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Anthropometric and other factors affecting respiratory responses to carbon dioxide in New Guineans

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A CO_2 rebreathing test was used to determine the breathing pattern and the ventilatory response to CO_2 in 15 Caucasians and 140 New Guineans (coastal and highland men and women, and male highlanders on the coast). The breathing pattern was analysed in terms of the slope and intercept (M and K) of the linear regression of ventilation on tidal volume: $\dot{V}_e = M(V_t - K)$, and of the interpolated tidal volume at a ventilation of 30 l min^{-1} ($V_{t,30}$). Each of these parameters bears a common relation to vital capacity throughout the groups studied. The CO_2 response was analysed in terms of the slope and intercept (S and B) of the linear regression of ventilation on P_{CO_2}: $\dot{V}_e = S(P_{CO_2} - B)$. B is lower in women than in men. S is a function of vital capacity, and this relation accounts for the difference in CO_2 sensitivity between men and women, and for part of the difference between the resident highland and coastal groups; part is attributable to altitude-adaptation and disappears on migration. In all these respects, New Guineans resemble Caucasians, and the results demonstrate the importance of the size of the vital capacity in influencing the setting of the respiratory control mechanisms. In addition, there is a residual difference between the ethnic groups, with the New Guineans having the lower CO_2 sensitivities and thus a greater tolerance of CO_2 loads.

The I.B.P. Expedition to New Guinea offered a remarkable opportunity to investigate respiratory control mechanisms in a population whose physique, lung function and environmental stresses were quite different from those of the Caucasian subjects commonly studied by respiratory physiologists. Recently, attention has been drawn to the biological significance of variations in respiratory responses to chemical stimuli and in ventilatory patterns.

Schaefer (1958) found that low CO_2 sensitivity was associated both with a pattern of breathing showing low frequencies and high tidal volumes, and also with larger vital and inspiratory capacities. Patrick & Howard (1972) found that age and lung size had specific effects on the breathing pattern, and suggested that the link with CO_2 sensitivity was a function of vagal lung-afferent activity. Low CO_2 sensitivity has been found in experienced divers (Schaefer 1958), endurance athletes (Rebuck & Read 1971), New Guinean highlanders (Beral & Read 1971) and Caucasian women (Patrick & Howard 1972). In addition, ethnic differences between Europeans, Indians and Africans have been demonstrated for lung volumes and ventilatory capacities, even after adjustment to allow for differences in lung and body size (Cotes 1968; Miller *et al.* 1972).

In the present study, a simple technique (Read 1967) has been used to determine CO_2 sensitivity and breathing patterns during hyperventilation at rest in coastal and highland New Guineans, and in a small control group of Caucasians. The indices have been analysed in relation to several other variables studied on the same populations.

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METHODS

Survey areas and subjects

Two contrasting New Guinean communities, each of about 1300 people, have been surveyed. Kaul is a coastal village on Karkar Island 15 km off the north coast of the mainland, and Lufa is in the Eastern Highlands at an altitude of about 2000 m. The villages also differ in their climate, their nutrition, and their patterns of employment and customary activity; further details of their human biology can be found in the other papers of this volume.

The main groups of subjects studied in both areas were young adults, both men and women. In addition, small groups of Caucasians were also tested at the coastal laboratory, and a further major group comprised young highland men who were indentured labourers on a coastal plantation on Karkar Island. These men were native to villages comparable in altitude and economy with Lufa but had been sojourners for between 3 and 24 months at sea-level, where they were studied. In Lufa the subjects were chosen at random from the young adult population, very few being rejected on grounds of chronic or current illness. In Kaul they were volunteers, but there is no reason to suppose that any serious bias was introduced by this method of sampling. Table 1 shows the numbers of subjects finally included in each group, and it summarizes their basic anthropometry and ventilatory capacities, which have been discussed in detail by Cotes, Anderson & Patrick (this volume, p. 349).

