ACTA NEUROBIOL. EXP. 1973, 33: 177-188

Lecture delivered at Symposium "Neural control of breathing"
held in Warszawa, August 1971

SOME OBSERVATIONS ON THE RELATION BETWEEN VENTILATION, TIDAL VOLUME AND FREQUENCY IN MAN IN VARIOUS STEADY AND TRANSIENT STATES

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Since the work of Hey, Lloyd, Cunningham, Jukes and Bolton (1966) it has been apparent that in intact man there is a unique relation between *mean* ventilation ($\dot{V}_E$) and the *mean* tidal volume (V_T) and frequency (f) (or its reciprocal, the time for a respiratory cycle T). This *steady-state* relation (the Hey relation) is essentially constant for any one individual whatever combination of common respiratory stimuli is contributing to the observed ventilation, except that in the case of hyperthermia there is a slightly increased emphasis on change of frequency. The Hey relation rarely survives conscious interference by the subject: thus when, in experiments of the kind described elsewhere (Cunningham et al., this Symposium), the experimenters suspected that a subject was unduly worried by the procedures or was paying too much attention to them, it was common to find subsequently that the Hey relation was not followed. Conversely, the results on relaxed subjects, especially those fully occupied with their reading material, nearly always showed little scatter when plotted in this way.

Any pair of the three primary variables $\dot{V}_E$, V_T, f (or T) may be plotted against each other, and constant values of the third variable can be indicated, e. g. Fig. 1: the faint dashed lines show the third variable. Hey et al. found the relation between $\dot{V}_E$ and V_T convenient since it is linear over the middle range, and the straight lines indicating constant frequency radiate from the origin (Fig. 1, top left). At the time when their paper

