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ANALYSES OF BREATH-BY-BREATH RESPONSES OF VENTILATION TO CO_2 EMPLOYING $\dot{V}$-PCO_2 LOOPS

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Abstract. Computer techniques were employed to construct a respiratory control model in which the variables treated were programmed according to a series of mathematical equations, with the purpose of eliciting the relationship of $\dot{V}$-PCO_2 (minute ventilation-partial pressure of carbon dioxide) on a transient time basis. It was discovered that the transient $\dot{V}$-PCO_2 relationship has the shape of a loop half of which is for on-CO_2 and the other half for off-CO_2. Breath-by-breath ventilation was calculated by means of a home-made computer and the $\dot{V}$-PCO_2 relationship was monitored on an XY plotter. The transient $\dot{V}$-PCO_2 course also showed a loop which was quite similar in the general shape to the one traced employing theoretical analysis with an analog computer. This $\dot{V}$-PCO_2 loop may have potential usefulness to reveal mechanisms of respiratory control which may not be shown by the conventional $\dot{V}$-PCO_2 response curves.

INTRODUCTION

One of the areas in respiratory physiology that enjoyed progress in the past 25 years is the regulation of ventilation. Perhaps the beginning of the "rapid" phase of progress in our understanding of the regulatory mechanisms involved in ventilation coincided with the work of Gray (1946, *see* 1950) who, with a stroke of genius, put forward the first empirical quantitative equation to describe the chemical control of breathing of the "chemostat". Although the equation of Gray (1950) was based on earlier observations made up to that time and although this equation intrinsically and explicitly did not describe the mechanisms, it did stimu-

late much experimental work. Consequently, with more observation, Nielsen and Smith (1951), employing the plot of $\dot{V}$-PCO_2 response curves revealed that PO_2 and PCO_2 acted not "additively" as stimuli to ventilation.

The work of Nielsen and Smith (1951) was followed by many more observations along the same vein; some were made by the Oxford group who made an attempt to quantitate ventilation as functions of PO_2, PCO_2 and H^+ also with empirical equations (Lloyd and Cunningham 1962, Lloyd et al. 1958).

With the aid of computer techniques, Grodins et al. (1954), Grodins (1959), Grodins and James (1963), Grodins (1964) and Grodins, Buell and Bart (1967) first analysed in a more detailed fashion the effect of CO_2 and other stimuli on ventilation. Their work also was followed by many (Defares et al. 1960, Yamamoto 1960, Defares 1964, Edwards and Yamamoto 1965, Milhorn et al. 1965, Yamamoto and Raub 1967, Milhorn and Brown 1970, Yamamoto and Hori 1970). It seems clear and important that with our improving knowledge of respiration on the analytical level, great strides have been made in the quantitation of the respiratory control system.

However, most of the analyses are based on the "steady state" responses or "transient" responses but limited to the behavior of some variables as functions of time.

It occurred to us that if one can perform a "transient" study employing breath-by-breath analysis of ventilation response to, e.g. CO_2, perhaps more information can be obtained. This we have tried and the results we obtained dealing with $\dot{V}$ as a function of PCO_2 employing breath-by-breath response with both theoretical exposition and experimentation were somewhat "astonishing". And this communication gives the abbreviated version of our study of the respiratory control employing computer techniques.

THEORY

Our respiratory control model has in essence three compartments similar to that of Grodins, Buell and Bart (1967): the brain tissue (the CO_2 of which affects ventilation), the non-brain tissue (the metabolic rate of which affects oxygen demand and CO_2 production), and the lungs (the function of which is here mainly considered as a CO_2 eliminator).

Ten fundamental equations describing the relationships of the variables listed below (Table I) were developed on the bases of previous work done by Grodins et al. (1954), Grodins and James (1963), Defares, Derksen and Duyff (1960) and Defares (1964). Some of the values of the con-

stants were selected also according to that employed by Grodins et al. (1954), Grodins and James (1963) and Grodins, Buell and Bart (1967) (Table II).

