Estimation of Expiratory Efficiency of Emphysematous Lungs on the Basis of Anatomical Findings

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Expiratory efficiencies of individual autopsied lungs, normal and emphysematous, were calculated with the expressions for expiratory mechanics derived in our previous report. The estimation of the pertaining parameters was possible on anatomical findings and by histometrical treatments. Estimated quantities were: elasticity constant \( a \), total lung volume in relaxation \( V_0 \), the mean density of elastic system \( E \), the standard deviation of the density of elastic system \( \sigma \), and total airway resistance \( R \). Emphysematous lungs were generally characterized by increased \( V_0 \) and reduced \( E \). Concomitant fibrosis elevated \( a \). The evidence was presented that \( R \) was rather reduced in emphysematous lungs when expiration proceeded without participation of thoracic activity.

Distinct deterioration of expiratory functions was demonstrated in all the examined emphysematous lungs. In extreme cases the expiratory efficiency was lowered to 20% of the normal value. The major cause of the disturbance was an increase of \( V_0 \). The reduction of \( E \) also impaired expiratory function. Increased \( \sigma \) exerted only insignificant influence on expiratory efficiency, but it effected an increase of transalveolar flow.

A rise in the value of \( a \) caused distinct elevation of intrapulmonary pressure at pulmonary expansion and improved expiratory efficiency. Enlarged thoracic cavities in emphysema also contributed to elevation of expired volume. These compensatory mechanisms could not, however, restore the expiratory efficiency in emphysema to the normal level.

In a previous report\(^1\) attempts were made to derive expiratory mechanics on the basis of anatomical findings on autopsied lungs. The expressions obtained on the assumption that the distribution of the density of intrapulmonary elastic system could be approximated by combination of a small number of different normal distributions were:

\[
V = \frac{P}{\sqrt{2\pi}} \sum_{j=1}^{n} \frac{V_{0j}}{\sigma_j} \int_{0}^{\infty} \frac{(1+x)^4 [(ax+a-2)e^{ax}+2]}{(e^{ax}-1)^2} e^{\left( \frac{P(1+x)^2 - E_j^2}{2\sigma_j^2} \right)x} dx
\]

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The parameters in the above derivations are:

\( a \): elasticity constant of pulmonary elastic system,

\( V_{oj} \): partial pulmonary volume in relaxation assigned to each normal distribution,

\( E_j \): mean density of the pulmonary elastic system in each normal distribution,

\( \sigma_j \): standard deviation of the elastic system in reference to the normal distribution with the mean \( E_j \), and

\( R \): total airway resistance.

The estimation of the parameters is necessary in advance of the calculation with the above expressions. Consequently, the present report is composed of two parts. The estimation of the parameters is discussed in the first part and the results of calculation are presented in the second.

**Estimation of the Parameters**

In the present investigations the left lungs were taken out of the thoracic cavities at autopsy and were gently expanded by intrabronchial formalin infusion through a cannula inserted into the main bronchus under a pressure not exceeding about 30 cm H₂O. The vessels at the pulmonary hilus were left unligated. The lungs were thus expanded to a state in which their pleural surfaces exactly fitted the costal surfaces of the thoracic cavities. The organs were then kept in 10% formalin in a large vessel for several subsequent days to complete fixation. The volume of individual lungs was then determined by water replacement, and the lungs were severed by a frontal section which passed the pulmonary hilus. Thick slices which covered the entire extension of the lung were taken and placed in 70% alcohol which filled a vessel large enough to avoid distortion of the slices. When the difference in pathological changes was remarkable between the dorsal and ventral pulmonary parts, the lung was further sliced with frontal sections and a number of frontal slices were taken so that the errors due to uneven distribution of anatomical changes were minimized. The slices were then separated into several pieces, embedded in paraffin and submitted to histological and histometrical examinations.

1) *Estimation of \( a \)*

The elasticity constant \( a \) of a certain tissue indicates its elastic property. It is practically determined by the elastic property of the main constituent fibers of the tissue. Elastic fibers are characterized by a low value of \( a \) below 5, while collagenous fibers have distinctly higher values of \( a \) over 10. The elasticity constant of the normal lung is estimated to be 5.5 for all the age groups. This indicates that the elastic system of the normal lung is practically made up of elastic fibers. Consequently, an increase of collagenous fibers in the lung will cause an elevation of its elasticity constant. In emphysematous lungs where pulmonary...
fibrosis is one of the commonest complications, higher values of elasticity constant are expected than in normal lungs.

It is mathematically impossible to express the effect of increased collagenous fibers over a wide range of pulmonary expansion by a single constant value of $a$, if we use the stress function in the form of $F = A(e^{ax} - 1)$. However, in the case where pulmonary expansion is limited to such an extent that an approximate application of Hooke's law is permissible, the elasticity constant for the whole lung is determined by the quantitative proportion of elastic and collagenous fibers.

If the volume and elasticity constants of elastic and collagenous fibers are $V_e, V_c, a_e$ and $a_c$, the elasticity constant of the total lung is given by:

$$ a = \frac{a_e V_e + a_c V_c}{V_e + V_c} = \frac{a_e + a_c (V_c/V_e)}{1 + (V_c/V_e)} \quad (3) $$

As the elastic system of normal alveolar septa is constituted to the major part by elastic fibers, the quantity of elastic fibers can be practically replaced by the volume itself of normal alveolar septa. On this assumption, the quantities of alveolar septa and collagenous fibers were estimated by means of line sampling on histological sections. The length of linear intercepts given by intersection of the sampling line with pulmonary structures was consecutively measured. The sum of intercepts delivered by normal alveolar septa gave $V_e$, and that by scarred alveolar septa including perivascular and peribronchial connective tissues made $V_c$. In normal lungs the ratio $V_c/V_e$ was about 0.2. On the other hand, the elasticity constant for normal lungs had been estimated to be 5.5 and for collagenous fibers 10.0 in a previous report of ours. Accordingly, the value obtained from (3) for $a_e$ was 4.6, $a$, $a_c$ and $V_c/V_e$ being 5.5, 10.0 and 0.2, respectively.

