EFFECTIVE BREATH HOLDING TIME IN THE MEASUREMENT OF THE PULMONARY DIFFUSING CAPACITY BY SINGLE BREATH METHOD

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Summary In the measurement of the pulmonary diffusing capacity $D_L$ by the single breath method the entire inspiration time has hitherto been included in the breath holding time. When the inspiration time is prolonged, this treatment leads to a considerable error in the $D_L$ value. In order to eliminate this error a correction factor of the inspiration time was newly introduced to obtain the effective inspiration time. The correction factor was a function of the ratio of the residual capacity to the total alveolar gas volume and the ratio of $D_L$ to the flow rate of inspiration. A nomogram was made for convenience to obtain the effective inspiration time.

Concerning the oxygenation velocity of the red blood cell Koyama and Mochizuki (1969) and Mochizuki (1966, 1970) have revealed that this velocity is significantly influenced by measuring conditions, above all by convection around the red cell in a rapid flow measurement. On the other hand, according to recent morphological studies made by Miyamoto and Moll (1968) the red cell changes its original biconcave shape to a cylindrical one during flowing through the pulmonary capillary. In addition, the convection of the blood plasma around the red cell in the capillary is considered markedly different from that in the rapid flow apparatus. Consequently, it has become necessary to measure the oxygenation velocity directly in vivo in the pulmonary capillary in order to ascertain the relationship between the oxygenation velocity and the $O_2$ uptake rate in the lung. For determining the oxygenation velocity in vivo, however, the transit time of the red cell through the pulmonary capillary, namely, the contact time, must be measured. The contact time in turn can not be determined at the present time without measuring the CO pulmonary diffusing capacity ($D_L$), the cardiac output and the reaction velocity of CO with the red cell. Thus, we attempted to determine
these three values as exactly as possible.

The $D_L$ has hitherto been measured to indicate grades of diffusion impairment in the lung. Because the single breath method elaborated by M. Krogh (1915) is rather simple and in addition because its accuracy has been improved by Forster et al. (1954), the $D_L$ is accepted in clinics as one of the screening tests of the pulmonary function. As reported by Forster (1964) and other authors (Burrows et al., 1960a, b; Piper and Sikand, 1966) the $D_L$ is, more or less, influenced by the uneven distribution of pulmonary gas volume and perfusion. Thus, for quantitative measurement of the contact time it becomes absolutely necessary to make these influences as small as possible. When cardiac output is measured by the single breath method using nitrous oxide or acetylene gases (Cander and Foster, 1959), the values of cardiac output should also receive the above influences. The extent of the influences depends on the uptake rate or solubility of the gas used, therefore, even when the $D_L$ and the cardiac output are measured at the same time, these influences appear to differently in magnitude on both the measured values of the $D_L$ and cardiac output. However, the influences due to solubility are considered to be equalized to some extent by selecting appropriate breath holding time, and the influences on the contact time value which is evaluated from the ratio of the $D_L$ to the cardiac output are thought to be eliminated. The uptake rate of CO is in general different from that of other gases. Therefore, it becomes desirable to select the optimum breath holding time as accurately as possible. Thus, we first studied the treatment of the inspiration time.

In the single breath method the $D_L$ has been evaluated according to the following formula:

$$D_L = \frac{-60 \cdot V_A}{t_b \cdot (P_B - 47)} \ln \frac{F_{A_{CO}}}{F_{A_{CO0}}}, \quad (1)$$

where $V_A$ is the gas volume (STPD) of the ventilating alveoli, $t_b$, the breath holding time, $F_{A_{CO0}}$ and $F_{A_{CO}}$ the CO concentrations in the alveoli at the outset and $t_b$ seconds of a breath holding respectively, and $P_B$, the barometric pressure. The calculation of Eq. (1) is based on the assumption that the inspiration is made so fast that the inspiration time becomes negligibly short compared with the breath holding time. Actually, the breath holding time has hitherto been counted from the outset of inspiration to the time of sampling on expiration. In some subjects, however, the inspiration time may be considerably prolonged and evaluation of the breath holding time often becomes very difficult.

