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THE RELATION BETWEEN TIDAL VOLUME AND INSPIRATORY AND EXPIRATORY TIMES DURING STEADY-STATE CARBON DIOXIDE INHALATION IN MAN

BY W. N. GARDNER

From the University Laboratory of Physiology, Parks Road, Oxford

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SUMMARY

1. Ambiguities and discrepancies in the published descriptions of the patterns of breathing in man have been re-investigated.

Steady-state hyperpnoea during rest was induced in normal subjects of both sexes by means of CO_2 inhalation, usually in high O_2, but sometimes in low ($P_{A,\,O_2} \sim 200$ and 55 torr respectively).

2. The relations between mean tidal volume $\bar{V}_T$ and mean times for inspiration $\bar{T}_I$ and expiration $\bar{T}_E$ were satisfactorily divided into lower and upper parts (ranges 1 and 2) in nineteen out of thirty-three experiments using an objective least-squares method, and polynomials were fitted separately to each of the following pairs of variables $\bar{V}_{T,\text{lower}}$, $\bar{T}_I$; $\bar{V}_{T,\text{lower}}$, $\bar{T}_E$; $\bar{V}_{T,\text{upper}}$, $\bar{T}_I$; $\bar{V}_{T,\text{upper}}$, $\bar{T}_E$.

3. The breakpoints occurred when $\bar{V}_T$ was about one third of vital capacity, but there was much variation between subjects.

4. In range 2, $\bar{V}_T$ was inversely related to both $\bar{T}_I$ and $\bar{T}_E$ and there appeared to be linkage between $\bar{T}_I$ and $\bar{T}_E$, all as described by Clark & Euler (1972). The relation suggested by Hey, Lloyd, Cunningham, Jukes & Bolton (1966) over range 2 was not confirmed.

5. The main part of the relation described by Hey *et al.* (1966) is concerned with range 1. Here the relation between $\bar{V}_T$ and $\bar{T}_I$ was variable; slight, but significant negative correlation predominated. $\bar{V}_T$ was, on the other hand, strongly and inversely related to $\bar{T}_E$, and plots of $(\bar{T}_E - \bar{T}_I)$ against $\bar{V}_T$ over both ranges showed even less scatter. Hence (*a*) $\bar{T}_E$ is probably related to $\bar{V}_T$ through two mechanisms, one involving a link with T_I and another prominent one being quite independent of T_I, (*b*) most changes of respiratory frequency in normal man are brought about by change of T_E rather than of T_I, and (*c*) there is no region of constant frequency as implied by Clark & Euler (1972).

INTRODUCTION

In conscious man, when mean ventilation ($\bar{V}$) changes, its constituent mean tidal volume ($\bar{V}_\mathrm{T}$) and breath duration ($\bar{T}_\mathrm{T}$) change in a highly predictable way that is characteristic for any one individual; in most situations it is independent of the nature of the drive or the combination of drives producing the ventilation (Hey *et al.* 1966; Patrick & Howard, 1972). In hypercapnia produced by rebreathing, the breathing pattern of anaesthetized cats (Euler, Herrero & Wexler, 1970; Clark & Euler, 1972; Widdicombe & Winning, 1974) and awake men (Clark & Euler, 1972) appears superficially to behave as described for the steady state by Hey *et al.* (1966). As Fig. 1 shows, however, separation of $\bar{T}_\mathrm{T}$ into its mean inspiratory and expiratory components ($\bar{T}_\mathrm{I}$ and $\bar{T}_\mathrm{E}$) reveals discrepancies between the descriptions of Hey *et al.* (1966) and of Clark & Euler (1972).

In Fig. 1 the over-all pattern of Hey *et al.* (1966) is shown diagrammatically by full lines on the left (*A*), plotted as $\bar{V}_\mathrm{T}$ versus $\bar{T}_\mathrm{T}$ for comparison with that of Clark & Euler (1972), for man, on the right (*B*). In Clark & Euler's description, the $\bar{V}_\mathrm{T}$, $\bar{T}_\mathrm{I}$ relation was divided into three ranges separated by breakpoints b_1 and b_2. In range 1, $\bar{T}_\mathrm{I}$ was constant and independent of $\bar{V}_\mathrm{T}$. The inverse relation that holds over range 2, which has been extensively studied in anaesthetized animals (e.g. Grunstein, Younes & Milic-Emili, 1973; Widdicombe & Winning, 1974; Bartoli, Bystrzycka, Guz, Jain, Noble & Trenchard, 1973; Bartoli, Cross Guz, Huszczuk & Jefferies 1975) was largely or entirely an expression of the time-dependence of the volume threshold of the Hering–Breuer inflation reflex. $\bar{T}_\mathrm{E}$, according to Clark & Euler (1972), was directly proportional to $\bar{T}_\mathrm{I}$ and so both were related to $\bar{V}_\mathrm{T}$ in the same way over all three ranges. This implies that, like $\bar{T}_\mathrm{I}$, $\bar{T}_\mathrm{E}$ (and hence $\bar{T}_\mathrm{T}$ and $\bar{f}$ should be constant over range 1 (Fig. 1, right, full lines; $\bar{T}_\mathrm{E}$ is shown on the left of the origin, cf. Kay, Petersen & Vejby-Christensen, 1975). The central part of Hey's relation, expressed as in Fig. 1 (left), appeared to Cunningham, Pearson & Gardner (1972) to be like Euler's range 2, in which case Hey's upper breakpoint would be Euler's b_2. Hey's breakpoint, however, occurred at values of $\bar{V}_\mathrm{T}$ about midway between those corresponding to Euler's b_2 and b_1.

In view of the confusion surrounding this subject the patterns of breathing in normal young people at rest have been re-examined using rigorous statistical methods. With regard to the problems set out in the figure, the new analysis provides a reasonable resolution different from that of Cunningham *et al.* (1972) (see fine dashed lines in Fig. 1). In general, for man, the inspiratory part of the pattern of ranges 1 and 2 shown on the right of Fig. 1 is confirmed, but the expiratory part is quite different. There is no information on Euler's range 3. A quantitative description of the factors influencing T_I and T_E that is more comprehensive than the simple equation of Hey *et al.* (1966) is presented in a companion paper (Cunningham & Gardner, 1977). Some of this work has appeared in abstract form (Cunningham & Gardner, 1972; Gardner, 1975).

