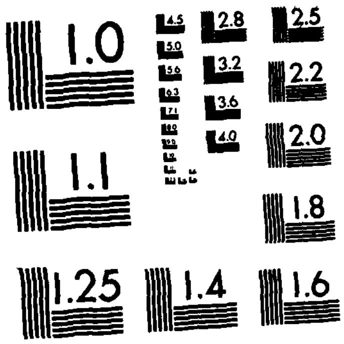
AD-A126 288 STRENGTH AND CYCLE TIME OF VENTILATORY OSCILLATIONS IN UNACCLIMATIZED HUM..(U) ARMY RESEARCH INST OF ENVIRONMENTAL MEDICINE NATICK MA T B WAGGENER ET AL. 04 MAR 83 USARIEM-M-11/83 1/1

UNCLASSIFIED F/G 6/19 NL

END

FILMED

DTIC



MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS-1963-A

unclassified

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER M11/83	2. GOVT ACCESSION NO. AD-A126288	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Strength and Cycle Time of Ventilatory Oscillations in Unacclimatized Humans at High Altitude		5. TYPE OF REPORT & PERIOD COVERED 6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Thomas B. Waggener, Paul J. Brusil, Richard E. Kronauer, Ronald A. Gabel, Gideon F. Inbar		8. CONTRACT OR GRANT NUMBER(s) NIH Grant 2R01 HL 1635-02 NIH Fellowship IF 22-01254-02
9. PERFORMING ORGANIZATION NAME AND ADDRESS US Army Research Institute of Environmental Medicine, Natick, MA 01760		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS US Army Medical Research & Development Command Ft. Detrick, MD 21701		12. REPORT DATE 4 March 1983 13. NUMBER OF PAGES 23
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office) Same		15. SECURITY CLASS. (of this report) Unclassified 15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Distribution of this document is unlimited.

DISTRIBUTION STATEMENT A
Approved for public release;
Distribution Unlimited

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

Same

DTIC ELECTE APR 1 1983 S D B

18. SUPPLEMENTARY NOTES

NA

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Periodic breathing, Cheyne-Stokes breathing, control of breathing, acclimatization to high altitude

20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Respiration was monitored with magnetometers in 12 healthy supine young adults at sea level, and in an altitude chamber at simulated high altitudes of 8,000, 9,000, 11,000 and 14,000 feet. Periodic breathing which was strong enough to include apnea at the time of minimum ventilation was seen in all subjects at high altitude. The cycle time of periodic breathing ranged from 12 to 34 seconds. On average across the population the incidence of periodic breathing increased with altitude. The cycle time of the periodic pattern increased as the strength of the

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

unclassified

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

20. (Cont)
pattern increased. After normalizing to a standard pattern strength, cycle time decreased as altitude increased. The study was repeated 3 weeks later on 7 of the subjects. The standard cycle time at 14,000 feet of each subject in the second series was the same as in the first series to within, on the average, 9%. The variation of standard cycle time for a given subject is less than the variation across the population, indicating characteristic cycle times for some individuals (one-way ANOVA, P <0.025).

Strength and Cycle Time of Ventilatory Oscillations in Unacclimatized Humans at High Altitude

Thomas B. Waggener, Paul J. Brusil, Richard E. Kronauer,
Ronald A. Gabel, Gideon F. Inbar

Division of Applied Sciences, Harvard University, Cambridge, MA 02138
Department of Anaesthesia, Harvard Medical School, Boston, MA 02115
U.S.Army Research Institute of Environmental Medicine, Natick, MA 01760
Department of Electrical Engineering, Technion-Israel Institute of Technology, Haifa 32 000, Israel

Please send reprint requests to: Thomas B. Waggener, Ph.D.
Department of Pediatrics
Children's Hospital Medical Center
300 Longwood Avenue
Boston, MA 02115

83 04 01 056

Waggener, et.al.