When the inspiration time is prolonged, the actual alveolar CO concentration at the end of inspiration may become smaller than the initial concentration, $F_{A_{CO0}}$ in Eq. (1) which is evaluated from both the He concentrations in inspired and alveolar gases, since the inhaled CO is taken up by the blood instantaneously during the course of inspiration. On the other hand, when the breath holding
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time is counted from the beginning of inspiration, the actual alveolar CO concentration may become larger at the end of inspiration than the CO concentration presumed according to Eq. (1) by taking $t_b$ for the inspiration time, since the uptake volume of CO is more in the model case of Eq. (1) than in the actual inspiration process. In the $D_L$ measurement, however, the alveolar gas can not be sampled at the end of inspiration, thus, estimation of the initial alveolar CO concentration $F_{ACO}$ by using He gas is indispensable. Therefore, to equalize the presumed alveolar CO concentration with the actual concentration at the end of inspiration a correction of the inspiration time, which should be included in the breath holding time $t_b$ in the calculation of Eq. (1), becomes absolutely necessary. In the present study a correction factor for obtaining the effective inspiration time from the actual time was studied.

THEORETICAL DERIVATION OF $F_{ACO}$ DURING INSPIRATION AND THE CORRECTION FACTOR OF INSPIRATION TIME

When the test gas containing CO is inhaled, the CO-free gas filling the dead space of the airway is inspired into the alveoli, and a definite time $t^*$, more or less, is required for the test gas to pass through the dead space. Let the volume of the dead space be $V_D$ and the flow velocity of the inspired gas be $V_I$. Then, the transit time $t^*$ may be expressed as follows:

$$t^* = \frac{V_D}{V_I}.$$  

Thus, the amount of CO gas inspired into the alveoli from the outset to $t$ sec of inspiration may be given by $F_{ICO} \cdot V_I (t - t^*)$, where $F_{ICO}$ is CO concentration of the inspired gas. During the inspiration time, on the other hand, a part of the CO in the alveoli is taken up by the blood flowing through the capillary at a rate $F_{ACO} \cdot D_L (P_B - 47)/60$. Consequently, the quantity of CO taken up by the blood during inspiration may be expressed as:

$$\frac{D_L \cdot (P_B - 47)}{60} \int_{t^*}^{t} F_{ACO} \cdot dt.$$  

Therefore, the CO remaining in the alveoli at the time $t$ may be given by

$$F_{ICO} \cdot V_I \cdot (t - t^*) \cdot \frac{D_L \cdot (P_B - 47)}{60} \int_{t^*}^{t} F_{ACO} \cdot dt.$$  

Let the residual gas volume in the alveoli at the start of inspiration be $V_R$, then, the alveolar volume at the time $t$ may be given by $V_R + V_I \cdot t$, and the $F_{ACO}$ is given as follows:

$$F_{ACO} = \frac{1}{V_R + V_I \cdot t} \left\{ F_{ICO} \cdot V_I (t - t^*) \cdot \frac{D_L \cdot (P_B - 47)}{60} \int_{t^*}^{t} F_{ACO} \cdot dt \right\}. $$  

(3)
Since $F_{ACO} = 0$ at $t = t^*$, Eq. (3) can be solved, and $F_{ACO}$ may be expressed as follows:

$$F_{ACO} = \frac{F_{ICO}}{(1 + \lambda)} \left\{ 1 - \left( \frac{V_R + V_D}{V_R + \dot{V}_I \cdot t} \right)^{1+\lambda} \right\}, \quad (4)$$

where

$$\lambda = D_L \cdot (P_B - 47)/60 \cdot \dot{V}_I. \quad (5)$$

Let the entire inspiration time be $t_0$, then, at the end of inspiration, namely, at $t = t_0$, the $F_{ACO}$ may be given by

$$F_{ACO} = F_{ICO}(1 - R^{1+\lambda})(1 + \lambda), \quad (6)$$

where

$$R = (V_R + V_D)/(V_R + \dot{V}_I \cdot t_0). \quad (7)$$

On the other hand, the initial alveolar CO concentration $F_{ACO0}$, which is obtained according to the method of FORSTER et al. (1954) may be given by,

$$F_{ACO} = \frac{\dot{V}_I \cdot (t_0 - t^*)}{V_R + \dot{V}_I \cdot t_0} F_{ICO} = (1 - R) \cdot F_{ICO}. \quad (8)$$

