The Number and Dimensions of Small Airways in Emphysematous Lungs

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The number of conducting airways less than 2 mm in internal diameter was only slightly reduced in the lungs of 12 patients with pulmonary emphysema and diminished flow rates. There was a change in the distribution of the smallest remaining airways, with a deficit of airways 0.4 to 0.6 mm in diameter and an excess of airways smaller than this. The change in airway caliber and number was small in emphysematous lungs and increased airway resistance in emphysematous lungs is more likely related to loss of elastic recoil, central flow limitation and associated chronic bronchitis (Am J Pathol 67:265–276, 1972).

ALTHOUGH it is generally thought that pulmonary emphysema is associated with airways obstruction, the site and mechanism of obstruction are far from clear. Pathologic studies are conflicting, and the available information is shown in Table 1.[1–7] The majority of these reports are purely descriptive and nonquantitative. On the other hand, the site of flow resistance has been demonstrated physiologically by Hogg *et al*[8] who partitioned airway resistance in excised postmortem lungs into a central (Rc) and a peripheral component (Rp) (in airways less than 2 mm in internal diameter). They showed that an increase in Rp was the common denominator in bronchitis, emphysema and bronchiectasis and that central resistance was inconstantly raised. We have, therefore, counted and measured airways less than 2 mm in internal diameter in the lungs of patients with emphysema to identify the nature of the lesions which might produce obstruction in these small airways.

Materials and Methods

Twenty-one emphysematous lungs from 12 patients, 11 of whom were male, were studied. The age range of the 12 patients was 51 to 74 years. All had had antemortem tests of pulmonary function and all had symptomatic obstructive lung disease which, in 10, was the cause, or the underlying cause, of death.

The number and dimensions of airways were determined as previously described for normal lungs.[9] In brief, the lungs were inflated at a transpulmonary pressure of 25 cm of 10% formalin for 18 to 24 hours. The volume of the distended

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Table 1—Obstruction or Narrowing of the Airway

Author(s)	Site	Nature
Spain, Kaufman[1]	Terminal bronchiole	Mural inflammation and fibrosis of bronchioles
Leopold, Gough[2]	Between a terminal bronchiole and an emphysematous space	Inflammatory fibrosis with narrowing of 60% of bronchioles supplying centrilobular emphysematous spaces
McLean[3]	Proximal order of respiratory bronchiole	Inflammation of airways and and mucous plugging
Wright[4]	First, second and third bronchi, distal to the segmental bronchi	Bronchial atrophy
Anderson, Foraker[5]	Non-respiratory bronchiole	Collapse of bronchioles (reduced bronchoalveolar attachment)
Pratt et al[6]	Bronchioles	Loss or distortion of the radial support of bronchioles
Bignon et al[7]	Bronchioles	Inflammatory bronchiolar narrowing

lung (total lung volume or TLV) was then measured by water displacement. The lungs were cut into sagittal slices 1.0 to 1.5 cm thick. The proportion of the lung occupied by emphysema and nonparenchyma was calculated from a stratified random point count over the slices of lung, after impregnation with barium sulfate, floated under water. The mid-sagittal slices were submitted for the paper-mounted whole lung sections, and the amount of emphysema was estimated on these, both by using a standard set of grading pictures[10] and the Ryder grid.[11] The former measurements were made by two observers who were unaware of the measurements of the small airways (Dr. George Massarella, Royal Post-Graduate School, London and Dr. M. W. Thurlbeck), and the mean score of the two observers was used. The latter measurements were made by Dr. Thurlbeck only.

