.95	265	545
13	130	12	1.26	1.16	120	455
16	155	21	1.67	1.95	280	700
17	112	180	1.19	1.17	260	660
18	147	65	2.00	1.90	510	850
19	140	2	2.04	2.07	530	970
20	119	9	1.35	1.34	570	780
Mean	133	37	1.65	1.55	325	678
±SE	±3.95	±14.8	±0.103	±0.111	±46.2	±60.6
P‡			<0.05		<0.01	

* Volume at Ptp 21 cm H_2O. † Volume of trapped gas at Ptp −6 cm H_2O. ‡ Paired t test of significance.

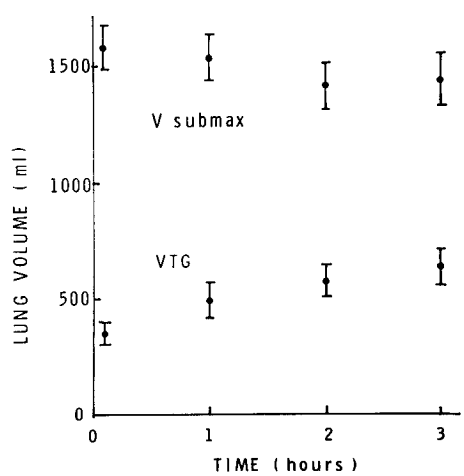

FIG. 1. Serial measurements of lung submaximal volume (V_{submax}) at Ptp 21 cm H_2O and volume of trapped gas (VTG) at Ptp − 6 cm H_2O at hourly intervals during perfusion in 10 lungs. Vertical bars indicate 1 SE of mean.

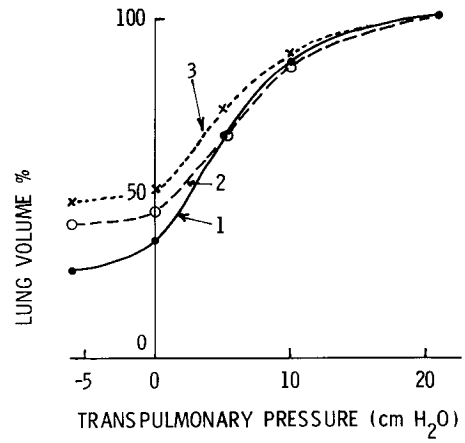

FIG. 2. Lung volume (as a percentage of submaximal volume) plotted against transpulmonary pressure during deflation from submaximal to minimal volumes. Serial measurements in time at 30, 90, and 150 min after start of perfusion in an isolated lung. Note how in later measurements (*nos. 2* and *3*) lung volumes are higher especially at lower distending pressures. V_{submax} did not change significantly (2.04, 2.04, and 2.07 liters, respectively).

In 10 lungs serial measurements of V_{submax} and VTG were obtained at approximately hourly intervals (Fig. 1). They show that significant changes in VTG occurred after only 1 hr of perfusion, and that these changes progressed as perfusion continued and as edema developed. Figure 2 is an example of the effect of perfusion time upon the deflation pressure-volume (PV) curve. The largest volume changes occur at the lowest distending pressures; above Ptp 5 cm H_2O the changes are initially comparatively small. Cook et al. (7) found that edema in dog lungs did not alter the deflation PV curve much in the range Ptp 20–5 cm H_2O.

Effect of Edema

Pulmonary edema of varying extent was seen in all preparations on macroscopic and histological examination at the end of the experiment. For the most part the changes correlated with the percentage weight gain. In six lungs (*nos. 7, 8, 13, 16, 19, 20*), interstitial edema was seen expanding the perivascular and peribronchial space; this effect was greatest in the dependent part of the lung, as previously described (13). There was no evidence of alveolar edema or airway foam. In the remaining lungs (*nos. 4, 6, 9, 11, 17, 18*) these changes were more severe and were usually accompanied by hemorrhage into the perivascular space and some alveolar edema; in these lungs some airway foam was seen on dissection. An analysis of lung weights and lung and tidal volumes of these two groups is presented in Table 2. The early measurements made on both groups are very similar although there is some difference in the lung weights. In the late measurements, made after several hours perfusion and just before dissection of the lung, several differences are apparent. The lungs with foam have a much larger percentage weight gain and much greater changes in all