We assume further that the elastic property of normal alveolar septa is still maintained unchanged in well-preserved alveolar septa even in emphysematous lungs. In this case, we can calculate the elasticity constant $a$ of individual emphysematous lungs, if we histometrically determine the ratio $V_c/V_e$ of each lung. The result is presented in Table 2. The elasticity constant $a$ is more or less enhanced in emphysematous lungs owing to concomitant fibrosis and attains a value over 6.5 in cases with advanced fibrosis.

The present estimation of $a$ is based on the assumption that Hooke's law is applicable. This condition is obviously not strictly satisfied even in emphysematous lungs where the ratio $TLC/V_a$ or the maximum pulmonary stretch is much lower than in the normal lung. We must be aware of some errors which may arise from the above assumption.
2) Estimation of $V_0$ and $V_{0j}$

Because $V_{0j}$ is the partial pulmonary volume obtained by the partition of the total lung volume $V_0$ to individual normal distributions, $V_0$ must be first estimated. The volume of the left lung expanded by intrabronchial formalin infusion is demonstrated in Fig. 1 in reference to age. As was mentioned in a previous report of ours, the total lung volume in relaxation is estimated to be about 1,000 cm$^3$ for healthy young adults. The value coincides quite well with that of expanded left lung. This means that the volume $V$ of the lung expanded under the conditions described above is approximately two times as large as $V_0$. If we assume that pulmonary expansion due to formalin infusion is of the same grade throughout all the examined cases, we can use the values in Fig. 1 immediately as the estimates of $V_0$ for both lungs.

![Fig. 1](image_url)

Fig. 1. The volume of the left lung expanded by intrabronchial formalin infusion is correlated to age. Solid circle: normal male. Open circle: normal female. Solid triangle: emphysema. All the cases of emphysema are those of male patients.

The volume of the normal lung increases remarkably with advancing ages especially in male subjects. It attains a value about two times of that in healthy young adults on the average, although the scatter of the individual estimates is very large. In female subjects, increase in pulmonary volume with age is much less pronounced. Emphysematous lungs have distinctly larger volumes than the normal lungs of the corresponding age group. The average value of the examined cases is around 3,000 cm$^3$.

The estimation of $V_{0j}$ is discussed later, since the distribution of the pulmonary elastic system is to be determined in advance.

3) Estimation of $E_j$ and $\sigma_j$

The density of the pulmonary elastic system in unexpanded lungs $E$ is given by the product of the density of alveolar septa $S_0/V_0$ and the density of the system on alveolar septa $\rho_0$ as:

$$E = (S_0/V_0) \cdot \rho_0$$

(4)
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When the pulmonary expansion due to formalin infusion is of the same grade in all the lungs, $S_0/V_0$ and $\rho_0$ can be substituted by the corresponding values of expanded lungs $S/V$ and $\rho$, so far as a comparative study of expiratory efficiency is concerned. The estimation of $E$ is consequently performed in the following two steps.

\textbf{a) Estimation of } S/V

The density of alveolar septa in the space or the alveolar surface area in a unit volume is estimated by line sampling on histological sections. If the length of the sampling line is $l$ and the number of intersections of the line with alveolar septa $C$, $S/V$ is given by:

$$\frac{S}{V} = 2 \frac{C}{l},$$

or writing $C/l$ as $C_u$:

$$S/V = 2 C_u.$$  \hspace{1cm} (5)

This simple relation\textsuperscript{3,4} indicates that the surface area of alveolar septa in cm\textsuperscript{2} in a pulmonary volume of 1 cm\textsuperscript{3} is two times of the count of intersections with a sampling line of 1 cm, provided that alveolar septa are sufficiently randomized in their orientation in the space.

The count $C_u$ was determined on 500 to 1,000 microscopical fields randomly taken over the whole extension of frontal sections of the lung. Representative patterns of the distribution of $C_u$ are presented in the histograms of Figs. 2–4. It is obvious that in normal lungs the distribution of $C_u$ is sufficiently

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig2.png}
\caption{The distribution of $C_u$ or $C/cm$ in a normal lung is demonstrated in the figure. The distribution can sufficiently be assimilated to a normal distribution.}
\end{figure}
Fig. 3. Even in the majority of emphysematous lungs the distribution of $C_u$ still retains its character as a normal distribution.

Fig. 4. In advanced emphysema the distribution of $C_u$ becomes distinctly asymmetrical and cannot be approximated to a single normal distribution. In the case of the diagram, it is partitioned into two different normal distributions, and the mean and standard deviation are determined in reference to each normal distribution.

approximated to a normal distribution. Even in emphysematous lungs the pattern of the distribution is essentially the same. Only in advanced emphysema, asymmetry in the distribution becomes apparent. This irregularity cannot be effectively corrected by usual transformations of the variable. In such a case, the distribution must be assimilated to the combination of a small number of different normal distributions. From the above results, it is now possible to
calculate the arithmetical mean $\bar{C}_u$ of $C_u$ and the standard deviation $\sigma$ based on the measurements on each lung.

Some comments will be necessary to the evaluation of $\sigma$ determined in this way. The value of $\sigma$ calculated directly from $C_u$ is the total deviation which is composed of two different kinds of deviation, namely within class deviation and between class deviation. The former, $\sigma_s$, is due to sampling errors from the same pulmonary portion of 1 cm$^3$. The latter, $\sigma_c$, is concerned with the difference of $C_u$ in different parts of the lung. The total deviation $\sigma$ is given by:

$$\sigma = \sqrt{\sigma_s^2 + \sigma_c^2}.$$  

What we need is in reality $\sigma_c$ and not $\sigma$. However, the influence of $\sigma$ on expiratory efficiency of the lung is only slight as will be seen later. Consequently, $\sigma$ is used instead of $\sigma_c$ in the following calculation for convenience.

