Studies on the Expired Alveolar Carbon Dioxide Tension in Chronic Pulmonary Emphysema with Special Reference to Pulmonary Arterial Hypertension

Atsushi SAKAMOTO, M.D. *and* Makoto MURAO, M.D.*

A total number of 68 cases were examined in the present study. Continuous analysis of expired alveolar CO₂ tension, using a rapid infrared meter, was made in 10 normal subjects and 20 patients with chronic pulmonary diseases. In 17 patients, an arterial blood was sampled simultaneously, while alveolar CO₂ tension was analyzed during quiet breathing. This allowed to make a direct comparison between blood and gas tensions. Cardiac catheterization was carried out in 38 patients with emphysema, and the mixed venous CO₂ tension and mean pulmonary artery pressure were measured. The mean pulmonary artery pressure exceeded 18 mm. Hg in 23 of 38 patients, and in all patients with a mixed venous CO₂ tension of more than 55 mm. Hg. The mixed venous CO₂ tension exceeded 50 mm. Hg in 23 of 38 patients, and the correlation between mixed venous CO₂ tension and pulmonary artery pressure was highly significant in these 23 patients ($R=+0.84$). These results indicate that the severity of pulmonary hypertension may be estimated by the expired alveolar CO₂ tension in patients with a mixed venous CO₂ tension of more than 55 mm. Hg.

WITH the recent availability of rapid CO₂ analyzers, DuBois and Fowler have explored a new field in continuous analysis of expired CO₂ tension for estimation of various values pertaining to mixed venous CO₂ tension, arterial CO₂ tension, uneven ventilation-perfusion relationship, ratio of pulmonary blood flow per equivalent lung volume, and also cardiac output.¹⁾⁻⁵⁾ These values are really essential in evaluating the respiratory insufficiency and pulmonary circulatory disturbance in patients with chronic pulmonary diseases,⁶⁾ and it seems very convenient for the clinical application that the values are obtained without hazardous procedures such as arterial puncture or cardiac catheterization. In this paper, an attempt has been made on normal subjects and patients with chronic pulmonary emphysema to reevaluate the continuous analysis of expired CO₂ tension following the method of Silvertson and Fowler, and clinical applicability of the methods is also discussed.

MATERIALS AND METHODS

Ten normal individuals were studied for the control, of whom 8 were men and 2

From the Second Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Tokyo.

* Associate Professor of Internal Medicine.

were women, ranging in age from 19 to 38 years. Twenty patients with chronic pulmonary diseases were also studied, 10 of whom had pulmonary emphysema, ranging in age from 41 to 67 years, with an average of 55 years. The other 10 cases of chronic pulmonary diseases included 4 cases of bronchial asthma, 2 cases of pulmonary fibrosis, 2 cases of chronic bronchitis, and one case each of beryllium poisoning and bronchiectasis.

The method used in this study was similar to that originally described by Sivertson and Fowler.⁴⁾ The infrared CO₂ meter* and its standard cell, through which the subject breathed, was set up as such that the distal end of the sampling tube of the CO₂ meter was connected to a prime mover of pneumotachograph. The prime mover was a Lilly type, which had an internal volume of 70 ml., and a flow resistance of 1.15 cm. H₂O per liter per second. The total volume of dead space was no more than 150 ml. The pick-up system of the prime mover was a type of wire resistance strain gauge differential manometer.** A warm-up period of 2 hours or more provided sufficient stability for sensitivity of the instruments. Then the infrared CO₂ analyzer was calibrated with mixtures of CO₂ in room air, which had been previously analyzed with a Scholander's apparatus. Dry gas concentrations were changed to tension by multiplying with the barometric pressure corrected for water vapor tension at body temperature. Calibrations were made before and after each test, and over-all accuracy of CO₂ tension described below was considered to be ± 1 mm. Hg. The CO₂ detector system was capable of 100% response in a 0.05 second and 0.2 second, when the rate of air flow was 500 ml. per second and 100 ml. per second respectively. Both CO₂ tension and ventilatory volume were recorded with an ink-writing oscillograph*** at a paper speed of 6 or 10 mm. per second. The area of the flow tracing, as it was deflected from zero line by each breath, was converted into a volume by planimetry or by counting squares. All volumes were corrected to BTPS.