TABLE 2. *Comparison of weights and lung and tidal volumes in preparations with and without airway edema at end of experiment*

	Lungs Without Foam (n = 6)			Lungs With Foam (n = 6)		
	Early	Late	Percent change	Early	Late	Percent change
V_{submax},[a] ml	1,600 ±114	1,550 ±150	−3.2	1,690 ±180	1,542 ±178	−8.8
V_0,[b] ml	494 ±57	687 ±96	+39	517 ±33	824 ±63	+59
VTG,[c] ml	328 ±75	601 ±105	+83	324 ±61	754 ±55	+132
VTG,[d] penult		511	+56		595	+69
VTG/V_{submax}, %	20.5	39		19	49	
Tidal vol,[e] ml	204 ±18	149 ±28	−27	201 ±25	125 ±21	−35
Inspiratory capacity,[f] ml	633 ±44	531 ±51	−16	632 ±58	490 ±62	−22.5
Lung wt, g	127 ±3.7	137 ±2.65	+8	140 ±6.1	219 ±25	+56

Values are means ±SE. [a] Volume at Ptp 21 cm H_2O. [b] Volume at Ptp 0 cm H_2O. [c] Volume of trapped gas at Ptp −6 cm H_2O. [d] Penultimate measurement of VTG. [e] Volume as Ptp altered from 5 to 10 cm H_2O at frequency 6/min. [f] Volume inspired from Ptp 5 to 21 cm H_2O.

lung volumes. The changes from the early measurement and the differences between the two groups are relatively small for V_{submax} and inspiratory capacity (IC) when compared to measurements made at lower distending pressures (tidal volume, V_0, and VTG). The penultimate measurement of VTG shows that the greater part of the final difference in VTG did not occur until the last measurement; the appearance of foam in the airways between these two measurements could have caused such a change.

Gas-dilution measurements of lung volume may be in error in the presence of airway foam. This problem was investigated by Cook et al. (7) in their study of pulmonary mechanics during induced pulmonary edema in dogs. In the presence of edema they found that the total gas volume estimated by helium or sulphur hexafluoride gas-dilution methods was 12–15% less than measurements by Boyle's law. There was good agreement in the nonedematous state. The amount of edema was much greater in their series (15 lungs with an average weight gain of 157% and a decrease in total gas volume of 23%). In this study V_{submax} in the lungs with airway foam decreased 8.8%, or 5.6% more than the group without airway foam. The result might mean inadequate penetration of xenon gas within or beyond the foam; on the other hand, if the surface area of the foam were large enough for complete equilibration, a genuine change of V_{submax} may have occurred. In fact the changes of V_{submax} are small and do not materially affect the results.

Regional Differences in VTG

The distribution of trapped gas in the lung before and after 4 hr perfusion is shown in Fig. 3. The trapped gas is low throughout the lung in the early measurement but more so at the apex. There is a generalized increase in trapped gas in the late measurement with a somewhat greater change in the dependent zones. In these vertical preparations the upper 10 cm of lung tissue was relatively unperfused at Ptp 10 cm H_2O; even in the late measurements pulmonary arterial pressure only increased by 1–2 cm H_2O. Consequently the increase in trapped gas at the apex seen in the late measurements appears somewhat out of proportion to its perfusion assuming that perfusion, edema, and trapped gas are related in this preparation. On the other hand, for the same overall flow pulmonary arterial pressure at Ptp 10 cm H_2O may be up to 12 cm H_2O less than that at Ptp 21 or −6 cm H_2O, so that the apical regions would be perfused at high and low lung volumes. Secondly, the increase of VTG in relatively unperfused areas may be related to factors other than edema (see DISCUSSION).