Either five or six stratified random blocks were taken from the lateral slice of each lung for counting and for measuring small airways as well as alveolar surface area. Correction was made for shrinkage during processing, and all results are corrected to formalin-fixed tissue. Conducting (*ie*, nonalveolated) airways, less than 2 mm in internal diameter, were counted, their diameters measured as described previously,[9] and the diameters used are those of all airways, rather than ideal airways. This was done because of the bias, in the latter method, toward smaller mean diameters.[9] In addition, the proportion of points falling on airway lumen (Q_{SAT}) (the lumen of airways less than 2 mm, irrespective of whether the lumen contained air, mucus or exudate), compared to the total number of points falling over lung tisue or it contents, was calculated.

A method of correction was devised for possible overinflation of emphysematous lungs, making the usual assumption that all structures expand equally in all directions. We had anticipated that emphysematous lungs would be overinflated, and, therefore, the number of small airways per unit area or volume would appear decreased. From previously described data,[9] it is possible to predict the ratio of TLV to the cube of body length at a given age. Thus, if body length is known, it is possible to predict TLV at age 20 (TLVp). Volumetric change corrections would be directly related to the ratio of observed TLV (TLV_c) to TLV_p. Two dimen-

sional changes, such as the number of airways per unit area, would be corrected to the two third power of the ratio, and one dimensional change, such as diameter, to the one third power of the ratio. Where structures would be expected to increase due to overinflation (for example, diameters), the correction would thus be $d_c = d \times (TLV_p/TLV_o)^{1/3}$, where d_c is corrected diameter and d is observed diameter. Where results might be artificially decreased by overinflation, such as number of airways per unit area, the correction would be $n_c = n \times (TLV_o/TLV_p)^{2/3}$, where n_c is the corrected number of airways per unit area and n is the observed number of airways per unit area.

Correction for the proportion of small airways lumen (Q_{SAT}) is difficult. Clearly, if the lung is overinflated, then the amount of air is increased in small, large and alveolated airways as well as alveoli. Thus the proportion of air (lumen) to tissue in the lung increases with overinflation. However, the ratio of small airways lumen to lumen of other structures will remain approximately constant, since the basic assumption, in all corrections, is that structures expand equally. Using these assumptions, it can be shown that (see Appendix):

$$Q_{SATc} = Q_{SAT} \times \frac{(TLV_p - V_t)}{(TLV_o - V_t)} \times \frac{(TLV_o)}{(TLV_p)}$$

Where Q_{SATc} is the proportion of small airways lumen corrected to TLV_p, Q_{SAT} is the proportion of small airways lumen as measured and V_t is the volume of tissue. When V_t is zero, or when TLV_p and TLV_o are the same, then Q_{SATc} is equal to Q_{SAT}. The degree to which the ratio of Q_{SATc}:Q_{SAT} varies from unity depends on the ratio of TLV_o:TLV_p and V_t. The variation is small. For example, when TLV_o is 1.5 times TLV_p and V_t 10% of TLV_p, $Q_{SATc} = 0.9642\ Q_{SAT}$. This represents the maximum change likely, since more than 50% overinflation is rarely found and V_t derived from the usually quoted density of the lung at total lung capacity (TLC)[12] and the density of air-free lung tissue[13] is 9.93% of TLV_p. Thus, while we have corrected Q_{SAT} for overinflation, it is unlikely to be of major significance.

The assumption that air-containing structures expand equally must be examined critically. Although it used to be thought that alveolar volume did not expand with lung volume[14] this is no longer thought to be true[15–17] and alveolar volume increases directly with lung volume.[16,17] The precise change in the dimensions of alveolar ducts with inflation is controversial,[16,17] but the most recent view is that the alveolar duct-volume fraction of the lung is constant throughout inflation.[17] By contrast, the dimensions of major bronchi[18] change little above functional residual capacity. All the above results were obtained in healthy animals. Since alveoli and alveolar ducts form, by far, the greatest proportion of the lung, and since they change in parallel with lung volume, it is likely that our method of correcting (n) for overinflation is appropriate. The elastic tissue of the small airways is in direct continuity with the elastic framework of the alveoli, and alveolar ducts; thus they are more likely to behave as do the alveoli and alveolar ducts than as major bronchi. If this is true, then our corrections of diameter (d_c) and of Q_{SA} are adequate. If the small airways behave like bronchi, diameter as measured (d) is the best measurement. Also, if small airways expand like major bronchi, then $V_{..p}$ is equal to $V_{..o}$ in equation 2, and, thus, $Q_{..p} = Q_{..o} \times (TLV_o/TLV_p)$. The effect of this latter assumption on our results is discussed below.