Fig. 5. The mean alveolar surface area in a unit pulmonary volume $S/V$ is demonstrated in reference to age. Solid circle: normal male. Open circle: normal female. Solid triangle: emphysema.

The mean density of alveolar septa $S/V$, obtained as $2C_u$, is presented in Fig. 5 in reference to age. In normal lungs the value takes its maximum at the birth and is continuously lowered with advancing ages. No sex difference is observed, and the scatter of the values is relatively small. In emphysematous lungs the value is distinctly lower than in normal lungs of the corresponding ages.

The product of $S/V$ and $V$ in Fig. 1 gives the total alveolar surface area $S_t$ of the left lung in the state of expansion due to formalin infusion. The results are shown in Fig. 6. The total effective respiratory surface area of alveoli will be approximately 4 times of $S_t$, because the value must be doubled to be related to both surfaces of alveolar septa and redoubled to express the quantity of both
Total surface area of alveolar septa of the left lung is determined as the product of $V$ and $S/V$. Solid circle: normal male. Open circle: normal female. Solid triangle: emphysema. No distinct reduction in the value of $S_t$ is observed even in emphysematous lungs in comparison with that of normal lungs.

Since the quantity of non-respiratory pulmonary structures such as large bronchi and vessels occupies about 10% of the total lung volume, the values of $S_t$ and the effective respiratory alveolar surface area would in reality be reduced to 90% of the above results.

In Fig. 6, $S_t$ increases after birth to the age of 30 years and remains hereafter essentially unchanged in normal lungs. An unexpected result in the figure is that $S_t$ of emphysematous lungs is not much different from that of normal lungs. Extensive alveolar destruction which characterizes emphysematous lungs is apparently not due to disappearance of alveolar septa but substantially to structural derangement and to detachment of alveolar junctions.

### Table 1

<table>
<thead>
<tr>
<th>Case</th>
<th>Age &amp; sex</th>
<th>$\bar{C}_u$</th>
<th>$\sigma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal lung</td>
<td>115-65</td>
<td>30 $\delta$</td>
<td>59.7</td>
</tr>
<tr>
<td></td>
<td>131-65</td>
<td>55 $\delta$</td>
<td>53.0</td>
</tr>
<tr>
<td>Emphysematous lung</td>
<td>299-62</td>
<td>62 $\delta$</td>
<td>40.7</td>
</tr>
<tr>
<td></td>
<td>134-64</td>
<td>68 $\delta$</td>
<td>36.3</td>
</tr>
<tr>
<td></td>
<td>148-65</td>
<td>76 $\delta$</td>
<td>32.2</td>
</tr>
<tr>
<td></td>
<td>388-64</td>
<td>69 $\delta$</td>
<td>30.2</td>
</tr>
<tr>
<td></td>
<td>178-65</td>
<td>62 $\delta$</td>
<td>27.2</td>
</tr>
<tr>
<td></td>
<td>93-65</td>
<td>75 $\delta$</td>
<td>26.2</td>
</tr>
</tbody>
</table>

The values of $\bar{C}_u$ and $\sigma$ of the cases in which $C_u$ is approximated by a single normal distribution are presented. Note essentially unchanged values of $\sigma$ even in emphysematous lungs.
We take now such emphysematous lungs in which the distribution of alveolar septa can be approximated to a single normal distribution and examine the values of the standard deviation. It is noteworthy that the standard deviations of the emphysematous lungs are not essentially larger than those of normal lungs (Table 1). This seems at first sight contradictory to anatomical appearance of emphysematous lungs where the dimension of alveoli or terminal air spaces is extremely divergent. For the correct understanding of the problem it is necessary to define the distribution of alveolar size. We assume that terminal air spaces can be assimilated to spheres of different diameters. We take a sphere of \( D \) in diameter and suppose that it is penetrated with an infinitely large number of parallel straight lines. The mean length \( l \) of intercepts delivered by intersection of the lines with the sphere is equal to \( \frac{2}{3} D \). Consequently, we obtain:

\[
\bar{l} = \frac{1}{\bar{C}_u} = \frac{2}{3} D.
\]

This result means that the distribution of \( D \) must be a reciprocal normal distribution, if the distribution of \( C_u \) is given by a normal distribution. When the distribution of \( C_u \) is written as:

\[
f_{C_u} = \frac{1}{\sqrt{2\pi}\sigma} \exp \left( -\frac{(C_u - \bar{C}_u)^2}{2\sigma^2} \right),
\]

with two parameters \( \bar{C}_u \) and \( \sigma \), that of \( D \) becomes:

\[
f_D = \frac{3}{2\sqrt{2\pi}\sigma} \cdot \frac{1}{D^2} \exp \left( -\frac{9(D - \bar{D})^2}{8(\sigma D)^2} \right),
\]