Effect of Bronchoconstriction

Because of the relatively large changes in VTG which occurred as a function of time while the lung was being perfused, we experienced some difficulty in interpreting the effects of stimuli which increased the volume of trapped gas. However, on a number of occasions (see Fig. 4) by infusing histamine into the pulmonary artery in relatively high concentrations (0.5–1.0 mg/min) for 5–7 min we were able to show an increase in the volume of gas retained at Ptp − 6 cm H_2O which was reversible. Regional measurements showed the increase of VTG was mainly in the dependent zones. The most likely explanation is that in the upright lung the dependent zones receive more blood flow per unit lung volume and therefore a greater concentration of histamine. Serotonin which is a potent vasoconstrictor in this preparation had no effect on the trapped gas volume when infused in a concentration of 0.1 mg/min nor did a bronchodilator, isoproterenol (0.03 mg/min).

Additional detail into the relations between transpulmonary pressure and lung volume was provided by *X-Y* plots. Figure 5 shows the effect of histamine infusion (1.0 mg/min) in a lung mounted horizontally. Absolute lung volumes were not measured but changes in V_{submax} can be inferred from results already presented. On deflation the

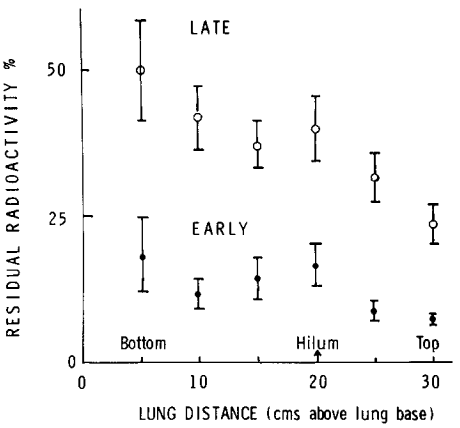

FIG. 3. Residual radioactivity is that remaining after deflation to Ptp − 6 cm H_2O as a percentage of that at Ptp 21 cm H_2O; it reflects percentage of gas trapped in vertical lungs from lower lobe (bottom) to apex (top). Average values in 9 lungs with vertical bars giving 1 SE of mean. In the early measurement residual radioactivity is low, especially at apex, but after 2 hr perfusion (late) there is an increase, most marked in dependent zone.

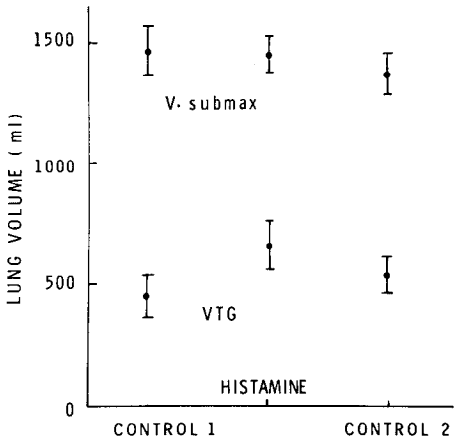

FIG. 4. Submaximal lung volume (V_{submax}) and volume of trapped gas (VTG), as in Fig. 1, before (*control 1*), during (*histamine*), and after (*control 2*) infusion of histamine (0.5–1.0 mg/min) for 5–7 min into the pulmonary artery. Mean value of 5 measurements in 3 lungs with 1 SE of mean. Histamine causes a partially reversible increase in VTG but no consistent effect on V_{submax}.

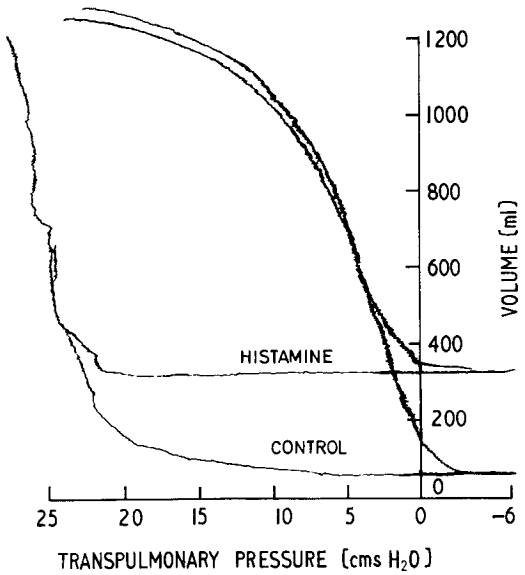

FIG. 5. *X-Y* plot of volume—not absolute lung volume—and transpulmonary pressure in an isolated lung before and during histamine infusion (1 mg/min) into the pulmonary artery. Note differences in PV diagrams at Ptp less than 3 cm H_2O, and the large distending pressure required to reinflate lung during histamine infusion.