Results

The complete data are shown in Table 2.

We have not illustrated the effect of sampling but, as in the normal

Table 2—Emphysematous Lungs

Case No.	Age (yr.)	Sex	Body length (cm)	Amount of emphysema: Standard set[10]	Amount of emphysema: Ryder grid[11]	Total lung volume (liter): TLV_o	Total lung volume (liter): TLV_p	No. of small airways/sq cm: n	No. of small airways/sq cm: n_c	Average diameter of small airways (mm): d	Average diameter of small airways (mm): d_c	Proporation of small airways lumen: Q_{SAT}	Proporation of small airways lumen: Q_{SAT_c}
1	74	M	167	45	16	—	4.93	0.94	—	.62	—	.0111	—
2	62	M	183	70	25	4.00	6.48	0.58	0.42	.88	1.03	.0111	.0119
3	64	M	168	41	18	5.20	5.02	1.03	1.05	.63	0.62	.0083	.0083
4	62	M	178	59	18	—	5.97	0.57	—	.90	—	.0096	—
5	73	M	167	54	17	4.46	4.93	0.58	0.54	.79	0.82	.0091	.0092
6	56	M	165	60	18	3.86	4.75	0.86	0.75	.59	0.63	.0096	.0098
7	70	M	182	34	14	8.59	6.38	0.40	0.49	.86	0.78	.0086	.0084
8	57	F	165	38	13	5.68	4.75	0.49	0.55	.73	0.69	.0067	.0066
9	62	M	188	60	20	6.19	7.03	0.50	0.46	.87	0.91	.0073	.0074
10	66	M	167	81	26	5.79	4.93	0.65	0.72	.75	0.71	.0095	.0096
11	68	M	177	44	14	9.27	5.87	0.53	0.72	.41	0.35	.0014	.0013
12	51	M	180	43	14	4.69	6.17	0.52	0.43	.82	0.90	.0116	.0120
Mean			173.9	52.4	17.8	5.773	5.601	0.638	0.613	0.738	.744	.00866	.00845
SE			±2.4	±4.1	±1.2	±.581	±.232	±.057	±.062	±.043	±.060	±.00071	±.00089

TLV_o = observed total lung volume
TLV_p = predicted total lung volume
n = observed number of small airways/sq cm
n_c = number of small airways/sq cm corrected to TLV_p
d = observed average diameter of small airways
d_c = average diameter of small airways corrected to TLV_p
Q_{SAT} = observed proportion of small airways lumen
Q_{SAT_c} = proportion of small airways lumen corrected to TLV_p

lung,[9] there was no significant difference between lungs or within lobes and five blocks of tissue provided reasonably precise data. Moderate to severe emphysema was present in all lungs.

Table 3 summarizes the findings in the 12 patients and contrasts these to the results in nonemphysematous lungs from 20 subjects.[9] The number of small airways per unit area (n) and the number of small airways per unit area corrected to total lung volume at age 20 (n_c) are significantly diminished in emphysema ($t = 2.3853$, $P < 0.05$ and $t = 2.9056$, $P < 0.01$, respectively). However, this difference is largely due to the fact that patients with emphysema were taller than our subjects without emphysema. Text-figure 1 shows that the majority of patients were more than 160 cm tall (average body length 173.9 cm) and that there is a negative correlation between (n) and body length ($r = -0.5851$, $P < 0.05$) as we have previously found in nonemphysematous lungs.[9] Text-figure 2 compares (n_c) observed in the emphysematous lungs to that predicted from body length in normal subjects.[9] It is apparent that most have a lower value for observed (n_c) than predicted, but the difference does not reach conventional levels of significance ($0.1 > P > .05$).