TABLE I

Definition of symbols

A = alveolar
b = brain tissue
B = non-brain tissue
C = concentration, volume/volume
E = expired
$\dot{F}$ = volume/time (cardiac output)
I = inspired
M = quantity/time (metabolic rate)
$\dot{Q}$ = quantity/time
v = venous
V = volume
$\dot{V}$ = volume/time (ventilation)
$\dot{V}O_2$ = quantity/time (oxygen consumption)

TABLE II

Values of K's used

K's	Units	Standard values used
K_1	$\frac{\text{liter } CO_2}{\text{liter blood}} / \frac{\text{liter } CO_2}{\text{liter air}}$	3.20
K_2	liter CO_2 / liter blood	0.33
K_3	$\frac{\text{liter air}}{\text{sec}} / \frac{\text{liter } CO_2}{\text{liter brain tissue}}$	980.00
K_4	$\frac{\text{liter air}}{\text{sec}} / \frac{\text{liter } CO_2}{\text{sec}}$	25.00
K_5	$\frac{\text{liter blood}}{\text{sec}} / \frac{\text{liter } O_2}{\text{sec}}$	6.50
K_6	liter blood / sec	4.20
K_7	$\frac{\text{liter blood}}{\text{sec}} / \frac{(\text{liter } CO_2)^4}{(\text{liter blood})^4}$	15.00

CO_2 continuity–lung reservoir

$$C_I\dot{V}\text{-}\dot{Q}_E + \dot{Q}v_B + \dot{Q}v_b - \dot{Q}a = \dot{Q}_A \qquad (1)$$

Alveolar–expired CO_2 equilibrium

$$C_A = \frac{Q_A}{V_A} = \frac{\dot{Q}_E}{\dot{V}} \tag{2}$$

Alveolar–arterial equilibrium

$$Ca = \frac{\dot{Q}a}{\dot{F}} = K_1 C_A + K_2 \tag{3}$$

Brain tissue reservoir CO_2 continuity

$$\dot{Q}_b = M_b + \dot{Q}_a - \dot{Q}v_B \tag{4}$$

Non-brain tissue reservoir CO_2 continuity

$$\dot{Q}_B = M_B + \dot{Q}a - \dot{Q}v_B \tag{5}$$

Brain tissue–venous CO_2 equilibrium

$$C_b = \frac{\dot{Q}v_b}{\dot{F}_b} = \frac{Q_b}{V_b} \tag{6}$$

Non-brain tissue venous CO_2 equilibrium

$$C_B = \frac{\dot{Q}v_B}{\dot{F}_B} = \frac{Q_B}{V_B} \tag{7}$$

$\dot{V}$ controller

$$\dot{V} = K_3(C_b - C_{b(O)}) + K_4 M_B \tag{8}$$

Cardiac output

$$\dot{F} = \dot{F}_B + \dot{F}_b = K_5 \dot{V}o_2 + K_6 \tag{9}$$

Brain arterial blood flow

$$F_b = K_7 \overset{4}{Ca} \tag{10}$$

Attempts were made to manipulate these equations in order to explicitly depict the behaviour relating $\dot{V}$-PCO_2 on the breath-by-breath basis. Since the variation made by a single breath is of a very complex nature, we simplified the situation by solving $\dot{V}$ and C_A (concentration of alveolar CO_2) as function of time without the breath-by-breath oscillation. Thus, by combining equations 3, 4, 6, 8 and 10 with rearrangements of terms, the following differential equation is obtained:

$$\dot{C}_b + \frac{K_7 C_a^4}{V_b} C_b = \frac{M_b + K_7 C_a^5}{V_b} \tag{11}$$

The coefficient of C_b makes this equation non-linear. However, since for ordinary purposes, Ca varies not to a great extent (to affect the equation), an average value of Ca can be chosen to calculate this coefficient without altering the results of this equation. This simplification leads to the solution of $\dot{V}$ as follows:

$$\dot{V} = K_3 \left\{ C_a(\infty) - C_a(O) + \frac{M_b}{K_7} \left(\frac{1}{C_a^4(\infty)} - \frac{1}{C_a^4(O)} \right) \right\} \left\{ 1\text{-}\exp\left(- \frac{K' K_7 C_a^4 O}{V_b \Delta C_I} t \right) \right\} + K_4 M_B \tag{12}$$

which can be simplified to yield:

$$\dot{V} = K_3 \Delta C_a \left[1\text{-}\exp\left(\frac{t}{\tau} \right) \right] + K_4 M_B \tag{13}$$

where

$$\tau = \frac{V_b \Delta C_I}{K' K_7 C_a^4(O)} \tag{14}$$

Alveolar concentration of CO_2 (C_A) as a function of time during CO_2 inhalation was obtained by combining equations 1, 2, 3, 5 and 7, with rearranging of terms:

$$\ddot{C}_A + \left(\frac{\dot{V}}{V_A} \right) \dot{C}_A + \left(\frac{\ddot{V}}{V_A} \right) C_A = \frac{C_I \ddot{V} - V_B \ddot{C}_B}{V_A} \tag{15}$$

Both equations 11 and 15 are non-linear.

By linearizing equation 15, we obtain a second order solution for C_A as function of time.

$$C_A = \frac{K_3 \Delta C_a \Delta C_I}{\tau} + \left\{ - \frac{K_3 \Delta C_a \Delta C_I}{\tau} + C_A(O) \right\} \exp - \left(\frac{K_3 \Delta C_a + \tau K_4 M_B}{2 K'' \tau V_A} t \right) \sin \left(\frac{K_3 \Delta C_a}{V_A \tau} \right)^{\frac{1}{2}} t \quad (16)$$

$$\text{where} \quad \tau = \frac{V_b \Delta C_I}{K' K_7 C_a^4(O)} \quad (17)$$

These two equations of $\dot{V}$ and C_A as functions of time were exposed in graph form as shown in Fig. 1. This was done employing a TR 48 analog computer.

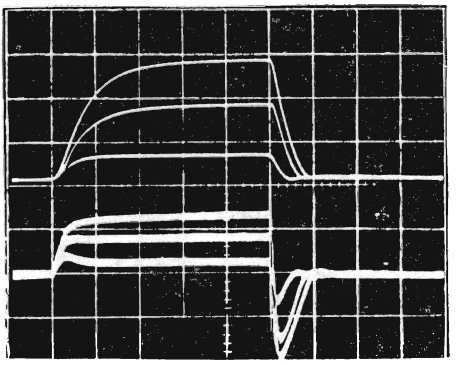

Fig. 1. The time course of $\dot{V}$ and $PACO_2$ traced as a function of time (each square=1 min). The upper three curves are $\dot{V}$'s for 0.07, 0.06 and 0.04 $FICO_2$. At the graded X-axis $\dot{V} = 0$, each square = 20 litres/min. The lower three curves are the $PACO_2$ responses. Each square = 10 mm Hg.

The complete diagram of the computer program is depicted in Fig. 2 which treats the system in accordance with the three-compartment concept.

The interesting point was: when V was plotted against C_A (which equals C_ACO_2 and with a factor can be changed into $PACO_2$) a loop appeared. Figure 3 shows five $\dot{V}$-$PACO_2$ loops when the F_ICO_2 is at 0.02, 0.04, 0.05, 0.06 and 0.07. The loops travel in a counter clockwise direction when CO_2 is on. In the graph at one o'clock (Fig. 3), ventilation reached a quasi "steady state".