histamine PV curve followed the control until about Ptp 4 cm H_2O was reached; the slope of the control curve continued unchanged to zero transpulmonary pressure where the compliance changed. Expulsion of gas ceased abruptly at Ptp −2.5 cm H_2O. Meanwhile during histamine infusion changes in the PV slope occurred at Ptp 3.5 and 2 cm H_2O as well as at zero Ptp. Small quantities of gas continued to be expelled until Ptp −3.5 cm H_2O. The pressures required to reopen the airways are quite high, especially during histamine infusion.

DISCUSSION

Perfused lungs at Ptp −6 cm H_2O retain considerable volumes of gas which increase as a result of edema or bronchoconstriction. For several reasons we believe that this gas volume is trapped by airway closure; for example, a further reduction of Ptp did not cause more gas to be expelled, and we have also observed closure of small airways under these circumstances (14).

Determinants of Trapped Gas Volume (VTG) in "Early" Measurements

The VTG in excised lungs reflects the properties of airways and air spaces, and since they are in series the relations between them. For instance, if airways were rigid the lung would empty completely apart from the anatomic dead space once the negative transpulmonary pressure exceeded that needed to collapse air spaces. If, on the other hand, airways closed at less negative transpulmonary pressures than alveoli VTG would reflect principally the parenchymal volume at that airway closing pressure. (If airway closure did not occur simultaneously throughout the lung, additional emptying of some alveoli might occur through collateral channels, although it has been suggested recently (28) that collateral channels in the dog lung are closed when Ptp is less than 2–3 cm H_2O.)

Experimental evidence favors the notion that airway closure may occur at transpulmonary pressures insufficient to collapse air spaces. Cavagna et al. (5) in open-chest animals compared airway pressure and lung volume in two situations; first, in air-filled lungs as air was withdrawn from the trachea with a syringe, and, second, in oxygen-filled lungs during gas absorption. Gas removal by syringe ceased at Ptp −2 cm H_2O although the alveoli still contained air. Further reduction of pressure was not accompanied by volume changes indicating that terminal air spaces were no longer in continuity with the trachea. During oxygen absorption changes of volume and pressure occurred together until the gas-free condition was reached at Ptp −2 to −6 cm H_2O. The authors argued that some airways must have remained open in this instance and that these pressures reflect the resistance of alveoli to collapse. Our PV diagrams of the lung (Fig. 5) are comparable to the syringe withdrawal experiments just described. In the control curve, for example, volume change ceased abruptly on deflation at Ptp −2.5 cm H_2O presumably because all airways have closed.

It is surprising perhaps that the pressures necessary to collapse airways and air spaces are so similar. On the other hand histological observations which we are presenting (14) suggest that the site of closure is in small bronchioles where structural differences between airways and air spaces are least. It follows that the VTG depends on the balance between airway and air-space closing. In the "early" measurements we often observed patchy atelectasis on the surface of the lung at Ptp −6 cm H_2O indicating that alveoli had collapsed at pressures insufficient to close their airways.

Effect of Perfusion

Minimal gas volumes in perfused lungs are greater than in lungs without blood flow. For instance it is commonly observed that anesthetized animals killed by exsanguination have very low lung gas volumes (equivalent to tissue volume)

when the thorax is opened. This represents approximately a volume equal to 8% of V_{submax} at Ptp 0 cm H_2O compared to the 20% V_{submax} at Ptp −6 cm H_2O we have reported for perfused lungs (Table 1). Kleinman et al. (16) measured the volume at Ptp 0 cm H_2O in dogs after opening the chest but with pulmonary perfusion continuing. Gas volumes were 2.5 times greater than tissue volume. Our own measurements shown in Fig. 3 are interesting in that VTG is less toward the apex of the lung, even in the "early" measurement where there was no pulmonary edema. In RESULTS we pointed out that pulmonary arterial pressure was on average sufficient only to perfuse the lung up to the level of the hilum so that the apex was relatively unperfused. We did not, however, find a gradient of VTG with vertical height in keeping with the gradient of perfusion pressures, but in the lower lobe this may have been obscured by collateral ventilation.

