

A QUANTITATIVE DESCRIPTION OF THE
PATTERN OF BREATHING DURING STEADY-STATE CO₂
INHALATION IN MAN, WITH SPECIAL EMPHASIS
ON EXPIRATION

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SUMMARY

1. Quantitative data on the pattern of breathing in normal men and women (Gardner, 1977) have been used to derive expressions that are based on known physiological mechanisms.

2. The relations between the applied chemical drive to breathing (expressed as $\Delta P_{A, CO_2}$ in high O₂) and the several components of the volume–time patterns described in the companion paper were examined. Neither mean tidal volume (\bar{V}_T), nor mean inspiratory nor mean expiratory times (\bar{T}_I , \bar{T}_E) were uniquely related to the chemical drive across the breakpoint, which could be demonstrated in two and suspected in the third of these plots.

3. Mean inspiratory flow (\bar{V}_T/\bar{T}_I) was linearly related to P_{A, CO_2} over the whole range and, like minute ventilation (\bar{V}), showed no breakpoint. The mean relation was $\bar{V}_T/\bar{T}_I = 0.11 (P_{A, CO_2} - 35.2)$. \bar{V}_T/\bar{T}_I was highly correlated with \bar{V} ; in individuals with healthy lungs and under relatively stable conditions of compliance and resistance it may be accepted as a wholly inspiratory alternative to \bar{V} as an index, on the efferent side, of the total prevailing chemical drive.

4. The description of the relation between \bar{T}_I and \bar{V}_T was essentially the same as that of Clark & Euler (1972): in range 1, $\bar{T}_I =$ either $1.29 - 0.07 \bar{V}_T$ or the constant 1.24 sec, and in range 2, $\bar{T}_I = 0.65/(\bar{V}_T - 0.88) + 0.59$.

5. Expiration was described by an equation based on the inverse linkage between \bar{T}_E and chemical drive and the direct link between both mean and breath-by-breath values of T_I and T_E : $\bar{T}_E = p\bar{T}_I + q/(\text{drive} - r)$ in which p was 0.64 ± 0.09 , q was 11.1 ± 2.64 sec. (torr CO₂)⁻¹ and r was -2.73 ± 1.09 torr CO₂. All three parameters were necessary for an adequate description.

6. It is argued that the first term of the T_E equation represents influences

related to lung volume exerted through the vagus, and that the second represents the effects of over-all chemical stimulation exerted through other pathways.

INTRODUCTION

In studies of the combinations of mean inspiratory and expiratory durations (\bar{T}_I , \bar{T}_E) and mean tidal volume (\bar{V}_T) that go to make up lung ventilation (\bar{V}) in man there is a need for a numerical standard of normality with which comparisons of the effects of experimental procedures and disease processes may be made (Cunningham, 1975). The equations of Hey, Lloyd, Cunningham, Jukes & Bolton (1966) and of Patrick & Howard (1972) make no provision for the division of cycle duration (T_T) into its inspiratory and expiratory components (T_I and T_E). The patterns of Clark & Euler (1972) were based largely on results with anaesthetized cats, and their application to man led these authors to underestimate the importance of independent influences on the expiratory half-cycle in determining cycle duration and thus minute volume (Gardner, 1977). It seems that the expiratory component needs individual quantification.

The relations between steady-state \bar{V}_T and \bar{T}_I , and \bar{V}_T and \bar{T}_E can be divided by breakpoints into lower and upper parts (ranges 1 and 2), three of the four parts being markedly curved (Gardner, 1977). When each part is treated separately at least eleven parameters are required for a complete though empirical description, five for inspiration and six for expiration.

In the present paper we consider the interrelations between the parts and we arrive at an adequate description of the whole steady-state pattern in terms of seven, eight or nine parameters. The description of inspiration differs little from that of Clark & Euler (1972); it requires four or five of the parameters. The description of expiration combines physiological with purely quantitative considerations; it treats both upper and lower ranges as a single continuum and thus requires three or four parameters instead of six. Development of this equation has required the presentation of more information on the breath-by-breath relations between T_E and T_I , and a consideration of some of the ways in which the respiratory drive may be represented in terms of measurable quantities.

METHODS

The details of the apparatus used, the experimental procedure and of some of the statistical methods appear in the preceding paper (Gardner, 1977). Ventilation was stimulated by CO₂ inhalation at rest, usually in high oxygen, but in several experiments hypoxia was combined with hypercapnia, especially when higher levels of respiratory drive were required. The thirty-three experiments described in the

preceding paper, supplemented as described below, comprise the data on which this further analysis is carried out.

For breath-by-breath analysis four of these original experiments were re-analysed, and another three experiments were carried out. These seven, together with two others in which step changes of drive were imposed (Gardner, 1974) provide the body of data on the relation between T_E and T_I .

In the three new experiments, T_I and T_E were derived from the points in time when flow, measured by pneumotachograph, crossed the zero line; the values were obtained with the aid of a Data General computer (Nova 8) used on-line.

In a later section of the paper, results are described of fitting hyperbolae of the kind

$$y = c^2/(x - a) + b \quad (1)$$

and

$$y = c^2/(x - a) + dz + b. \quad (2)$$

Equations were fitted with the help of an ICL 1906A computer using standard multiple regression techniques. Different values of a were inserted until a minimum sum of squares emerged; experiments in which it was not possible to obtain a clear minimum were omitted from further consideration (e.g. 4 out of 33 for eqn. (7)).

The parameters of such equations usually show some degree of mutual correlation. In the Appendix a method is described for obtaining an extra parameter L that expresses this correlation.

RESULTS AND DISCUSSION

The interrelations of \bar{V}_T , \bar{T}_I , \bar{T}_E , \bar{V} and respiratory drive

Gardner (1977) showed that as respiratory drive was made to vary (usually as a result of varying P_A, CO_2 in high O_2) the relations between \bar{T}_I and \bar{V}_T , and \bar{T}_E and \bar{V}_T exhibited discontinuities. For the series as a whole, these breakpoints were significant for both relations. We now examine briefly the separate relations of all three variables to the chemical drive; a preliminary account of this work has already been given (Gardner, 1975).

The relation between \bar{T}_E and P_A, CO_2 in high O_2 was inverse (Fig. 1C). In the series as a whole the tendency for there to be a breakpoint approached but did not reach full statistical significance, i.e. $P < 0.1$; the same test when applied to the \bar{T}_E, \bar{V}_T plots, showed the presence of a breakpoint significant at $P < 0.025$ (Gardner, 1977).

