Anatomic Changes in Lung Parenchyma Due to Aging Process*

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The structure of the air passage of the lungs, including alveoli, is usually divided into two portions, i.e., the airway and the respiratory portion. Although the latter is morphologically subdivided into the respiratory bronchioli, alveolar ducts, alveolar sacs and alveoli, it will be much more useful to divide the respiratory portion into two parts, i.e., the central ducts succeeding the airway and alveoli surrounding the central ducts.

In 1961 we found morphologically the dilatation of the central ducts in the senile lungs. Recently, Weibel investigated the volume contribution of the central ducts and alveoli for five excised lungs from patients from 8 to 74 years old. He found that the volume contribution of the alveoli, corresponding to the alveolar air, was higher (62 per cent) than that of the central ducts in three younger individuals. On the contrary in two older individuals this value decreased by 56 per cent. In his paper he stated, “The small number of cases obviously does not justify conclusive statement with respect to changes of volume proportion of the lung generally attributable to age.”

At this point, it is necessary to notice that in his estimation of volume contribution, the volume fraction of the respiratory bronchioli was not included. It would be due to the difficulty to estimate the volumetric fraction of this part by means of his modified method, applying Delesse and Rosiwal’s principles.

The purpose of this paper is to estimate the variation of the volume contribution between the alveoli and central ducts including respiratory bronchioli by means of our new method with respect to the aging process.

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Method

We used nine necropsied lungs which did not show any pathologic changes. These lungs were selected with respect to greatest freedom from dust deposit as possible, although in some regions, especially in the senile lungs, a small amount of dust was deposited. The age range of the individuals whose lungs were excised was from four days to 68 years. After the lungs were excised, we induced a 10 per cent formalin solution through the trachea with the intratracheal pressure of 25 cm H₂O, they were then fixed for one week, keeping the intrabronchial pressure constant by means of Heard’s method. Then macrosections of 100 µ thick were made by the method similar to Gough’s. We used transparent celluloid board instead of filtering paper in order to make the macrosection specimen adhere. We called this macrosection “celluloid macrosection.” The macrosection was projected on photographic paper, which was cut into about 5, ~6,000 parts along the margin of the respiratory portion. We calculated the individual weight of each part by means of the gravimetric method. Based on this calculated weight, we constructed the distribution of volumetric fraction of the respiratory portion by the following process:

\[ F(w) \ d \log w = 1 \quad \ldots \ldots \quad (1) \]
\[ F(w) = w \times n \quad \ldots \ldots \quad (2) \]

where \( w \) and \( n \) represents the weight of each part and number of the parts corresponding to the weight respectively.

It was possible to standardize each excised lung according to equation (1) and (2).

We plotted the calculated weight on the horizontal axis, which is logarithmic. Therefore, a unit of the horizontal axis is \( \log w = 0.1 \), and on the vertical axis, the ratio of \( \Sigma F(w) \Delta \log w \) to \( \Delta \log w \) respectively.
For the other purpose, we took the slice nearest that of the "celluloid macrosection" specimen from five necropsied lungs (Cases 1, 3, 5, 6 and 8). Then we embedded these slices in paraffin, and prepared the paraffin section with 6 μ thickness for each case.

RESULTS

Case 1, a boy four days old. The standardized distribution of the volumetric fraction of the respiratory portion in this case ranged 0.1~17.6 mg (-1<log w≤1.3) of the calculated weight and we found that the highest value for the ratio of the ΣF (w) Δ log w to Δ log w was in the range of 2.0~2.5 mg (0.3<log w≤0.4) and the contribution of the heavy weighted part was relatively higher than that of the light one. These findings are shown in the upper portion of Fig. 1.

Case 2, a boy one year old. The distribution range was 0.1~18.7 mg (-1.0<log w ≤1.3) of the calculated weight and the highest value was in the range of 0.8~1.0 mg (-0.1<log w≤0), which is much shorter compared to case 1, but, as a whole, the distribution seemed to be more even than that in case 1.

Case 3, a girl of seven years. The distribution range was 0.1~49.2 mg (-1.0<log w≤1.7) and the highest value was found in the range of 0.8~1.0 mg (-0.1<log w ≤0), although this value was much smaller than that of case 2. Moreover, it was characteristic for this case that the contribution of the light weighted part was higher than that of the heavy one.

Case 4, a boy 17 years old. The range of distribution was 0.1~45.3 mg (-0.1<log w≤1.7). There were three highest values and the ranges of these were 0.8~1.0 mg (-0.1<log w≤0), 2.0~2.5 mg (0.3<log w≤0.4) and 7.9~10.0 mg (0.9<log w≤1.0) respectively.