Other workers have measured lung volumes in the presence of normal and high pulmonary venous pressures. Using an open-chest dog preparation Borst et al. (2) found that at Ptp 0 cm H_2O a sudden lowering of left atrial pressure was accompanied sometimes by substantial further emptying of the lung. PV diagrams in cat's lungs (9) showed that at low distending pressures volumes were slightly greater when vascular pressures were high. All these observations are consistent with von Basch's original proposal in 1887 (1) that pulmonary vascular pressures give mechanical support to the lung parenchyma. This would mean in the case of VTG that for the same airway closing pressure parenchymal volume would be greater at higher vascular pressures. Alternatively pulmonary vascular pressures could alter the pressures at which airways close or open.

Determinants of Trapped Gas Volume (VTG) in "Late" Measurements

Large increases in VTG took place while the excised lungs were being perfused, though changes in vascular pressures and resistance were small. Possible reasons for this will be discussed below.

Change in air-space properties. A loss of the surface active material (surfactant) from air spaces would tend to lower lung volumes at low distending pressures rather than raise them. Edema of alveolar walls might alter parenchymal compliance. On the other hand changes in lung recoil in the range Ptp 21 to 5 cm H_2O were small compared to the increases of VTG making it unlikely that significant changes in the elastic properties of lung parenchyma had occurred.

Change in airway properties. SURFACTANT. Airway closure in excised rabbit lungs occurs at the same pressure whether gas or liquid filled (25) suggesting that closure is largely independent of surface properties. This notion is supported by recent evidence (19) showing that in lungs flushed with a solution of Tween 20 bronchioles dissected free from the surrounding parenchyma close at higher pressures than in the control situation; these bronchioles appeared to be lined with a substance similar to alveolar surfactant. Therefore at low volumes the tension at the surface will be low and the contribution of surface forces to their closing pressure must be very small. To the extent that the site of airway closure in our preparation is in such bronchioles, loss of airway "surfactant" might cause the increase of VTG we have found. This may explain certain features of the VTG, for instance the increase of VTG at the apex of the lung (late curve in Fig. 3) which seems out of proportion to the perfusion that area received, the dependence of VTG on the time taken to deflate the lung from maximal volumes (S. Permutt, personal communication), and the fact that unperfused lungs do eventually trap gas. On the other hand, the rate of increase and the absolute volumes of trapped gas are in our experience much greater in perfused preparations. We would also expect bronchioles to be replenished with surfactant from the alveolar pool each time the lung is deflated to low lung volumes; our evidence from PV curves (Fig. 2), admittedly indirect, suggests no significant loss of alveolar surfactant.

EDEMA. It is easy to see that fluid within the airways may obstruct them and form menisci especially when bronchial diameter is reduced at low lung volumes. Table 2 shows that large increases in VTG occurred at the time foam appeared in the airways. Equally important from the point of view of airway closure may be the appearance of interstitial edema in the peribronchial and perivascular spaces. In the sequence of fluid accumulation in the lung edema appears first in these interstitial spaces (24). In our experiments an increase in VTG occurred within the first hour of perfusion (Fig. 1) in lungs where weight gain was minimal (Table 2) and where no alveolar edema was visible on histological examination with conventional techniques. Edema of the perivascular and peribronchial spaces was always seen, and there was a correlation between the VTG of the region 5 cm above the lung base and the width of the perivascular cuffs in specimens taken for histological examination immediately afterward.