Both \bar{V}_T and \bar{T}_I (expressed as $1/\bar{T}_I$) plotted against P_A, CO_2 in high O_2 showed significant breakpoints ($P < 0.001$ and $P < 0.05$ respectively). In the example shown in Fig. 1A, B and C the break occurs at about 48 torr P_A, CO_2 . \bar{V}_T was usually clearly linearly related to \bar{P}_A, CO_2 on both sides of the break (cf. also Gardner, 1977); $1/\bar{T}_I$ vs. P_A, CO_2 , for which the bend at the break was much shallower, was often only approximately so.

Unlike \bar{V}_T and \bar{T}_I in isolation, the ratio \bar{V}_T/\bar{T}_I appeared to be continuous over both ranges 1 and 2. Fig. 2 shows the data of Fig. 1A, B and those from three other experiments (each with a clear breakpoint in the

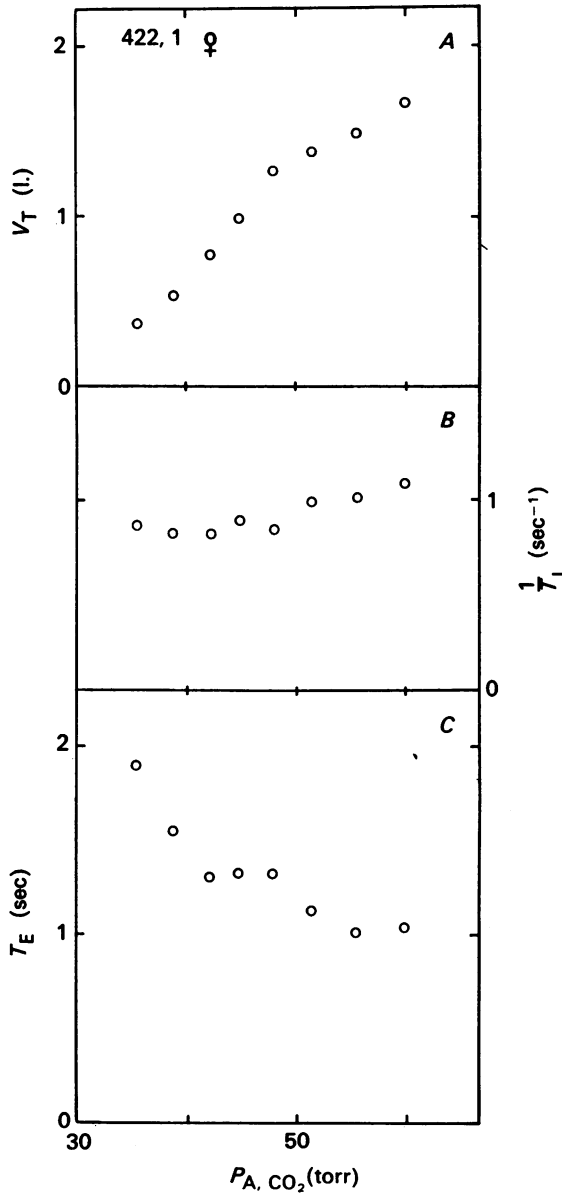


Fig. 1. Shows tidal volume (\bar{V}_T), the reciprocal of inspiratory time ($1/\bar{T}_I$) and expiratory time (\bar{T}_E) each plotted against P_{A, CO_2} for one of the experiments illustrated in Fig. 4 of Gardner (1977). Each symbol is the mean of approximately thirty breaths; all are in hyperoxia. Note the strong suggestion of a breakpoint in all three plots. The data of this experiment appear in Figs. 2A and 3A, and also in Figs. 4A and 6A of Gardner (1977).

\bar{V}_T , \bar{P}_{A,CO_2} and $1/\bar{T}_I$, \bar{P}_{A,CO_2} plots) plotted as \bar{V}_T/\bar{T}_I against \bar{P}_{A,CO_2} ; here a single straight line fits the data right across the region of breakpoint, of which in this plot there is no sign. It seems that the breakpoints exemplified in Fig. 1 cancel each other in the variable \bar{V}_T/\bar{T}_I . Out of the twenty-two experiments in which the relation of \bar{V}_T/\bar{T}_I to drive was statistically analysed significant breakpoints were seen in five. However, of the five, three breaks

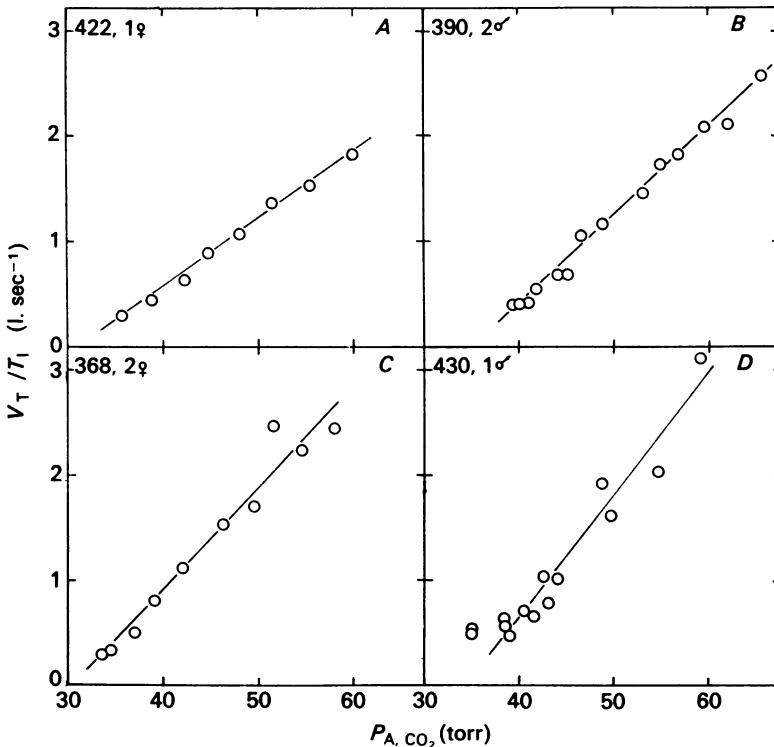


Fig. 2. \bar{V}_T/\bar{T}_I (on the ordinate) related to P_{A,CO_2} in high O_2 (on the abscissa) for four of the experiments shown in Fig. 4 of Gardner (1977). Symbols are described in Fig. 1. Least-square regression lines are shown.

were in one direction and two in the other; averaging over all experiments showed no significant deviation from linearity. Moreover, \bar{V} against drive, a relation generally accepted as linear, showed very similar results, with six significant and cancelling breakpoints, when analysed in the same way.