where \( D \) is equal to \( 1/\bar{C}_u \). In Fig. 7, varying patterns of \( f_D \) is demonstrated when \( \sigma \) is fixed to a certain value and only \( \bar{C}_u \) is allowed to change. The values of \( \bar{C}_u \) are taken as 80, 60, 40 and 20, corresponding to infantile, young adult, senile and emphysematous lungs, respectively. In normal lungs of young subjects the distribution of alveolar diameter is confined within a very narrow range. In other words, the alveoli in such lungs are practically uniform in size. On the contrary, alveolar diameter becomes widely scattered with progressive reduction of \( \bar{C}_u \). When \( C_u \) is lowered to 20 corresponding to emphysematous lungs, the curve is so extended to the region of large diameters that the incidence of alveoli over several millimeters in diameter is no more negligible. The peak of the curve is only moderately shifted to a larger value, so that the asymmetry of the curve becomes very remarkable. Anatomical characteristics of emphysematous lungs are sufficiently reproduced, even if the standard deviation of \( C_u \) remains the same as in the normal lung.
Fig. 7. The distribution of alveolar diameter $D$ is given by a reciprocal normal distribution, when the distribution of $C_u$ is defined by a normal distribution. The curves in the figure represent the shift in the pattern of the distribution of $D$. The values of the mean, $C_u$, are taken as 80, 60, 40 and 20, and the corresponding curves in the figure are (1), (2), (3) and (4), respectively. The standard deviation of $C_u$ is fixed to 6 irrespective of the variations in $C_u$.

\[ \text{(6)} \]

h) Estimation of $\sigma$

The total length of the elastic system or practically that of elastic fibers on a unit surface area of alveolar septa can be determined from:

\[ \rho = \frac{\pi}{2} \cdot \frac{C'}{\lambda}. \]

In the above expression, $\lambda$ is a certain adequate length taken along the section of alveolar septa, and $C'$ is the count of the sections of elastic fibers. The derivation of the expression will be discussed in a forthcoming report.

This apparently simple determination is in reality fraught with a difficulty. In histological sections, elastic fibers of the lung are not of uniform thickness. Thick fibers are composed of a number of fine fibrils, which, however, cannot always be discerned even under high magnification. The difference in the thickness of elastic fibers must be adjusted by weighting the count $C'$ with the thickness of individual fibers. In this respect, the absolute values of $\rho$ in Fig. 8 are of significance only in studies made by the same investigator, because they are influenced by the standard of the elementary fibrils, which must be more or less arbitrarily determined by each investigator.

In spite of the difficulty, a definite tendency is observed in the values of $\rho$. They increase remarkably with advancing ages and attain in senile lungs a level about two times as high as that in young adults. The result is in good agreement with the chemical determination of elastin by Pierce and Hocott.7
Fig. 8. The total length of the elastic system on alveolar septa of a unit surface area is correlated to age. Solid circle: normal male. Open circle: normal female. Solid triangle: emphysema. The values of $\rho$ are of significance only in the comparison of individual cases.

Relatively high estimates of $\rho$ in infantile lungs in the present histometrical study are probably due to a larger tissue quantity against a unit alveolar surface area in this age. Infantile lungs are histologically characterized by thick alveolar septa. In emphysematous lungs the values of $\rho$ are somewhat lower than in normal lungs of corresponding ages. This is because elastic fibers are rarified in over-stretched alveolar septa adjacent to the foci of alveolar destruction or because they can be destroyed in scarred alveolar septa. In none of the examined cases of emphysema, however, the value of $\rho$ is lower than the level of normal young adults. The result makes the often asserted development of emphysema from primary attenuation or degeneration of elastic fibers rather improbable.

c) Estimation of $E_j$ and $\sigma_j$

With the determinations of $C_u$ and $\rho$ it is now possible to estimate $E_j$ and the standard deviation of $E_j$. In a volume of 1 cm$^3$ the deviation of $\rho$ is not expected to play an important part, because the unevenness of $\rho$ is a problem in a volume of much smaller dimension. Accordingly, the standard deviation of $\rho$ is neglected and only its mean is taken into consideration. In the case where the distribution of $C_u$ is given by a single normal distribution, the product of $2C_u$ and $\rho$ is taken as $E$. The standard deviation of $E$ is determined from that of $C_u$ and $\rho$ and also designated as $\sigma$ hereafter for simplicity. When the distribution of $C_u$ is irregular it is partitioned into a number of different normal distributions, and $E_j$ and $\sigma_j$ are estimated in reference to each normal distribution. It is further preferable to determine the overall arithmetical mean $\bar{E}$ even in asymmetrical distributions of $C_u$.

In Table 2, overall $\bar{E}$, overall $S/V$ and $\rho$ are entered. In all the estimates
Table 2

<table>
<thead>
<tr>
<th>Case</th>
<th>Age &amp; sex</th>
<th>$\alpha$</th>
<th>$V_0$ ($10^4$ cm$^2$)</th>
<th>$S/V$</th>
<th>$\rho$</th>
<th>$\tilde{E}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal lung (young adult)</td>
<td>68.5</td>
<td>5.5</td>
<td>1.0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Senile lung</td>
<td>5.5</td>
<td>2.0</td>
<td>0.67</td>
<td>2.00</td>
<td>1.34</td>
<td></td>
</tr>
</tbody>
</table>


Elasticity constant $\alpha$, total lung volume in relaxation $V_0$, overall mean of the alveolar surface area in a unit volume $S/V$, density of elastic system on alveolar surface $\rho$ and overall mean of the density of elastic system in the space $\tilde{E}$ are presented. In $S/V$, $\rho$ and $\tilde{E}$ the values of the normal lung of young adults are taken as the standard and regarded as 1. The cases of emphysema are arranged in the descending order of $\tilde{E}$.

The values of the normal lung of young adults are taken as the standard and regarded as 1. Under physiological conditions, $\tilde{E}$ takes its minimum value in young adults. In senile lungs its value is increased on account of high $\rho$, although $S/V$ is lowered. In emphysematous lungs elevation of $\rho$ cannot sufficiently compensate remarkable reduction of $S/V$, and $\tilde{E}$ is lowered with progressive emphysematous process down to half the value of normal young adults.