Case 5, a man 20 years old. The range of the distribution was 0.1~99.8 mg (-1.0<log w≤2.0). In the range between 2.0~2.5 mg (0.3<log w≤0.4), and 20.0~25.0 mg (1.3<log w≤1.4), we found two highest values and there were two different dis-

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**FIGURE 1**: Case 1, four-day-old boy. Upper figure represents the gravimetric distribution which indicates the respiratory portion and lower figure, the histometric distribution which indicates the alveolar portion.

**FIGURE 2**: Case 6, 38-year-old woman. Upper figure represents the gravimetric distribution which indicates the respiratory portion and lower figure, the histometric distribution which indicates the alveolar portion.
tribution patterns along these two highest values. But the contribution of the light weighted part ranging 0.1~7.9 mg (−1.0 < \log w \leq 0.8) seemed to be two times higher than that of the heavy weighted part ranging more than 8 mg (0.8 < \log w).

Case 6, a woman 58 years old. The distribution range was 0.1~53.7 mg (−1.0 < \log w \leq 1.8). In the range of 2.0~2.5 mg (0.3 < \log w \leq 0.4) and 15.8~19.9 mg (1.2 < \log w \leq 1.3) there were two highest values. The contribution of the light weighted part ranging 0.1~5.0 mg (−1.0 < \log w < 0.7) was about 1.5 times higher than that of the heavy one ranging more than 5.1 mg (0.7 < \log w). These findings are shown in the upper portion of Fig. 2.

Case 7, a woman 41 years old. The range of the distribution was 0.1~51.8 mg (−1.0 < \log w \leq 1.8). In the range of 0.8~1.0 mg (−0.1 < \log w \leq 0) 2.0~2.5 mg (0.3 < \log w \leq 0.4) and 12.5~15.8 mg (1.1 < \log w \leq 1.2), there were three highest values and there were two different distribution patterns excepting the first highest value. The range of the first pattern was 0.1~6.3 mg (−1.0 < \log w \leq 0.8) and that of the second one, more than 6.4 mg (0.8 < \log w). The contribution of the first part seemed to be about two times higher than that of the second one.

Case 8, a man 63 years old. The distribution range was 0.2~181.0 mg (−0.7 < \log w \leq 2.3). In the range of 15.8~19.9 mg (1.2 < \log w \leq 1.3) there was the highest value and along this value there was one distribution pattern. This was quite contrary to casts 5, 6 and 7 in which there were two different patterns, but as a whole, the contribution of the heavy weighted part seemed to be relatively higher than that of the light one. These findings are shown in the upper portion of Fig. 3.

Case 9, a man 68 years old. The range of the distribution was 0.2~351.8 mg (−0.7 < \log w \leq 2.5). In the range of 25.1~31.6 mg (1.4 < \log w \leq 1.5) there was highest value. Along this value there was one distribution pattern which is quite similar to the upper portion of Fig. 3 which was shown in case 8.

We found the characteristic differences in terms of the distribution of the volumetric...
fraction of the respiratory portion for each age group. In order to clarify how these differences were related to the aging process, the following study was made.

For this purpose the paraffin section was used, and according to Weibel's method, the average diameter of 150 alveoli for each case were measured. For the comparison, it was necessary to correct these values by the amount which corresponded to the value obtained from the gelatin section for the macrosection specimen because there was a difference in the grade of the tissue contraction between the paraffin and gelatin section. According to our study, the ratio of the length of the tissue embedded in gelatin to that in paraffin was 10:8. Therefore, the value for average alveolar diameter for the paraffin section, which corresponds to the value for the gelatin section, can be obtained by multiplying a factor of 1.3.

Assuming that all alveoli would be circles with a calculated average diameter, it was possible for us to calculate the area (S) of each alveoli. On the other hand, the weight of a photographic paper was almost constant, in spite of differences in the magnitude of printing and humidity, and we found that the average weight per unit cm² was 20.1±0.2 mg (W'). Then, we are in a position to calculate the weight of each alveolus printed on a photographic paper by multiplying S and W', and furthermore, to construct the distribution of alveolar area by calculating the weight of each alveolus and the corresponding number of them. This distribution could be compared to the distribution which constructed by the macrosection specimen, but for a comparison, again, we had to standardize each case according to equation (1) and (2). It would be worthwhile to notice at this point that the distribution constructed by the histometric method using a paraffin section represents that of alveoli. On the other hand, the distribution constructed by the gravimetric method using a macrosection specimen represents that of the respiratory portion including alveoli.