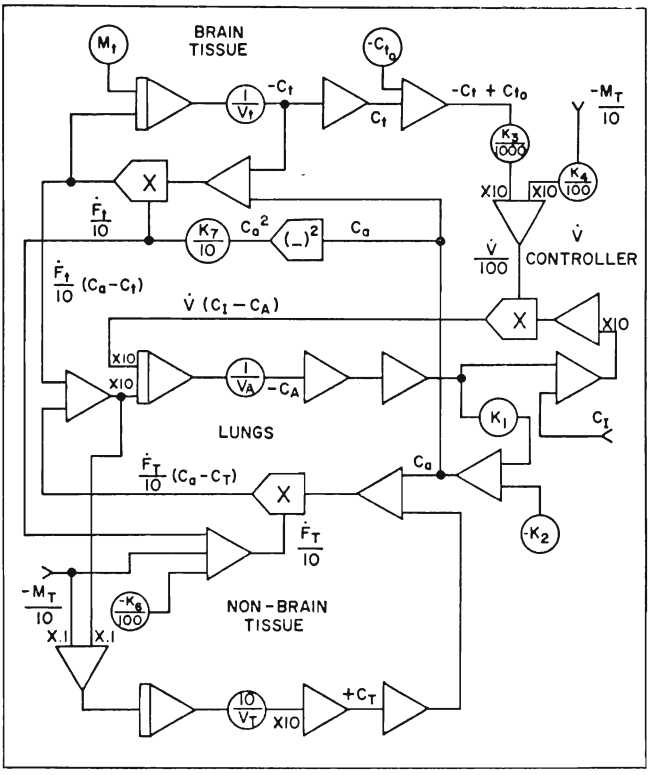

Fig. 2. Computer model of the respiratory system constructed from the fundamental equations. C_{α}^{2} reads C_{α}^{4}; t reads b; T reads B.

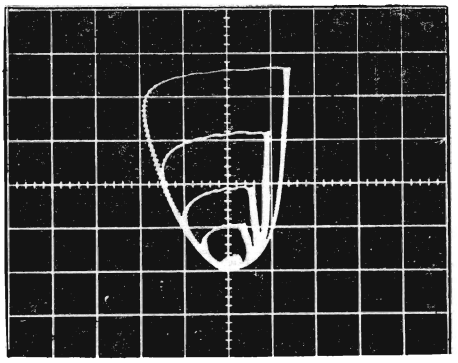

Fig. 3. Computer tracing of $\dot{V}$-PCO_2 loops with $F_ICO_2 = 0.02$ (smallest loop), 0.04, 0.05, 0.06 and 0.07. The graded Y-axis cuts the X-axis at 40 mm Hg PCO_2. Each square = 10 mm Hg PCO_2; increase to right and decrease to left. Ventilation at rest is 5 litres/min at a PCO_2 of 40 mm Hg. Each square of the Y-axis = 10 litres/min. The loop starts at 40 mm Hg PCO_2 and travels to right and upward when CO_2 is on. At "one o'clock" CO_2 is off. The sharp turn at one o'clock indicates a $\dot{V}$-PCO_2 loop travels anti-clockwise.

EXPERIMENTAL

Our experimental design was comparatively simple. Tidal volume was measured by means of a Fleisch-type pneumotachograph, the volume was integrated by a home-made computer (Fig. 4). Respiratory frequency was monitored by recording the duration between the beginning of inspiration of one breath to that of the following breath. The quotient of the tidal