Wearing a nose clip, subjects sat in chairs during a suitable rest period. Then they breathed room air through a mouth-piece attached to the sampling tube. CO₂ and tidal volumes were recorded for several natural breaths and for a forced maximal expiration following normal inspiration (Fig. 1). Recordings were made for a maximal expiration following breathholding at the inspiratory level of the normal ending (Fig. 2). The period of breathholding was intended to be 25 seconds or longer, as could be tolerated. All the procedure mentioned above was repeated and recorded. Then recordings were also made before and during 30 seconds of voluntary hyperventilation terminated by a forced maximal expiration (Fig. 3). For hyperventilation, subjects were directed to take approximately 12 breaths in 30 seconds.

Thirty-eight patients with chronic pulmonary emphysema were studied by right heart catheterization, and the partial pressure of CO₂ in the mixed venous blood and the mean pulmonary artery pressure were measured.⁷⁾ In 17 patients, an indwelling needle was inserted into the brachial artery and arterial blood was sampled, while the expired alveolar gas was analyzed continuously during natural breathing. The whole blood was analyzed for CO₂ and O₂ by the method of Van Slyke and Neill.

* Liston-Becker Model 16 Beckman Co.

** Toyosokki Co. DLPU-0.03.

*** Nihonkoden Co. W 1-40.

Fig. 1. Record of expired CO₂ tension analysis during normal respiration and forced expiration.

Fig. 2. Estimation of $P_{\dot{V}CO_2}$ by the CO₂ tension curve during forced expiration after breathholding (19 sec.).

The pH was determined with Cambridge pH meter* and the packed cell volume by the method of Wintrobe. The CO₂ tension of blood was determined from the nomogram of Singer and Hastings.⁸⁾

RESULTS

Data of routine pulmonary function tests and that of CO₂ tension which represent the maximal value for any single expiration are summarized in Table I.

Results in Normal Subjects—

The largest variations in end-tidal CO₂ tension during a 45 second-

* 4427 Cambridge pH meter, portable pattern.

Fig. 3. Record of expired CO_2 tension analysis during hyperventilation and terminal forced expiration.

period in 10 normal subjects were ranging from 1.0–3.0 mm.Hg. During quiet breathing prior to a forced expiration, there was a plateau observed at each end-expiration (Fig. 1). The mean of average end-tidal values for each subject was 38.5 mm.Hg. At the end of normal inspiration following quiet breathing, the breathing was held for an average of 23 seconds. In this case, the alveolar plateau by succeeding forced expiration was essentially horizontal during an expiration of a liter or more for several seconds (Fig. 2). As mixed venous CO_2 tension has been essentially unchanged for 23 seconds or more in these cases, the maximal values of CO_2 tension of maximal expiration after the breathholding were considered to represent the mixed venous CO_2 tension (oxygenated).⁴⁾ The average value of estimated mixed venous CO_2 tensions was 45.7 mm.Hg in normal subjects. With maximal expiration following natural breathing, there always occurred slight increase in CO_2 tension (Fig. 1), reaching an average value of 41.8 mm.Hg, at the average value of 2,050 ml. of expired volume (Table I). Assuming that the observed rate of increase in expired alveolar CO_2 tension is equal to that of alveolar CO_2 tension, after about 500 ml. of gas was expired and anatomic dead space was washed out, Fick's principle may be applied to the observed rate of increase in expired alveolar CO_2 tension as a function of time. This expression was shown in the papers of DuBois and Fowler as follows⁴⁾⁹⁾:

$$\frac{\Delta P_{\text{ACO}_2}}{\Delta t} = \frac{(P_{\text{VCO}_2} - P_{\text{ACO}_2})(\text{diss. slope}) \dot{Q} (P_B - 47)}{\text{ELV}} \quad (1)$$

P_{ACO_2} : partial pressure of CO_2 in the alveolar gas at given time.

P_{VCO_2} : partial pressure of CO_2 in the mixed venous blood, oxygenated.

diss. slope: the mean slope of the dissociation curve for CO_2 and oxygenated whole blood, normally about 0.46 volume per cent per mm.Hg.

$\dot{Q}$: rate of alveolar blood flow.

P_B : barometric pressure, expressed in mm.Hg (760 ± 8 mm.Hg in Tokyo, Japan).