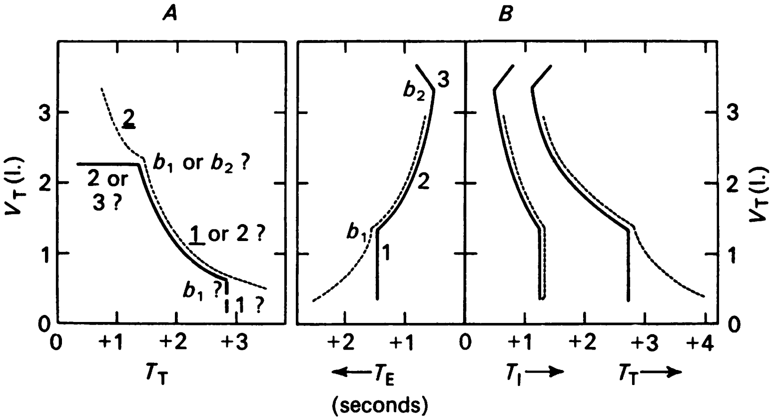

Fig. 1. The problem and its solution. Diagrammatic representations of the volume–time patterns as described by Clark & Euler (1972) (*B*), and as reconstructed for data of Hey *et al.* (1966) by Pearson & Cunningham (1973) (*A*). Ordinates, tidal volume V_T; abscissae, times for cycle T_T, inspiration T_I and expiration T_E. T_E is plotted leftwards from the origin in *B* (after Kay *et al.* 1975). Thick dashed vertical line in plot *A* represents suggested patterning at low V_T. 1, 2 and 3, and b_1 and b_2 beside the lines refer to Clark & Euler's ranges and breakpoints. The solution provided in this paper is shown with fine dashed lines and, in *A*, underlined range numbers.

METHODS

Apparatus

The apparatus was essentially a simple form of that used by Ward & Cunningham (1977). Gas mixtures of adjustable composition were supplied in excess to the subject's inspiratory valve by way of a T-tube and blow-off. Expiratory volume was detected with a dry gas meter (Parkinson & Cowan type CD 4) and a wedge spirometer (Oxford Instruments, Oxford) in series; the latter was emptied by suction early in inspiration through a solenoid-operated stopcock. In a few experiments volume was measured by a pneumotachograph head (Fleisch Type 2, P. K. Morgan, Chatham, Kent) connected through a T-piece directly into the line from the rotameters. Mouth pressure, transduced with a capacitance manometer (M.D.C. 301, Hilger-I.R.D. Ltd, London), signalled the transitions between inspiration and expiration as swings of pressure across zero: these swings triggered the solenoid stopcock and also the time ramp (see below). Alveolar gas composition was measured with a mass spectrometer (VG-Micromass Ltd, Winsford, Cheshire, England). The variables were recorded on moving paper with a multi-channel recorder (M8, Devices Instruments Ltd, Welwyn Garden City, Herts, England).

Recording of T_T, T_I and T_E

A slowly charging capacitor circuit was used to generate a ramp on the recorder trace the height of which increased at a constant rate until the capacitor was discharged and the ramp re-started. The discharge was triggered by the end-expiratory mouth-pressure signal, and so the height of the ramp on the trace was proportional to cycle duration (Fig. 2). Visual estimates of time are easy at slow paper speeds with this method (M. G. Howson, private communication).

At the end of inspiration another pulse from a Schmidt trigger was superimposed on the display of the time-ramp voltage; the resulting break in the otherwise linear rise of voltage with time divided T_T into T_I and T_E (Fig. 2).

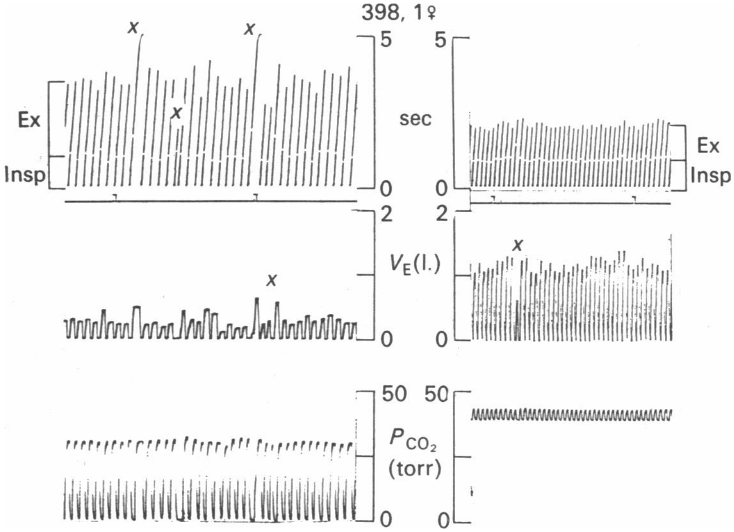

Fig. 2. Examples from an experimental trace at low and high levels of ventilation. Top: heights of sloping lines are cycle durations, T_T, interrupted at the transitions from inspiration to expiration, T_I. Centre: expiratory volume, V_E, the peaks giving tidal volume, V_T. Bottom: P_{CO_2} at the mouth swinging between inspiratory P_{I,CO_2} and end-expiratory P_{A,CO_2}. When an excursion for V_T, T_I or T_E was approximately one third or more away from its run mean as estimated by eye, the whole breath was discarded (e.g. at *x*).

Note that the shortening of cycle duration on the right is achieved by shortening T_E, T_I remaining unchanged.

Experimental design

The subjects were healthy young adult volunteers, eleven men and seven women; twelve of them were used more than once. Many knew no physiology; they were told of the general form of the procedures but the details and aims of the experiments were withheld.

Great emphasis was placed on avoiding or minimizing disturbance of the subjects by, for example, unnecessarily high levels of ventilation, noises or clicks in the apparatus, or uncomfortable surroundings. They were encouraged to read throughout. Those who admitted to being anxious or tense were rejected completely and so too were experiments in which subjects did not read for the greater part of the time. The duration of each experiment was about 3 hr including an initial period of air breathing during which the subjects were allowed to settle; often there were rest periods at intervals of about an hour.