Abstract

Respiration was monitored with magnetometers in 12 healthy supine young adults at sea level, and in an altitude chamber at simulated high altitudes of 8,000, 9,000, 11,000 and 14,000 feet. Periodic breathing which was strong enough to include apnea at the time of minimum ventilation was seen in all subjects at high altitude. The cycle time of periodic breathing ranged from 12 to 34 seconds. On average across the population the incidence of periodic breathing increased with altitude. The cycle time of the periodic pattern increased as the strength of the pattern increased. After normalizing to a standard pattern strength, cycle time decreased as altitude increased. The study was repeated 3 weeks later on 7 of the subjects. The standard cycle time at 14,000 feet of each subject in the second series was the same as in the first series to within, on the average, 6%. Each subject studied at 11,000 feet in both series reproduced his cycle time to within, on the average, 9%. The variation of standard cycle time for a given subject is less than the variation across the population, indicating characteristic cycle times for some individuals (one-way ANOVA, $P < 0.025$).

less than

Index terms: periodic breathing

Cheyne-Stokes breathing

control of breathing

acclimatization to high altitude

INTRODUCTION

Periodic breathing, a regular waxing and waning of respiration, is brought about by various conditions of stress, specifically heart disorders, neurological disorders, premature birth and high altitude (3). The periodic pattern seen with heart and neurological disorders, so-called Cheyne-Stokes breathing, is often accentuated as the patient's state of health deteriorates. The periodic patterns exhibited at high altitude and in premature infants are accepted as a normal response to an abnormal situation. An accurate description of these breathing patterns is prerequisite to understanding their causes and consequences, similarities and dissimilarities. In this paper we characterize the strength and cycle time of high altitude breathing patterns.

Breathing patterns of adults at an altitude of 10,000 feet have been characterized by Brusil, et al. (1). Low amplitude oscillatory breathing patterns in adults at sea level have been observed and characterized by Goodman (4), Priban (10), and Lenfant (9). In this study we observed breathing patterns at barometric pressures corresponding to sea level, 8,000, 9,000, 11,000 and 14,000 feet and report how the pattern characteristics change with altitude. The experiments were repeated three weeks later on the same subjects to determine the reproducibility of these patterns.

METHODS

We studied 12 healthy young adults who had volunteered to participate in this investigation approved by the Human Use Review Committee. The study was performed in an altitude chamber (U.S. Army Research Institute of Environmental Medicine, Natick, MA) at simulated high altitudes ranging from 8,000 to 14,000 feet. Using magnetometers to monitor respiration, we studied each supine subject at sea level, several altitudes, and then sea level again. The rate of ascent was 2,000 feet per minute and the entire protocol lasted 7 hours. The magnetometers measured anterior-posterior dimensions of the thorax at xiphoid level and the abdomen at close to umbilical level. They were calibrated to give changes in lung volume using isovolume maneuvers and a spirometer (1).

A second set of experiments was conducted on 7 of the subjects. The second set occurred three weeks after the first and used a similar protocol.

The high altitude chamber had 2 rooms. Breathing patterns were monitored in one, while in the other, the subjects not currently being monitored were free to talk, play cards, watch television, etc. Although altitude changes were not announced, we assume the subjects were aware of such changes because of the noise associated with changing the pressure in the chamber. The subjects were naive as to the explicit purposes of the experiments, verified by a postexperiment questionnaire, although they were aware that changes in altitude were involved.

Two prominent characteristics of periodic breathing patterns are the cycle time and the strength of the pattern. Cycle time is the time between successive points of maximum ventilation in the periodic pattern (Figure 1). The strength is a measure of how much the ventilation changes as the pattern goes from its point of maximum ventilation to its point of minimum ventilation. A strong pattern has greater changes of ventilation than does a weak pattern. Periodic breathing patterns which are so strong that during points of minimum ventilation the subject doesn't breathe at all (apnea) we call apneic oscillations.

We have defined a strength parameter M which conforms to the above concepts of periodic patterns, with large M corresponding to large swings in ventilation and small M corresponding to small swings in ventilation (12). M is defined for non-apneic oscillations as the fractional modulation of the signal, i.e. the ratio of the modulation amplitude over the mean value of ventilation (Figure 1 and Appendix I). This means that patterns which do not include apnea always have an M value of less than 1.