Respiratory drive

In CO₂ inhalation the input or drive to the system has been regarded as proportional to P_{A, CO_2} , but when hypoxia is present as well drive is represented more accurately by an expression like that of Lloyd & Cunningham (1963). For the manipulations that follow, however, it is desirable to have an index of drive that is less cumbersome than theirs and others like it.

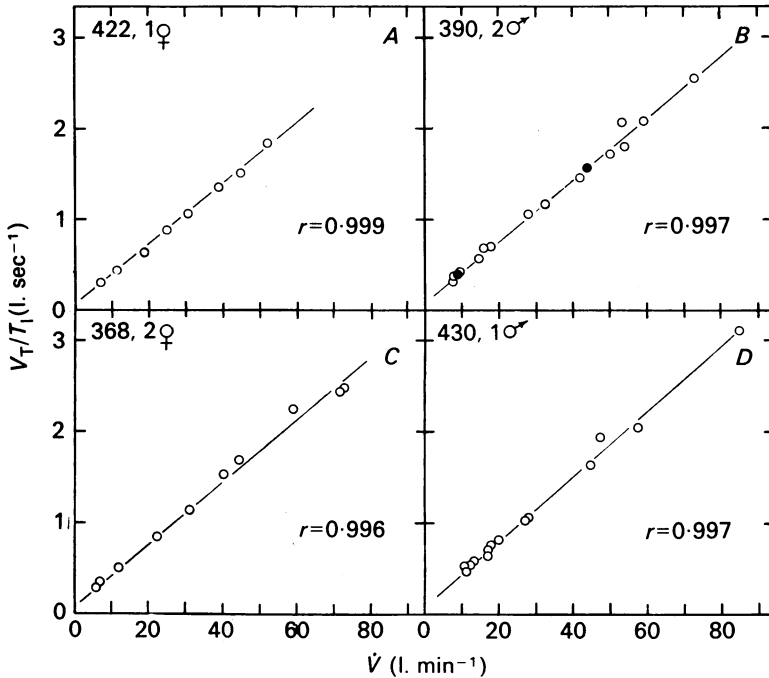


Fig. 3. \bar{V}_T/\bar{T}_I (on the ordinate) related to \bar{V} (on the abscissa); r is correlation coefficient and other symbols are as described in Fig. 1. Note the close correspondence between the two even under hypoxic conditions (filled symbols) and when the \bar{V}_T/\bar{T}_I vs. P_{A, CO_2} plot tends to flatten at the bottom (e.g. Fig. 2D). Least-square regression lines are shown indicating that the relationship is nearly linear, although perfect linearity is of course impossible because the ratio $\bar{T}_I/(\bar{T}_I + \bar{T}_E)$ is not constant (e.g. Fig. 4).

Total ventilation \dot{V} has conventionally been regarded as a measure of the total output of the respiratory system partly because in experiments on CO₂ inhalation in high O₂ it is so well correlated with P_{A, CO_2} . However, Euler, Herrero & Wexler (1970) and Clark & Euler (1972) have suggested that the rate of increase of inspiratory activity (measured as the slope of the integrated phrenic discharge or as the slope of the line relating inspired

volume and T_I , i.e. \bar{V}_T/T_I), is also a good index of drive. \bar{V}_T/T_I , like \dot{V} , will depend on factors other than respiratory drive, e.g. lung and chest wall compliance, airway resistance and initial length of the respiratory muscles. In situations where these factors are unpredictable (e.g. patients with lung disease) other indices, such as the early part of the inspiratory volume-time slope or $P_{0.1}$ (Milic-Emili, 1974) or dP/dt_{\max} (Matthews & Howell, 1975) may be preferable. In our experiments in healthy young subjects the correlation of P_{A, CO_2} with \bar{V}_T/T_I was just as good as with \dot{V} ($\bar{r} = +0.978$ and $+0.980$ respectively), and the two quantities appeared to measure almost the same thing, as Fig. 3 shows: panel *B* includes data obtained in hypoxia and *D* a few points when P_{A, CO_2} appeared to be below the CO_2 threshold of Nielsen & Smith (1952). Neither the hypoxic nor the below-threshold points stand out as different from the others in these or any other experiments of the series; nor for that matter do the points around the few significant breakpoints (see preceding section). The question of whether these indices of inspiratory activity are (Bartoli, Cross, Guz, Huszczuk & Jefferies, 1975) or are not (Euler and co-workers, e.g. Bradley, Euler, Marttila & Roos, 1975; Callanan, Dixon & Widdicombe, 1975) influenced by vagal activity need not concern us here. If, then, we regard \bar{V}_T/T_I , which is a wholly inspiratory variable as being related to the whole of the respiratory drive even when components other than CO_2 are present, it is possible to use it to obtain an 'effective' $\Delta P_{A, CO_2}$: the effective $\Delta P_{A, CO_2}$ may be defined as the $\Delta P_{A, CO_2}$ that would, operating alone in the absence of all other stimuli, give the observed value of \bar{V}_T/T_I . The effective $\Delta P_{A, CO_2}$ may be read off the plots of \bar{V}_T/T_I against P_{A, CO_2} in high O_2 (Fig. 2) or calculated from the appropriate regressions. The Δ is used because in eqn. (5) it is important to have drive expressed as change of P_{CO_2} ; the point of reference from which the change is measured has been made the intercept of the \bar{V}_T/T_I , P_{A, CO_2} line produced to the P_{A, CO_2} axis (cf. parameter *B* of Lloyd & Cunningham, 1963, with which this intercept is nearly identical). As in earlier work, the use of such an intercept does not in any way pre-judge issues such as the existence or otherwise of apnoea points or thresholds outside the range of the observations: it is purely pragmatic.

In the remainder of this paper the input variable 'drive' is expressed as effective $\Delta P_{A, CO_2}$.

Quantitative description of the pattern

Inspiration

Assuming that end-expiratory volume ($V_{L,E}$) remains constant, tidal volume is determined in inspiration by inspiratory time and slope of inspiratory activity (Clark & Euler, 1972). The effect of increasing drive

on the rate of increase of inspiratory activity \bar{V}_T/\bar{T}_I during CO₂ inhalation has been discussed earlier.