Nine of the thirteen experiments were designed exclusively to study the pattern over the lower range of ventilation, using tidal volumes of up to about one third of the vital capacity and including the region of ventilation not studied by Hey *et al.* (1966) at and just above resting. Stress was minimal or absent in these nine. Inspiratory $P_{\mathrm{CO_2}}$ was increased in steps of approximately 5 torr every 10–12 min, in all cases with $P_{\mathrm{A,O_2}}$ at about 200 torr. In some experiments, at the end of every such period, $P_{\mathrm{A,O_2}}$ was reduced for about 2 min to between 50 and 65 torr, usually about 55. $P_{\mathrm{A,CO_2}}$ was maintained at the same level as before throughout the periods of hypoxia by adjustment of the inspiratory $P_{\mathrm{CO_2}}$. Once moderate levels of hypercapnia had been reached a number of downward steps of $P_{\mathrm{A,CO_2}}$ were introduced in a fairly arbitrary way.

The other twenty-four experiments were designed to study specifically the patterning at higher levels of ventilation and its relation to the patterning at lower levels, the upper limit being set by the tolerance of the subject. Because the number of points to be determined in a session was greater, 7–8 min 'steady states' were employed. Again, determinations were made in a rather arbitrary order, but care was taken to avoid unduly large, and therefore detectable, leaps in chemical drive. The whole range was often covered in both directions a number of times. In each experiment, the number of determinations ranged from seven to twenty, commonly ten to fourteen.

Treatment of data

$P_{\mathrm{A,CO_2}}$, V_{T}, T_{I}, T_{E} and T_{T} were averaged for the 30 (or 40) consecutive breaths from the 6th (or 8th) min after each step, or, in the case of hypoxia, for the 30 (or 40) breaths before the end of the hypoxic period; the bracketed figures refer to the first nine experiments. In the following text, $\bar{V}_{\mathrm{T}}$, $\bar{T}_{\mathrm{I}}$, $\bar{T}_{\mathrm{E}}$ etc. refer to these averages. If either V_{T}, T_{I} or T_{E} for any one breath was more than approximately one third outside the mean for the whole section, judged by eye, all the variables for that breath were rejected, as were obvious coughs and swallows. Whenever there was any doubt, breaths were left in rather than removed. Whole runs were eliminated if there appeared to be no obvious steady level or if more than one in five breaths needed to be eliminated. Each such average represented one point on a plot.

Much of the analysis was concerned with the general shape of the lines relating $\bar{T}_{\mathrm{I}}$ and $\bar{T}_{\mathrm{E}}$ to $\bar{V}_{\mathrm{T}}$, $\bar{V}_{\mathrm{T}}$ being regarded as the independent variable. Linear correlation, and linear and curvilinear regression analyses were performed for each experiment using standard methods (e.g. Bailey, 1959). Over-all correlations were expressed as the common correlation coefficients ($\bar{r}$), obtained by means of the z-transformation (Fisher, 1944).

'Breakpoints', e.g. Fig. 1, were localized objectively by applying, to a series of points, a computer program designed to fit two contiguous straight lines (Dr J. A. Anderson, private communication). The intersection of the two least-square regression lines was constrained to lie between successive pairs of values of the abscissae; the co-ordinates of the breakpoint were taken to be those of the intersection of the pair of lines with the smallest combined residual sum of squares. The significance of the improvement of fit of the two lines over one (and thus also the over-all nonlinearity or otherwise of the data) was determined by analysis of variance. Over all experiments, the two slopes, weighted appropriately by their variances, were also compared by paired t test. In these calculations it was convenient to regard $\bar{V}_{\mathrm{T}}$ as the independent variable, but in the figures, following the conventions of others, it is plotted as the ordinate.

The existence of significant curvature in individual sets of points was tested by fitting simple curves of the kind

$$y = a+bx+cx^2 \qquad (1)$$

and assessing the improvement of fit, compared to a straight line, by analysis of variance; significance of the mean value of the coefficient of the squared term was also determined by t test.

Both in this and in the two-line analysis of variance described above, P-values for the individual experiments were pooled to obtain a mean P-value by the exact method of Fisher (Fisher, 1944). The resulting mean P-values took no account of the direction of curvature and so the experiments were sometimes divided into groups containing only positive or negative values of the curvature coefficient c; the pooled P value was then calculated for each group. The results of analysis of variance and t test were usually in agreement.

In all cases, the use of the word 'significant' implies a P value less than 0·05. All volumes have been corrected to b.t.p.s.

At all stages of the analysis use was made of an ICL 1906A computer, and a statistical package compiled by Oxford University Computing Service.

RESULTS

Conscious man shows more variation in his breathing than the anaesthetized cat, and thus more data are required to obtain a statistically significant result. With steady-state techniques, the number of mean determinations in each session is often limited. Thus, in the present results, few single experiments were suitable for examination of all features of the pattern. Pooling all data (or even all data for one subject) before analysis was found to obscure an unacceptable amount of information that was obvious on visual inspection of the individual experiments; the results were therefore pooled only after each experiment had been analysed separately, and thus there were sometimes insufficient points after various divisions and manipulations of the data for any meaningful analysis. Furthermore, odd 'rogue' points, if included in the analysis, could cause large artifacts in the pattern but if they were eliminated on objective criteria the number of points remaining for calculation sometimes became critically small. For these and other reasons, the numbers of experiments submitted to the different types of analysis varied from one test to another. Since this paper is concerned with statistical validation of a pattern, all data, 'good and bad', have been included in the analysis with the exception of those excluded on the few objective criteria already stated and those whole experiments or parts of experiments in which the sets of values were too few for proper statistical treatment. The questions asked concerned the presence or absence of a breakpoint, its position, and whether or not there was significant curvature in the $\overline{V}_T$, $\overline{T}_I$ and $\overline{V}_T$, $\overline{T}_E$ plots above and below it (see Fig. 1).

The general pattern

Two typical experimental records are shown in Fig. 2, with zero and high inspiratory CO_2 concentrations on the left and right respectively, both at $P_{A,\,O_2} \sim 200$ torr. The crosses mark breaths that were 'edited out' (see Methods). Both records show the great breath-by-breath variation that characterizes normal human breathing. Both also show that the breath-by-breath volumes and total breath durations tend to be positively correlated (Priban, 1963; Cunningham *et al.* 1972; Newsom Davis & Stagg, 1975; Kay *et al.* 1975). Most of the variation of T_T arose from variation of T_E in this example. The effect of raising $P_{A,\,CO_2}$ was to increase mean V_T and shorten mean T_T; the top traces show that the latter was accomplished by markedly shortening mean T_E while mean T_I remained unchanged.