Table I. Characteristics of Several Types of Breathing

	Normal			Chronic pulmonary diseases					
				Emphysema			Miscellaneous		
	No.	Mean	Range	No.	Mean	Range	No.	Mean	Range
Rest	10			10			10		
V _T (ml.)		570	380~ 850		500	300~ 750		580	330~ 790
V (L./min.)		9.0	5.3~13.5		9.0	5.9~15.0		10.2	8.4~13.3
f (resp./min.)		16	9~ 19		18	13~ 22		18	11~ 30
Max. Pco ₂ (mm.Hg)		38.5	35~ 44		39.0	31~ 48		35.9	29~ 43
Max. expiration									
Vol. (ml.)		2,050	1,060~2,870		1,340	740~2,480		1,890	1,320~2,410
Dur. (sec.)		7.7	3.4~11.5		9.9	5.5~17.6		9.3	3.2~13.8
Max. Pco ₂ (mm.Hg)		41.8	36~ 46		52.9	45~ 67		44.2	35~ 50
Hyperventilation	10			10			10		
Pco ₂ before HV (mm.Hg)		37.1	31~ 43		38.5	33~ 44		34.4	30~ 40
Dur. (sec.)		29	27~ 32		30	25~ 37		31	28~ 35
V _T (ml.)		1,840	1,150~3,120		780	460~1,690		1,580	840~3,220
V (L./min.)		43	23~ 77		18	10~ 47		31	16~ 55
f (resp./min.)		23	18~ 33		23	13~ 36		21	13~ 40
Max. Pco ₂ (lowest 3 end-tidal)		20.8	17~ 26		31.9	24~ 38		24.6	20~ 28
Max. expiration after HV									
Vol. (ml.)		3,210	2,000~5,230		1,600	820~3,380		2,340	1,470~3,140
Dur. (sec.)		4.9	2.6~ 7.8		10.0	3.4~11.3		8.7	4.7~16.9
Max. Pco ₂ (mm.Hg)		26.3	20~ 35		46.5	37~ 58		33.2	25~ 43
Breathholding	10			10			10		
Dur. BH. (sec.)		23	17~ 36		9	19		22	14~ 27
Max. exp. after BH									
Vol. (ml.)		1,880	1,220~2,520		1,270	690~1,950		1,740	1,120~2,400
Dur. (sec.)		6.1	2.7~12.0		7.8	3.3~17.5		6.4	3.9~16.0
Max. Pco ₂ (mm.Hg.)		45.7	41~ 51		55.6	48~ 66		48.1	40~ 52
RV/TLC (%)		23	19~ 28		61	52~ 68		38	24~ 48
MBC (L./min.)		126	89~ 166		9	33		56	27~ 107
MBC (% of predicted)			>100		43	26~ 72		57	33~ 95
MMF (L./sec.)		4.1	2.6~ 5.9		0.50	0.18~1.22		1.37	0.28~ 4.2
Sao ₂ (%)					91	75~ 98		96	93~ 100
pHa					7.38	7.33~7.46		7.42	7.38~7.46
Paco ₂ (mm.Hg)					49.3	39~ 62		39.3	35~ 44

Note: CO₂ tensions are maximal values of any single expiration.

V_T : Tidal volume

MBC : Maximal breathing capacity

V : Minute volume

MMF: Maximal midexpiratory flow

f : Respiratory frequency

Sao₂ : Arterial blood oxygen saturation

RV : Residual volume

pHa : Arterial blood pH

TLC : Total lung capacity

Paco₂ : Arterial carbon dioxide tension

ELV: 'Equivalent lung volume for CO₂ at a given time' includes the capacity of the alveolar gas, pulmonary capillary blood and tissue for CO₂.

The integrated form of the equation (1) is:

$$P_{ACO_2} = P_{\bar{V}CO_2} - (P_{\bar{V}CO_2} - P_{A_0CO_2}) e^{-kt} \quad (2)$$

P_{A₀CO₂}: the value of P_{ACO₂} at zero time.

$$k = \frac{(\text{diss. slope}) \dot{Q} (P_B - 47)}{\text{ELV}}$$

The difference between the mixed venous tension and the successive alveolar tension was measured on several points of each record of maximal expirations and the logarithm of the difference was plotted against the time from the onset of expiration, as illustrated in Fig. 4. As seen in Fig. 5,

Fig. 4. Mixed venous-alveolar CO_2 tension gradient during forced expiration on the record shown in Fig. 1. The arrows show the points of the initial alveolar CO_2 tension of 2nd and 3rd phase. Estimation of P_{VCO_2} is based on the breath-holding method shown in Fig. 2.