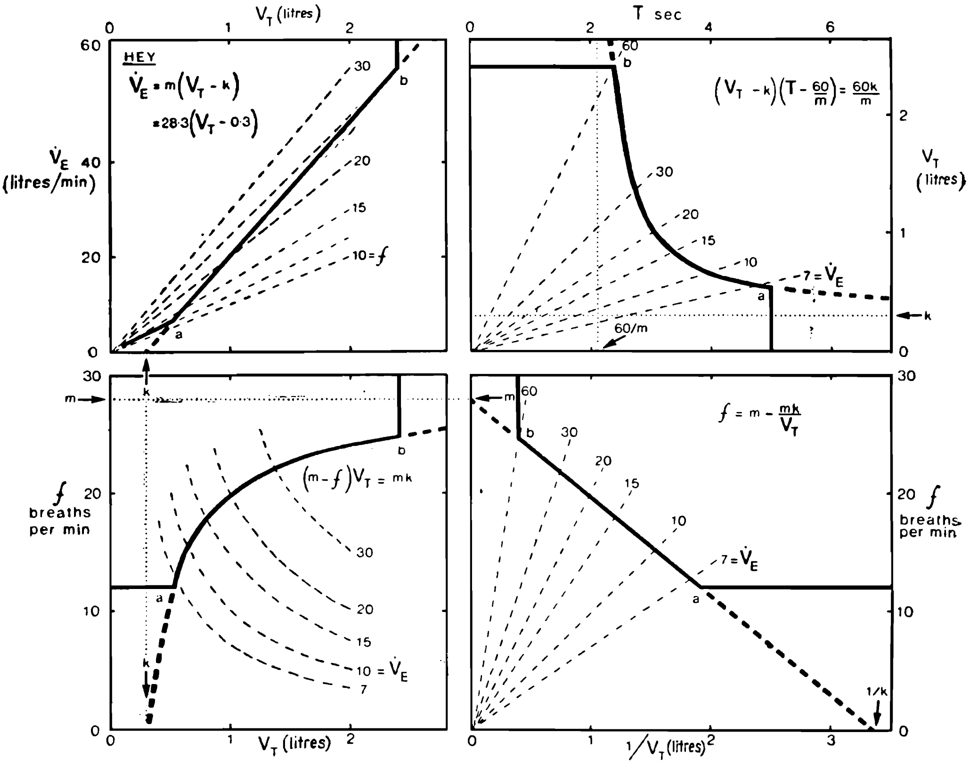

Fig. 1. Four versions of the Hey–Euler relation. The heavy full lines are based on the mean experimental results of Hey et al. (1966). Over a middle range (between *a* and *b* in the Figures) the mean values found for the slope (*m*) and intercept (*k*) in the top left panel define the lines drawn in the other three panels. In each panel, the equation of the curve for the middle range is shown in terms of parameters *m* and *k*. At low ventilation $\dot{V}_E$ (lower than at point *a*), frequency *f* is shown as constant, and at high ventilation (higher than at point *b*) tidal volume V_T is shown as constant. The heavy dashed lines are extrapolations, outside the physiological range, to intercepts and towards asymptotes which are indicated by dotted lines. The thinner dashed lines indicate constant values of the third variable which is not represented along the axes: *f* at the top left and $\dot{V}_E$ in the other three Figures. Parameter *m* in the top left Figure, besides being the slope of the heavy line, is the limiting value of respiratory frequency for so long as the relation governing the middle range holds: therefore *m* is also the horizontal asymptote is the lower left Figure, and the vertical intercept in the lower right Figure, and its reciprocal $60/m$ is the vertical asymptote in the upper right Figure. *k* and its reciprocal $1/k$ are the horizontal intercepts on the V_T axis (upper and lower left) and the $1/V_T$ axis (lower right) respectively; *k* is also the horizontal asymptote in the upper right. Area constants and slopes are 60 k/m, mk and $-mk$ for top right, and lower left and right respectively.

was published Hey et al. were unaware of the paper of Milic Emili and Cajani (1957) in which essentially the same plot appeared, probably for the first time. In accordance with the views of Euler and his collaborators (Euler et al. 1970, Clark and Euler 1970) we would agree that Hey's linear plot describes the situation over only the middle range. At high ventilation a break point b is reached, beyond which V_T increases no further, only *f* changing. As ventilation falls towards resting values, a point or region may be reached (*a* in Fig. 1, top left) below which mean *f* is constant and change of mean $\dot{V}_E$ is attributable solely to change of mean V_T: we emphasize mean values because in this region there is usually great variation from one breath to another. Recent work on man and cat (Clark and Euler 1970) provides a physiological basis for regarding the low-ventilation, constant-frequency part as being distinct rather than continuous with the middle region. It will not be discussed further in this communication. The middle region was described by Hey et al. (1966):[1]

$$\dot{V}_E = m(V_T - k)$$

Figures 2 and 3 show three examples from a large number of experiments that indicate how well a single straight line describes data such as these: it appears to us that the relation is also effectively linear in the anaesthetised cat during CO_2 inhalation at normal or raised body temperature (Fig. 2*A*, 3 and 4 of Euler et al. 1970), though the authors themselves expressed uncertainty on this point.

A consequence of this linearity is that the other ways of expressing the inter-relations of the three variables over the middle range, whether themselves linear or hyperbolic, can all be described explicitly in terms of the two parameters *m* and *k*. Three such other forms are shown in Fig. 1. Before outlining their special features its is, perhaps, worth mentioning that parameter *m* (Euler's *k*) appears to be a limiting frequency which *f* approaches but never reaches until after the break point, *b*, has been reached and passed. Hey et al. found that *m* is well correlated with parameter *D* of Lloyd, Jukes and Cunningham (1958), which expresses ventilatory sensitivity to CO_2 in the complete absence of hypoxia (possibly pure central chemosensitivity, *see* Loeschcke, this Symposium). Thus two different types of control, namely of pattern and of overall ventilation volume, may be physiologically linked in some way as yet unknown: *m* therefore could be of some general physiological significance. The significance of parameter *k* (V_0 of Euler) remains obscure.

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[1] Note that Euler et al. (1970) used *k* for the slope constant of the same linear relation. Their published equation is $V_E = k\,(V_T - V_0)$.

Figure 1, top right, illustrates a plot like that used by Euler et al. (1970). A closely related plot, in which the abscissa is time for inspiration T_i, is the basis for an elegant model (Clark and Euler 1970). We would readily agree that conceptually this plot is in most respects preferable to that of Hey. Two points should, however, be stressed. First, inasmuch as Hey's parameter m has reality (*see* above) the V_T, T plot must incorporate a minimum value of $T = 60/m$, to which the curve is asymptotic, as shown in the Figure. A corresponding asymptote in a plot involving f was recognised by Euler et al. (1970). It may further be shown that, given the effective linearity of Hey's plot, a vertical asymptote at a positive value of inspiratory time T_i (homologous to $60/m$ in Fig. 1, top right) is a necessary part of the expression for the relation between V_T and T_i of Clark and Euler (1970). Secondly, Euler proposed that the middle hyperbolic range of, e.g. Fig. 1, top right, is a manifestation of the Hering–Breuer reflex. If this is so, it is plausible to suggest that the area constant, $60\ k/m$, is related quantitatively to Hering–Breuer reflex sensitivity.