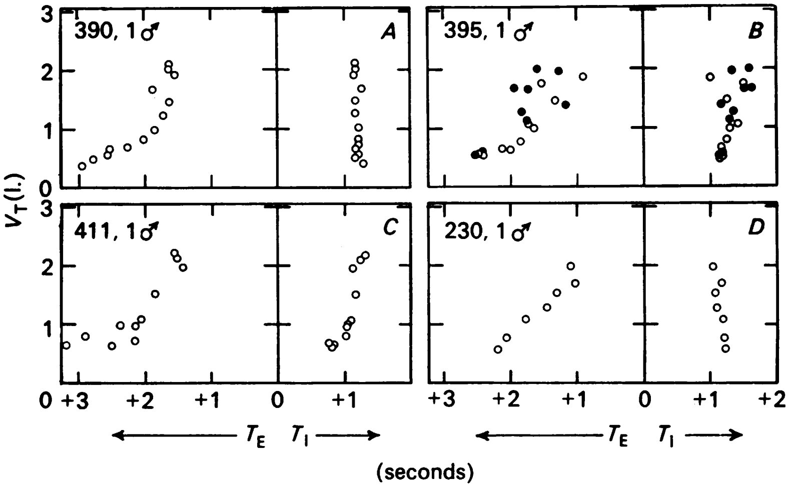

Fig. 3. Four examples of volume, time plots of experiments covering a restricted range of $\bar{V}_T$. Note that T_E is plotted backwards from the origin (cf. Fig. 1). Each symbol is the mean of forty breaths at one level of $P_{A,\,CO_2}$; open circles represent hyperoxia ($P_{A,\,O_2} \sim 200$); filled circles hypoxia ($P_{A,\,O_2} \sim 55$). Subject number (with experiment number) in LH upper corner. Note that with increasing $\bar{V}_T$ the changes in $\bar{T}_E$ are much greater than the changes in $\bar{T}_I$, which are small and variable.

The lower range

$\bar{T}_I$ remained effectively constant as $\bar{V}_T$ increased in eight of the nine experiments in which change of $\bar{V}_T$ was kept to modest proportions (Fig. 3; see also Fig. 1 of Cunningham & Gardner (1972) and Fig. 5 of Cunningham *et al.* 1972). In five the correlation coefficient was not significant (e.g. Fig. 3*A*), in one it was significantly negative (Fig. 3*D*), in two significantly positive (Fig. 3*B*, *C*) and the common correlation coefficient $\bar{r}$ was not significant (0·166). $\bar{T}_E$, on the other hand, shortened markedly with increasing volume and was significantly and negatively correlated with $\bar{V}_T$ in all eight experiments; the common correlation coefficient was highly significant ($\bar{r} = -0{\cdot}865$; $P < 0{\cdot}001$). There was no region of constant frequency including and just upwards from the resting state (contrast Fig. 3 with Fig. 1, right, continuous lines, and with Fig. 10 of Clark & Euler, 1972).

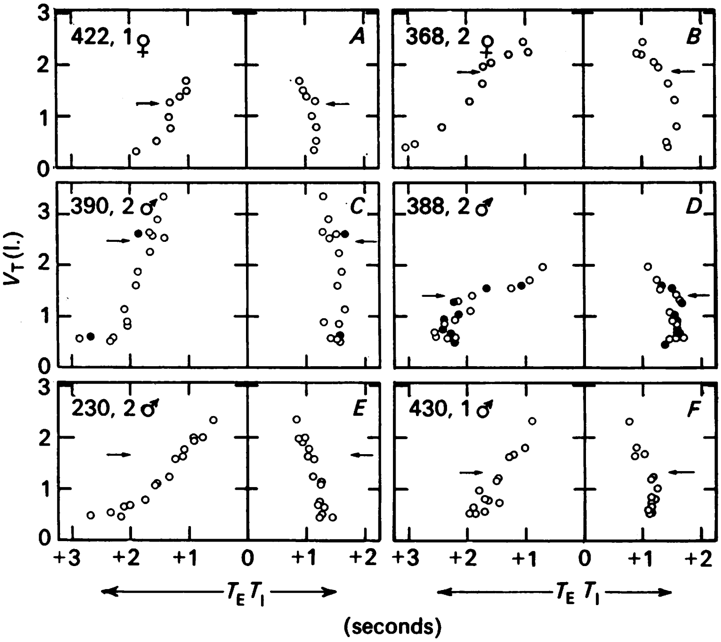

Fig. 4. Six representative full-range experiments. Conventions as in Fig. 3, except that each point is the mean of about thirty individual breaths. Arrows show breakpoints calculated from the $\bar{V}_T$, $\bar{V}_T/\bar{T}_I$ relation (Fig. 6).

In the ninth experiment, with a rise of $\bar{V}_T$ beyond only double its resting value (Fig. 4*D*), $\bar{T}_I$ shortened significantly: at quite a low level of respiratory drive there appeared to be a break point as in those described below.

In the other twenty-four experiments, employing larger changes of $\bar{V}_T$, the lower parts of the $\bar{V}_T$, $\bar{T}_I$ and $\bar{V}_T$, $\bar{T}_E$ relations were in general like those just described (Fig. 4), but $\bar{T}_I$ less often increased with increases of $\bar{V}_T$. In this respect, the results of the more relaxed experiments may be more reliable. Any changes of $\bar{T}_I$ were always much less than the corresponding changes of $\bar{T}_E$ (e.g. Fig. 4*E*).

The upper range

There appeared to be a break in the relations between $\bar{V}_T$ and both $\bar{T}_I$ and $\bar{T}_E$, usually at values of $\bar{V}_T$ slightly less than half the vital capacity (as quoted by Hey *et al.* 1966); above the break $\bar{T}_I$ was inversely related to $\bar{V}_T$ (cf. Clark & Euler, 1972), and $\bar{T}_E$ appeared to be closely linked to $\bar{T}_I$ (e.g. Fig. 4*A*). On both inspiratory and expiratory sides the relative changes in times and volumes varied widely from subject to subject; ventilation increased with changes predominantly of $\bar{V}_T$ in some (Fig. 4*C*) and of times in others (Fig. 4*D*); but neither component was ever entirely absent as was described by Hey *et al.* (Fig. 1, left) and by Kelman & Watson (1973).