we divided each record of forced expirations into three phases. After an average value of 480 ml. had been expired (designated as '1st phase'), the rate of decrease (per cent per second) in the tension difference, $P_{VCO_2} - P_{ACO_2}$, became constant for the period during which an average of 1,030 ml. was expired (designated as '2nd phase'). In Fig. 6, the mean rate of increase in expired alveolar CO_2 tension in the 2nd phase ($\Delta P_{ACO_2}/\Delta t$) was plotted against each initial gradient, which represented the difference at the initial P_{ACO_2} in the 2nd phase ($P_{VCO_2} - \text{initial } P_{ACO_2}$). In this Fig. 6, the percentage rate of change in the initial gradient was represented by the angle of the straight line connected with the zero point. The average value of $\dot{Q}/ELV$ was calculated from the mean percentage rate of decrease for each group by substitution in the equation (1), and these values were shown in Table II. In normal subjects, the mean rate of increase in P_{ACO_2} in the 2nd phase had an average value of 11 mm.Hg and decreased about 21 per cent per second. It was corresponding to an average value of 3.8 liters blood flow per minute per liter of lung volume (Table II). The upward slope of the alveolar plateau decreased progressively toward the end of forced expirations. In the 3rd phase, the

Subject: M.M. Normal.

Fig. 5. CO₂ tension curve during normal and forced expiration on the record shown in Fig. 1. The arrows show the same points indicating the initial alveolar CO₂ tension in Fig. 4.

Fig. 6. Correlation between mean rate of increase in alveolar CO₂ tension and mixed venous-initial alveolar CO₂ tension gradient in the 2nd phase.

plateau was almost horizontal, although it showed small variations (Fig. 5). As noted by the more horizontal course of the last three points of Fig. 4, semilogarithmic plots of $P\bar{V}CO_2 - P_{ACO_2}$ showed that the percentage rate of decrease became less in the 3rd phase. Similar analyses were made for maximal expirations following hyperventilation (Fig. 7).

Fig. 7. CO_2 tension during hyperventilation and terminal forced expiration. The arrows show the points indicating the initial alveolar CO_2 tension.

With voluntary hyperventilation, 10 normal subjects increased their minute volume to an average value of 43 liters per minute, as such of 4.8 times at rest. During hyperventilation, end-tidal values of P_{ACO_2} decreased for the first several breaths and then decreased little as long as the respiratory rate was similar. The mean value for the average P_{ACO_2} of the lowest three expirations for each subject was 20.8 mm.Hg, as presented in Table I. On the succeeding forced expiration, maximal CO_2 tension had an average value of 26.3 mm.Hg, at average expired volume of 3,210 ml. during the period of 4.9 seconds. In some records of some cases, maximal values of expired CO_2 tension were observed prior to the end of expiration (Fig. 7). The semilogarithmic plots of $P\bar{V}CO_2 - P_{ACO_2}$ showed a period of constant percentage rate of decrease, during which an average 2,100 ml. of gas was expired (2nd phase). With hyperventilation, the values of the initial gradient and mean rate of change in P_{ACO_2} increased in the 2nd phase, but the percentage rate of change was about—18 per cent per second (Table II). Average values of durations were shortened in three phases.

Results in Chronic Pulmonary Diseases—

After comprehensive case history and pulmonary function tests including

Table II. Average Values of Volume, Time, and Changes in CO₂ Tension During Expiration.

Type of expiration	Normal		Chronic pulmonary diseases			
	Max. expiration after normal respiration	Max. expiration after hyperventilation	Max. exp. after norm. respiration		Max. exp. after HV	
			Emphysema	Miscellaneous	Emphysema	Emphysema
Tot. expiration volume (ml.)	2,040 (1,060~2,870)	3,210 (2,000~5,230)	1,340 (240~2,480)	1,870 (1,320~2,410)	1,610 (820~3,380)	
Vol. of 1st phase (ml.)	480 (260~730)	500 (200~900)	470 (240~780)	520 (250~1,100)	590 (290~1,430)	
Alveolar gas	2nd (10) 3rd (9)	2nd (10) 3rd (9)	2nd (10) 3rd (9)	2nd (10) 3rd (10)	2nd (9) 3rd (9)	
Volume (ml.)	1,030 (360~1,440)	520 (130~1,070)	440 (190~660)	870 (480~1,330)	590 (190~1,150)	440 (100~890)
Duration (sec.)	2.3 (0.5~3.7)	4.5 (0.5~7.5)	2.4 (1.1~3.6)	2.4 (1.4~4.1)	2.4 (1.5~3.2)	6.2 (4.0~7.4)
Mean rate of increase (mm.Hg/sec.)	2.2 (1.0~3.0)	0.4 (0.~1.0)	4.3 (2.6~6.4)	2.9 (1.0~4.6)	3.8 (2.1~5.5)	0.9 (0.3~1.3)
Initial P _{ACO₂} (mm.Hg)	36 (33~38)	39 (36~43)	38 (31~44)	34 (30~42)	33 (23~43)	41 (30~50)
Init. gradient, P _{̇V} -P _A (mm.Hg)	11.0 (5~15)	6.4 (3~9)	18.8 (14~30)	14.4 (8~20)	22.1 (16~30)	13.6 (6~23)
Change in P _{̇V} -P _A (% per sec.)	-21 (-12~-41)	-5 (0~-13)	-24 (-15~-34)	-20 (-10~-29)	-18 (-11~-25)	-7 (-3~-11)
Calc. $\dot{Q}/\dot{V}_{ELV}$ $\left(\frac{L./min.}{L.}\right)$	3.8	0.9	4.4	3.7	3.3	1.4