For the series as a whole (hyperoxic points only, number of experiments = 33) the relation can be described by the equation

$$\bar{V}_T/\bar{T}_I = 0.11 (P_A, \text{CO}_2 - 35.2) \quad (3)$$

the s.e. of the slope and intercept being $\pm 0.005 \text{ l. sec}^{-1} \cdot \text{torr}^{-1}$ and $\pm 2.0 \text{ torr}$ respectively.

Inspiratory duration. Euler and his colleagues (e.g. Bradley *et al.* 1975) have discussed and quantified the \bar{V}_T, \bar{T}_I relation very fully and we have no major experimentally based reason for disagreeing with them. In particular, there are good physiological reasons for treating T_I as a function of volume rather than of drive. From the results in the preceding paper (Gardner, 1977) we may write, for both ranges,

$$\bar{T}_I = T_{I_0} \text{ or } e/(\bar{V}_T - f) + g, \quad (4)$$

whichever is the smaller. T_{I_0} was $1.24 \pm 0.04 \text{ sec}$ ($n = 33$). This is an adequate description for most purposes; a slightly more accurate description in range 1 is

$$\bar{T}_I = a + b\bar{V}_T. \quad (5)$$

The mean values (\pm s.e.) of the parameters of eqn. (5) for range 1 are $a = 1.29 \pm 0.006 \text{ sec}$, $b = -0.07 \pm 0.03 \text{ sec. l.}^{-1}$ ($n = 33$); for range 2 (eqn. (4)) they are $e = 0.65 \pm 0.37 \text{ sec. l.}$; $f = 0.88 \pm 0.39 \text{ l.}$; $g = 0.59 \pm 0.11 \text{ sec}$ ($n = 10$). It should be noted that g , the T_I asymptote, regarded as unnecessary by Clark & Euler (1972), is significantly positive. The area constant e is the volume-time product (cf. Clark & Euler, 1972), the reciprocal of which might be regarded as an index of the sensitivity of the inflation reflex.

Expiration

In general, if $V_{L, E}$ is constant expiratory tidal volume is determined by purely inspiratory factors (see above). A new equation describing the independent behaviour of expiratory time will be described.

Initially we sought a single variable such as the chemical drive that would be uniquely related to \bar{T}_E right across the breakpoint. As is shown by Fig. 1C and the text related to it, and also by Table 2 (see later), the use of drive as the only independent variable provided a tolerable description of \bar{T}_E . The impression persisted, however, that there was some sort of breakpoint though, as reported above, its existence could not be proved statistically. Furthermore, inspiratory factors such as \bar{T}_I or inspiratory \bar{V}_T undoubtedly influenced the positions of the individual points in relation to the fitted \bar{T}_E, \bar{V}_T curve both above and below the breakpoint (Fig. 5 of

Gardner, 1977). It seems that two independent variables are required and we should write

$$\bar{T}_E = \text{function}(\bar{T}_I, 1/\text{drive}). \quad (6)$$

It may be that the T_I term really reflects an influence of V_T . \bar{V}_T is, however, also related to drive (Fig. 1A) and when it and drive are the two independent variables difficulties arise in the separation of the components. These difficulties do not arise when \bar{T}_I is the second independent variable.

Additive and multiplicative forms of such equations may be written

$$\bar{T}_E = p\bar{T}_I + q/(\text{drive} - r) + s \quad (7)$$

and

$$\bar{T}_E = q'\bar{T}_I/(\text{drive} - r') + s' \quad (8)$$

respectively. Though the equations are derived from mean values of the variables, at each single value of mean drive the equation should also describe the relation between the individual breath-by-breath values of T_I and T_E as they 'hunt' around their means (e.g. Fig. 4; see also Newsom Davis & Stagg, 1975 and Kay, Petersen & Vejby-Christensen, 1975). If we accept that this is so, the breath-by-breath data give us a means for discriminating between the two equations. Both state that when drive is constant (as in each of the 341 steady states) then breath-by-breath values of T_E plotted against the corresponding T_I yield a straight line. When a separate plot is made for each steady state of one experiment, eqn. (7) predicts that these straight lines should be parallel, with slope p and vertical intercept $s + q/(\text{drive} - r)$, whereas eqn. (8) predicts a fan of straight lines radiating from a single intercept s with slopes $q'/(\text{drive} - r')$, i.e. their slopes should vary inversely with drive.

Fig. 4 shows \bar{T}_E plotted against \bar{T}_I for a single experiment. The proportionality of mean T_E to T_I , indeed, their near-equality (cf. Clark & Euler, 1972), is apparent as long as both are less than about 1.5 sec, that is to say, over what appears to be range 2. In range 1, however, where \bar{T}_E was longer than this, the proportionality broke down, there being little further lengthening of \bar{T}_I , as has been shown already (Gardner, 1977).

Breath-by-breath linkage between T_E and T_I (e.g. Newsom Davis & Stagg, 1975; see also Fig. 3 of Kay *et al.* 1975) was significant in only the minority of subjects who showed a large amount of scatter: even in them it was demonstrable in only some of the runs. In Fig. 4, twelve of the nineteen steady states showed no significant linkage even though between 40 and 100 consecutive breaths were measured for each steady state. The seven significant regression lines are centred on the corresponding steady-state points and span ± 2 s.d. of T_I . The slopes of these lines are not significantly different from one another and they lie nearly parallel to the spread of the *mean* T_E , T_I points that comprise range 2. The lines in range 1 lie above those in range 2. In the seven experiments analysed in this way

there appeared to be a slight tendency for the slopes to increase systematically with decrease of drive (i.e. with lengthening of mean \bar{T}_E), but it was not statistically significant. The intercepts on the T_E axis, however,