Why should peribronchial edema cause airways to close at higher distending pressures than normally? It might well be argued that the cuff of fluid would bulge out into the surrounding air spaces rather than compress the airway. Fenn (8) has analyzed the situation where a volume of gas is introduced into a closed system between two elastic structures—the chest wall and the lung in pneumothorax. Changes of volume and pressure can be predicted if the compliances of lung and chest wall are known. A similar situation exists in the interstitial space when fluid accumulates between the bronchial wall and the limiting membrane which forms the outer boundary of the peribronchial sheath. As an example, an analysis of this using a modified "Campbell" diagram (4) is shown in Fig. 6 where the volume of a hypothetical bronchus is plotted against peribronchial pressure. Intrabronchial pressure is atmospheric. At peribronchial pressures of −3 cm H_2O and 0 cm H_2O we have illustrated the sequence of changes in bronchial volume and in the volume of the peribronchial space (equal to the vertical distance between the curves for the bronchus and the limiting membrane), as fluid accumulates. For instance at a peribronchial pressure of −3 cm H_2O and at zero interstitial fluid volume the limiting membrane volume has the same percentage volume as that of the bronchus. In this situation the limiting membrane is being distended by lung recoil forces (assume as a first approximation that pleural and peribronchial pressures are similar) equivalent to 3 cm H_2O which are balanced by a peribronchial pressure

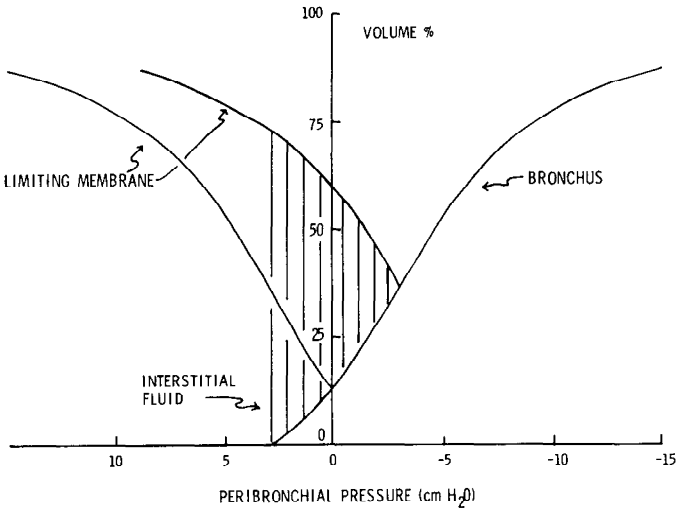

FIG. 6. Hypothetical pressure-volume relationship of a small airway (bronchus) and its peribronchial space as fluid accumulates between bronchial wall and limiting membrane which forms outer boundary of peribronchial sheath. Pressure refers to that within peribronchial space; alveolar and airway pressures are atmospheric. Volumes of bronchus and limiting membrane are expressed as percentages of that at maximal inflation (Ptp 30 cm H_2O). Volume of interstitial fluid in peribronchial space is given by vertical distance between curves for limiting membrane and bronchus. Effect of fluid accumulation on volumes of bronchus and limiting membrane, while transpulmonary pressure remains constant, is shown starting from peribronchial pressures of -3 cm H_2O and 0 cm H_2O. See text for explanation.

of -3 cm H_2O. Similarly the bronchial wall is recoiling with a pressure of 3 cm H_2O against the peribronchial pressure. As fluid forms in the interstitial space the peribronchial pressure will increase. In the presence of fluid an increase of peribronchial pressure affects the limiting membrane and bronchus in opposite ways, expanding the former and compressing the latter. As sufficient fluid accumulates to alter peribronchial pressure from -3 cm H_2O to -2 cm H_2O, for example, the limiting membrane expands because on its outer surface it is still exposed to lung distending forces (3 cm H_2O) but the opposing forces on its inner surface are now only equivalent to -2 cm H_2O. The bronchus contracts because its recoil pressure (3 cm H_2O) now exceeds its surface pressure (-2 cm H_2O). Provided transpulmonary pressure remains constant this sequence of events continues until peribronchial pressure equals airway closing pressure (3 cm H_2O). If the initial peribronchial pressure is 0 cm H_2O a much smaller cuff of fluid suffices to bring about airway closure. At low distending pressures the width of cuff needed to bring about airway closure, shown in Fig. 6, is not very great. At 0 cm H_2O initial peribronchial pressure the width of the cuff of peribronchial fluid when airway closure occurs equals about 34% of the original bronchial diameter.