Unless otherwise stated, the former will appear as histometric method and the latter, as the gravimetric method. The following results stemmed mainly from the comparison of two distributions for the same case.

Case 1: The range of the volumetric fraction of the alveoli according to the histometric method corresponded almost to that of 0.1~1.0 mg (−1.0<log w≤0) according to the gravimetric method (Fig. 1).

Case 3: The range of the volumetric fraction of the alveoli corresponded to that of 0.1~2.0 mg (−1.0<log w≤0.4) according to the gravimetric method and the highest value for the volumetric fraction of alveoli was also included in this range.

Case 5: The range of volumetric fraction of alveoli corresponded to 0.1~3.9 mg (−1.0<log w≤0.6), which is the first peak in the gravimetric distribution. Therefore, this finding made it clear that the first peak in the gravimetric distribution corresponded to the volumetric fraction of the alveoli. On the other hand, the second peak corresponded to that of the central duct.

Case 6: The range of the volumetric fraction of the alveoli corresponded to 0.1~6.3 mg (−1.0<log w≤0.8), which is almost the first peak in the gravimetric distribution. Again, it is clearly seen that the first peak in the gravimetric distribution corresponded to the volume fraction of alveoli and the second one, that of central duct (Fig. 2).

Case 8: The range of the volumetric fraction of alveoli was 0.2~6.9 mg (−0.7<log w≤0.9) of the gravimetric distribution (Fig. 3).

Based on these results, the volume fraction of the alveoli to that of total respiratory portion for each case could be estimated: 21 per cent in Case 1, 42 per cent in Case 3, 57 per cent in Case 5, 63 per cent in Case 6, 44 per cent in Case 8 (Fig. 4). These results gave us the following conclusion. As far as the volumetric fraction of the alveoli is concerned, it was increasing ever remarkably in the infant and child lung, then it reached the highest value.
in the young adult lung. On the contrary in the older adult lung, it again decreased. But these findings should be referred to the volumetric fraction of the central ducts, that is, in the infant and child lung the volumetric fraction of the central duct showed relatively high value, but in the young adult lung, it decreased and again in the older adult lung it increased relatively.

**DISCUSSION**

According to the recent reports it has been known that the lungs continue to develop after birth. Emery and Mithal showed that the postnatal development of the lungs involved not only the airway, but also the respiratory portion, from the quantitative study of the terminal respiratory unit for the infant and child lungs. These findings were assured by our gravimetric method. In case 1 (the fourth day after birth), the contribution of the volumetric fraction of the respiratory portion was shown to be much higher in the range of the heavy weighted portion, but in case 2 (one year) the highest value for the contribution shifted to the range of the light weighted portion and this tendency was shown clearly in case 3 (seven years) with the higher contribution in the range of the light weighted portion. Furthermore, taking the results of the histometric investigation into consideration, the pattern of the volumetric fraction shown in these cases clearly indicates the process of the postnatal development of the alveoli.

In three cases aging from 20 to 40 years, the volumetric fractions showed a typical distribution pattern with two phases. In case 4 (17 years), the distribution pattern was just between that in case 3 and case 5 (20 years). These findings made it clear that the respiratory portion continued to develop until 20 years of age, then the development was maintained almost constant until 40 years of age.

Frank and associates and Pierce and associates showed that the static compliance of the lungs was rapidly ever increasing until about 20 years of age. Then this value was maintained almost constant for the young adults. It seems remarkable that there is a good deal of similarity between our results and their findings, in terms of the pattern of development of the lung. At this point we have to take the thickness of our macrosection specimen used in gravimetric method into consideration. The thickness was 100 μ. Therefore, it would be assumed that there might be some alveoli which are unmeasurable in our section, especially in the infant lung because it has been shown that in the infant lungs there were some alveoli, of which the diameter was less than 100 μ. Therefore, we made the following correction for the infant lungs.

Assuming that a number of small spheres with the diameter of 2r are distributed at random in the space, and we obtain a slice with the thickness of d(d>2r), the ratio of the number of spheres, which appear as a cross section on the slice (A), to that of sphere which are embedded completely in the slice (B), can be obtained from the following equation.

\[
\frac{A}{B} = \frac{2 \pi 2r}{d - 2r}
\]

Applying this equation to the macrosection of case 1, taking the values for the thickness of a slice as 100 μ and the average diameter of the alveoli as 80 μ, we can estimate that the ratio of the unmeasurable alveoli, which are embedded in the slice, to the total alveoli, is about 13 per cent. Therefore, if we take this value into the volumetric fraction of the alveoli, the corrected value for the volumetric fraction does not exceed more than 30 per cent in case 1. As far as the adult lungs are concerned, it should not be necessary to make such a correction, because most of the alveoli have a diameter more than 100 μ.