Table 3 indicates that the mean diameter of airways less than 2 mm in diameter is similar in controls and in emphysema, whether corrected or not. Text-figure 3 compares the distribution of diameters of the small airways. This shows that in emphysema there is an excess of airways less than 0.2 mm in diameter, a small excess in airways 0.2–0.4 mm in diameter and a deficit in airways between 0.4 and 0.6 mm. The distribution of the remaining airways is essentially similar in emphysematous and nonemphysematous lungs.

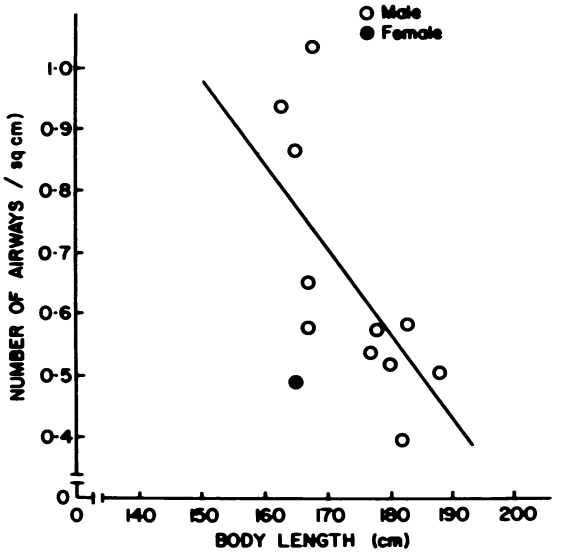
The proportion of small airways lumen (Q_{SAT}) is diminished in emphysema ($t = 3.9052$, $P < 0.001$). There were no significant correlations between any of the measurements of small airways and either measurements of flow rates or amounts of emphysema.

Discussion

Our results show that there are alterations in the number and dimensions of small airways in emphysema but that these changes are

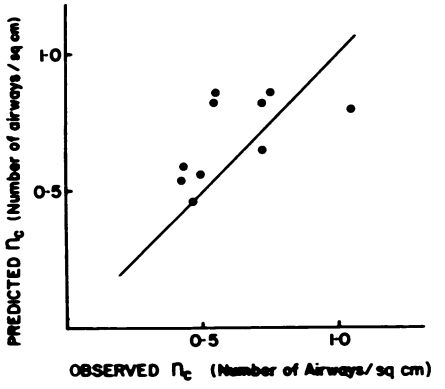
Table 3—Comparison of Nonemphysematous and Emphysematous Lungs

Lung	n	n_c	Q_{SAT}	d	d_c
Nonemphysema	0.840	0.931	0.0142	0.756	0.723
Emphysema	0.638	0.613	0.0087	0.738	0.744

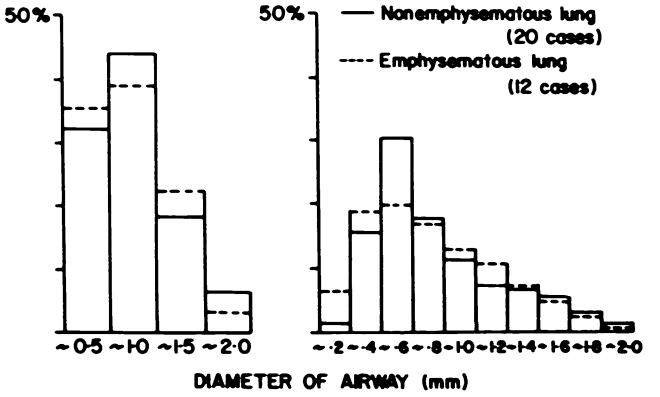


TEXT-FIG 1—The relationship between the number of small airways/sq cm and body length ($r = -0.5851$, $P < 0.05$).