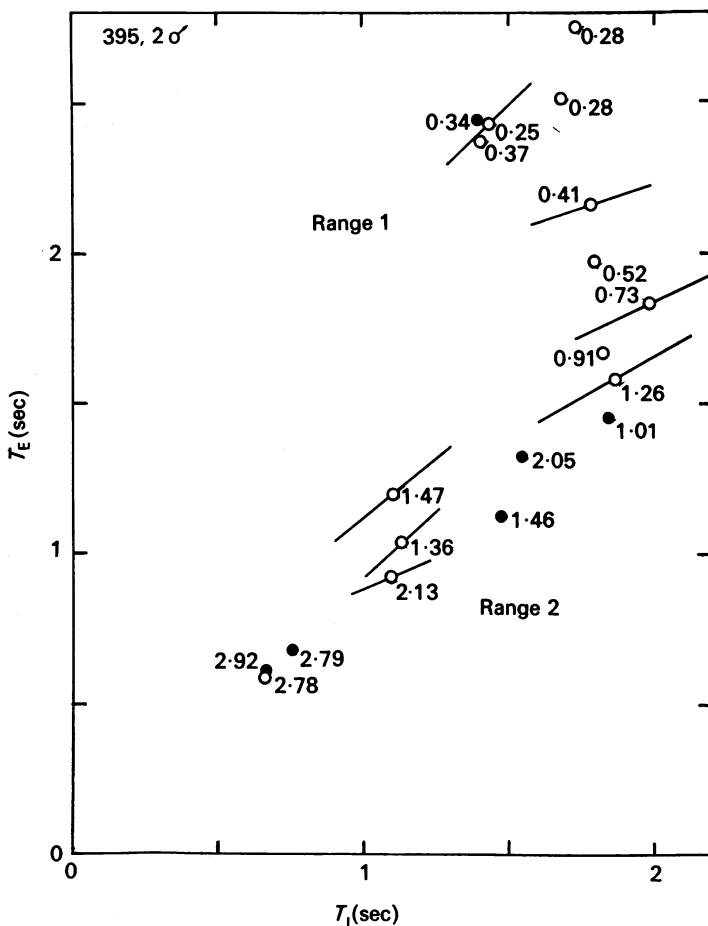


Fig. 4. T_E plotted against T_I for one experiment covering both ranges 1 and 2 (this experiment is also shown in Fig. 5 of Gardner, 1977). Symbols represent mean values as in Fig. 1; the filled symbols represent hypercapnic hypoxia ($P_A, O_2 \sim 55$). The short lines are the regressions of individual T_E on individual T_I values (i.e. breath-by-breath T_E vs. T_I) for the steady states represented by the associated points; their extents show ± 2 s.d. of breath-by-breath T_I . Only significant correlations are so represented. The numbers beside the symbols are \bar{V}_T/\bar{T}_I l. sec $^{-1}$.

Note (1) that mean T_I and mean T_E are well correlated over range 2 ($T_E < 1.5$ sec) but not in range 1, and (2) that the breath-by-breath regressions of T_E on T_I within each steady state are largely independent of mean T_I .

were negatively correlated with the respiratory drive ($r = -0.46$, $P < 0.01$). It was possible to test the effects of drive on the slopes and intercepts of these breath-by-breath T_E , T_I lines in another way. The data from nine experiments were such as to allow grouping of slopes and intercepts into those obtained at high and at low levels of drive respectively. As Fig. 5 shows, the means of the slopes at high drive did not differ systematically from those obtained at low drive, whereas the means of the intercepts showed a significant tendency to be smaller when drive was high (Wilcoxon's rank order test, $P < 0.025$). Thus, the relations between T_I and T_E fulfil the predictions of eqn. (7) better than of eqn. (8).

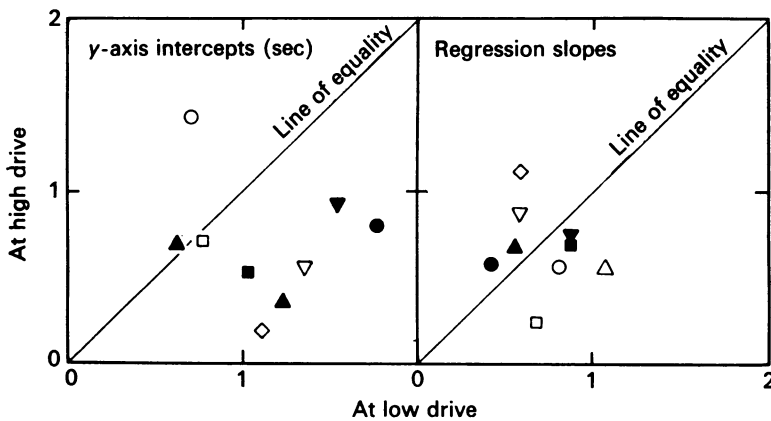


Fig. 5. The effect of changing respiratory drive on the slopes and intercepts of the breath-by-breath T_E vs. T_I regression lines, (e.g. Fig. 4). Nine experiments are shown; each experiment is represented by a separate symbol. The slopes and vertical intercepts have been divided into roughly equal groups, averaged and compared for high and low levels of drive. The left-hand panel shows that the intercepts tend to increase as drive decreases whereas the right-hand panel shows that the slopes do not change consistently. This is in accordance with predictions of eqn. (7) but not those of eqn. (8).

Eqn. (7) was fitted separately to the data of all thirty-three experiments. Four of the fits were rejected because parameter r was indeterminate (no minimum residual sum of squares emerged, see Methods). A fifth fit was excluded from the averages that follow on the grounds that the drive parameter q lay more than six s.d.s from the mean; its inclusion in the averages distorted what we regard as the proper representative values. The averages for the remaining twenty-eight are presented in Table 1.

Mean s was not significantly different from zero (see also Table 2) and the second line of the Table shows the effects of recalculating the other parameters with s set at 0.

In all calculations, \bar{V}_T/\bar{T}_I has been used as a measure of drive, and $\Delta P_{A, CO_2}$ has been derived by dividing \bar{q} and \bar{r} by the mean slope of the $\bar{V}_T/\bar{T}_I, P_{A, CO_2}$ relationship (see eqn. (3)). The drive parameters in Table 1 are expressed in terms of both V_T/T_I and $\Delta P_{A, CO_2}$. It would, of course, be possible to calculate $\Delta P_{A, CO_2}$ first and then use it directly in the equation instead of \bar{V}_T/\bar{T}_I .