TABLE 1. GROUPS OF SUBJECTS STUDIED IN NEW GUINEA, GIVING BASIC ANTHROPOMETRIC AND LUNG FUNCTION DATA FOR EACH GROUP

		means and standard deviations									
subject group	no.	age/years		height/m		mass/kg		t.l.c./l		f.v.c./l	
1. Coastal men	28	24.7	4.1	1.651	0.047	58.50	4.29	5.15	0.61	3.83	0.53
2. Coastal women	27	22.2	4.3	1.559	0.063	53.02	5.00	3.91	0.39	2.86	0.37
3. Highland men (resident)	28	24.8	3.9	1.657	0.046	60.04	4.46	6.00	0.64	4.22	0.44
4. Highland women	25	21.9	3.8	1.551	0.059	50.14	7.80	4.31	0.62	3.16	0.42
5. Highland men (migrant)	32	23.8	4.7	1.598	0.057	63.14	5.55	5.28	0.68	4.05	0.60
6. Caucasian men	8	28.9	5.1	1.833	0.043	73.75	8.51	7.79	0.43	5.89	0.32
7. Caucasian women	7	23.0	4.1	1.729	0.052	61.07	5.83	5.65	0.56	4.17	0.57

Laboratory procedures

The test procedures reported here were part of a battery of lung-function and work-capacity tests made during the day or two that each subject spent in the air-conditioned laboratory. The other results are being reported elsewhere (Patrick, Cotes & Saunders 1973; Cotes *et al.* 1973; Cotes, Anderson & Patrick, this volume). Tests were performed in various orders and care was taken that there could be no interference of the results of one test by another. Vital capacity (v.c.) and total lung capacity (t.l.c.) were measured with a McDermott bellows spirometer and a Meade–Saunders Respirometer.

Respiratory regulation was investigated using the rebreathing procedure of Read (1967) in which the seated, resting subject rebreathes a CO_2/O_2 mixture for about 5 min. The expired volume, tidal P_{CO_2} and tidal F_{O_2} were continuously recorded as the subject hyperventilated in response to the rising CO_2 stimulus. The practical details of the procedure were very similar to those described by Patrick & Howard (1972). Twenty of the original subjects were excluded from the final analysis either because they failed to complete the rebreathing procedure or because their hyperventilation response was irregular or unsustained.

Values for minute ventilation ($\dot{V}_e$), mean tidal volume (V_t), and tidal P_{CO_2} were obtained from the trace for successive $\frac{1}{2}$ min periods after the first minute, which was ignored. These values were plotted in the conventional way to give a Hey plot of the breathing pattern ($\dot{V}_e$ against V_t; Hey *et al.* 1966) and a CO_2 response line ($\dot{V}_e$ against P_{CO_2}). Allowance was made for certain occasional but characteristic non-linearities (cf. Patrick & Howard 1972; Pearson & Cunningham 1972), and regression lines were calculated for the linear portions of each relation.

The respiratory responses are expressed as the numerical values for the slopes and intercepts of the two regression lines for each subject. The breathing pattern can conveniently be described by the equation

$$\dot{V}_e = M(V_t - K),$$

whose parameters represent the notional maximum respiratory frequency (the slope, M) and the minimum tidal volume (K, the intercept on the tidal volume axis; Hey *et al.* 1966). In addition, the tidal volume at a ventilation of 30 l min^{-1} ($V_{t,30}$) has been calculated as an alternative index to the two parameters M and K (cf. Cotes, Johnson & McDonald 1970). The parameters of the CO_2 response line are the slope S representing the sensitivity to CO_2 in the absence of hypoxia, and the intercept B representing the CO_2 threshold. The regression equation is

$$\dot{V}_e = S(P_{CO_2} - B).$$

Patrick & Howard (1972) have discussed the relation between the values for the parameters obtained during the present non-steady-state method, and those previously established using steady-state procedures. All the parameters obtained here were treated as variables in a statistical analysis in which the subject groups were compared, and cross-correlation and covariance analyses were performed.