4) Estimation of $R$

Increased airway resistance, which is the most important symptom of pulmonary emphysema, is observed only in forced expiration. Whether airway resistance is enhanced in expiration without the participation of thoracic activity is an entirely different problem. Geometrical configuration of bronchial trees is evidently the decisive factor in determining intrabronchial resistance to air flow. Intrabronchial pressure gradient can be calculated on the basis of analytical treatments of bronchial casts. For this purpose our derivations are already available. The result with a normal lung is presented in Fig. 9. It is clearly demonstrated that in the normal lung the greater part of intrabronchial resistance is inserted in the region of terminal airways. In this respect, it is important to investigate the behavior of terminal airways in emphysematous lungs.

As the problem will be more extensively discussed elsewhere, the treatment in the present paper is restricted to the presentation of the typical cases. It is demonstrated in Figs. 10–12 that the total length of terminal airways is remarkably reduced in emphysematous lungs. The incidence of abnormally
narrowed bronchioli is more or less increased in the majority of emphysematous lungs. But their total length is by far smaller than that of normal terminal airways. These results indicate a rather extensive transformation of terminal airways, probably because terminal and respiratory bronchioli with attenuated walls are distended, and their walls are absorbed and incorporated into the pulmonary elastic system. Since terminal airways represent the site of the major intrapulmonary resistance to air flow, their destruction would contribute much to reducing airway resistance in emphysema. The total airway resistance in expiration by pulmonary retractive force alone must be as a rule lower in emphysematous than in normal lungs.

However, an exact quantitative evaluation of intrapulmonary airway resistance in emphysema is at present difficult on account of the anatomical irregularity of bronchial trees. Consequently, it would be rather practical to take the extreme case into consideration. In normal subjects, the total airway resistance is the sum of the resistance of the upper respiratory tract and that of the intrapulmonary airways. As is demonstrated in Fig. 9, intrabronchial pressure drop from the terminal bronchioles to the main bronchus of the normal lung is about 8 mm H₂O under airflow of 1 liter per second. On the other hand, clinically determined total airway resistance is about 16 mm H₂O/liter/sec. Accordingly,
Fig. 10. The count $C$ of bronchial sections on histological slides of a normal lung is distributed according to bronchial diameters. The value of $C$ is directly proportional to the total length of the bronchi of the corresponding diameters in a unit volume. The dots connected by lines give theoretical values of $C$ calculated on a geometrical model of the normal bronchial tree.

Fig. 11. A typical pattern of the distribution of bronchial sections in emphysema is presented. The dots indicate theoretical values of the normal lung. Note distinct reduction of the count in the region of terminal airways. The total count of bronchial sections of every possible diameter is also reduced.

Fig. 12. In some cases of emphysema, the incidence of abnormally narrowed bronchioi (shadowed in the diagram) is increased. Their count, however, cannot usually account for the remarkable reduction of the count of normal terminal airways. Note the reduction of the total count.
The input data for the computation are tabulated. In the cases where the data of \( V_0, E \) and \( \sigma \) are written in two lines, the distribution of \( E \) is approximated by two different normal distributions, and the values of the three parameters are given in reference to each normal distribution. \( V_{\text{max}} \) is the initial pulmonary volume at expiration and is given as the sum of \( V_0 \) and 4.5 liters.

Initial \( P \) in the table is obtained from the expression (1) when \( V \) in the expression is equal to \( V_{\text{max}} \). The values of \( P \) obtained in this way give the initial conditions for the differential equation (2). The results of the computation for \( P \) are merely of relative significance, because the units of pertaining parameters are not taken into consideration. To express \( P \) in cm H\(_2\)O the values must be multiplied by a coefficient 1.5. The adjusted pressures are given in parentheses. The determination of the coefficient is explained in our previous report.\(^1\)

In the computation with an electronic computer it is not absolutely necessary to calculate the expression (2). The derivative \( dt/dP \) can be transformed as follows:

\[
\frac{dt}{dP} = \frac{dt}{dV} \frac{dV}{dP} = -\frac{R}{P} \frac{dV}{dP}.
\]

If \( a \) is a certain positive value, the time interval \( t_a \) required for the expiration from the pressure \( P \) to \( a \) is given by:

\[
t_a = \int_a^P \frac{R}{P} \cdot \frac{dV}{dP} dP = R \left[ \frac{V}{P} \right]_a^P + \int_a^P \frac{V}{P} dP.
\]

The data necessary for the calculation of this expression are already available in the course of the computation of (1).
Fig. 13. The normal lung of a 30-year-old woman is demonstrated in a thick frozen section. The lung was stained for elastic fibers prior to gelatin embedding. For input data see Table 3.
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Fig. 14. The calculated time-pressure curve of the normal lung of young adults. Note the high initial pressure of expiration and precipitating pressure drop with time.

Fig. 15. The expired volume of the same pulmonary model as in Fig. 14 is demonstrated. The rise of expiratory volume is rapid, and the expiration approaches to its practical termination in a short time.

the resistance of the upper respiratory tract is approximately equal to that of intrapulmonary airways. When we assume that in extreme cases intrapulmonary resistance in emphysema is so lowered that it is practically zero, the total airway resistance would be half the normal, provided that the resistance of the upper respiratory tract remains unchanged. In the present study, the total
Fig. 16. A case of moderate emphysema is presented. Dyspnea was not clinically noticed. The histological picture is one of the so-called 'centrilobular emphysema'. Case 134–64. For input data see Table 3.
Fig. 17. The calculated time-pressure relation of the case in Fig. 16 is demonstrated. The upper curve is that of the normal lung. The initial pressure of expiration attains only about 6 cm H₂O even after the inspiration of 4,500 cm³. Note retarded pressure drop in the case of emphysema.

Fig. 18. The calculated expired volume of the case in Fig. 16 is compared with that of the normal lung. The latter is represented by the uppermost curve in the diagram. The lowermost curve is that of the transalveolar flow of this case of emphysema. Note the slow elevation of V₁ₚ with time.