Note: Number of persons in parentheses in column headings. Range of values in parenthesis in table. One normal and one patient showed no change of rate in late expiration.

fluoroscopic examination, 20 patients were divided into 2 groups which consisted of 10 typical pulmonary emphysema and 10 cases with other forms of pulmonary disease. Data listed in Table I indicate that pulmonary insufficiency is compensated better by hyperventilation in the miscellaneous group than in the emphysema group at rest. In these patients, the breath-to-breath variation in resting end-tidal P_{ACO_2} was greater than that of normal subjects, ranging from 1.3–4.8 mm.Hg during a 45-second period. In many cases of pulmonary disease, resting end-tidal P_{ACO_2} was frequently less than normal. However, with a forced expiration, an increase in P_{ACO_2} of about 10 mm.Hg was observed, reaching average values of 52.9 and 44.2 mm.Hg in emphysema group and others respectively. In patients with emphysema listed in Table I, maximal expirations following natural breathing were prolonged (an average value of 9.9 seconds of duration) and the expired volumes were smaller (an average value of 1,340 ml.) than normal. Nine of 10 patients with emphysema held their breath for 12 to 27 seconds, averaging 19 seconds. The alveolar plateau of maximal expirations after breath-holding was essentially horizontal during an expiration of the last 0.8 liter during several seconds (Fig. 8). In these patients, as well as in normal sub-

Fig. 8. Estimation of $P\bar{V}_{CO_2}$ by the CO_2 tension curve during forced expiration after breathholding (21 sec.).

jects, the maximal values of these alveolar plateau tensions appeared to represent $P\bar{V}_{CO_2}$, averaging 55.6 mm.Hg (Table I). The semilogarithmic plots were made for maximal expirations and they also showed a constant percentage rate of decrease in the 2nd phase, during which an average 440 ml. of gas was expired (Fig. 9). In cases of emphysema, the mean rate of increase in P_{ACO_2} in 2nd phase had an average value of 4.3 mm.Hg per second, which was equal to that observed in normal subjects in the 2nd phase of maximal expiration following hyperventilation. The relatively large average value of 18 mm.Hg of initial gradient was observed, and it decreased at the rate of about 24 per cent per second. In the 3rd phase, the mean rate of increase in P_{ACO_2} had an average value of 1.0 mm.Hg per second, which was similar to that

Fig. 9. CO₂ tension curve during normal and forced expiration. Estimation of $\overline{P\dot{V}CO_2}$ is based on the breathholding method shown in Fig. 8. Arrows show the points of the initial alveolar CO₂ tension.

value observed in normal subjects in the same 3rd phase of the maximal expiration following hyperventilation (Table II).

The patients with emphysema showed less response to voluntary hyperventilation than normal subjects and their average minute value was 18 liters per minute. As the reductions of end-tidal values did not exceed several mm.Hg during hyperventilation, it appeared that an effective alveolar ventilation of emphysematous lungs could not be increased voluntarily. With the succeeding forced expiration, the increase in the expired volumes was smaller in patients with emphysema than in normal subjects. The maximal P_{ACO_2} of the succeeding forced expiration, with a mean of 46.5 mm.Hg, exceeded the resting end-tidal value in all cases. These expirations were plotted semilogarithmically and divided into three phases (Fig. 10). In many cases of emphysema, the maximal value of expiratory flow rate of each forced expiration was observed within the 1st phase (Fig. 11). In the 2nd phase of maximal expiration following hyperventilation, an average value of 590 ml. for the expired volume was obtained, and the increase in expired volumes was far less than normal. An average duration remained unchanged throughout three phases, after hyperventilation. The mean rate of increase in P_{ACO_2} in the 2nd phase had an average value of 3.8 mm.Hg per second, which was similar to those observed during a forced expiration after natural breathing. The initial gradient was slightly increased, averaging 22.1 mm.Hg. This resulted in the value of about -18 per cent per second for the calculated percentage rate of decrease (Table II). Ten patients with miscellaneous pulmonary diseases showed intermediate values of the gradient and its rate of change.