The $M<1$ definition could be extended to values of $M>1$ by allowing modulation amplitude to exceed mean value of the signal and considering the resulting negative values of ventilation as apnea. However, such an extension is unstable, i.e. M goes to infinity as the duration of apnea becomes 1/2 of the cycle time. Because the apneas are sometimes this long or longer M was redefined for apneic oscillations as the ratio of cycle time over the difference between cycle time and length of apnea (Appendix I and Figure 1).

The breathing patterns reported here are so strong as to be obvious as a regular periodicity in the strip chart recording of lung volume versus time, so the cycle time and strength of the patterns were measured directly off of the strip chart recordings. Although there are other aspects of these patterns which may be of interest, as in Brusil, et al. (1), this report deals only with changes of cycle time and pattern strength with altitude. We did not look for other, more subtle, periodicities in these data.

RESULTS

Although from subject to subject there is considerable variation, on the average, the higher the altitude, the greater the percentage of time a subject would spend in periodic breathing (Figures 2 and 3). All subjects showed sustained apneic oscillations at high altitude; some even at the lowest altitude studied, 8,000 feet (Figure 3). No subjects showed sustained apneic oscillations at sea level.

The cycle time of the periodic breathing patterns ranged from 12 to 34 seconds and increased as the strength of the pattern increased, i.e. strong patterns had longer cycle times than did weak patterns (Figures 4 and 5). To determine the relationship between cycle time and altitude, the influence of strength of the pattern on cycle time had to be removed. This was accomplished by using the cycle time vs. strength relationships seen in Figure 5 to adjust the cycle time of each pattern to that expected if the pattern were of a standard strength, chosen as M=1.

The cycle time of the standard, M=1, pattern increases slightly as altitude decreases (Figure 6). The cycle times reported by Brusil et al. (1) for 10,000 feet altitude agree with the cycle time versus altitude relationship reported here. Linear extrapolation shows that the standard cycle time of the high altitude periodic breathing would be on the order of 30 to 35 seconds if it were seen at sea level. Sea level Cheyne-Stokes cycle times are typically said to range from 60 to 200 seconds, although there are data showing cycle times of approximately 30 seconds for some individuals (6).

Comparison of the second set of high altitude experiments with the first, indicates that periodic breathing characteristics are quite reproducible. The standard cycle time at 14,000 feet of each subject in the second series was the same as that seen in the first series to within 6% on the average (Table 1). Each subject studied at 11,000 feet in both series was found to reproduce his standard cycle time at that altitude to within 9% on the average. Hence the reproducibility of standard cycle times was in general quite good and showed improvement with increase of altitude. Comparison of standard cycle times between subjects shows a standard deviation of 14% at 11,000 feet and 11% at 14,000 feet. Thus, at a given altitude, the variation of standard cycle time for a given subject is less than the variation across the population. Using one way analysis of variance, the hypothesis that there is no difference in cycle times between individuals at 14,000 feet or at 11,000 feet was rejected at the $P \leq 0.0025$ and $P \leq 0.025$ levels respectively. This indicates that individual subjects may have distinct, characteristic cycle times.

DISCUSSION

The incidence of apneic oscillations was greater in this study than in our previous study of adults at high altitude (1) despite the fact that our respiratory monitoring techniques were identical. We assume this difference is due to lack of acclimatization in our current subjects. In the previous study subjects were monitored during 2 weeks at high altitude, with only 1 subject monitored within five hours of reaching altitude, while in the current study the total altitude exposure lasted only 7 hours, the longest time spent at any altitude was 3 hours, and subjects were monitored soon after arrival at each altitude, with some subjects monitored during the ascent. The rate of ascent was also much faster in this study, 2000 feet per minute, than in the earlier study, when subjects drove in an automobile from Madison, Wisconsin to a laboratory at Echo Lake, Colorado.