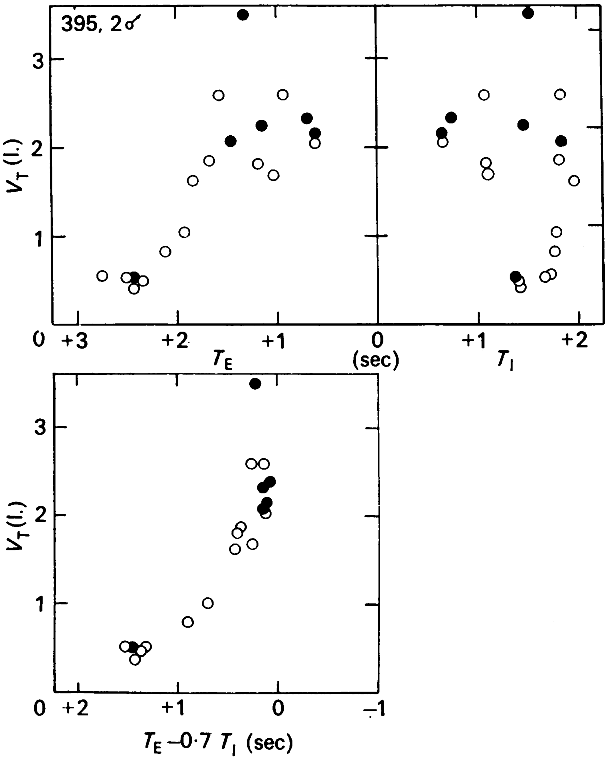

Fig. 5. The upper panel shows one of the full-range experiments with a particularly large degree of scatter, displayed as in Fig. 4. The lower panel shows $\bar{T}_E$ replotted after subtraction of a proportion of $\bar{T}_I$ (see Cunningham & Gardner, 1977); the scatter has been substantially reduced showing that most of the scatter of $\bar{T}_E$ was linked to scatter in $\bar{T}_I$.

Linkage between mean T_I and mean T_E

Above the break but not below it, $\overline{T}_I$ and $\overline{T}_E$ were closely correlated ($\bar{r} = 0{\cdot}90$, $P < 0{\cdot}001$) and the two times were nearly equal, as reported by Clark & Euler (1972). A less obvious form of linkage extended over both lower and upper ranges: when an individual $\overline{V}_T$, $\overline{T}_I$ point lay to one side of the calculated line of best fit, the paired $\overline{V}_T$, $\overline{T}_E$ point was usually displaced in the same direction by a corresponding amount (see Fig. 5 which shows a well marked example). The mean correlations between these displacements of $\overline{T}_I$ and $\overline{T}_E$ were $+0{\cdot}57$ below and $+0{\cdot}54$ above the break ($P < 0{\cdot}001$ in each case).

Reproducibility

Many of the subjects on whom more than one experiment was performed showed minor but recognizable idiosyncracies of pattern (e.g. compare Figs. 3*D* and 4*E*, Figs. 3*B* and 5, Figs. 3*A* and 4*C*). This was usually but not always the case for breakpoints (see below).

Statistical testing of pattern

To facilitate analysis of this rather complex pattern, the data for each experiment were divided into two groups, with tidal volumes above and below the estimated breakpoint. In order to locate this breakpoint objectively, its presence was sought in a variety of rearrangements of the data, in forms amenable to linear or bilinear analysis (see Methods).

Location of breakpoint

The most consistent functions for locating the breakpoint were $\overline{P}_{A,\,CO_2}$ *vs.* V_T (high oxygen points only) and $\overline{V}_T/\overline{T}_I$ versus $\overline{V}_T$, both of which were usually bilinear (see Gardner, 1975; Cunningham & Gardner, 1977). The discontinuity between the two lines in both plots corresponded well with the breakpoint as estimated by eye from the volume–time plots. $\overline{V}_T/\overline{T}_I$ (or mean rate of increase of inspiratory activity) was highly correlated with $P_{A,\,CO_2}$ in high oxygen and allowed inclusion of hypoxic points in the analysis; the $\overline{V}_T/\overline{T}_I, \overline{V}_T$ relation (Fig. 6) was thus preferred. As determined by bilinear regression analysis, the slope was greater below than above the breakpoint in twenty-three out of twenty-five full range experiments and significantly so in nineteen. The mean of the value of $\overline{V}_T$ at which breaks occurred corresponded to 37 % of the vital capacity (cf. Hey *et al.* 1966 'in the region of half the vital capacity'; Clark & Euler's (1972) b_1 in Fig. 1, right; approx. 33 % of vital capacity). The arrows in Fig. 4 indicate breakpoints derived in this way.

In many subjects the position was reproducible from one experiment to another, in a few it was not detected even though $\bar{V}_T$ exceeded 60% of vital capacity, and in a few its position and even its presence was variable from one experiment to another.

The breakpoint and T_E

The above relations described the T_I breakpoint; it was next necessary to investigate the visual impression that a corresponding breakpoint also occurred in the $\bar{V}_T$, $\bar{T}_E$ relation. It was not so easy to arrange the data involving $\bar{T}_E$ in any simple linear form and so a different approach was tried. A single polynomial (eqn. (1)) was fitted across the entire range for each experiment, and the position corresponding to the inspiratory break marked. It was found that the two points closest to the mark lay to the left of the line (i.e. $\bar{T}_E$ was too long) in eighteen out of twenty-three

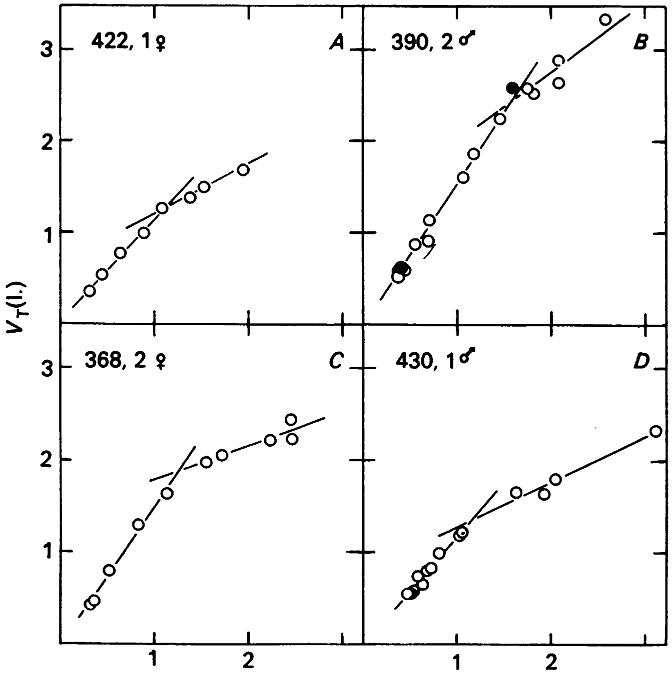

Fig. 6. Four of the full-range experiments of Fig. 4 plotted as $\bar{V}_T$ (on the ordinate) against respiratory drive or $\bar{V}_T/\bar{T}_I$ (see Cunningham & Gardner, 1977) on the abscissa. The symbols are the same as in Fig. 3. Note the bilinearity of the points with a clear bend corresponding well with the visually estimated breakpoints in Fig. 4. The lines are computed by the two-line regression technique (see Methods); their intersections objectively locate the breakpoints.