Airway resistance of the normal lung is regarded as 1. Under this condition, the possible range of R for emphysematous lungs is from 1 to 1/2.
Fig. 19. A case of advanced emphysema is presented. Extensive alveolar destruction as in 'panlobular emphysema' is associated with fibrosis. Distinct dyspnea and obstructive expiratory distress were clinically observed. Case 111-05. For input data see Table 3.
Fig. 20. The calculated time-pressure curve of the case in Fig. 19 is demonstrated in comparison with that of the normal lung, which is given in the upper part of the diagram. Note drastically lowered initial pressure and extremely slow pressure drop in the case of emphysema.

Fig. 21. The calculated expired volume of the case 111-65 is presented. The uppermost curve is that of the normal lung and the lowermost represents the transalveolar flow of this case. Note almost linear $V_{e}$ curve of this case. The expired volume rises very slowly, and a practical termination of expiration is not attained in a time interval compatible with the respiratory activity of the organism.

**CALCULATED EXPIRATION CURVES OF EMPHYSEMATOUS LUNGS**

With the estimation of the parameters we are now ready to calculate the expressions (1) and (2) with the input data of Table 3 employing an electronic computer. For the
comparison of expiratory efficiency of individual lungs expiration must be started after
the same quantity of air is inspired. Throughout the following calculations, the initial
pulmonary volume is determined as the sum of \( V_0 \) and 4,500 cm\(^3\). In other words, every
lung is assumed to have inspired 4,500 cm\(^3\) of air when expiration is started.

Another condition which must be considered in the calculation is the time scale.
Since there is no reliable way to check an absolute time scale, we take the time interval
in which the normal adult lung expires 3,000 cm\(^3\) after an inspiration of 4,500 cm\(^3\) as the
unit time. Practically this would not be much different from a second.

In Figs. 14 and 15, the expiration curves of the normal lung in young
adults are presented. The initial pulmonary pressure of expiration attains a
very high level over 30 cm H\(_2\)O. With the progress of expiration, intrapulmonary
pressure drops so rapidly that a practical termination of expiration is reached
in a short time. Corresponding to the precipitating time-pressure curve, expired
volume rises steeply in the initial phase of expiration, and the curve rapidly
approaches to its plateau.

In contrast to the normal lung, a distinct deterioration of expiratory function
is demonstrable even in the case of moderate emphysema as in Fig. 16. The
initial pressure of expiration in this case remains very low even after the
inspiration of 4,500 cm\(^3\). On the other hand, the pressure drop is distinctly
retarded, and the t-P curve crosses the corresponding curve of the normal lung.
The practical termination of expiration is not reached in such a short time as
in normal lungs. The rise of expired volume is also remarkably hampered. At
the point \( t=1 \), where 3,000 cm\(^3\) out of 4,500 cm\(^3\) are already expired by normal
lungs, only about 1,200 cm\(^3\) are expired. When checked at \( t=1 \), expiratory
efficiency of this case is lowered to 40% of the normal.

With advancing emphysematous changes, deterioration of expiratory function
becomes still severer. In the case demonstrated in Fig. 19 the curve of \( t-V_{\phi} \)
is so flattened that only 600 cm\(^3\) out of 4,500 cm\(^3\) are expired at \( t=1 \). Expiratory
efficiency is lowered to 20% of the normal.

In Table 4, expired volumes at \( t=1 \) and \( t=2 \) of all the examined emphy-
sematous lungs are presented. As is easily comprehended from the expression
(2), \( R \) is directly proportional to \( t \). It takes exactly two times as much time
to attain the same state of expiration, when \( R \) is increased to two times.
Accordingly, if expiratory efficiency is checked at \( t=2 \) in the case of \( R=1 \), it is
equivalent to the expiratory efficiency at \( t=1 \) with \( R=0.5 \). In none of the
examined emphysematous lungs the expired volume attains the level of 3,000 cm\(^3\)
even at the point of \( t=2 \). This means emphysematous lungs cannot drive out
a sufficient volume even after the lapse of twice as long time as required for the
normal lung, or even if the intrapulmonary airway resistance is brought to zero.
TABLE 4

<table>
<thead>
<tr>
<th>Case</th>
<th>( V_{sp} ) (10^3 cm³)</th>
<th>Percent expiratory efficiency</th>
<th>( \varphi ) (10^4 cm³)</th>
<th>( V_{sp} ) (10^3 cm³)</th>
<th>Percent expiratory efficiency</th>
<th>( \varphi ) (10^4 cm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal lung</td>
<td>3.00</td>
<td>100.0</td>
<td>0.04</td>
<td>3.78</td>
<td>100.0</td>
<td>0.07</td>
</tr>
<tr>
<td>(young adult)</td>
<td>1.94</td>
<td>64.7</td>
<td>0.04</td>
<td>2.91</td>
<td>77.0</td>
<td>0.07</td>
</tr>
<tr>
<td>Senile lung</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>93-65</td>
<td>1.21</td>
<td>40.3</td>
<td>0.06</td>
<td>1.96</td>
<td>51.9</td>
<td>0.12</td>
</tr>
<tr>
<td>134-64</td>
<td>1.16</td>
<td>38.7</td>
<td>0.07</td>
<td>1.95</td>
<td>51.6</td>
<td>0.14</td>
</tr>
<tr>
<td>138-64</td>
<td>1.06</td>
<td>35.3</td>
<td>0.12</td>
<td>1.80</td>
<td>47.6</td>
<td>0.24</td>
</tr>
<tr>
<td>388-64</td>
<td>0.91</td>
<td>30.3</td>
<td>0.08</td>
<td>1.56</td>
<td>41.3</td>
<td>0.16</td>
</tr>
<tr>
<td>299-62</td>
<td>0.87</td>
<td>29.0</td>
<td>0.07</td>
<td>1.52</td>
<td>40.2</td>
<td>0.14</td>
</tr>
<tr>
<td>149-65</td>
<td>0.86</td>
<td>28.7</td>
<td>0.10</td>
<td>1.51</td>
<td>39.9</td>
<td>0.18</td>
</tr>
<tr>
<td>178-65</td>
<td>0.79</td>
<td>24.9</td>
<td>0.07</td>
<td>1.54</td>
<td>34.1</td>
<td>0.14</td>
</tr>
<tr>
<td>124-61</td>
<td>0.69</td>
<td>23.0</td>
<td>0.09</td>
<td>1.54</td>
<td>32.8</td>
<td>0.18</td>
</tr>
<tr>
<td>110-65</td>
<td>0.69</td>
<td>23.0</td>
<td>0.07</td>
<td>1.32</td>
<td>32.3</td>
<td>0.14</td>
</tr>
<tr>
<td>111-65</td>
<td>0.56</td>
<td>18.7</td>
<td>0.07</td>
<td>1.03</td>
<td>27.2</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Expiratory volume \( V_{sp} \), expiratory efficiency in percentage against the normal, and transalveolar flow \( \varphi \) are registered in the table. Because the expiration in emphysema is characterized by a retarded rise in \( V_{sp} \), expiratory efficiency is improved with the progress of time. Note also larger values of \( \varphi \) in emphysematous than in normal lungs.