The lower left Figure shows what are usually regarded as the fundamental variables V_T and f plotted against each other. This plot has the practical disadvantage that both the lines of equal ventilation and the heavy line that represents Hey's relation are curves.

The lower right-hand Figure is a double reciprocal plot of the top right-hand Figure, $f(= 1/T)$ against $1/V_T$. In it the Hey relation appears as a straight line of negative slope while the constant ventilation lines are also straight, radiate from the origin and have a positive slope. Linear regressions and correlations may be used on this diagram, as will appear later.

The remainder of this paper is concerned with the analysis of experimental data in terms of these diagrams. The analysis has emerged as a by-product of experimental work designed for other purposes. We propose to deal first with the effects of patterns of blood gas oscillation on the Hey relation, secondly, with the breath-by-breath behaviour of V_T and T and its interaction with the Hey relation, and thirdly, with the response to respiratory transients.

Steady state

The effects of various patterns of blood-gas oscillation on the ventilation were described in our paper on Tuesday morning. Figure 2 shows two Hey plots of results obtained during simulated tube breathing, and Fig. 3 shows a Hey plot and a plot of f against $1/V_T$ for another experiment from the same series. *Mean* V_T and *mean* f or T during such periods

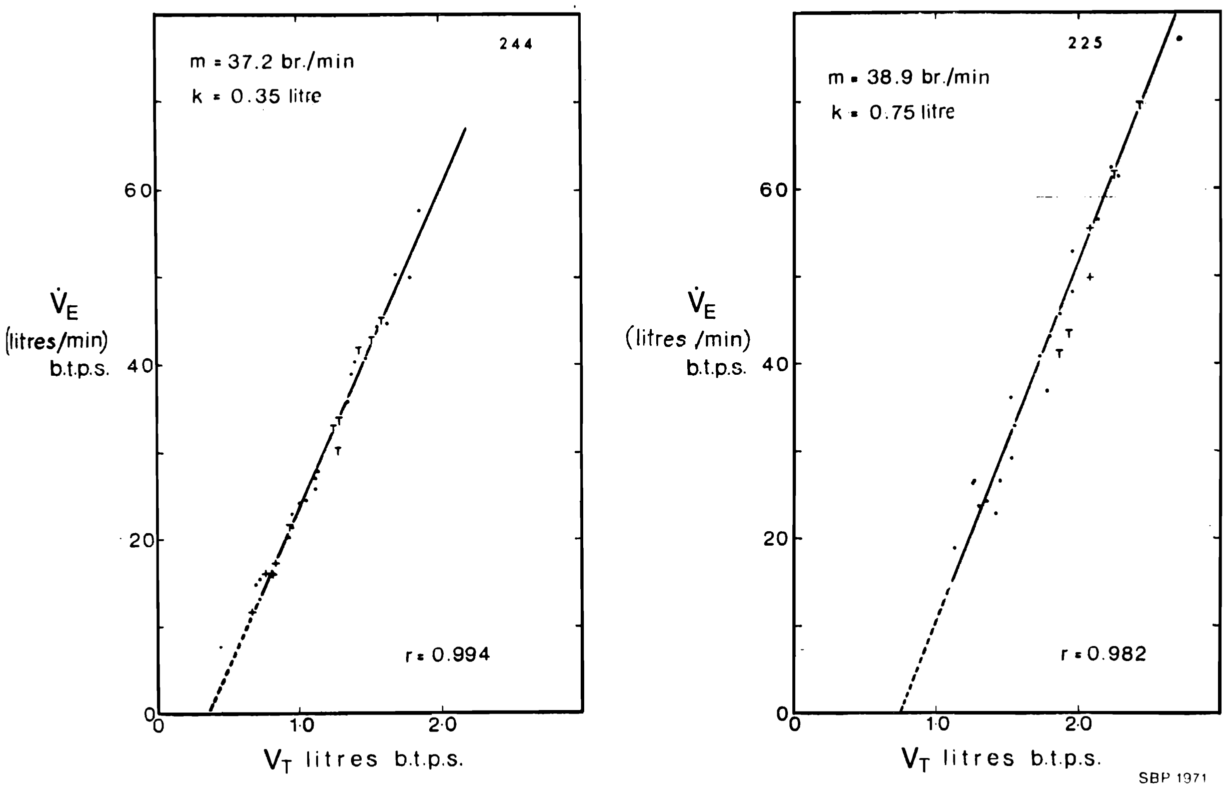

Fig. 2. Hey plots ($\dot{V}_E$ against V_T) for two subjects in whom comparisons were made between *T* "simulated tube breathing"; +, "reversed simulated tube breathing"; and ●, conventional CO_2 inhalation, all in moderate hypoxia (*see* Cunningham et al., this Symposium). The different kinds of points, all of them mean values in steady states, appear to lie on single straight lines, and thus the peculiar time pattern of alveolar PCO_2 found in tube breathing, while it affects the level of ventilation, does not affect the unique relations between $\dot{V}_E$, V_T and *f*.

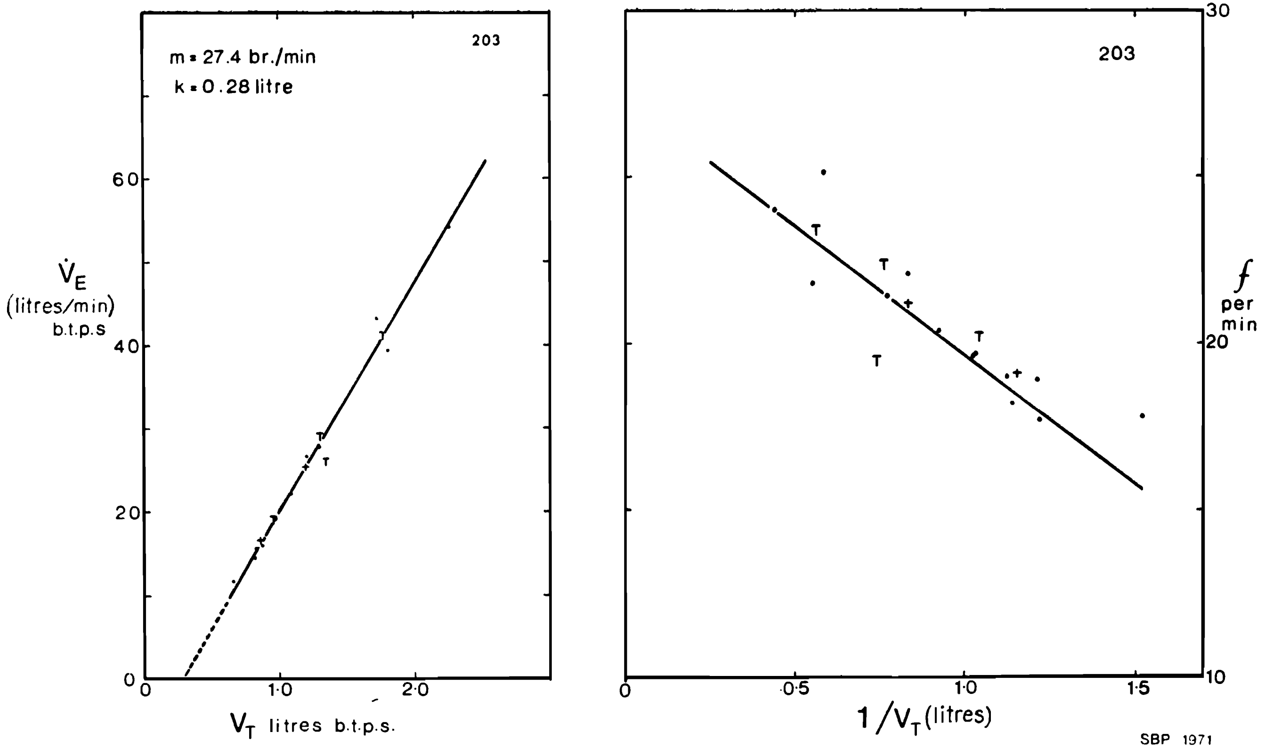

Fig. 3. Left: Hey plot for another subject; explanation as for Fig. 2. Right: same points plotted as f vs. $1/V_T$.

of tube breathing, simulated tube breathing, or reversed tube breathing, with enhanced or depressed ventilation, follow the Hey relation however plotted. In other words, the oscillatory component of the chemical drive is treated *on average* in the same way as the steady component in the computation by the respiratory centre of the combination of V_T and T required for any given $\dot{V}_E$ in the steady state. In the short term, however, the relation is unstable, i.e. shows hunting, especially in tube breathing, and the breath-by-breath V_T, f relation, which we shall now describe is very different from the steady-state relation dealt with so far.