Increase in alveolar CO₂ tension (ΔP_{ACO_2}) and volume of expired alveolar

Fig. 10. Mixed venous-alveolar CO_2 tension gradient during forced expiration on the record shown in Fig. 3. Estimation of $\text{P}\bar{\text{V}}\text{CO}_2$ is based on the breathholding method shown in Fig. 8. Arrows show the points of the initial alveolar CO_2 tension of 2nd and 3rd phase.

Fig. 11. CO_2 tension curve during hyperventilation and terminal forced expiration on the record shown in Fig. 3. The arrows show the same points indicating the initial alveolar CO_2 tension in Fig. 10.

gas in the 2nd phase of maximal expiration were plotted in Fig. 12. In patients with emphysema, the differences from normal findings were larger $\Delta\text{P}_{\text{ACO}_2}$ and smaller volumes of expired alveolar gas. These 2 components

Fig. 12. Increase in alveolar CO₂ tension plotted against volume of expired alveolar gas (2nd and 3rd phase).

were divided by a duration of the 2nd phase for each subject, and a correlation between the mean rate of increase in alveolar CO₂ tension ($\Delta P_{ACO_2}/\Delta t$) and mean rate of air flow in the 2nd phase was obtained (Fig. 13). As shown in Fig. 13, $\Delta P_{ACO_2}/\Delta t$ and the mean rate of air flow increased in normal subjects after hyperventilation, but did not increase in patients with emphysema. As plotted in Fig. 14, a significant correlation between $P_{\bar{V}CO_2}$ and mean pulmonary artery pressure was observed in 38 patients with emphysema ($R=+0.67$). The mean pulmonary artery pressure exceeded 18 mm.Hg in 23 of 38 patients, and in all patients with a $P_{\bar{V}CO_2}$ of more than 55 mm.Hg. The $P_{\bar{V}CO_2}$ exceeded 50 mm.Hg in 23 of 38 patients, and the correlation between $P_{\bar{V}CO_2}$ and pulmonary artery pressure was highly significant in these 23 patients ($R=+0.84$).

DISCUSSION

In general, the difficulty of forced expiration in patients with emphysema is due to the check valve mechanism.¹⁰⁾ This is well demonstrated by the fact that a forced expiration shows a peaking of expiratory flow early in expiration, followed by a rapid decrease to the lower rate of flow, namely the 'leakage flow'. By a forced maximal expiration after deep inspiration, these characteristics of the pattern of expiratory flow were distinguished in patients with emphysema (Fig. 11). In normal subjects it has been known that the rate of

Fig. 13. Mean rate of increase in alveolar CO_2 tension plotted against mean rate of air flow in the 2nd phase.

Fig. 14. Correlation between mixed venous CO_2 tension and pulmonary artery pressure (Mean) in the patients with pulmonary emphysema. Values shown in this figure are measured by catheterization techniques.

air flow of forced expiration decreases progressively after peak flow, but that a fairly large rate of flow is maintained for the major part (Fig. 7).¹¹⁾ In normal subjects the initial alveolar gas of the 2nd phase was always delivered on the ascending stage of the peak flow. On the contrary, in many patients with emphysema, the initial alveolar gas of the 2nd phase was delivered with suggestive POC (Point Of Closure by check valve mechanism) after the peak flow (Fig. 11). This accounts for the results that the mean rate of air flow in the 2nd phase of maximal expiration remained almost unchanged with hyperventilation in emphysema cases, despite an increasing rate of the peak flow. According to Sivertson and Fowler,⁴⁾ the patients with emphysema showed an increased mean rate of change in P_{ACO_2} in the 2nd phase of forced expiration after hyperventilation than that after normal breathing. However, in the present study, no significant change was observed. In emphysema it is well known that an expiratory level is elevated during hyperventilation. Furthermore, airway resistance and pulmonary pressure should be increased within the succeeding forced expiration. This appeared to reduce the pulmonary blood flow and the ratio of pulmonary blood flow per alveolar lung volume, in a manner similar to that observed with the Valsalva maneuver.¹³⁾⁻¹⁸⁾ In this study, knowledge relating to the ratio of rate of pulmonary blood flow per alveolar lung volume throughout the entire respiratory cycle was not available, since events were limited to the expiratory phase of a single respiratory cycle.