relatively slight. There is also a paradox in our data. At first sight, it appears that there is a marked change in the number of airways per unit area and no change in diameter. The striking diminution in number of small airways per unit area (n) is due primarily to the fact that our patients with emphysema were taller than the nonemphysematous subjects used in a previous study.[9] Since body length and (n) are negatively correlated, this would diminish (n) in emphysema, as opposed to the nonemphysematous subjects. The latter were shorter than the patients with emphysema since the controls were selected primarily because they did not have emphysema. Becaust emphysema is much less common in women, we have more female controls, hence the smaller



TEXT-FIG 2—In 7 cases, the observed n_c is less than that predicted from body length in normal subjects.



TEXT-FIG 3—In emphysematous lungs, there are more airways less than 0.5 mm in diameter. When the diameter of airways is examined at 0.2 mm intervals, it becomes apparent that there is an excess of airways of less than 0.4 mm in diameter and a deficit of airways between 0.4 and 0.6 mm diameter in emphysema.

average body height of the group without emphysema. When allowance is made for height, the change in our emphysematous subjects is small and does not reach conventional levels of significance. For reasons discussed below, a real loss of airways is likely.

Another feature of the paradox is that no change in average diameter was noted, yet there was a small shift in distribution of airway diameter with an excess number of very small airways in emphysema. A simple example will show how this apparent contradiction may arise. Let us imagine that a normal subject had nine airways per unit area and that these airways were 1, 2, 3, 4, 5, 6, 7, 8 and 9 mm in diameter, respectively. The average airway diameter would be 5 mm. If the two smallest airways (1 and 2 mm in diameter) were destroyed, then the average diameter would be increased to 6 mm. There could be considerable narrowing of the remaining airways, yet the average diameter would be unchanged if the smallest airways were lost. That this is not speculation is shown by the alteration of proportion of small airways lumen (Q_{SAT}). This represents the sum effect of airway number per unit area and airway volume, and it is an accurate and reproducible measurement. Since there is no reason to suspect that there is loss of airway length, diminution of Q_{SAT} indicates diminution of airway diameter and/or airway number. The reduction in Q_{SAT} is significantly larger than that of (n_c) and thus airway lumen must also be compromised. It follows that the airways which are lost must be the smallest ones, otherwise average diameter would have diminished. Reference to Text-figure 3 shows that the narrowing of airways also involves only the smallest ones (<0.6 mm in diameter) and thus the overall effect

on average diameter will be small. However the change in Q_{SAT} is not likely to have a major effect on airway resistance. Since normally airways less than 2 mm only contribute some 10% of resistance to air flow in the lung,[8] the smallest airways, which are affected, contribute even less. Thus, the changes we recorded would make little difference to total resistance, even allowing for the fact that increase in resistance increases to the fourth power of the reduction in radius. Even in our patients with the most severe airway abnormalities, the change in total airway resistance would have been only doubled.

It follows that the changes we observed and which we would like to refer to as fixed airways disease, are insufficient to account for the high levels of airway resistance found in some patients with emphysema. There are several other mechanisms of increased resistance to flow which have been described. Since our measurements were made under isopressure conditions, there was no loss of force acting on the airways. We would anticipate that under isovolume conditions, diminished elastic recoil of emphysematous lungs would result in narrowed airways. Another mechanism is flow limitation of central airways which occurs in about half of patients with emphysema.[19] However, the most important cause of increased resistance is likely to be due to associated chronic bronchitis. There is evidence that patients with the "bronchial type" of airways obstruction have higher levels of airways resistance, particularly on inspiration, than patients with emphysema and mild or no bronchitis.[20] It seems likely that this is due to mucous plugging in the small airways although it may, in part, be due to encroachment on the lumen by enlarged bronchial glands. Our methodology (intrabronchial distension) was not appropriate to assess intrabronchiolar mucus and we are presently investigating the extent of mucous plugging in bronchitis, using fixation via the pulmonary artery. We would emphasize that our definition of bronchial lumen included mucus—*ie,* hits on the lumen were counted as hits, irrespective of the content.