The effect of acclimatization on incidence of apneic oscillations can be explained if one accepts that the oscillations represent instability in the blood gas feedback control system. Respiratory control system modeling by Khoo et al (8) has shown that such instability is compatible with the characteristics of the oscillations reported here. The more unstable the control system is, the stronger will be the periodic breathing pattern and the higher the incidence of apneic oscillations. The ventilatory response to changes in arterial P_{CO_2} and P_{O_2} is an important part of this control system and is affected by acclimatization. Specifically, during acclimatization plasma bicarbonate is lost through renal excretion with a consequent drop in plasma pH at any given level of $P_{a_{CO_2}}$. This will shift the ventilation - CO_2 response curve to the left with either no change or a slight decrease in slope (5,7), i.e. ventilation is higher at any given $P_{a_{CO_2}}$ but the change in ventilation for any given change in $P_{a_{CO_2}}$ is the same. Both the shift and the decrease in slope, if any, will tend to stabilize the control system (8,13) and thus reduce the incidence of apneic oscillations. Acclimatization also allows the maintenance of a slightly higher P_{aO_2} and lower $P_{a_{CO_2}}$ than is possible upon first reaching altitude. Both of these changes will tend to stabilize the control system.

The change of pattern cycle time with altitude is in the direction to be expected. Increased cardiac output with progressive hypoxia will decrease convective delay times between the lungs and chemoreceptors thus leading to shorter cycle times at higher altitudes. Also, and perhaps more importantly, both increased pulmonary blood flow and hyperventilation due to hypoxia will decrease the time constant for washout of CO_2 and washing in of O_2 in the lungs, again leading to shorter cycle times.

At a given altitude, stronger breathing patterns have slightly longer cycle times. In a respiratory control system model a stronger pattern corresponds to increased loop gain at a phase angle of 180 degrees. As shown by Khoo, et. al. (8), the changes in physiological parameters most likely to account for such an increase in loop gain are increased chemoreceptor gain, increased circulatory delay between the lungs and chemoreceptors, and increased functional residual capacity. Of these three possibilities only increased circulatory delay will also cause an increase in pattern cycle time, while both of the other changes will cause a decrease in cycle time. So our results suggest that variations in pattern strength at a given altitude are related to variations in cardiovascular parameters which affect circulatory delay between the lungs and chemoreceptors.

The breathing patterns we report here are most likely due to a high gain control instability mediated by the peripheral chemoreceptors. Modeling by Khoo, et al has shown that the breathing pattern characteristics we observed are compatible with decreased respiratory control system stability due primarily to peripheral chemoreceptors with very little contribution from the medullary chemoreceptors (8). This agrees with the estimate of Crawford and Severinghaus that respiratory drive at an altitude of 12,000 feet is 80% due to peripheral chemoreceptors and 20% due to central chemoreceptors (2,11).

Breathing pattern cycle times seem to be highly reproducible. That the variability from one study to another, 3 weeks later, is less than the variability across subjects indicates that individuals may have their own distinct characteristic cycle times. If the breathing pattern is characteristic of the circulatory and respiratory control systems, then variations in the parameters of those systems could account for individual variations in cycle time. Parameters such as functional residual capacity, cardiac output, lung to chemoreceptor circulation time, and chemoreceptor sensitivity are known to vary from person to person and may account for person to person variation in pattern cycle time.

Cycle times were slightly more reproducible at higher altitudes suggesting that the greater the stress the more reproducible will be the respiratory system response. Conversely, under less stressful conditions ventilatory responses may be more flexible leading to more variability in the cycle time of breathing patterns.

ACKNOWLEDGMENTS

Supported in part by NIH Grant 2R01 HL 1635-02 and NIH Fellowship IF 22 01254-02.

Some of these data have been presented as an abstract (12).

Human subjects participated in these studies after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.

References

1. Brusil, P.J., Waggener, T.B., Kronauer, R.E., Gulesian, P.. Methods for identifying respiratory oscillations disclose altitude effects. J. Appl. Physiol., 1980, 48: 545-556.

2. Crawford, R.D., Severinghaus, J.W.. CSF pH and ventilatory acclimatization to altitude. J. Appl. Physiol., 1978, 45: 275.