TABLE 2. RESPIRATORY RESPONSES OF THE GROUPS OF SUBJECTS STUDIED IN NEW GUINEA

The means and standard deviations of the parameters are given.

		pattern of breathing						response to CO_2			
		K/l		M/min^{-1}		$V_{t,30}$		B/Torr		S/l min^{-1} Torr^{-1}	
subject group	no.										
1. Coastal men	28	0.42	0.22	35.5	8.1	1.31	0.19	43.6	4.7	1.66	0.44
2. Coastal women	27	0.29	0.18	36.6	11.3	1.18	0.15	38.1	7.4	1.16	0.38
3. Highland men (resident)	28	0.44	0.21	32.4	5.6	1.39	0.18	42.4	3.7	1.94	0.52
4. Highland women	25	0.35	0.19	35.1	10.6	1.30	0.22	40.2	5.4	1.52	0.55
5. Highland men (migrant)	32	0.42	0.23	32.4	6.7	1.38	0.18	41.9	6.5	1.64	0.58
6. Caucasian men	8	0.63	0.19	25.6	6.4	1.87	0.34	45.3	5.4	2.86	1.14
7. Caucasian women	7	0.24	0.31	26.9	8.6	1.47	0.28	41.9	6.6	2.44	1.37

RESULTS

Table 2 summarizes the values obtained for the parameters of the respiratory responses in each of the seven subject groups.

Figures 1 and 2 show, for men and women separately, the breathing patterns and the CO_2 response lines for the groups. The lines have been constructed using the mean slope and mean intercept for the individual groups. In fact, there are no significant differences between the intercepts in any of the figures (parameters K and B), so the inter-group variation can be roughly represented by fans of lines. The same pattern of variation is shown by both sexes. For the $\dot{V}_e$, $\dot{V}_t$ plot (figure 1) the coastal people have the steepest lines followed by the highlanders, and then the Caucasians, who have significantly the flattest line, i.e. the lowest values for the slope M. For the CO_2 response (figure 2), however, the order is reversed. The Caucasians, the highland residents and the coastal dwellers in descending order of CO_2 sensitivities (S) are significantly different from one another.

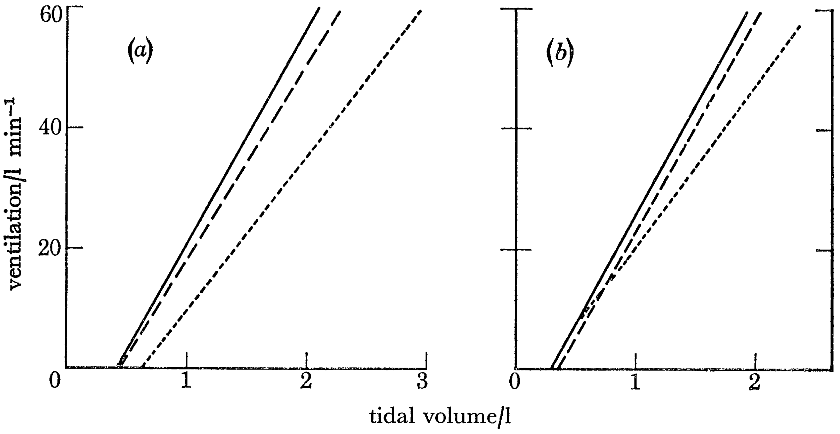

Figure 1. Relation between ventilation and tidal volume in (a) men and (b) women. ——, coastal New Guineans; – –, highland New Guineans; · · · ·, Caucasians. The line for the male highland migrants has been omitted for clarity. On this scale it is indistinguishable from the dashed line for the male highland residents in (a).

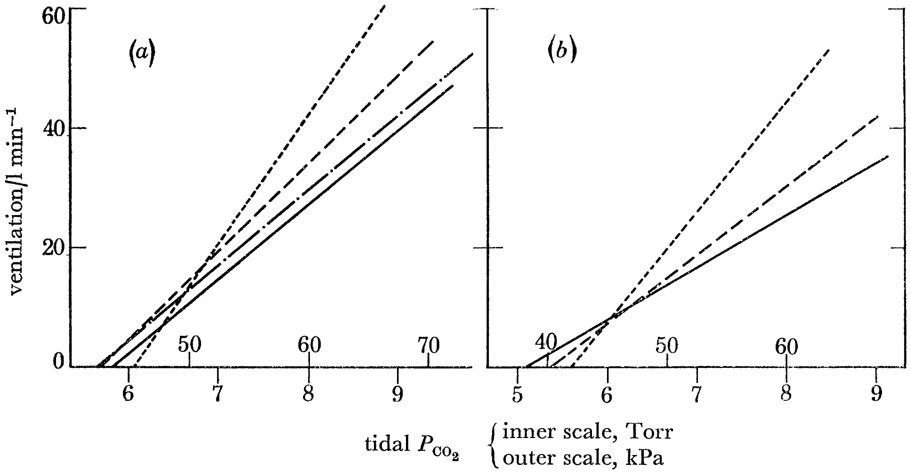

Figure 2. Relation between ventilation and P_{CO_2} in (a) men and (b) women. ——, coastal New Guineans; —·—, migrant highland New Guineans; – –, resident highland New Guineans; · · · ·, Caucasians.