We have considered, and dismissed, two possible reasons for the small difference between controls and emphysema. First, it is possible that some patients with emphysema have a diminished number and caliber of airways while others do not. One might anticipate that the latter patients would be relatively asymptomatic. Thus, if one studied random necropsies, it is possible that such a series might include patients with limited symptoms and normal airways. Our series is not random and all patients were symptomatic with demonstrable airways obstruction, as determined by FEV or MMFR. Second, our method of measuring only airways less than 2 mm in diameter, while it is the only practical

method, has inherent disadvantages, as discussed elsewhere.[9] In particular, if airways that were normally greater than 2 mm in diameter were reduced to less than 2 mm in diameter in emphysema, then these airways would be included in our count and would tend to obscure a difference between emphysema and normals. This is unlikely to have a major effect. We have shown [9] that about 5% of the airways less than 2 mm in diameter are in the size range, 1.5–2.0 mm, and it is likely that perhaps half of this number (*ie*, 2.5%) are in the range of 2.0–2.5 mm. Thus, even if all this class of airways were rearranged and then included in our counts, it would make no material difference.

Our methodology contains another potential error. If airways were dilated in emphysema, some airways normally less than 2 mm in diameter would be increased over our arbitrary limit and the number of airways less than 2 mm in diameter per unit area would be decreased. However, for the reasons listed previously, this effect is likely to be small, affecting less than 5% of the airways, and cannot account for the marked reduction in proportion of airways lumen. It should also be noted that if large airways were excluded then the average diameter would be reduced, which was not the case.

A point of minor technical interest is the fact that 5 of the 10 patients with emphysema had smaller measured lung volumes than those predicted from body length. Bignon *et al* have had similar experience.[7] The likely reasons include the fact that terminal pulmonary infection is common in emphysematous lungs and this tends to make them stiff. The lack of anticipated lung overinflation made our attempts at correction largely unnecessary. Using the assumption of uniform inflation of all components of the lung, the mean values for observed and corrected (d), (Q) and (n) were essentially identical. If the alternative assumption is made that airway dimensions are not affected by overinflation, only Q_{SAT} is changed significantly, and the mean value in the emphysematous subjects becomes 0.00797 as opposed to 0.00866 uncorrected and 0.00845 when corrected to assumed uniform pulmonary overexpansion. In the section on methods, we have pointed out why we do not favor the assumption of fixed airway dimension. Even using this assumption, which maximizes the change in emphysema, changes in dimensions of airways are insufficient to account for observed alterations in airway resistance, strengthening the conclusions drawn earlier.

Appendix

Where TLV = total lung volume (volume of air plus tissue in lung)
V = volume, Q = proportion, t = tissue, a = air, o = observed, p = predicted and sa = small airways.

By definittion:

$$TLV_p = V_t + V_{ap},\ V_{ap} = TLV_p - V_t,\ TLV_o = V_t + V_{ao},\ V_{ao} = TLV_o - V_t$$

thus:

$$\frac{V_{ap}}{V_{ao}} = \frac{TLV_p - V_t}{TLV_o - V_t} \tag{1}$$

since by definition:

$$Q_{sap} = \frac{V_{sap}}{TLV_p}$$

therefore:

$$V_{sap} = Q_{sap} \times TLV_p$$

similarly:

$$Q_{sao} = \frac{V_{sao}}{TLV_o}$$

therefore:

$$V_{sao} = Q_{sao} \times TLV_o$$

thus:

$$\frac{V_{sap}}{V_{sao}} = \frac{Q_{sap} \times TLV_p}{Q_{sao} \times TLV_o} \tag{2}$$