experiments, a distribution that was not random (Wilcoxon's rank test, $P < 0{\cdot}02$). Furthermore, hyperbolae fitted to the $\overline{T}_E$, $\overline{V}_T$ points exclusively below the break value of $\overline{V}_T$ predicted larger values of $\overline{T}_E$ above the break than those observed ($P < 0{\cdot}02$). It may be concluded that there is probably a breakpoint on the expiratory side that corresponds to that demonstrated on the inspiratory side.

The pattern above and below the breakpoint

Having established the positions of the breakpoints it was desirable to test the four segments of the $\overline{V}_T$, $\overline{T}_I$, $\overline{T}_E$ patterns for direction, if any, of the general trends and for the presence and direction of curvature.

The results of this analysis, which are summarized in Table 1, confirm in most respects the qualitative descriptions of Figs. 3 and 4 given earlier. Over the upper range, the relations between $\overline{V}_T$ and $\overline{T}_I$, and $\overline{V}_T$ and $\overline{T}_E$, and over the lower range between $\overline{V}_T$ and $\overline{T}_E$ showed strong negative correlations (columns 2–4), and both upper and lower relations involving $\overline{T}_E$ were significantly curved, with the convexities facing the origin (columns 6–10). Probably as a result of an insufficiency of data, the tests for curvature in the upper $\overline{V}_T$, $\overline{T}_I$ relation gave less definite results. However, $\overline{T}_I$ is usually accepted as being curved in range 2 in animals (e.g. Clark & Euler, 1972; Milic-Emili, 1974) and Clark & Euler and Garrard & Lane (1975) described similar curvature in man; thus, further experiments designed solely to strengthen the evidence on this point do not seem to be necessary.

The deviation from the vertical of the $\overline{V}_T$, $\overline{T}_I$ relation over the lower range was very much less than in the cases of the other three, and the directions of the slopes was more nearly random (column 5). Nevertheless, for all thirty-three experiments the common correlation coefficient, though low, was negative and highly significant. Furthermore, there was a slight but significant curvature which, unlike the others, was curved with the concavity facing the origin (negative sign of parameter c in eqn. (1); Table 1, column 10). Such curvature is attributable to the positions of a few points at the bottoms of a few of the lines (e.g. Fig. 3*C*, Fig. 4*B* and *D*); it does not imply that curvature over the whole range is a regular feature. Having recorded the fact of curvature, it is closer to reality to regard this relation as essentially straight with, at most, a slight negative slope.

The new and most prominent feature of the present description, which this analysis emphasizes further, is the marked curvature in the lower part of the relation between $\overline{V}_T$ and $\overline{T}_E$ over the range where the $\overline{V}_T$, $\overline{T}_I$ relation is straight, or curved in the opposite direction. These curves and their coefficients are simpler to compute than those derived in the companion paper (Cunningham & Gardner, 1977). The description they afford is, however, entirely empirical and the physiological meaning, if any, of the twelve parameters given in Table 1 is obscure.

TABLE 1. Stastical analysis of relations between tidal volumes and inspiratory and expiratory times in lower and upper ranges

Dependent variable	No. of expts (points) (1)	Linear				Curvilinear regression (T_{I} or $T_{\mathrm{E}} = a+bV_{\mathrm{T}}+cV_{\mathrm{T}}^2$)				
		Correlation			Regression					
		$\bar{r}$ (2)	+ve (sig./all) (3)	−ve (sig./all) (4)	b ± S.E. (5)	+ve (sig./all) (6)	−ve (sig./all) (7)	a ± S.E. (8)	b ± S.E. (9)	c ± S.E. (10)
Lower										
T_{I}	33 (319)	−0·34***	2/10	11/23	−0·07*** ± 0·03	0/12	2/21	+1·22*** ± 0·07	+0·20 ± 0·12	−0·18* ± 0·07
T_{E}	33 (319)	−0·87***	0/0	28/33	−0·78*** ± 0·07	6***/28	0/5	+3·01*** ± 0·18	−1·86*** ± 0·34	+0·61** ± 0·19
Upper										
T_{I}	12 (68)	−0·87***	0/0	5/12	−0·44*** ± 0·05	0/9	0/3	+4·80* ± 1·66	−3·46* ± 1·49	+0·79* ± 0·34
T_{E}	12 (68)	−0·81***	0/0	4/12	−0·76*** ± 0·15	1*/10	0/2	+8·03*** ± 2·37	−6·94* ± 2·39	+1·72* ± 0·68

*** $P < 0{\cdot}001$; ** $P < 0{\cdot}01$; * $P < 0{\cdot}05$.

Column (1) shows the numbers of experiments and, in parentheses, corresponding numbers of individual points in each group.

Columns (2–5) establish the general trends of the relationships, in (2–4) by linear correlation analysis and in (5) by linear regression analysis. Column (2) shows common correlations coefficients ($\bar{r}$) and their significance based on the total number of points. Columns (3) and (4) show the division into +ve and −ve values of r and the numbers significant in each group. Column (5) shows the arithmetic mean (± S.E.) of individual linear regression coefficients of the relation Time $= a + b\,V_{\mathrm{T}}$. Note that the regression slope for $T_{\mathrm{I,\,lower}}$, though significant, was much smaller than the others. The T_{I} intercept for this regression was 1·28 ± 0·06 sec.

Columns (6–10) show the degree and directions of curvature in each relationship. Columns (6) and (7) show the numbers of individual experiments with convexity facing towards the origin (6) and away from it (7), and the numbers significant in each group (as determined by comparison with a straight line using analysis of variance). The asterisks denote over-all significance for each group derived by pooling individual values with the Fisher Exact test. Columns (8–10) show over-all mean (± S.E.) values of the coefficients of the fitted parabolas (eqn.(1)); curvature coefficient in (10).