TABLE 1. Mean values (\pm s.e.) of parameters of eqn. (7) with and without s , the \bar{T}_I independent component of the \bar{T}_E asymptote. Twenty-eight experiments, 341 determinations

$$\bar{T}_E = p\bar{T}_I + q/(\text{drive} - r) + s$$

	p	q (l. ⁻¹)	q' (sec. torr ⁻¹)	r (l. sec ⁻¹)	r' (torr)	s (sec)	L
	+0.70	+0.90	+8.18	-0.22	-2.00	+0.001	+0.95
s.e.	\pm 0.11	\pm 0.17	\pm 1.55	\pm 0.09	\pm 0.82	\pm 0.14	\pm 0.03
	+0.64	+1.22	+11.09	-0.30	-2.73	0	+0.98
s.e.	\pm 0.09	\pm 0.29	\pm 2.64	\pm 0.12	\pm 1.09		\pm 0.04

The drive components are expressed in units of V_T/T_I , i.e. l. sec⁻¹ (q, r) and as 'effective $\Delta P_{A, CO_2}$ in high O_2 ' (q', r') derived for each experiment by division of mean q and mean r by the mean slope parameter of eqn. (3), i.e. 0.11.

Both forms of the equation (i.e. with and without s) are equally acceptable (see Table 2). The 7th column gives the mean and s.e. of the combined parameter L (see Appendix) calculated here from the V_T/T_I drive parameters; note that the s.e. of L in each case is less than that of any of the individual parameters.

Fig. 6 shows the mean relation between \bar{T}_E and drive according to eqn. (7); the relation between \bar{T}_I and drive is not shown, but the separate components of the equation, including $p\bar{T}_I$ as a function of drive, are indicated. Over range 1 (upper left in the Figure) the systematic change in \bar{T}_E is determined almost entirely by change of drive, the corresponding change in \bar{T}_I being minimal. The shortening of \bar{T}_I is seen to affect the \bar{T}_E curve at and beyond the transition to range 2, causing \bar{T}_E to diverge from the continuation of the simple hyperbola that comprises range 1. The divergence is small, in keeping with the finding that the supposed breakpoint in the \bar{T}_E , drive relation, unlike that for \bar{T}_E vs. \bar{V}_T , did not reach overall significance though it appeared to be present in most of the experiments with breakpoints in other plots.

The relative importance of each parameter. Table 2 is an F -ratio matrix which shows how the description provided by eqn. (7) deteriorates as individual parameters or pairs of parameters are omitted. In each case the appropriate equation was fitted to all experiments individually and the resulting residual sums of squares compared by analyses of variance. The Table shows the resulting F -ratios and their significances. Omission of either p or q markedly reduced the goodness of fit, implying that \bar{T}_E

could not be described adequately in terms of either \bar{T}_I or drive alone. This was true even for the ten experiments in which no breakpoint and thus no range 2 was present (separate calculations like those in Table 2).

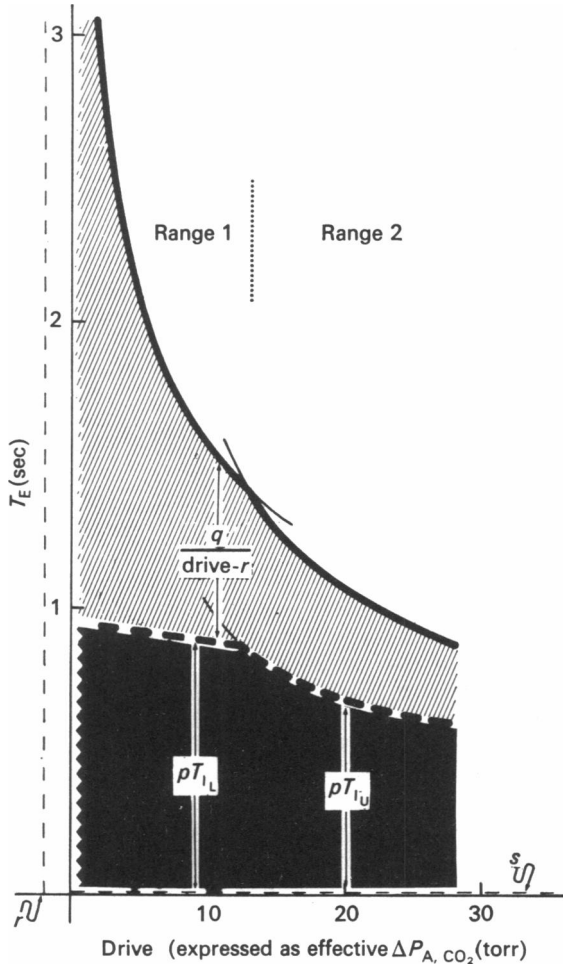


Fig. 6. A two-dimensional representation of eqn. (7), averaged for twenty-eight experiments. T_E is shown as a function of drive (which is the major independent variable) expressed as $\Delta P_{A, CO_2}$ (see text, and legend, Table 1). For purposes of representation only, the contribution of the second independent variable \bar{T}_I (suffixes U for upper or Clark & Euler's (1972) range 2; and L for lower or their range 1) was calculated from equations analogous to eqns. (4) and (5), but relating \bar{T}_I to drive rather than to \bar{V}_T . The contribution of drive and \bar{T}_I are shown by the upper and lower shaded areas respectively, and their sum (+ parameter s) is the continuous heavy line. Mean values of p , q , r and s given in Table 1 have been used. Note that the mean of the vertical asymptote r is negative and s is negligible. The shallow break in the continuous line is due entirely to the break in \bar{T}_I .

Of the two, the figures indicate the superior importance of drive. With regard to the asymptotes, s could be omitted with little loss of precision provided p was retained, but omission of r rendered the description significantly worse; inspection of eqn. (7) shows that r is especially important when drive is small and \bar{T}_E long, e.g. in eupnoea at rest. We conclude that three of the parameters of eqn. (7) are necessary to provide an adequate prediction of \bar{T}_E in healthy young adults. The description is greatly superior to the corresponding equation of Clark & Euler (1972; see their Table 1), which is tested in column 8 of our Table 2.