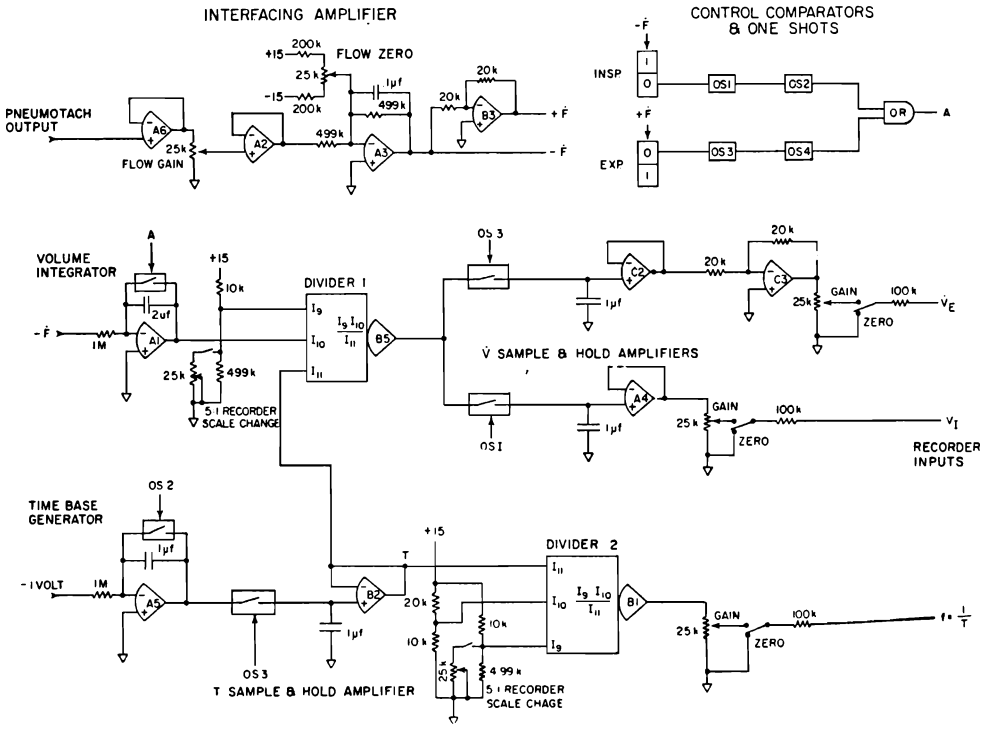

Fig. 4. Schematic diagram of a home-made computer for breath-by-breath computation of ventilation.

volume and the duration to the next breath (Fig. 5) gives the breath-by-breath ventilation. The tracings obtained by this simple computer are shown in Fig. 6 as exposed on a memoscope.

The breath-by-breath changes of ventilation as a function of PCO_2 is exhibited on an XY plotter. One of the experiments is shown in Fig. 7. This experiment was done on one of the authors (FFK) while breathing 5% CO_2 in the inspired air.

There are distinctively four phases (if not more) which can be identified on this V-PCO_2 loop which is in very close agreement to that obtained by means of the computer respiratory control model.

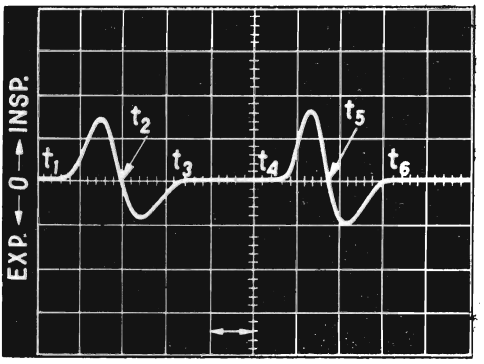

Fig. 5. The actual oscillographic tracing of two successive breaths employing a pneumotachograph, inspiration upward, expiration downward. $\leftarrow\rightarrow$=1 sec; $T = t_5 - t_2$; $f = \frac{1}{T}$

When CO_2 is off, CO_2 decreases sharply while ventilation changes very little (the horizontal portion of the loop). If one connects the sharp bend at one clock of the loops, a usual $\dot{V}$-PCO_2 response curve is obtained.

It can be seen from the graph that when CO_2 is on at zero time (Fig. 7), ventilation changed little while $PACO_2$ increased significantly. This is the first phase: the on-CO_2-iso-ventilation phase. After 30 sec from the onset of CO_2 administration $PACO_2$ changed little while ventilation

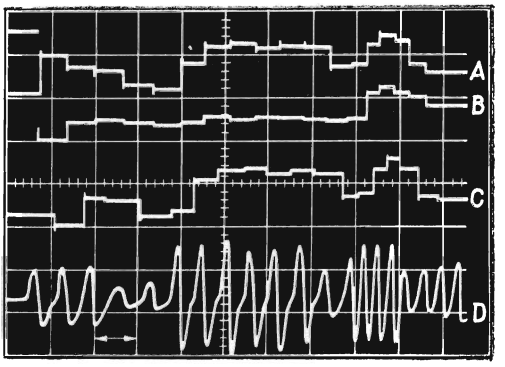

Fig. 6. Oscillographic tracings. *A*, V_I; *B*, *f*; *C*, $\dot{V}_E$; *D*, pneumotachogram; $\leftarrow\rightarrow$, 1 sec.