The highland men have been studied in two localities: the breathing pattern of the migrants to the coast is very similar to that of the residents at the altitude from which they had come. However their CO_2 response slope resembles that of the coastal people among whom they were currently living and is significantly less steep than that of the altitude residents (figure 3). When the two sexes are compared, both S and B are found to be consistently greater in men than in women, and the difference is significant in most of the paired groups (figure 4). K and M, however, show no such sex difference.

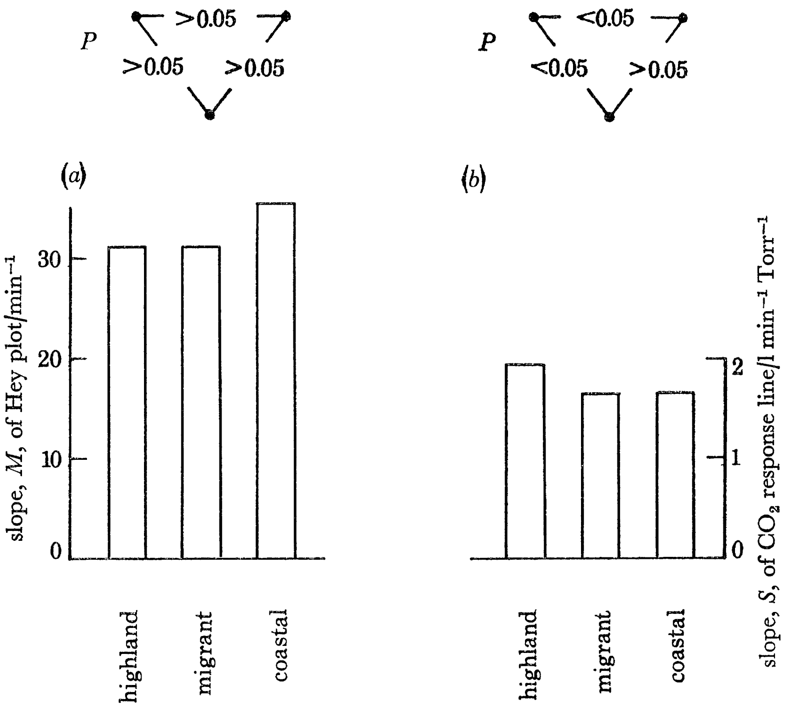

Figure 3. Comparison of (*a*) the slope *M* of the Hey plot and (*b*) the slope *S* of the CO_2 response line between groups of New Guinean men at different altitudes. *P* values in the *t* test are given for each comparison.