TABLE 2. Analysis of variance

	(1) <i>pqr</i> s	(2) <i>pqr</i> -	(3) <i>pq</i> - <i>s</i>	(4) <i>-qr</i> s	(5) <i>pq</i> ..	(6) <i>-qr</i> -	(7) <i>-q</i> - <i>s</i>	(8) <i>p</i> .. <i>s</i>
(A) <i>pqr</i> s		1.11 n.s.	1.78 $P < 0.01$	3.44 $P < 0.001$	1.94 $P < 0.001$	2.94 $P < 0.001$	10.2 $P \ll 0.001$	27.9 $P \lll 0.001$
(B) <i>pqr</i> -			—	—	2.80 $P < 0.001$	4.73 $P < 0.001$	—	—
(C) <i>pq</i> - <i>s</i>			—	—	2.00 $P < 0.001$	—	7.73 $P \ll 0.001$	49.9 $P \lll 0.001$
(D) <i>-qr</i> s					—	1.94 $P < 0.01$	5.29 $P \ll 0.001$	—

An analysis of variance matrix showing the F -ratios and significances of the deteriorations of fit as various coefficients or pairs of coefficients are successively omitted from the full equation. F -ratios were calculated from residual mean-squares and 28/229, 28/257, 28/285 or 28/313 degrees of freedom, as appropriate. (1) q and p are the fundamental parameters (Table lines A, B, C), q being by far the more important (line A, columns 4, 5 and 8; and line C). (2) Asymptotes r and s : omission of r always had significant effects (A3, B5, D7); if other important parameters were already absent, omission of s had significant effects (C5, D6), but the effect of omitting s only was not significant (A2). *Conclusions*: (1) it is legitimate to use the three parameters p , q and r , omitting s ; (2) the performance of the equation of Clark & Euler (1972) (column 8) is markedly inferior to that of several others.

The inclusion of drive as an important factor in the equation is in accordance with the observation that the frequency parameter m of the \bar{V}_E , \bar{V}_T relation is well correlated with CO_2 sensitivity (Hey *et al.* 1966; Patrick & Howard, 1972).

Milic-Emili & Grunstein (1976) recognize the importance of T_E , but they appear hesitant in according it independent status, as we have done; their equation emphasizes the ratio of T_I to T_{total} rather than mentioning T_E explicitly. The relations of \bar{T}_I/\bar{T}_E and \bar{T}_I/\bar{T}_T to both \bar{V}_T and drive were examined at an early stage in the present work. Both ratios changed in a curvilinear fashion over range 1 and were roughly constant over range 2;

the mean value of \bar{T}_I/\bar{T}_E was about 1.0 in range 2 (e.g. Fig. 4). Nevertheless, in comparison with the relation of drive to \bar{T}_E , which was consistently curved in one direction, the ratios showed inconsistent and sometimes bizarre behaviour and the breakpoints estimated visually from these plots corresponded poorly with those derived by other means. Eqn. (7) could, of course, be modified to express the behaviour of either ratio, if so desired.

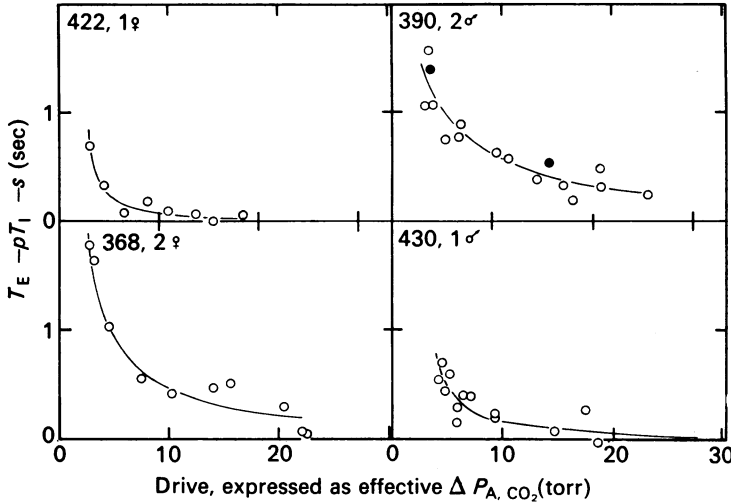


Fig. 7. Eqn. (7) fitted to the four experiments of Figs. 2 and 3. $(\bar{T}_E - p\bar{T}_I - s)$ is shown as a function of drive expressed as $\Delta P_{A,CO_2}$.

Goodness of fit

Fig. 7 shows the results of fitting eqn. (7) to four typical experiments. The ordinates are the part of \bar{T}_E attributable to the drive term, expressed as $(\bar{T}_E - p\bar{T}_I - s)$, and the abscissae are drive. The points are reasonably close to the lines and the scatter appears to be random. The magnitude of the drive-dependent part of \bar{T}_E varied from subject to subject and did not seem to be related to vital capacity. A reasonable approximation to these curves may be obtained without computing p and s by assuming them to be +0.7 and 0 respectively (Table 1).

Fig. 8 is a plot of \bar{T}_E calculated from eqn. (7) against the observed \bar{T}_E for sixteen experiments (the nineteen with significant divisions into ranges 1 and 2, less three in which it was not possible to fit eqn. (7) as described above). In the Figure the values have been standardized along the line of equality so that all the breakpoints are superimposed. No trend across the breakpoint is apparent. The statistical details appear in the legend to the Figure; they suggest that the correspondence between observed and calculated \bar{T}_E is slightly better in range 1 than in range 2.

Correlations between parameters

The main parameters p and q tend to be negatively correlated and, as is liable to occur with hyperbolae, q is negatively correlated with the asymptotes r and s . Thus, though the standard deviations of all parameters are substantial, there is the expectation that when, for example, q is large, p and/or r and s will be more negative. Therefore, when two populations of drive vs \bar{T}_E data are being compared it would be possible to find each individual parameter to be within 'normal' limits, yet for the interrelations of one or more of the sets of parameters to be abnormal. This idea can be expressed quantitatively by deriving another parameter L

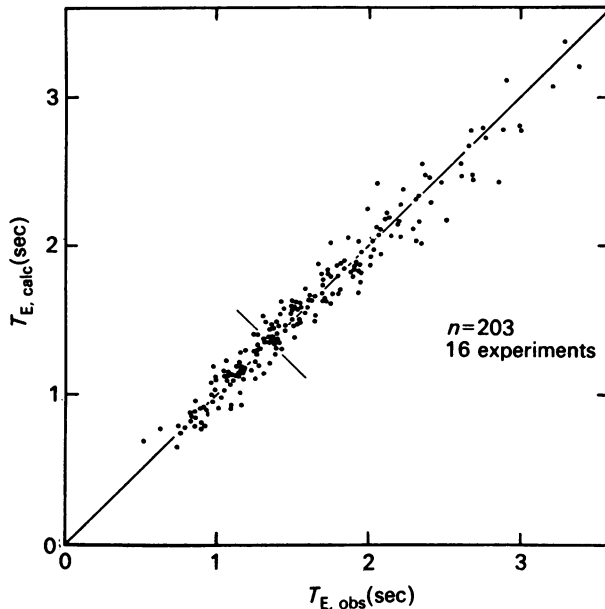


Fig. 8. Goodness of fit of eqn. (7). The Figure shows the actual values of mean T_E in relation to T_E calculated from the individual equation for each of sixteen experiments (nineteen with significant breakpoints less three which could not be fitted by the equation). To show more clearly any possible trends across the breakpoint, all experiments have been superimposed at a common breakpoint (crossed line) by bodily shifting the individual experiments up or down the line of equality. The mean correlation coefficient over these sixteen experiments was 0.981, and 0.980 when calculated for all twenty-eight experiments fitted by eqn. (7). The mean value of the difference between the observed and calculated value of \bar{T}_E , i.e. an estimate of the confidence limits of the equation was 0.12 sec for the lower range ($n = 276$) and 0.10 sec for the upper ($n = 65$). The corresponding coefficients of variation (i.e. after division by the means of $\bar{T}_{E, \text{lower}}$ and $\bar{T}_{E, \text{upper}}$, 1.73 and 1.05 respectively) were 0.07 and 0.09.