changed significantly. This is the second phase: the iso-$PACO_2$ phase. It should be noted that when F_ICO_2 is more or less than 0.05, this second phase of the $\dot{V}$-PCO_2 loop may bend inward or outward (*see* Fig. 3). With the termination of CO_2 inhalation $PACO_2$ decreased significantly while ventilation changed little. This is the third phase: the off-CO_2-iso-ventilation phase. Then the ventilation travelled roughly along the isometabolic hyperbola and returned to the control value. This is the restitution phase.

There was definitely oscillatory phenomenon. The general direction of this $\dot{V}$-PCO_2 loop is counter-clockwise and it oscillates along this general direction. For example, the ventilation value along phase two at 70 sec

after onset was lower than that at 60 sec and at 170 sec was lower than at 150 sec (Fig. 7).

Figures 8 and 9 show some additional $\dot{V}$-PCO_2 loops in sheep during CO_2 inhalation. With and without vagotomy, these loops are different from that in man vagotomy in sheep seems to disturb this $\dot{V}$-PCO_2 loop. Further experimentation is necessary to reveal the "obscure" shapes, if any, of the $\dot{V}$-PCO_2 loops caused by abnormal states. For example, in these sheep on autopsy there was inevitably pulmonary oedema. And during these experiments the sheep were on their backs, it was not impossible that fluid may accumulate in the lungs during experiments. If

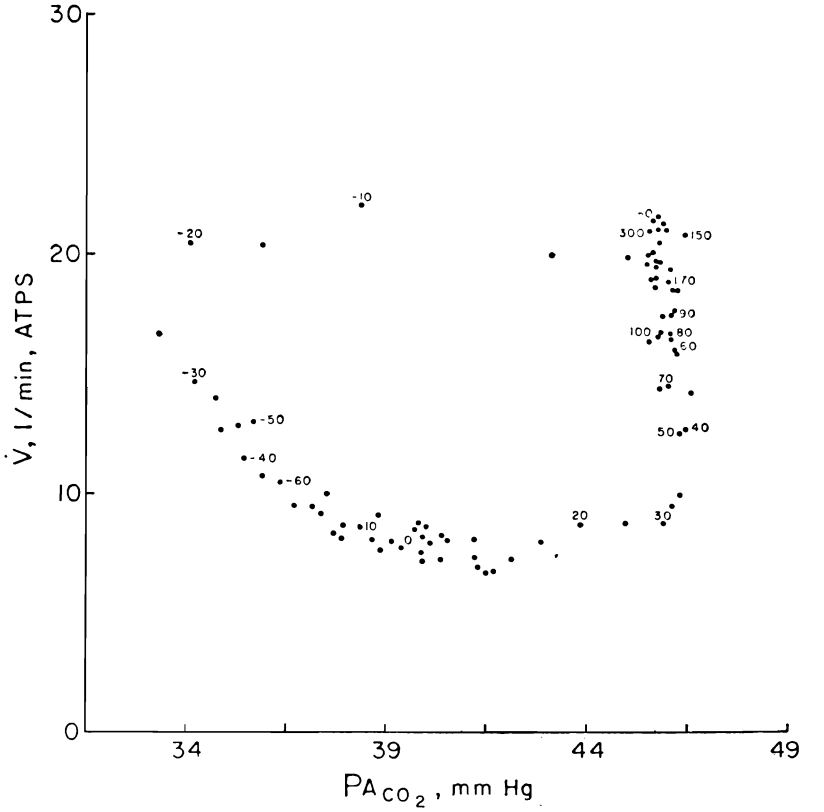

Fig. 7. $\dot{V}$-$PACO_2$ loop in man with $FICO_2 = 0.05$ (FFK subject). The numbers in the graph are time in seconds after the administration of CO_2 in the inspired air (without −), and after the termination of CO_2 (with −). Note the four possible components of this loop for analysis: (i) the on-CO_2-iso-ventilation phase (during the mixing of CO_2 intrapulmonarily); (ii) the iso-$PACO_2$ phase (during diffusion and mixing of blood, which eventually "saturates" the chemoreceptors); (iii) the off-CO_2-iso-ventilation phase (during CO_2 evacuation from lungs), and (iv) the restitution phase (blood gas and alveolar PCO_2 both returned to the resting point).