When the alveolar CO concentration is abruptly increased to $F_{ACO0}$ at $t = t^*$, the $F_{ACO}$ at $t = t_0$ is given according to Krogh’s formula of Eq. (1) as follows:

$$F_{ACO} = F_{ACO0} \exp \left\{ - D_L \cdot (P_B - 47) \left( t_0 - t^* \right)/60 \cdot \dot{V}_I \right\}. \quad (9)$$

The value calculated according to Eq. (6) shows the actual $F_{ACO}$ expected at the end of inspiration time and is essentially smaller than the $F_{ACO0}$ of Eq. (8) which is calculated under the assumption that the inspiration is made so fast that the CO uptake during the course of inspiration may be disregarded. But it is greater than the value of Eq. (9), where the CO uptake is more than in the actual inspiration process. In order to obtain the true $D_L$, therefore, the $F_{ACO}$ of Eq. (6) should be inserted into the Krogh’s formula of Eq. (1) as the $F_{ACO0}$, where the inspiration time must be entirely excluded from the breath holding time. However, since it is troublesome to calculate the $F_{ACO}$ in each measurement by using Eq. (6), a simpler method to correct the breath holding time in Eq. (1) was considered, leaving the value of $F_{ACO0}$ unchanged. The actual $F_{ACO}$ of Eq. (6) is greater than the presumed $F_{ACO}$ of Eq. (9), therefore, in order to equalize them, inspiration time $t_0 - t^*$ in Eq. (9) is necessary to be corrected to a smaller value. In detail, when the corrected inspiration time is taken as $t_x$, $t_x$ must satisfy the following relation:

$$(1 - R^{1+\lambda})(1 + \lambda) = (1 - R) \exp \left\{ - \lambda (1 - R) \cdot t_x/(t_0 - t^*) \right\}, \quad (10)$$

or
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Therefore, for obtaining the true $D_L$ the actual inspiration time ($t_0 - t^*$) must be multiplied by the ratio of $t_d/(t_0 - t^*)$ of Eq. (11).

EVALUATION OF THE CORRECTION FACTOR

The ratio of CO concentration in alveolar gas to that in inspired gas, $F_{Aco}/F_{ICO}$ can be obtained numerically according to Eq. (3), when the residual volume $V_R$, the dead space $V_D$, the inspiration rate $V_I$ and the $D_L$ are known. The ratios shown in Fig. 1 were obtained at five different inspiration times, whereas the residual gas volume was invariably taken as 1 liter, the total inspired gas volume was 4 liters, the dead space was 0.2 liters and the $D_L$ was 30 ml·min⁻¹·mmHg⁻¹. $F_{Aco}$ at the end of inspiration always had lower values than those measured.

Fig. 1. Ratio of the CO concentration in alveolar gas to that of inspired gas calculated along the inspiration and subsequent breath holding time. The curves were obtained at five different inspiration times of 1, 2, 3, 4 and 5 sec, where $V_R = 1$ liter, $V_D = 0.2$ liters, $V_I - t_0 = 4$ liters, and $D_L = 30$ ml·min⁻¹·mmHg⁻¹. Broken lines illustrate the $E_{Aco}$'s which may be assumed when the test gas is abruptly inhaled at respective outset points of inspiration.
by Forster's method, which is shown by a line at 76%, and these decreased as the inspiration time was prolonged. However, \( F_{ACO} \) during the breath holding period becomes greater as the inspiration time was prolonged. The broken lines depicted in Fig. 1 were obtained by extrapolating the \( F_{ACO} \) curves in the breath holding period to the reversed direction. The intersections of these curves and the \( F_{ACO0} \) line at 76% is located between \( t^* \) and \( t_0 \), indicating that the actual inspiration time \( t_0 - t^* \) is too long to evaluate the actual \( F_{ACO} \) value at the end of inspiration according to Eq. (9). Insofar as the \( F_{ACO0} \) of Eq. (8) is used for evaluation of it, the inspiration time \( t_0 - t^* \) in Eq. (9) should be shortened to the time intervals between these intersections and the end inspiratory time point, which will be referred to as the effective inspiration time.