Breath-by-breath analysis: individual breaths

The breath-by-breath relation between V_T and T or f in resting man breathing air has been described by Priban (1963) and by Dejours et al. (1966), and for hypercapnic man by Priban (1963). In 9 out of 13 experiments on 11 normal subjects, Priban found a significant negative correlation ($p < 0.05$ or better) between V_T and f (*see* Fig. 1, lower left, faint dashed constant-$\dot{V}_E$ line). Dejours et al. (1966) found effectively the same thing, namely a significant positive correlation between V_T and T (*see* Fig. 1, upper right, faint dashed constant-$\dot{V}_E$ line, $p < 0.05$) in 8 out of 11 periods of air breathing in 4 subjects. The implication of these findings is that breath-to-breath variations in $\dot{V}_E$ are less than would occur if V_T and T were varying independently. A good example of such behaviour is shown by the anaesthetised vagotomised cat under conditions of thermal polypnoea in high oxygen (von Euler et al. 1970). Any form of Hey's plot will demonstrate that such hunting in V_T and f at constant $\dot{V}_E$ is across rather than along the line describing the steady-state relations at various levels of chemical drive. The f vs. $1/V_T$ version of the plot (Fig. 1, lower right) has the advantage for this purpose that both Hey's steady-state and Priban's breath-to-breath relations appear as straight lines with negative and positive slopes respectively, and that the plot involves the two primary variables.

There are, then, these two opposed relations, one for the steady state and the other over short periods, and we shall now consider them in relation to experimental values of $\dot{V}_E$, V_T and f on 6 of our subjects in three situations: first, alternate breaths of high and low CO_2 in hypoxia (PAO_2 ~ 55 torr) given in such a way as to produce an alternate-breath oscillation in $PACO_2$ with an amplitude of about 12–13 torr, secondly, conventional CO_2 breathing in hypoxia (PAO_2 ~ 55 torr), and thirdly, alternate breaths of high and low CO_2 in high oxygen. In the last of these states, as already described (Cunningham et al. 1973), the ventilation does not follow the oscillations, probably because the arterial chemoreceptors are inactivated by the hyperoxia and the intracranial receptors probably see only the mean blood PCO_2. Such periods may therefore be regarded as indistinguishable from periods of response to steady hypercapnic hyperoxia.

We have determined the correlation between f and $1/V_T$ for the breath-by-breath values of these variables in the three states with the following results. In 7 out of 11 periods (50 or more consecutive breaths) of conventional CO_2 breathing in hypoxia and in 5 out of 6 periods of hyperoxic alternate-breath CO_2 oscillations significant positive correlations ($p < 0.05$ or better) were found. Significant positive correlations were also seen in 6 out of 10 periods of hypoxic alternate-breath CO_2 oscillations; it will be recalled that only in the latter did the oscillatory signal produce reflex ventilatory oscillations. In general, it appears that, on a breath-to-breath basis, the Priban-type positive correlation takes precedence over the Hey-type negative correlation. A further significant point emerges, however, when the common correlation coefficients for each type of experiment are calculated by means of Fisher's Z transformation. The results may be summarized as follows:

Table of common correlation coefficients between f and $1/V_T$ (Fisher Z transformation)

	$\bar{r}$	95% confidence limits
Hypoxic alternate-breath CO_2 oscillations	+0.191	0.120-0.259
Hyperoxic alternate-breath CO_2 oscillations	+0.386	0.309-0.458
Hypoxic conventional CO_2 breathing	+0.327	0.265-0.386
Hypoxic tube breathing	+0.635	0.586-0.679

All the common correlation coefficients are positive and significantly different from zero. The correlation coefficients for the hyperoxic alternate-breath CO_2 oscillations and the hypoxic conventional periods are not significantly different from each other. This is to be expected from the hypothesis that the respiratory system is insensitive to alternate breaths of high and low CO_2 in high oxygen, only the mean CO_2 level being detected. The correlation coefficient for the hypoxic alternate-breath CO_2 oscillation, however, though itself significant, is nevertheless significantly lower than the other two. This finding may be interpreted as being a compromise between the attempts of the respiratory system to follow a fluctuation in chemical drive which, in the steady state, would be associated with a Hey-type negative correlation, and the Priban-type positive correlation seen when chemical drive is constant, which tends to minimise breath-to-breath variations in $\dot{V}_E$.