PARAMETER ANALYSIS

Pronounced deterioration of expiratory function in emphysematous lungs is demonstrated by the above calculations. Because five parameters exert their combined effects on the expiration, it is desirable to analyze the effect of individual parameters.

1) \( V_0 \) and \( E \)

We consider two pulmonary models. In one of them, \( E \) is reduced to half the normal, and the other four parameters are left to be normal. In the other model, only \( V_0 \) is increased to 2,000 cm³, namely to two times of \( V_0 \) of the normal lung, the other parameters being fixed to the normal. In both models expiration is started after the inspiration of 4,500 cm³. The curves of expiration are presented in Figs. 22 and 23. In the former model in which \( E \) is reduced to half the normal, the initial pulmonary pressure is lowered almost exactly to a half of the normal value. Expiratory efficiency checked at \( t=1 \) is depressed to about 70% of the normal. In the latter model where \( E \) remains normal and only \( V_0 \) is increased to two times, the depression of the initial pulmonary pressure is much more pronounced, and expiratory efficiency at \( t=1 \) is lowered to 50% of the normal. In emphysematous lungs \( V_0 \) often exceeds 3,000 cm³, or it is increased over three times of the normal value, while the lowest value of \( E \) in the present study is only a little smaller than half the normal. It is easy to understand, that an increase of the volume in unexpanded lungs plays the most important role in
Fig. 22. The influences of reduced density of elastic system and increased pulmonary volume in relaxation on the time-pressure curves are calculated on the corresponding pulmonary models and presented in comparison with the curve of the normal lung. The models are: (1) normal lung, (2) $E=0.5$ and $V_0=1.0$, and (3) $E=1.0$ and $V_0=2.0$.

Fig. 23. The expiratory volumes are calculated with the models in Fig. 22. Note the serious effect of increased $V_0$ on the expiratory efficiency.

the deterioration of expiratory efficiency in emphysema.

2) Effect of $\sigma$

The fluctuation in the value of $\sigma$ has only a little influence on the expiratory efficiency. As $E$ or the density of elastic system cannot take a negative value, the largest possible value of $\sigma$ is practically limited to a third of the mean $E$. In Figs. 24 and 25, the effects of increasing $\sigma$ are demonstrated. Even when $\sigma$
Fig. 24. The effects of varying $\sigma$ or standard deviation of $E$ are demonstrated. The effect of increasing $\sigma$ is revealed in a slight depression of intrapulmonary pressure. However, the difference in the pressure is practically negligible even when $\sigma$ takes its largest possible value.

Fig. 25. Corresponding to the results in Fig. 24, expired volume is not essentially influenced by $\sigma$. The significance of increasing $\sigma$ consists rather in its effect to increase transalveolar flow $\varphi$. The models of this diagram are: (1) $E=1.0$ and $\sigma=0.100$ (normal lung), and (2) $E=1.0$ and $\sigma=0.333$. The transalveolar flow at $t=1$ of the second model is over 4 times of that of the first model.

takes the largest possible value, its influence is practically negligible.

The significance of increasing $\sigma$ consists rather in its effect to enhance transalveolar flow*. This is demonstrated in the model of Fig. 25. When the

* For the concept and determination of transalveolar flow, see our previous report.1
Fig. 26. The distribution of $C_u$ in a case of emphysema is demonstrated. The scatter of $C_u$ is relatively limited in this case.

Fig. 27. The distribution of $C_u$ in another case of emphysema is demonstrated in comparison with that of the case in Fig. 26. Note distinctly larger scatter of $C_u$ in this case. The distribution cannot any more assimilated to a single normal distribution.

lung operates in the region of lower pressure as in the case of emphysema, the proportion of transalveolar flow to expired volume becomes still larger. In Figs. 26 to 29, two cases of emphysema are presented. Expiratory volumes are nearly the same in both cases. However, the scatter of the density of alveolar septa and accordingly that of $E$ is much larger in the case of Figs. 27 and 29. Transalveolar flow in this case attains about 11% of the expired volume at $t=1$ in contrast to 6% of the other case in which the standard deviation of $E$ is much
3) **Effect of a**

The elevation of elasticity constant $a$ due to pulmonary fibrosis has a pronounced effect to increase intrapulmonary pressure at a certain pulmonary expansion. In Fig. 30, the volume-pressure relation is presented with a series of
different $a$. It is further noteworthy that an increase of $a$ from 5.5 to 6.5 can compensate almost completely a reduction of $E$ to half the normal. Pulmonary fibrosis, which is in its nature a definitely pathological process, may improve functional disability of the lung in some situation.