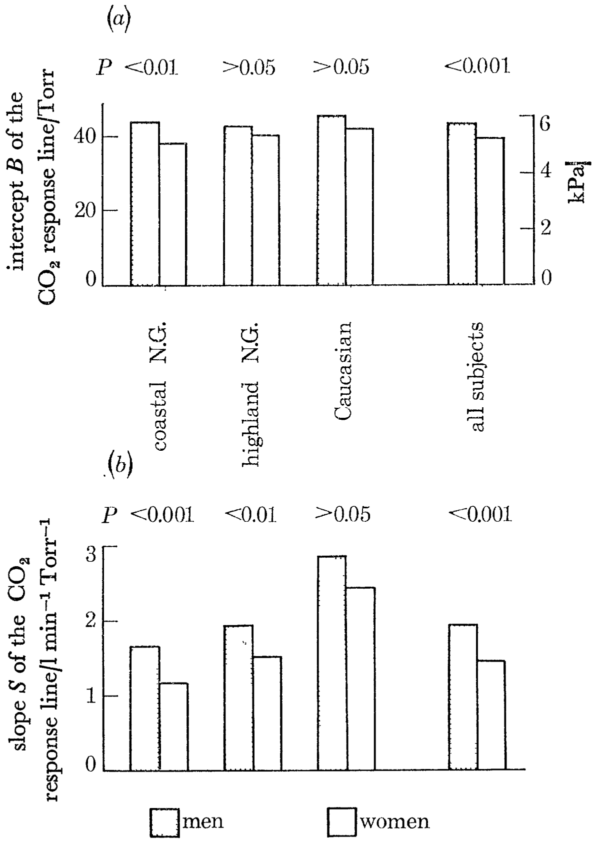

Figure 4. Comparison of (*a*) the intercept *B* and (*b*) the slope of the CO_2 response line between men and women. *P* values in the *t* test are given for each group comparison.

A cross-correlation matrix for the relevant variables is given in table 3. The values have been calculated for all the subjects pooled, and only those coefficients significant at the 0.05 level of probability are shown. The relation of lung volume, including vital capacity (v.c.), with height has been discussed by Cotes *et al.* (this volume); here the respiratory parameters K, M, $V_{t,30}$ and S are shown to be moderately strongly correlated with v.c.

TABLE 3. CROSS-CORRELATION MATRIX FOR EIGHT VARIABLES IN ALL SUBJECTS STUDIED IN NEW GUINEA

Only coefficients significant at the 5% level are shown.

	age	height	v.c.	K	M	$V_{t,30}$	B	S
age	—							
height	—	—						
vital capacity	0.30	0.67	—					
K	—	0.22	0.33	—				
M	—	—	−0.31	0.51	—			
$V_{t,30}$	0.32	0.41	0.60	0.36	−0.55	—		
B	—	—	—	0.26	—	0.22	—	
S	—	0.36	0.55	0.38	—	0.33	0.44	

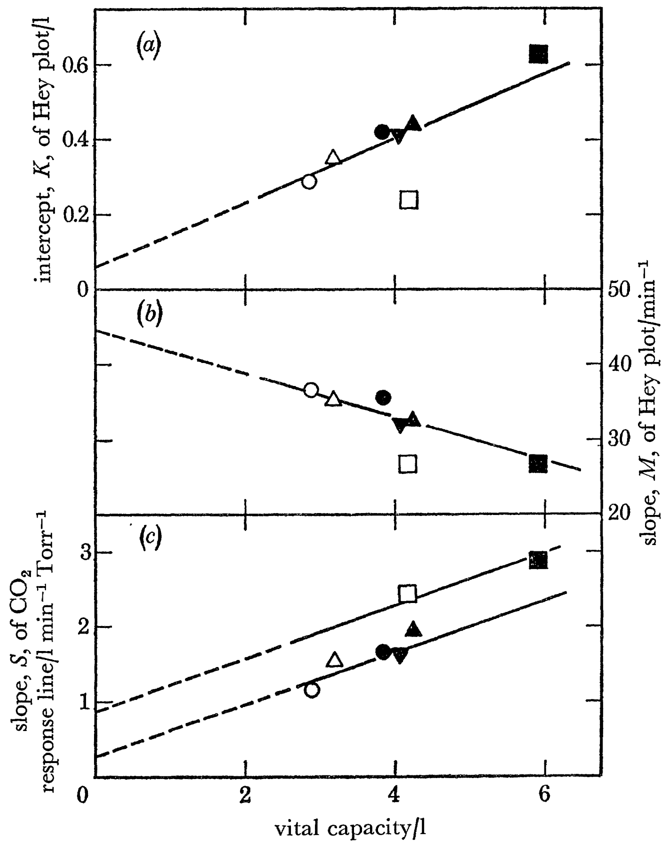

FIGURE 5. Relation with vital capacity of (*a*) intercept K and (*b*) slope M of Hey plot, and (*c*) slope S of CO_2 response line. Mean values for subject groups are shown. Filled symbols represent males, unfilled symbols females. ●, ○, coastal New Guineans; ▲, △, highland New Guineans; ▼, highland migrants; ■, □, Caucasians. Common regressions for all the subject groups are shown, except in (*c*) where the intercept for the Caucasians is significantly greater than that for the New Guineans.