On the analysis of an individual case, the value of initial P_{ACO_2} in the 2nd phase was slightly lower than the end-tidal P_{ACO_2} ; and the average value of expired volumes in the 1st phase was subtracted from the average value of tidal volumes. During natural breathing, normal subjects and patients with emphysema delivered 90 ml. and 30 ml. of pure alveolar gas respectively in each tidal air. During hyperventilation, the former delivered 1,340 ml. of pure alveolar gas and the latter 190 ml. (Table I, II). This indicates the limited ability of patients with emphysema to increase an effective alveolar ventilation voluntarily. In the same patients, the large difference between $P_{\overline{VCO_2}}$ and P_{ACO_2} observed in the 2nd phase indicates that the gas exhaled must have largely come from the alveoli with a high ventilation/perfusion ratio. The expired alveolar gas may present apparent rates of increase in P_{ACO_2} that to some extent exceed the intrapulmonary rates of increase in P_{ACO_2} . However, they afford a convenient means of contrasting the normal and emphysematous state. According to Sivertson and Fowler,⁴⁾ the normal or large apparent values of $\dot{Q}/ELV$ indicate that perfusion is not reduced but that ventilation must be increased in the overventilated alveoli. In their description, "increasing the ventilation of overventilated alveoli is relatively less effective in CO₂ elimination from the blood than is a proportionate increase in normally ventilated alveoli." These characteristics of hyperventilated alveoli have been mentioned as 'alveolar dead space.'¹⁹⁾

In patients with emphysema, it is well known that there is a marked

variation in ventilation/perfusion ratios in different parts of the lung. As DuBois¹³⁾ has described, the P_{ACO_2} have fluctuations according to 'time' or 'phase of the respiratory cycle,' in addition to distribution according to ventilation and blood flow. It has been theorized by Riley²⁰⁾ that the mean arterial CO_2 tension should be identical with the mean alveolar CO_2 tension. This theoretical mean tension has been designated as 'ideal' tension by Riley.²¹⁾ Rahn²²⁾ has shown that the P_{ACO_2} obtained by sampling from the last fraction of each tidal volume is in very close agreement with the arterial CO_2 tension in normal subjects. On the other hand, they observed on the average of a 3–4 mm.Hg higher CO_2 for the Haldane technique of sampling air than the arterial blood in normal subjects.²⁰⁾²²⁾ Even at present, a puncture method is commonly used for the analysis of arterial blood. However, this requires an arterial puncture and considerable skill in the determination of arterial CO_2 tension, since any single determination of arterial CO_2 tension by the bubble method can only be read with an accuracy of ± 3 mm.Hg CO_2 tension.²³⁾ On the other hand, methods of analyzing alveolar gas continuously offer many practical advantages, with the recent availability of the rapid infrared CO_2 analyzer (its accuracy is ± 1 mm.Hg). A rapid infrared gas analyzer has been used for the determination of $P_{\bar{V}CO_2}$ by a bag rebreathing method.¹⁾²⁾⁵⁾ According to Collier,¹⁾ if gas mixtures carefully adapted to individual requirements are used, the plateau CO_2 tension as obtained by rebreathing of a small volume of a CO_2 mixture during spontaneous breathing in about 18 seconds may represent $P_{\bar{V}CO_2}$. By this method, $P_{\bar{V}CO_2}$ can be adequately determined in patients with heart and/or lung disease, with an accuracy of ± 3 mm.Hg CO_2 tension.¹⁾ Although it is customary to represent the degree of hypercapnia by arterial CO_2 tension, the mixed venous blood CO_2 is equally representative. The findings shown in Fig. 14 suggest that the degree of pulmonary hypertension varies directly with the severity of hypercapnia, and that hypercapnia as well as anoxia may be important in the genesis of pulmonary hypertension in patients with chronic emphysema.^{7)16)24)–26)} This is supported by the general knowledge that hypercapnia is the consequence of ineffective alveolar ventilation and is always associated with anoxia unless the individual is inhaling oxygen with a partial pressure greater than that in room air. The correlation between $P_{\bar{V}CO_2}$ and pulmonary artery pressure will be useful in estimation of the pulmonary hypertension from the value of expired P_{ACO_2} instead of catheterization procedure in patients with a $P_{\bar{V}CO_2}$ of more than 55 mm.Hg.