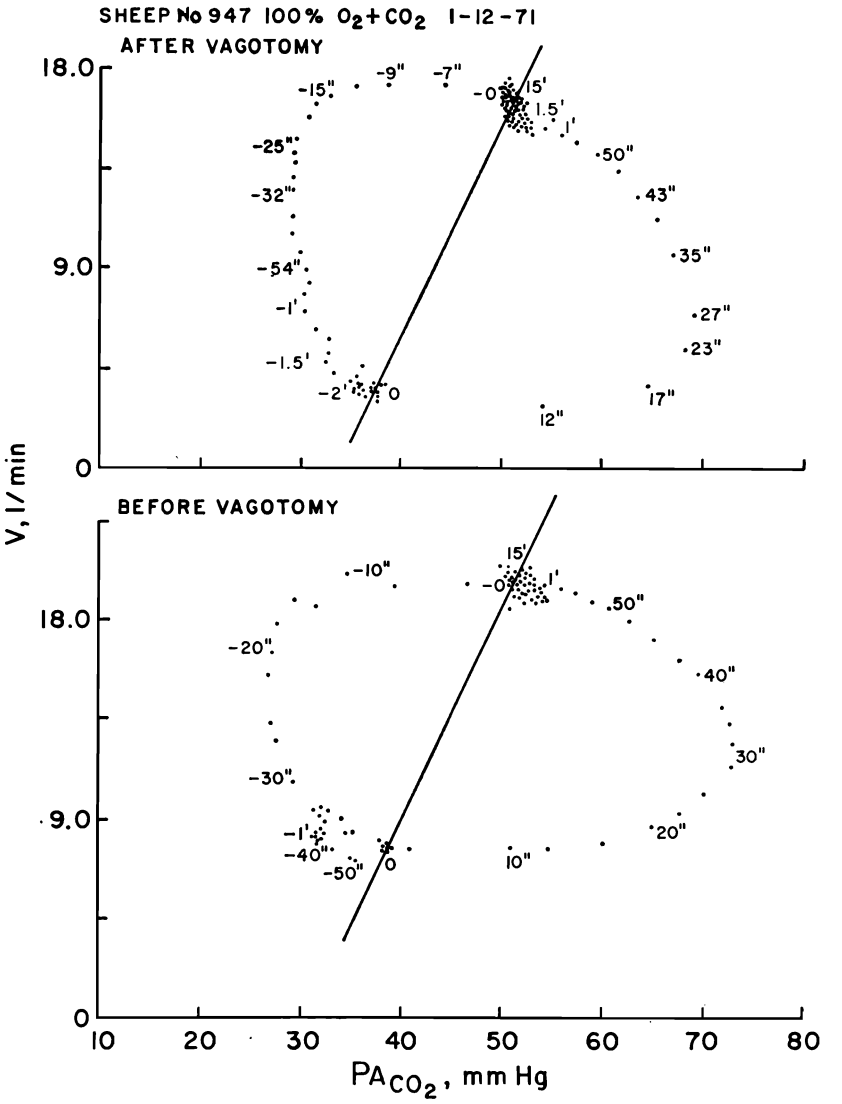

Fig. 8. $\dot{V}$-$PACO_2$ loops in sheep with and without bilateral cervical vagotomy. The numbers in the graphs are seconds (") and minutes ('). The numbers with (—) signs in front of them are times after CO_2 termination. The lines in the graph are the $\dot{V}$-PCO_2 response curves.

so, the slanting path of the second phase could be "attributed" to pulmonary oedema which may impede diffusion.

It can be said, however, that there seems to be potential usefulness in applying the $\dot{V}$-PCO_2 loop for experiments in which before we "only" use V-PCO_2 curves.