Although several assumptions and simplifications are implicit in the illustration shown in Fig. 6, we believe that it is reasonably realistic. For example, we have chosen the compliance of the bronchus on deflation to be the same as that of lung tissue. For bronchioles and very small airways this may not be unreasonable since the distensibility of 2-mm bronchi in vitro is fairly similar to that of the lung (20). This is also convenient for the analysis because if bronchus and lung tissue expand equally peribronchial pressure will be the same as pleural pressure. Airway closing pressure is taken as 3 cm H_2O (5). We have neglected the pressure drop across the limiting membrane (Mead et al. (21) have suggested that it is small at normal lung volumes) and assigned the limiting membrane the same compliance as that of the bronchus and lung tissue. The structure of the limiting membrane is similar to that of alveolar tissue although it contains more collagen fibers (10). In fact assuming a constant bronchial wall thickness percent volume changes of the bronchus and limiting membrane in the absence of fluid must be the same. Changes in bronchial wall thickness may be important especially at low and zero airway volumes (by definition the limiting membrane cannot reach zero volume as long as the bronchial wall remains); in general this effect would shift the curve for the limiting membrane at zero interstitial fluid volume to the left of that for the bronchus.

To the extent that the compliances of the airway and the limiting membrane differ from those in Fig. 6—and it is obvious that they will be somewhat different—more or less interstitial fluid will accumulate before airway closure occurs. If the fibers in the limiting membrane were at their resting length an increase in radius of 100% by means of accumulation of fluid in the peribronchial space would increase the surface area and length of the fibers in the same proportion. Radford (23) in length-tension studies on lung tissue slices found maximum extension in the neighborhood of 80%. The implication is that limiting membranes may become very rigid under certain circumstances and exceed the capacity of their airways in resisting further deformation.

A reduction in the effective bronchial distending pressure may also accompany interstitial fluid accumulation. According to a recent analysis (21), the radial stress on cylindrical structures within the lung is related to the distending forces, the number of tissue attachments transmitting these forces, and the area acted upon. As the surface area of the limiting membrane increases, the force per unit area (the effective distending pressure) will become less. A cuff of peribronchial fluid equivalent in thickness to 50% of the diameter of the bronchus would double the circumference of the limiting membrane and reduce the effective distending pressure by half. However, this mechanism would not lead to positive peribronchial pressures.

BRONCHOCONSTRICTION. Histamine infused into the pulmonary artery of dogs and cats (intact chest) causes a fall of dynamic compliance measured during tidal breathing (6). In cats with open chest at Ptp 3.5 cm H_2O marked constriction of alveolar ducts and bronchioles has been demonstrated histologically (6), but quasi-static PV curves and the volume of trapped gas have not been measured. We have shown a reversible increase in VTG during infusions of histamine into the pulmonary artery (Fig. 4); the compliance curve of the lung on deflation (Fig. 5) was similar to that of the control curve except at low distending pressure (Ptp less than 3.5 cm H_2O). Quasi-static PV curves were reported by Woolcock et al. (28) during bronchoconstriction induced by vagal stimulation in dogs with open chest. There were decreases in vital capacity in some animals of up to 20% but no volume increase at Ptp 0 cm H_2O. These results do not agree with our own and suggest that the site of constriction with vagal stimulation differs from that

brought on by histamine infusion. An increase of VTG with histamine suggests critical closure of airways, by which we mean closure occurring as a result of increases in active tension while transmural pressure remains constant (3).

Closure occurring in small airways should not be confused with the increased resistance to collapse from compressing pressures which has been shown for the trachea and large bronchi when constricted with histamine (22). In the histamine PV curve (Fig. 6) small quantities of gas are expelled from the lung until Ptp -4.5 cm H_2O suggesting that complete airway closure occurs at a lower Ptp than in the control. Probably most airways have closed at higher Ptp but because the trapped gas volume is high compared with the control, the relatively well-expanded parenchyma contained by the first airways to close may be maintaining the patency of some neighboring units. In other words, the spectrum of airway closing pressures was probably much greater in the presence of bronchoconstriction.

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