Suskind and Rahn²⁷⁾ pointed out that the A-V CO_2 difference was reasonably constant in a respiratory steady state despite a wide variation in cardiac output. In view of this finding, Collier and his coworkers²⁾ assumed a constant A-V CO_2 tension difference of 6 mm.Hg in both normal subjects and patients with heart or lung disease. They employed a 'rebreathing method' for determination of $P_{\bar{V}CO_2}$, and estimated the arterial CO_2 tension, subtracting a fixed A-V CO_2 tension difference of 6 mm.Hg from the $P_{\bar{V}CO_2}$. In our

17 patients, the arterial blood and expired alveolar gas were sampled simultaneously. The arterial CO₂ tension was compared with the end-tidal P_{ACO₂}, the P_{ACO₂} of maximal expiration following natural breathing and the estimated P _{$\bar{V}$ CO₂} (the maximal value of forced expiration after breathholding). The end tidal-arterial CO₂ tension difference was calculated for patients with emphysema, and an average value of -10 mm.Hg was obtained (Table I).²⁸⁾ In 15 of 17 patients studied, the P_{ACO₂} of maximal expiration following natural breathing equaled or exceeded the arterial CO₂ tension. On the other hand, the measured arterial CO₂ tension never exceeded significantly the estimated P _{$\bar{V}$ CO₂} in all cases. Though Defares⁵⁾ recently calculated the cardiac output using the indirect Fick's principle in normal subjects, with the aid of the rebreathing method for the estimation of P _{$\bar{V}$ CO₂} and sampling the end-tidal air for the substitution of arterial CO₂ tension, the precision of the rebreathing method, as well as breathholding method, appeared to be too unsatisfactory for the determination of cardiac output. As mentioned above, the A-V CO₂ tension difference at rest is about 6 mm.Hg, and an accuracy of about 0.5 mm.Hg would be necessary for the determination of cardiac output. Moreover, the end-tidal P_{ACO₂} may be considerably lower than the arterial CO₂ tension in patients with pulmonary emphysema, which would make the determination of cardiac output by this method impractical or less accurate.

SUMMARY AND CONCLUSION

Continuous analysis of expired alveolar CO₂ tension, using a rapid infrared meter, was made in 10 normal subjects, and 20 patients with chronic pulmonary diseases. An analytical method similar to that previously described by Sivertson and Fowler was used. Arterial blood was sampled and arterial CO₂ tension was measured in 17 patients simultaneously with expired alveolar CO₂. Right heart catheterization was carried out in 38 patients with pulmonary emphysema.

(1) In many patients, the resting end-tidal CO₂ tension was frequently less than normal. In both normal subjects and patients, the upward slope of alveolar CO₂ tension decreased toward the end of forced expiration. However, in patients with emphysema a larger rate of increase in expired alveolar CO₂ tension, smaller expired volumes and the prolonged duration of forced expiration were observed. In patients, the apparent values of the difference between mixed venous and alveolar CO₂ tension were large and the percentage rates of decrease in the difference were normal. This probably indicates that perfusion is not reduced in the overventilated alveoli of the emphysematous lung. These results well coincided with Fowler's observations.

(2) In cases of pulmonary emphysema, the mean rates of increase in expired alveolar CO₂ tension observed during a forced expiration after hyperventilation, remained similar to those observed during a forced expiration after normal breathing. An expiratory level was elevated in patients with emphysema during

hyperventilation. Within the succeeding forced expiration, air-way resistance and pulmonary pressure must have been increased, consequently the ratio of pulmonary blood flow per alveolar lung volume should be reduced.

(3) In many patients, the end-tidal CO_2 tension was lower than the arterial CO_2 tension, but the maximal CO_2 tension of the forced expiration following normal breathing equaled or slightly exceeded the arterial CO_2 tension. On the other hand, the measured arterial CO_2 tension never exceeded the estimated mixed venous CO_2 tension significantly.

(4) In pulmonary emphysema, the elevated values of mixed venous CO_2 tension well correlated with the degree of pulmonary hypertension. This correlation is proposed for the use in estimating the pulmonary hypertension from the value of expired alveolar CO_2 tension in patients with a mixed venous CO_2 tension of more than 55 mm.Hg.

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