'Anomalous' (i.e. −ve) curvature of $T_{\mathrm{I,\,lower}}$ (see text) was slight; curvature of $T_{\mathrm{I,\,upper}}$ is not firmly established here because data were few, but the curvature of both sections of the T_{E} plots, especially the lower, is established.

The $\overline{\dot{V}}_E$, $\overline{V}_T$ *relation*

The pattern of breathing has been expressed as the relation between $\dot{V}_E$ and $\overline{V}_T$ by several authors (e.g. Milic-Emili & Cajani, 1957; Hey *et al.* 1966; Cotes, Johnson & McDonald, 1970; Gilbert, Auchincloss, Baule, Peppi & Long, 1971; Patrick & Howard, 1972; Freedman, Dalton, Holland & Patton, 1972). For the present results the relation was generally nearly linear or bilinear as described by Hey *et al.* (1966) except that the part above the breakpoint usually showed a finite slope rather than being vertical. For the lower region the mean slope *m* and the mean horizontal intercept *k* were 24·1 ± S.E. 1·46 breaths/min, and 0·19 ± 0·03 l. respectively, which are close to the values given by Hey *et al.* (1966) and by Patrick & Howard (1972). Over the upper range *m′* and *k′* were larger and varied to a greater extent, in keeping with the greater variation in patterning seen in the upper range (94·2 ± 26·2 breaths/min and 1·22 ± 0·53 l.). Within each range, *m* and *k*, and *m′* and *k′* respectively were significantly correlated but there was no correlation between lower and upper parameters. In some subjects a single continuous curve could have been fitted to the $\overline{\dot{V}}_E$, $\overline{V}_T$ data (cf. Gilbert *et al.* 1971) especially in cases with a 'splayed' breakpoint; nevertheless in most cases two straight lines were adequate.

Patterns in low and high oxygen

As in previous work from this laboratory (e.g. Lloyd, Jukes & Cunningham, 1958; Hey *et al.* 1966) the patterns of response during hypoxia and hyperoxia were indistinguishable (e.g. Figs. 3, 4, 5, and Fig. 1, Cunningham & Gardner, 1972).

DISCUSSION

The present analysis is consistent with descriptions given by others of the curvilinearity of the upper parts of the $\overline{V}_T$, $\overline{T}_I$ and the $\overline{V}_T$, $\overline{T}_E$ relations and of the near-constancy of $\overline{T}_I$ over the lower range of $\overline{V}_T$. It affords support for, but not proof of, there being discontinuities or breakpoints between the lower and upper parts of these relations (Clark & Euler, 1972; Garrard & Lane, 1975).

The pattern described here is, however, quite different from that of these authors for $\overline{V}_T$ and $\overline{T}_E$ over their range 1 (Fig. 1, right). Nevertheless, the lower range described above is clearly their range 1 because it includes and extends upwards from resting values of $\overline{V}_T$ and $\overline{T}_T$ and it lies wholly below the first breakpoint b_1, which occurs at broadly similar values of $\overline{V}_T$ in all three sets of results. Thus, under the present conditions, $\overline{T}_E$ varies markedly in range 1 while $\overline{T}_I$ remains nearly constant and so the two times are not uniquely related. Nor is there a zone of constant frequency including and extending upwards from the state of complete eupnoea.

Curved dashed lines can therefore be substituted for the full vertical straight lines describing $\bar{V}_T$ *vs.* $\bar{T}_E$ and $\bar{T}_T$ over range 1 in Fig. 1, right. Likewise, the lower range described above, henceforward called range 1, may now be identified with the lower range studied by Hey *et al.* (1966) for three reasons: (1) the only breakpoint described by them was at levels of $\bar{V}_T$ as high or higher than those corresponding to Clark & Euler's first breakpoint; (2) over the range below it there were substantial changes of frequency, thus the upper break in Fig. 1, left, is b_1, not b_2; and (3) the parameters m and k of the $\bar{\dot{V}}$, $\bar{V}_T$ relation over range 1 in these experiments are essentially the same as those for the lower range of Hey *et al.* (1966), while the corresponding parameters for range 2 are much larger than Hey's and show much more scatter. An earlier attempt at reconciling the discrepancies of Fig. 1 (Pearson & Cunningham, 1973; Cunningham *et al.* 1972) can now be regarded as wide of the mark.

In range 2, above the first breakpoint, both $\bar{V}_T$ and $\bar{f}$ increase to a greater or lesser extent as ventilation increases, and the claim by Hey *et al.* (1966), supported by Kelman & Watson (1973), that $\bar{V}_T$ is constant in this range was probably based on insufficient data.

The breakpoint

The argument that the breakpoint was justified statistically in most cases in which its presence was suspected is permissive rather than conclusive. The grounds for retaining a breakpoint are as follows. First, visual inspection of most plots covering the full range appear by eye to show it (e.g. Fig. 4). Secondly, while a continuous function can be fitted to some of the $\bar{V}_T$, $\bar{T}_I$ plots, only an elaborate one could describe the sharp transition between a curve and a vertical line seen in several experiments. When the discontinuity was less obvious, this may merely have been the result of splay produced by the action in parallel of a large number of stretch receptors with an unusually large spread of volume thresholds, some of which might vary with time; indeed this may be part of the explanation for the reported absence of clear $\bar{V}_T$, $\bar{T}_I$ breakpoints in excerise (Kay *et al.* 1975).

Thirdly, there are experimental reasons for supposing the existence of two separate mechanisms. Guz and co-workers (summarized in Guz, Noble, Eisele & Trenchard, 1970), extending earlier work of Widdicombe (1961), found a substantial inflation reflex in anaesthetised man only at tidal volumes over approximately 1 l., corresponding roughly to the level of the breakpoint described above. In conscious man, they found little change in resting pattern in response to vagal blockade, and more recently in response to selective local anaesthetic block of the airways (Cross, Guz, Jain, Archer, Stevens & Reynolds, 1976). Likewise, in conscious dogs the inflation reflex is weak and can be weakened further or abolished by auditory or visual stimulation of higher nervous centres (Nadel, Phillipson, Fishman & Hickey, 1973). Clark & Euler (1972) regard the break as occurring at the intersection of the Hering–Breuer volume-time threshold curve with a vertical line corresponding to the constant frequency of a postulated bulbo-pontine pacemaker, revealed more clearly in anaesthetized cats after vagotomy (but see also Widdicombe & Winning, 1974). The new results, however, indicate that such a control structure would hold constant only the inspiratory component of time, and as such the term pacemaker is a misnomer. It is perhaps this structure, if it exists, whose 'time keeping' may be influenced not only by change of central temperature but also by the moment-to-moment variation in the activity descending from higher levels that may be a characteristic of consciousness.