(personal communication, Dr M. G. Bulmer) which combines the four (or three) basic parameters and also expresses the correlations between them. For a set of parameters to be judged 'within the normal range' not only must they lie individually within 2 s.d. of the appropriate means, but they must be mutually related normally as judged from the value of L (Table 1, column 7). The usefulness or otherwise of this parameter will only be testable when two populations of data are available for testing. The method of calculating L is given in an appendix.

Concluding remarks

We now envisage the effects of drive as being exerted on T_E by two mechanisms. The first, an indirect one, is expressed in terms of $p\bar{T}_I$ in eqn. (7). The primary inspiratory effect of drive is on the rate of increase of inspiratory activity (mean inspiratory flow rate \bar{V}_T/\bar{T}_I in human experiments). This, in conjunction with the 'central clock' and the volume-time threshold mechanisms that are thought to determine T_I over ranges 1 and 2 respectively, determines \bar{V}_T (Clark & Euler, 1972; Grunstein, Younes & Milic-Emili, 1973). In the conscious animal it is probably the breath-by-breath variations in T_I that give rise to the breath-by-breath variations in \bar{V}_T ; i.e. the longer the time allowed for filling the bigger the tidal volume. The two in combination show a 'hunting' pattern along a \bar{V}_T/T_I line; the hunt centres on the mean of the steady state which lies on the steady-state \bar{V}_T, \bar{T}_I relation discussed here and in the preceding paper and is roughly at right angles to it (Cunningham, Pearson & Gardner, 1972; Newsom Davis & Stagg, 1975; Kay *et al.* 1975). \bar{V}_T can affect T_E both mechanically (the greater the volume the longer is the time required to empty the lungs through the prevailing airway resistance) and reflexly (Breuer, 1868; Knox, 1973; Bartoli, Bystrzycka, Guz, Jain, Noble & Trenchard, 1973), and it is probably through its breath-by-breath effect on \bar{V}_T that T_I is linked weakly to T_E (Fig. 4; cf. also the weak *positive* breath-by-breath correlation of \bar{V}_T with T_E , Newsom Davis & Stagg, 1975). On the other hand, the steady-state relation between mean values of these variables at various levels of drive is quite different (see Figs. 1, 3 and 4 of Gardner, 1977, in which \bar{V}_T and \bar{T}_E are *inversely* related) and it is with steady-state data that eqn. (7) is concerned.

The second mechanism, expressed as q /drive in eqn. (7), acts directly in the sense that it can operate independently of inspiratory events (Gardner, 1975, 1977); indeed, it can even be made to operate out of phase with inspiration (Ward & Cunningham, 1977). We think of the mechanism as modifying the emptying curve of the lungs (Gautier, Remmers & Bartlett, 1973; see Fig. 5 of Kay *et al.* 1975); this it does by varying the combination of braking by inspiratory muscles early in expiration, of

propulsion by expiratory muscles and of the values of the resistances in the lower and upper airways, including the larynx, very much as described by Gautier *et al.* (1973), and Remmers (1976).

The direct desensitising effect of CO_2 on the stretch receptor endings may be important for T_E in the dog (Bartoli, Cross, Guz, Jain, Noble & Trenchard, 1974; Bradley, Noble & Trenchard, 1976), but what may be the corresponding effect in man is small (Cunningham, Drysdale, Gardner, Jensen, Petersen & Whipp, 1977). It follows that, on the afferent side, a large part of the effect of drive on T_E is exerted by some means other than the inhibitory effect of CO_2 on the pulmonary stretch receptors. For example, drive from the arterial chemoreceptors seems to operate on T_E with a very short latency (Drysdale & Ward, 1976).

In summary, the drive, acting through afferent pathways that have yet to be established, 'sets' the lung emptying curve, and also contributes, through the inspiratory variables, to the tidal volume and thus to the determination of the positions on the emptying curve that the individual breaths or series of breaths will occupy. Both influences are expressed in eqn. (7).

APPENDIX

Derivation of the extra parameter L

As stated above, L is an extra parameter which combines the four (or three) basic parameters of eqn. (7) and also expresses the correlations between them (Dr M. G. Bulmer, personal communication). Based on the simplified form of eqn. (7) which omits s ,

$$L = \bar{p} + w_2 \bar{q} + w_3 \bar{r}, \quad (9)$$

w_2 and w_3 are weighting factors; \bar{p} , \bar{q} and \bar{r} are means for the whole series of experiments.

$$\text{Var of } L = \text{Var}_p + w_2^2 \text{Var}_q + w_3^2 \text{Var}_r + 2w_2 \text{Covar}_{pq} + 2w_3 \text{Covar}_{pr} + 2w_2 w_3 \text{Covar}_{rs}, \quad (10)$$

which is a standard formula for estimating the variance of a sum; Var and Covar are variances and covariances.

This variance formula is then successively minimized with respect to w_2 and w_3 :

$$\frac{\partial \text{Var}_L}{\partial w_2} = 2w_2 \text{Var}_q + 2 \text{Covar}_{pq} + 2w_3 \text{Covar}_{qr} = 0, \quad (11)$$

$$\frac{\partial \text{Var}_L}{\partial w_3} = 2w_3 \text{Var}_r + 2 \text{Covar}_{pr} + 2w_2 \text{Covar}_{qr} = 0. \quad (12)$$

Solving for w_1 and w_2 gives values at which Var_L is at a minimum.

A corresponding procedure, involving a w_4 and parameter s may be used if it is thought necessary to include parameter s .

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