Covariance analysis of S and vital capacity shows that a common relationship describes all the subjects studied except that there is a significant difference between the Caucasians and the New Guineans. For men and women together

$$S = 0.89 + 0.35\ \text{v.c.} - 0.61\ \text{N.G.},$$

where the final term represents the reduction of the intercept in the New Guinean subjects (figure 5*c*). Thus, some of the difference in S between the ethnic groups seen in figure 2 reflects the difference in vital capacity, but some is due to the fact that at a given v.c., the Caucasians have a significantly greater CO_2-sensitivity than New Guineans. Figure 5*c* also shows that the highlanders have, at a given v.c., a value for S that is greater than that for lowlanders, and this difference is significant when the sexes are pooled in the analysis.

If parallel regressions of S on v.c. are fitted to the data of men and women separately, keeping the lines for New Guineans and Caucasians a fixed distance apart, the intercepts for the two sexes are not significantly different. That is, the sex difference in S seen in figure 4 can be entirely accounted for by differences in vital capacity.

Both the parameters of the $\dot{V}_e$, V_t relation (the Hey plot) are significantly correlated with vital capacity (figures 5*a*, *b*) but not with any other relevant anthropometric variable. Covariance analysis shows that for neither M nor K in their relation with vital capacity is there any difference between the sexes, between the ethnic groups, or between the New Guinean subgroups. For all subjects, therefore, these parameters are described by the following equations:

$$M = 44.6 - 2.91\,\text{v.c.}$$

$$K = 0.067 + 0.084\,\text{v.c.},$$

and the influence of vital capacity on the pattern of breathing during CO_2-hyperventilation is independent of sex, ethnic group and altitude of residence within the ranges studied.

The alternative parameter, $V_{t,30}$, which varies directly with K but inversely with M, is also significantly related to vital capacity and, for all subjects pooled, this relation is described by the equation:

$$V_{t,30} = 0.72 + 0.166\,\text{v.c.}$$

Unlike M and K, $V_{t,30}$ is also significantly related to age, and the simple and multiple regressions are given by

$$V_{t,30} = 0.91 + 0.019\ \text{age}$$

and

$$V_{t,30} = 0.55 + 0.009\ \text{age} + 0.15\,\text{v.c.}$$

Discussion

The pattern of breathing

Several factors have previously been shown to influence the parameters of the Hey plot relating ventilation, tidal volume and frequency during CO_2 hyperventilation in man. M is raised by hyperthermia (Hey *et al.* 1966) and lowered by increasing age (Patrick & Howard 1972). K is a function of body size (Hey *et al.*), most conveniently expressed as vital capacity (Patrick & Howard 1972). K, M and S (the slope of the CO_2 response line) are all affected by experimental vagal block (Guz & Widdicombe 1970; Guz *et al.* 1966), and their parallel pattern of inter-individual variation in man suggests that 'vagal tone' may help to set the normal pattern of the hyperventilation response to respiratory stimuli (Patrick & Howard).

The present study shows that variations in vital capacity account for a substantial part of the inter-subject variation in the intercept and slope of the Hey plot. The parameters K and M of Hey's equation can therefore be replaced by expressions containing v.c., and the equation reduces to

$$\dot{V}_\mathrm{e} = (44.6-2.91\ \mathrm{v.c.})\,V_\mathrm{t}+0.244(\mathrm{v.c.})^2-3.55\,\mathrm{v.c}-3.0.$$

Over the range of v.c. from 2 to 7 l, this equation is adequately represented by the empirical formulation

$$\dot{V}_\mathrm{e} = (44.6-2.91\,\mathrm{v.c.})\ (V_\mathrm{t}+0.45)-28.0,$$

which describes a fan of lines originating at a point whose coordinates are $(-0.45,\ -28.0)$ on the $\dot{V}_\mathrm{e}$, V_t plot (figure 6). The slopes of these lines are a negative function of v.c., and still correspond exactly with Hey's M. The original K is now represented merely by the points at which the fan cuts the V_t axis, giving larger values for this intercept as the vital capacity increases. Figure 6 also shows how well the equation above represents the mean data for three of the subject groups studied in New Guinea whose mean vital capacities range from less than 3 to almost 6 l.