The assumption is made that volume changes are equally distributed throughout the lung. Thus:

$$\frac{V_{ap}}{V_{ao}} = \frac{V_{sap}}{V_{sao}} \tag{3}$$

Substituting (1) and (2) in (3) yields:

$$\frac{TLV_p - V_t}{TLV_o - V_t} = \frac{Q_{sap} \times TLV_p}{Q_{sao} \times TLV_o}$$

and:

$$Q_{sap} = Q_{sao} \times \left(\frac{TLV_p - V_t}{TLV_o - V_t}\right) \times \left(\frac{TLV_o}{TLV_p}\right)$$

References

1. Spain DM, Kaufman G: The basic lesion in chronic pulmonary emphysema. Am Rev Tuberc 68:24–30, 1953
2. Lepold JG, Gough J: The centrilobular form of hypertrophic emphysema and its relation to chronic bronchitis. Thorax 12:219–235, 1957
3. McLean KH: The pathogenesis of pulmonary emphysema. Am J Med 25: 62–74, 1958
4. Wright RR: Bronchial atrophy and collapse in chronic obstructive pulmonary emphysema. Am J Pathol 37:63–77, 1960

5. Anderson AE Jr, Foraker AG: Relative dimensions of bronchioles and parenchymal spaces in lungs from normal subjects and emphysematous patients. Am J Med 32:218–226, 1962
6. Pratt PC, Jutabha O, Klugh GA: Quantitative relationship between structural extent of centrilobular emphysema and postmortem volume and flow characteristics of lungs. Med Thorac 22:197–208, 1965
7. Bignon J, Khouri F, Even P, André J, Brouet G: Morphometric study in chronic obstructive bronchopulmonary disease: Pathologic, clinical and physiologic correlation. Am Rev Resp Dis 99:669–695, 1969
8. Hogg JC, Macklem PT, Thurlbeck WM: Site and nature of airway obstruction in chronic obstructive lung disease. N Engl J Med 278:1355–1360, 1968
9. Matsuba K, Thurlbeck WM: The number and dimensions of small airways in non-emphysematous lungs. Am Rev Resp Dis 104:516–524, 1972
10. Thurlbeck WM, Dunnill MS, Hartung W, Heard BE, Heppleston AG, Ryder RC: A comparison of three methods of measuring emphysema. Human Pathol 1:215–226, 1970
11. Ryder RC, Thurlbeck WM, Gough J: A study of inter-observer variation in the assessment of the amount of pulmonary emphysema in paper-mounted whole-lung sections. Am Rev Resp Dis 99:354–364, 1969
12. Fraser RG, Pare JAP: Diagnosis of disease of the chest—an integrated study based on the abnormal roentgenogram. Philadelphia, London, Toronto, WB Saunders Co, 1970, p 86
13. Hogg JC, Nepszy S: Regional lung volume and pleural pressure gradient estimated from lung density in dogs. J Appl Physiol 27:198–203, 1969
14. Macklin CC: Musculature of bronchi and lungs. Physiol Rev 9:1–60, 1929
15. Storey WF, Staub NC: Ventilation of terminal air units. J Appl Physiol 17: 391–397, 1962
16. Dunnill MS: Effect of lung inflation on alveolar surface area in the dog. Nature 214:1013–4, 1967
17. Forrest JB: The effect of changes in lung volume on the size and shape of alveoli. J Physiol 210:533–547, 1970
18. Marshall R: Effect of lung inflation on bronchial dimensions in the dog. J Appl Physiol 17:596–600, 1962
19. Macklem PT, Fraser RG, Brown WG: Bronchial pressure meaurements in emphysema and bronchitis. J Clin Invest 44:807–905, 1965
20. Burrows B, Saksena FB, Diener CF: Carbon dioxide tension and ventilatory mechanics in chronic obstructive lung disease. Ann Intern Med 65:685–700, 1966

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