4) **Maximum pulmonary expansion**

The parameter analysis is concluded with the consideration of the initial lung volume of expiration. Even with emphysematous lungs of definitely lowered expiratory capacity, a sufficient expiratory volume is theoretically obtainable in a limited time, if the lung is further expanded by increasing inspiratory volume. The enlargement of thoracic cavity in patients with emphysema can be regarded as a compensatory process. The problem is, however, to what extent the lung volume must be increased at the beginning of expiration, in order that an expiratory volume of 3,000 cm$^3$ may be obtained at $t=1$. Fig. 32 demonstrates the initial volumes of the examined emphysematous lungs, which are required to afford the above expiratory volume at $t=1$. In none of the cases the required initial volume is smaller than 10 liters. In extreme cases it exceeds 15 liters. The inspiratory volume necessary to obtain the required initial volume is larger than 8 liters throughout the examined cases. This requirement is obviously not fulfilled in the organism. Clinical experiences have demonstrated that the vital capacity is distinctly reduced in emphysema. The quantity is approximately equivalent to the inspiratory volume in the present study. Emphysematous lungs are after all incompetent to drive out a sufficient quantity of inspired air in a time interval compatible with physiological respiratory activities.
Fig. 31. An elevation of $a$ from 5.5 to 6.5 can almost completely compensate the effect of a reduction of $E$ to half the normal. The models in the diagram are: (1) $a=6.5$ and $E=1.0$, (2) $a=6.5$ and $E=0.5$, (3) $a=5.5$ and $E=1.0$, and (4) $a=5.5$ and $E=0.5$. Note the almost identical volume-pressure curves in (2) and (3).

Fig. 32. The initial pulmonary volume $V_{\text{max}}$ required to afford an expiratory volume of 3,000 cm$^3$ at $t=1$ is calculated with each emphysematous lung. The white part of the column represents inspired volume.

COMMENTS

In the present investigation attempts were made to demonstrate lowered expiratory efficiency of emphysematous lungs on the basis of anatomical findings and independent of clinical function tests. The lungs were assumed to operate without the participation of thoracic activity. Although the condition is
Fig. 33. The time-pressure curve of an emphysematous lung from an initial volume which affords an expiratory volume of 3,000 cm$^3$ at $t=1$ is presented as the thick curve in the diagram. The uppermost curve is the volume-pressure curve of the normal lung from the initial volume of 5,500 cm$^3$ or after an inspiration of 4,500 cm$^3$. The lowermost curve represents the time-pressure relation of this case of emphysema from an initial lung volume of 7,900 cm$^3$ or after the inspiration of 4,500 cm$^3$. Even at the initial volume of 15.5 liters the initial pressure attains only about 16 cm H$_2$O.

Fig. 34. The expired volume of the case in Fig. 33 from the initial volume of 15.5 liters is given by the thick curve in the diagram. The uppermost slender curve is that of the normal lung after inspiration of 4,500 cm$^3$, and the lowermost curve is that of this case of emphysema after inspiration of the standard volume of 4,500 cm$^3$. The thick curve crosses the curve of the normal lung at $t=1$ and still continues to rise without essentially reducing its gradient.
not realized in the organism, such an attempt is useful in the establishment of theoretical basis of pulmonary functions.

When expiratory efficiency is depressed below a certain level, an aid of thoracic contractile force becomes indispensable to sustain a physiologically necessary expiratory volume. The lung is thus compressed by an extraneous force. This force is transmitted through intrapulmonary air pressure on bronchial walls without reducing its strength. If the bronchial walls are rigid enough, expiration proceeds without noticeable disturbance. However, when the structures are attenuated, increased transmural pressure incites the check valve mechanism. The resulting obstructive expiratory distress makes emphysema a clinical problem for the first time.

How decisive the check valve mechanism may be in the development of dyspnea in emphysema, the condition is brought about only after the lung is no more competent to drive out a necessary volume of air on account of its impaired retractive force. The pulmonary disability of this type is not necessarily disclosed in clinical function tests, but it is nevertheless important especially when we want to understand the pulmonary expiratory function in the strict sense of the word.

In the present situation the endeavor of clinicians does not seem to be concentrated on an attempt to isolate pulmonary, from thoracic, activities. Although the combined effects are of significance in the respiration of living organisms, a well-founded analytical study of pulmonary functions is possible only when the lung is treated as an independent system. It is desirable that the concepts and theories on pulmonary functions are substantiated by adequate correlations of anatomical findings to functions.

Apart from the clinicopathological correlation, it is further of greater importance to notice that expiratory functions of the lung are determined not only by the property of its constituent elements, but rather by the configuration of the elements in the space. In the present pulmonary model, elasticity constant $a$ is the sole parameter which defines the character of pulmonary constituent elements. Its determination requires a non-morphological treatment. All the other parameters, $V_0$, $E$, $\sigma$, and $R$ are related to, or determined by, the spatial configuration of the elastic system and are susceptible of entirely morphological or geometrical analyses, except for the viscosity coefficient of air in the determination of $R$. The present investigation demonstrates that the spatial orientation of the elastic system may have a serious influence on the expiratory function of the lung, even when the property of the elastic system remains unchanged. Analytical treatments of organ structures above the level of constituent elements are not only effective but also indispensable for a correct understanding of organ functions in general. The principle of such structural analysis is fundamentally independent of the analysis of the constituent element. The
latter can be put between brackets and disregarded in the course of the theoretical treatment. Structural analyses of this sort are expected to open the way to morphological approaches to organ functions which have not hitherto arrested due attention.

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References