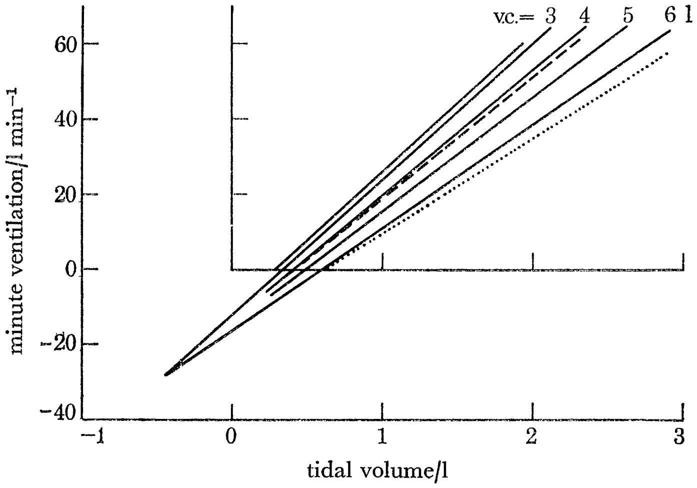

FIGURE 6. Relation between ventilation and tidal volume. The fan of four lines represents the relation predicted at v.c. = 3, 4, 5 and 6 l from the empirical equation $\dot{V}_\mathrm{e} = (44.6-2.91\ \mathrm{v.c.})\ (V_\mathrm{t}+0.45)-28.0$. Upper right area shows conventional Hey plot (cf. figure 1) with actual relation found in three illustrative subject groups: ——, coastal females (v.c. = 2.86 l); – –, highland males (v.c. = 4.22 l); · · · ·, Caucasian males (v.c. = 5.89 l)

The suggestion in our results that $V_{\mathrm{t},30}$ varies with age carries little weight on its own because the relation is only significant among the men, because it is not reflected by corresponding variations in either M or K with age, and because the age range of the subjects was deliberately kept narrow. Nevertheless, the change in $V_{\mathrm{t},30}$ with age is equivalent in direction to the decline of M with age seen by Patrick & Howard (1972), who, however, did not calculate a multiple regression of M on both age and vital capacity.

It has previously been suggested that the position of the upper point of inflexion on the $\dot{V}_\mathrm{e}$, V_t plot, beyond which Hey's equation no longer applies, depends on the subject's vital capacity (Hey *et al.* 1966; Cotes, Johnson & McDonald 1970). It now appears that the location of the whole of the linear part of the Hey plot below the inflexion is also a function of the vital capacity in several diverse subject-groups. This highlights the importance of the capacity of the respiratory apparatus in determining the setting of the control system for the respiratory pattern. The striking outcome of this New Guinea survey is that this relationship between the breathing pattern and the vital capacity seems to be independent of sex, altitude and ethnic origin, and appears, therefore, to represent a control mechanism that is suited to a wide variety of environmental situations.

The CO_2 *response*

The well-established finding of a lowered CO_2 threshold (B) in women is confirmed in this study. There is a highly significant difference between the sexes of about 400 Pa (3 Torr), revealed by comparing men and women in each main subgroup, or by comparing all the men with all the women (figure 4*a*). This sex difference cannot be accounted for by anthropometric variation, and is presumably attributable to progesterone-induced hyperventilation during the normal menstrual cycle in women. The biological value of this mechanism lies in promoting the gas exchange of the potential foetus. In this respect New Guinean women appear to respond just like their Caucasian counterparts; no ethnic differences were found.

The CO_2 sensitivity appears to be influenced by three factors studied: vital capacity, altitude and ethnic group. The vital capacity accounts for the difference in parameter S between the sexes and for part of the difference between the ethnic groups in S. The larger the vital capacity, the steeper is the CO_2 response line (figure 5*c*). Patrick & Howard (1972), reviewing the data then available in the literature, concluded that the sex difference in S was not dependent on differences in body size or lung size. The more detailed statistical analysis and the wider range of the present data, however, demonstrate clearly the importance of vital capacity as a factor influencing CO_2 sensitivity in adult men and women.