The last line in the table is from subjects breathing a mildly hypoxic gas mixture through a 1200 cc dead space. The mean steady values follow the Hey relation (Fig. 2 and 3; f and $1/V_T$ *negatively* correlated), but the high *positive* correlation coefficient for the breath-by-breath values in any one steady state indicates that in this situation too the hunting occurs reciprocally between V_T and f, and thus breath-by-breath variation in $\dot{V}_E$ is minimised, as described by Priban.

Mean breath-by-breath responses to step changes of inspired gas

For the last part of this communication we make use of the first set of experiments described in our other paper in this volume, namely $\dot{V}_E$, V_T and f for the eight breaths immediately following sudden removal of CO_2 against steady backgrounds of hypoxia or hyperoxia, or sudden relief of hypercapnic hypoxia by two breaths of CO_2-containing oxygen[2]. In this analysis we use mean values, each mean comprising from 23 to 52 individual breaths at a nearly constant interval after the step change of inspired gas mixture. It may be argued that this kind of averaging minimises the Priban-type variations in V_T and f which, for the present purpose, may be regarded as random: thus the effects of the changing chemical drive are clarified and may be compared with a standard Hey-type relation. Two examples are shown in Fig. 4. Below $\dot{V}_E$ is plotted against V_T (*see* Fig. 1, top left). The dashed line is the probable Hey line, as explained in the legend. The full line is the reduced major axis (Kermack and Haldane 1950): 6 out of 9 such lines are clearly not significantly different from the constant frequency line (which, unlike the Hey line, passes through the origin (*see* Fig. 1, top left). At the top of Fig. 4 the same data are plotted as f against $1/V_T$ and here the direction of movement appears to be nearly parallel to the $1/V_T$ axis rather than to the Hey line. This was so for 6 out of the 9 plots. It thus appears that the immediate response of the ventilation to step change of chemical drive may often be achieved by a temporary departure from the Hey relation, the fall of V_T being unaccompanied by the appropriate fall in frequency for the first eight breaths. There are as yet no data which indicate how long it takes for the combination of mean V_T and mean f appropriate to the new level of chemical drive to be re-established. However, Loeschcke et al. (1963) have reported that at the on- and off-transient of CO_2 inhalation in man V_T becomes steady more quickly than $\dot{V}_E$ and thus than f. Their experiments were conducted over a larger time scale than ours, and were not concerned with breath-by-breath changes.

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[2] We are grateful to Dr J. P. Miller for permission to use these data.