If we accept that a break exists on the inspiratory side, it is simplest to regard any breakpoint at similar levels on the expiratory side as a secondary manifestation of the same phenomenon.

Consciousness

The pattern described could well be a function of consciousness; Gautier, Remmers & Bartlett (1973) reported this form of patterning in conscious cats in contrast to the range 2 type patterning under anaesthesia. However, it is unlikely to be a direct result of conscious manipulation by the subject. Unlike the anaesthetized cat, conscious man breathes in an unpredictably irregular fashion, presumably at least partly because of variations in mental state. It was commonly observed, for example, that at lower levels of ventilation, stress and probably heightened awareness tended to shorten $\bar{T}_I$ and $\bar{T}_E$. While there were often large variations in scatter and in the detail of the patterning between experiments, the basic form of the pattern was nevertheless reproducible between subjects and was seen as often at the time of a subject's first acquaintance with CO_2 inhalation as in later experiments. Subjective responses to the experiment could only be determined by cautious questioning after the experiment: too much would render a subject unsuitable for further experiments. Nevertheless, subjects immersed in their books appeared to be unaware of changes in their breathing over at least the lower third of the total range of ventilations studied; this is the part of range 1 over which the greatest change of $\bar{T}_E$ occurred.

It is conceivable that the breakpoint is a function of anxiety induced by the high levels of ventilation. However, the onset of awareness appeared not to correlate well with the level of the breakpoint. Moreover, at these higher levels of ventilation it is difficult to breathe in any way other than that dictated by physiology.

A different and, from the present point of view, possibly a more reliable way of studying the pattern has been reported (Gardner, 1974). Repeated step changes were made between two levels of alveolar P_{CO_2} sufficiently close (5–10 torr) to ensure that the subjects were in general unaware of the resulting changes in ventilation. The final pattern averaged from between 10 and 20 such steps for each subject showed the essential constancy of $\bar{T}_I$ and the curvilinear change of $\bar{T}_E$ exactly as reported here for range 1. Likewise simultaneous changes of V_T and T_E, often of opposite sign, were seen in the alternate breath oscillation experiments of Ward & Cunningham (1977) in which there was no question of awareness. T_E here was obviously independent of inspiratory events.

Inhalation of CO_2, though an outstandingly fruitful experimental procedure, is not an everyday occurrence outside the laboratory (nor for that matter is acute hypoxia), and it is of interest that in the hyperpnoea of exercise the pattern is like that described here (Kay *et al.* 1975).

Hypoxia, hypercapnia and end-expiratory volume

Descriptions from different laboratories of the patterns in man often show real discrepancies, especially over the identity or otherwise of the responses to hypoxia and to hypercapnia (e.g. Haldane, Meakins & Priestley, 1919; Rebuck, Rigg & Saunders, 1976). At least two sources of difference appear to be involved. In the first place, transients consisting of steps of $P_{A,\,CO_2}$ in high O_2 often have paradoxical effects on T_T and T_I, but not on T_E (Cunningham *et al.* 1972; Gardner, 1974), and quick rebreathing runs, besides being often more stressful, can be regarded as a continuous succession of transient changes of stimulus. Nevertheless the range 1 pattern described in this paper has also been found for man by Jennett, Russell & Warnock (1974) using rebreathing techniques.

Secondly, there is the question of lung volume. Most workers measure V_T as the volume variable, but presumably the pulmonary stretch receptors report a quantity related to lung volume. The importance of the distinction has been shown recently (Garrard & Lane, 1975), and the discrepancy between the hypoxic-hyperoxic comparison in the present paper and those of others may be due to a difference of behaviour of end-expiratory lung volume $V_{L,E'}$ with differing techniques (Kellogg & Mines, 1975; Garfinkel & Fitzgerald, 1975; Saunders, Betts & Rebuck, 1975). Kellogg & Mines, who reported no change of $V_{L,E'}$ in an isopnoeic comparison, seem also to have used steady-state techniques. The results of Garrard & Lane (1975) suggest that the changes reported by Rebuck *et al.* (1976) should be thought of in terms of the vagal volume–time component as much as the drive component (see the two terms in eqn. (7) of Cunningham & Gardner, 1977), but it is changes in the latter that have been implied in the writings of most observers of hypoxic tachypnoea.

Physiological interpretations

T_E, to which so much space has been devoted, is itself far from being a simple quantity. The time taken to empty the lungs down to about $V_{L,E'}$ depends upon the volume of gas to be expelled (i.e. the end-inspiratory volume) and the resultant of all the expiratory forces (passive recoil supplemented by more or less pushing from the expiratory muscles and opposed by less or more braking by the diaphragm and other inspiratory muscles) operating through the lower and upper airway resistances, including that of the larynx. The subject has been well reviewed by Gautier *et al.* (1973) and Bartlett, Remmers & Gautier (1973). However, even the attainment of some fitted $V_{L,E'}$ need not necessarily operate some notional expiratory off-switch; end-expiratory pauses (seen in the present experiments only at resting ventilation, and then only occasionally) may follow, and anyway, $V_{L,E'}$ itself is not a stable quantity (Hlastala, Wranne & Lenfant, 1973; Cunningham & Ward, 1975; Ward & Cunningham, 1977).

In animals there appears to be dispute about the afferent pathways controlling these effector mechanisms, whether activity of pulmonary stretch fibres modulated by P_{CO_2}, or other vagal pathways excluding the stretch fibres and/or afferents from intercostal muscles (e.g. Guz *et al.* 1970; Nadel *et al.* 1973; Callanan, Dixon & Widdicombe, 1975; Cross *et al.* 1976; Bradley, Noble & Trenchard, 1976). Attractive though the airway P_{CO_2}-stretch-receptor hypothesis may be (Bartoli, Cross, Guz, Jain, Noble & Trenchard, 1974), the effects in man that might correspond to it are small (Cunningham, Drysdale, Gardner, Jensen, Petersen & Whipp, 1977); the work of Drysdale & Ward (1976) shows that a major chemical factor affecting T_E in man operates with a latency probably too long for the airway receptors. This is another situation in which similarity of response should not be taken to imply identity of mechanism.

We have come to view the Hering–Breuer inflation reflex as an important feature of volume regulation in the supine, anaesthetized and perhaps hypercapnic animal; its role in the healthy air-breathing moderately active human is less clear.

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