![Fig. 2. Differences between the actual and effective inspiration times versus the inspiration time obtained at three different values of \( R = (V_R + V_D)/V_A \): 0.2, 0.3 and 0.4.](image)

The effective inspiration time was always shorter than the actual \( t_0 - t^* \), and the longer the inspiration time, the greater the difference between these became. The difference varied with the changes of \( V_R, \ V_D, \ \dot{V}_L \) and \( D_L \) as expected from Eq. (11). Figure 2 shows the difference between \( t_0 - t^* \) and \( t_x \) against the inspiration time. These were calculated at three different ratios of the residual volume to the total lung volume of 0.2, 0.3 and 0.4, whereas the total alveolar gas volume was taken as 5 liters and \( D_L, 30 \text{ ml min}^{-1} \text{ mmHg}^{-1} \). As shown in Fig. 2, the time differences ranged from 0.5 to 0.7 sec at the usual inspiration time of 2 sec. When the \( D_L \) is measured during a 10 sec period of breath holding including inspiration time, the error caused by taking \( t_0 - t^* \) instead of \( t_x \) may become 5 to 7%. Especially, the error should increase in subjects with large residual volume.
As seen in Eq. (11) the ratio of $t_x/(t_0-t^*)$ is a function of $\lambda$ and $R$. Thus, we calculated the ratio by changing $R$ from 0.15 to 0.75 and also the $\lambda$ value from 0.05 to 0.5. The results are seen in Fig. 3, where $t_x/(t_0-t^*)$ is plotted against $\lambda$ by taking $R$ as a parameter. As shown in Fig. 3, the ratio decreased linearly as $\lambda$ increased. Furthermore, on the basis of Fig. 3, a nomogram was made for obtaining $t_x/(t_0-t^*)$ from both the ratios of $R = (V_R + V_D)/V_A$ and $\lambda = D_L \cdot (P_B - 47)/60 \cdot \dot{V}_I$, as shown in Fig. 4.

In the use of the nomogram of Fig. 4 the $\lambda$ value should be obtained provisionally by using the $D_L$ value calculated without the correction of the inspiration time. Since the slight variation of $\lambda$ as well as $D_L$ has no large effect on the $t_x/(t_0-t^*)$ ratio, the correction of $\lambda$ may not be needed for obtaining the true $D_L$ value.

**DISCUSSION**

Concerning the error in the measurements the breath holding time, FORSTER et al. (1954) reported that this error was less than 1 sec because the inspiration and expiration periods together took less than 2 sec. Insofar as the breath holding time was measured by recording the volume curve on a spirometer,
Fig. 4. Nomogram for obtaining the ratio of the effective to the actual inspiration time. First, from the measured He concentrations of inspired and expired gases the total alveolar volume $V_A$, the dead space $V_D$ and the alveolar residual volume $V_R$ are calculated and then the ratio $(V_R + V_D)/V_A$ is obtained. Secondly, the provisional diffusing capacity $D_L$ is obtained without correction of the inspiration time, and the ratio of it to the inspiration rate $V_I$ is obtained. Thirdly, connecting two points on the $(V_R + V_D)/V_A$ and $D_L/V_I$ scales a line is drawn and extrapolated to the scale of $t_0/(t_0 - t^*)$ ratio. This ratio is read from the intersection. Finally, the transit time of inspired gas through the dead space $t^*$ is calculated by dividing the dead space by $V_I$, and the effective inspiration time is obtained by multiplying the ratio on the $t_0/(t_0 - t^*)$ by the time interval $t_0 - t^*$, where $t_0$ is the actual inspiration time.

$V_A$: alveolar volume
$V_D$: dead space
$V_R$: alveolar residual volume
$t_0$: actual inspiration time
$t^*$: transit time through dead space
$t_e$: effective inspiration time
$D_L$: diffusing capacity
$V_I$: inspiration rate
the time could be measured with an accuracy on the order of 0.1 sec, and the sampling time during expiration also was measured with the same accuracy. However, as for the inspiration time, even when accurate measurement could be made by spirometry, the entire inspiration time should not be included in evaluation of the breath holding time. When the inspiration time is about 2 sec, the difference between the effective and actual breath holding times may be 0.7 sec or thereabouts, as shown in Fig. 2, which actually corresponds to 7% of the 10 sec period of breath holding. Recently, Takahashi (1970) found that the inspiration time was distributed around 2 sec and the effective breath holding times which were obtained by the use of the nomogram of Fig. 4 were shorter by about 0.7 sec than the actual. Thus, even though the CO concentration could be measured within an error of a few percent, the error due to the breath holding time exceed, this error range, when the correction of the inspiration time is disregarded. This error is not too small to be ignored, when the physiological range of the membrane component of the \( D_L \) is studied.

**REFERENCES**