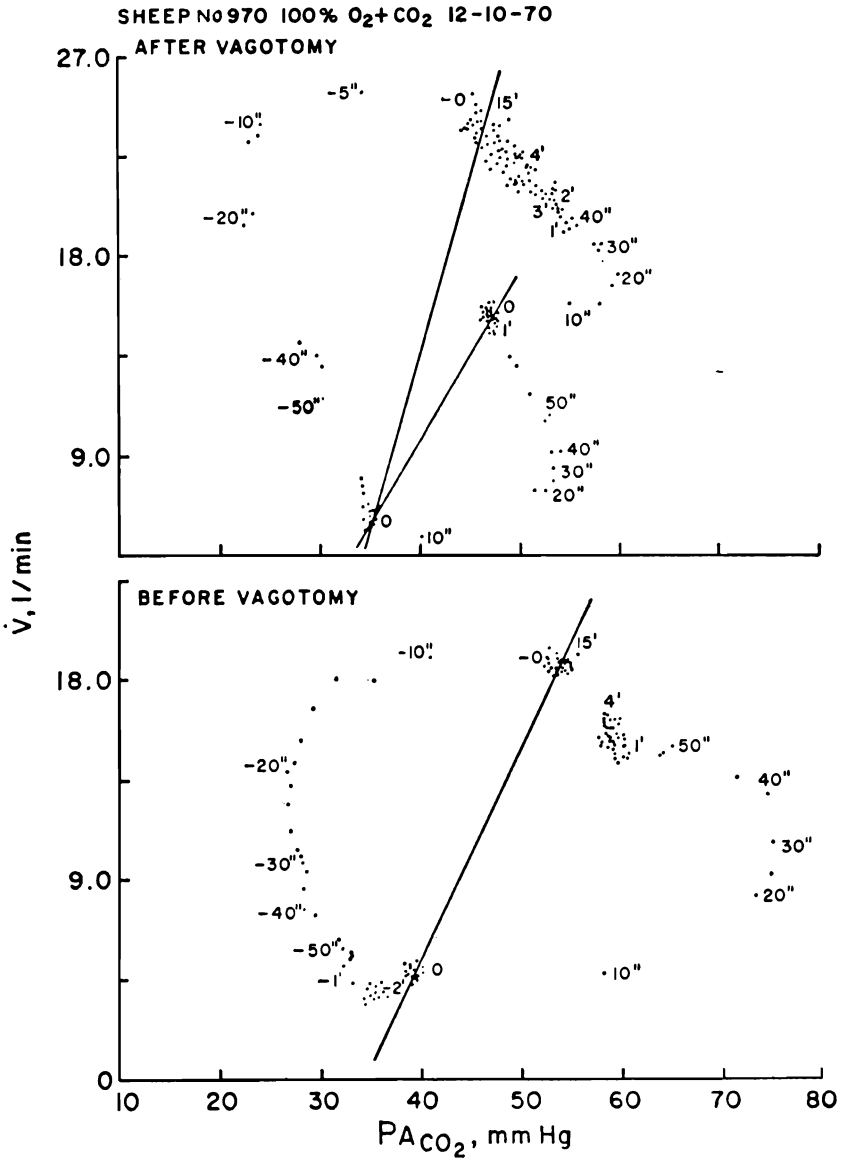

Fig. 9. $\dot{V}$-PCO_2 loops in sheep with and without bilateral cervical vagotomy (for details *see* legend of Fig. 8), with two levels of CO_2 inhalation. The second level of CO_2 was super imposed on the first one, so there is no restitution phase for the first level of low CO_2. The $\dot{V}$-PCO_2 response curve is higher after vagotomy.

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ERRATA

Page 155, line 11 of Abstract:
instead of (V/V_T) *should be* $(\dot{V}/V_T)$

Page 173 first line from bottom should read:
use $\dot{V}$-PCO_2 curves.

Page 191, line 19 from top:
instead of bandpass 8–1,0000 cycle/sec *should be* bandpass 8–1,000 cycle/sec