In the young adult lungs, we obtained the value for the volumetric fraction of the alveoli to the respiratory portion, being about 60 per cent. This value corresponds reasonably to the value (62 per cent), obtained by Weibel for the two lungs of
patients 16 and 34 years old. His value is the ratio of the alveoli to the respiratory portion, including the interstitial tissue. On the contrary, our value was obtained without taking the interstitial tissue into our calculation. If we take this portion into our calculation, our value for the volumetric fraction of the alveoli would be smaller. At this point we faced the discrepancy between our value and Weibel's, but it will be due to the difference in the morphologic range for the respiratory portion, that is, in our estimation the respiratory bronchioles were included as the respiratory portion, but Weibel did not.

On the other hand, we found in senile lungs a relative decrease in the volumetric fraction of the alveoli and simultaneously a relative increase in that of the central ducts. This finding proved quantitatively our previous study and Giese's in which the morphologic dilatation of the central ducts were shown in the senile lung (it might be attributable to the decrease in the elastic recoil).

The relative increase in the volumetric fraction of the central duct was also shown in the infant lungs. Then the question arises: What does this common feature imply? In our histometric method, the average alveolar diameter in the infant lungs was smaller than that in young adult lungs, but much smaller than that in senile lungs. In other words, the average alveolar diameter is getting larger with aging. Here we have the following solution. In the infant lung, the reason for the relative decrease in the volumetric fraction of the alveoli is straightforward, that is, the smaller average alveolar diameter, because of the prematurity. On the contrary, in the senile lungs it seems more complex, because, as already shown, both the average diameter of the alveoli and the volumetric fraction of the central ducts, increase simultaneously. But the most important feature for the senile lungs is the relatively higher increase in the volumetric fraction of the central ducts, compared to that in the alveoli, due to the increase in the average alveolar diameter.

It has not been clearly shown which mechanism is involved in the dilatation of the central ducts in the senile lungs. Generally speaking, it has been shown that the ductal organs, for example, the vessels, were getting dilated through aging. Such a mechanism might partly involve dilatation of the central ducts in the senile lungs.

In our gravimetric method, all estimations of the distribution of the alveoli and central duct were, strictly speaking, obtained in terms of the area instead of the volume. In 1842, Delesse presented the following principle: "If a section is placed through a tissue volume containing a given component, the fraction of the area covered by transsections of the component will be equal to the volume occupied by the component." Therefore, our estimation can be extended to the volumetric fraction based on his principle.

**SUMMARY**

We studied the volumetric fraction of the respiratory portion (respiratory broncholi, alveolar ducts, alveolar sacs and alveoli) for nine autopsied lungs aging from the fourth day after birth to 68 years old, by means of gravimetric method, using the macrosection specimen. All lungs did not show any pathologic changes. Furthermore, in order to analyze the distribution of the volumetric fraction, the histometric method for the same lung was used.

We found that the alveoli developed rapidly in the infant and child lungs and the development of the respiratory portion continued until about 20 years of age. In the range of 20-40 years of age, the volumetric fractions were maintained almost constant, i.e., about 60 per cent for the alveoli and 40 per cent for the central ducts. On the other hand, in the senile lungs, the volumetric fraction of the central ducts was relatively higher than that in the young adults. The important feature for the senile lungs is the relative higher volumetric fraction of the central ducts, compared to that of the alveoli. This would be due to the dilatation of the central ducts.
RESUMEN
Hemos estudiado la fracción volumétrica del segmento respiratorio (Bronquiolos respiratorios, conductos alveolares, sacos alveolares y alveolos) en nueve pulmones obtenidos en autopsias de individuos desde cuatro días a 68 años de edad, por medio del método gravimétrico, usando macrosecciones. No todos los pulmones mostraron cambios patológicos. Además, en orden a analizar la distribución de la fracción volumétrica, empleamos el método histométrico en el mismo pulmón.
Hemos observado que los alveolos se desarrollan rápidamente en el niño y que el desarrollo de la porción respiratoria continua hasta los 30 años. Entre los 20 y los 40 años las fracciones volumétricas se mantuvieron casi constantes, esto es alrededor del 60 por ciento para el alveolo y 40 por ciento para el conducto central. Por otra parte, en el pulmón senil la fracción volumétrica del conducto central es relativamente más elevada que en el adulto joven. Pero la característica importante del pulmón senil es el volumen relativamente mayor de la fracción volumétrica del conducto central, comparada con la del alveolo. Esto sería debido a la dilatación de los conductos centrales.

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REFERENCES

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