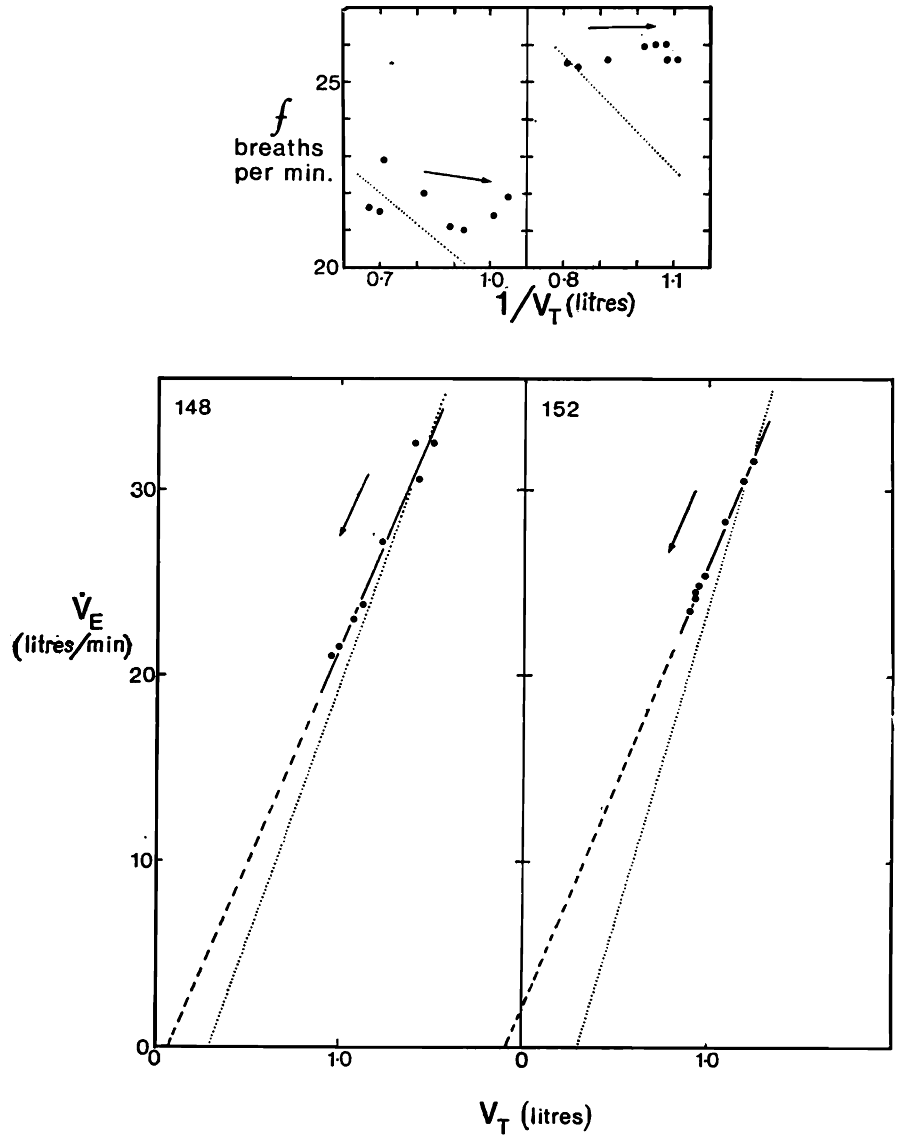

Fig. 4. The first 8 breaths of a respiratory transient (sudden withdrawal of CO_2 from a hypercapnic hypoxic gas mixture), mean values for 29 and 52 determinations on subjects 148 and 152 respectively. As explained in the text, the averaging of many determinations for each breath eliminates the "Priban-type" scatter and makes it easier to judge whether the initial change follows the Hey relation. Below: $\dot{V}_E$, vs. V_T. The dotted lines show the probable vicinities of the Hey lines, which were not determined experimentally: these lines join the mean values for the first three (left) and the first two points (right) to an assumed horizontal intercept (k) of 0.3 litre. The full lines and their dashed extensions are the reduced major axes. Since these pass close to the origin it appears that the transient fall of V_E occurs at essentially constant f. Above, same data plotted as f vs. $1/V_T$, which shows more clearly the tendency of f to remain constant. It thus appears that the initial change of $\dot{V}_E$ is due to a fall of V_T with no concomitant change of f. Four out of seven other sets of determinations followed the same trend (From Miller 1966.)

CONCLUDING REMARKS

The experiments referred to were designed for other purposes and the data are in some respects incomplete. Nevertheless, certain broad conclusion are possible: (i) The adjustment of mean V_T and f to that "appropriate" to the level of ventilation occurs with the strange alveolar time pattern of tube breathing just as in "conventional" breathing. (ii) This adjustment applies only to mean, steady-state values: from moment to moment, V_T and f commonly vary reciprocally in a way that results in a stabilisation of V_E, as described by Priban. (iii) In response to certain kinds of step changes of chemical drive although the ventilation was high enough for the values to fall on the hyperbolic part of von Euler's curve (*see* Fig. 1, top right) the early changes in pattern commonly follow neither Hey's nor Priban's relation, being achieved by change of V_T at nearly constant frequency.

The work of Euler et al. (1970) shows that the vagus is necessary for the maintenance of the Hey–Euler relation in the anaesthetised cat: the Priban-type hunting, however, was seen by these workers in a vagotomised animal.

The ultimate description of the respiratory neural organization will have to include a mechanism which shows the properties described in this communication. There are clues as to the nature of the peripheral part of the mechanism, but apparently none at present as to the exact location or nature of the central components.

Dr C. von Euler kindly read the manuscript of this communication: while in no way associating him with the views expressed here, we wish to express our gratitude for his helpful comments. S. B. Pearson was supported by the Medical Research Council.

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