The second factor affecting the slope of the CO_2 response line is altitude of residence. For both young men and women, S is greater for the residents at 2000 m than for the resident lowlanders close to sea-level. Furthermore, the migrant group of male highlanders have a mean value for S close to that of their sea-level neighbours, significantly less than their compatriots in the highlands. There are no comparable differences for B or for the other parameters studied. These differences are still apparent when variations in vital capacity between the groups are taken into account (figure 5*c*).

This difference reflects a difference in sensitivity to carbon dioxide, not to hypoxia, because the P_{O_2} during the rebreathing was enough (27 kPa; 200 Torr) to eliminate virtually all the hypoxic drive to breathe, both at sea-level and at 2000 m altitude (Cunningham, Patrick & Lloyd 1964). Higher values for true CO_2 sensitivity at altitude in both sojourners and residents have been reported by Rahn, Stroud, Tenney & Mithoefer (1953), Milledge (1963) and Sorenson & Severinghaus (1968*a*, *b*). The present findings for S in New Guineans fit well with these when allowance is made for the different altitudes for each study. Sorenson and Severinghaus's results show a small though non-significant difference in S when migrants from 3000 m to sea-level (2.23) are compared with highland residents (2.43 $\mathrm{l\ min^{-1}\ Torr^{-1}}$). This is comparable with the present difference between New Guinean highlanders resident at 2000 m and those at sea-level.

It is likely then that the observed differences in S are due to altitude-induced changes in true CO_2 sensitivity. These changes are reversible within months of return to sea-level, and persist in natives of high altitudes. This is in contrast to hypoxial sensitivity, which is lost during exposure to low P_{O_2} in early life, and which does not change with altitude in adults (Sorenson & Severinghaus 1968*a*, *b*). New Guineans, therefore, appear to show the same type of reversible adaptation of their CO_2 sensitivity to changes in altitude as the Caucasians and Andean Indians previously studied. This is one aspect of the homeostatic response to relative ambient hypoxia, and contributes towards the improved alveolar-tissue gradient for oxygen transport that appears at altitude. This is the lowest altitude at which this phenomenon has been seen, and it suggests that there is no threshold to the response of the respiratory control system to mild degrees of chronic hypoxia.

TABLE 4. INTER-ETHNIC COMPARISONS FOR THE SLOPE (S) OF THE CO_2 RESPONSE LINE IN YOUNG ADULT MALES

	non-Caucasian	Caucasian control (sea-level)	ratio of non-Caucasian to Caucasian	P value	reference
New Guinea lowlanders	1.66	2.86	0.58	0.02	present study
New Guinea highlanders	1.94	2.86	0.68	0.02	
New Guinea highlanders	1.37	2.51	0.55	0.01	Beral & Read (1971)
E. Indians in Jamaica	2.25	2.79	0.81	n.s.	Edwards *et al.* (1972)
W. Africans in Jamaica	2.35	2.79	0.85	n.s.	

The third factor affecting S is an ethnic one. Even when allowance has been made for the differences in vital capacity, New Guineans, both men and women, have a lower CO_2 sensitivity than their Caucasian counterparts. This has previously been reported for a different group of New Guinea highlanders by Beral & Read (1971), who like us could offer no explanation. Edwards *et al.* (1972) measured S using a similar method in smaller groups of subjects in Jamaica, and found the Europeans to have the largest mean value, the East Indians next and those of West African origin the lowest (see table 4). Although the differences were not significant, when seen in conjunction with the data on New Guinean subjects they reinforce the suggestion that non-Caucasian ethnic groups show less ventilatory sensitivity to carbon dioxide than Caucasians. This means that the homeostatic set-point for P_{CO_2} while breathing air at rest is slightly lower in Caucasians, and being more tolerant rises in P_{CO_2}, the New Guineans do less respiratory work in situations where the CO_2 load is high. This might offer biological advantage during heavy physical exercise, and it is noteworthy that other groups showing lower than usual CO_2 sensitivity include endurance swimmers and runners (Rebuck & Read 1971). It is possible therefore that the lower sensitivity represents an adaptation to a way of life demanding greater habitual activity, but other environmental or even heritable factors cannot be excluded.

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