3. Dowell, A.R., Buckley, C.E., Cohen, R., Whalen, R.E., Siber, H.O.. Cheyne-Stokes respiration - a review of clinical manifestations & critique of physiological mechanisms. Arch. Intern. Med., 1971, 127: 712-726.

4. Goodman, L.. Oscillatory behavior of ventilation in resting man. IEEE Trans. Biomed. Eng., 1964, BME-11:81-93.

5. Irsigler, G.B., Stafford, M.J., Severinghaus, J.W.. Relationship of CSF pH, O_2, and CO_2 responses in metabolic acidosis and alkalosis in humans. J. Appl. Physiol., 1980, 48: 355-361.

6. Karp, H.R., Sieker, H.O., Heyman, A.. Cerebral circulation and function in Cheyne-Stokes respiration. Am. J. Med., 1961, 30: 861-870.

7. Kellog, R.H., Pace, N., Archibald, E.R., Vaughn, B.E.. Respiratory response to inspired CO_2 during acclimatization to an altitude of 12,470 feet. J. Appl. Physiol., 1957, 11: 65-71.

8. Khoo, M.C.K., Kronauer, R.E., Strohl, K.P., Slutsky, A.S.. Factors inducing periodic breathing in humans: a general model. J. Appl. Physiol., 1982, 53:644-659

9. Lenfant C.. Time-dependent variations of pulmonary gas exchange in normal men at rest. J. Appl. Physiol., 1967, 22: 675-684.

10. Priban, I.. An analysis of some short term patterns of breathing in man at rest. J. Physiol.,1963, 166:425-434.

11. Severinghaus, J.W., Crawford, R.D., Regulation of respiration. Acta. Anaesth. Scand., 1978, Suppl. 70: 188-191.

12. Waggener, T.B., Brusil, P.J., Kronauer, R.E., Gabel, R.A.. Strength and period of ventilatory oscillations in unacclimatized humans at high altitude (Abstract). Physiologist 20:98, 1977.

13. Waggener, T.B.. Breathing patterns of newborn infants (PhD thesis). Cambridge, MA. Harvard University, 1979.

Appendix I

We define the ventilatory strength index, M, for non-apneic oscillations as the fractional modulation of the data string, i.e. the modulation amplitude divided by the mean value.

Let $\bar{\dot{V}}_E$=mean value of ventilation

A= amplitude of the modulation of ventilation

(insert figure A1 here)

We define the ventilatory strength index,M, for apneic oscillations as ratio of the cycle time of the oscillation over the cycle time minus duration of apnea.

Let Tc= cycle time

Ta= duration of apnea

(insert figure A2 here)

If the modulation amplitude is allowed to exceed the mean value, i.e. $A>\bar{\dot{V}}_E$, and the resulting negative values of ventilation are considered apnea, then definition (1) can be used for apneic oscillations as well. As seen in Figure A3, where sinusoidal modulation is assumed, when M is only slightly greater than 1 the two definitions give similar results. However as the duration of apnea approaches one half of the cycle time, $M \rightarrow \infty$ under definition (1) and $M \rightarrow 2$ under definition (2). Because the apneas we observed were sometimes one half of the cycle time and longer, definition (2) was used for all apneic oscillations.

(insert figure A3)

FIGURE LEGENDS

Figure 1

Definition of ventilatory oscillation strength index M. These definitions are discussed further in Appendix I.

Figure 2

Incidence of ventilatory oscillations as a function of altitude. Individual data are labelled according to subject number and experiment number. To avoid obscuring average values, not all of the individual data are shown.

Figure 3

Incidence of apneic ventilatory oscillations as a function of altitude. Individual data are labelled according to subject number and experiment number. To avoid obscuring average values, not all of the individual data are shown.

Figure 4

Example of the relationship between oscillation cycle time and strength index M for subject number 12. Vertical translation of the curve shows that cycle time at a given strength falls with a rise in altitude (see Figure 7). Data are labelled according to subject number, experiment number, and measurement number within an experiment.

Figure 5

Relationship between oscillation cycle time and strength index M for entire study population. Data are labelled according to subject number and experiment number.

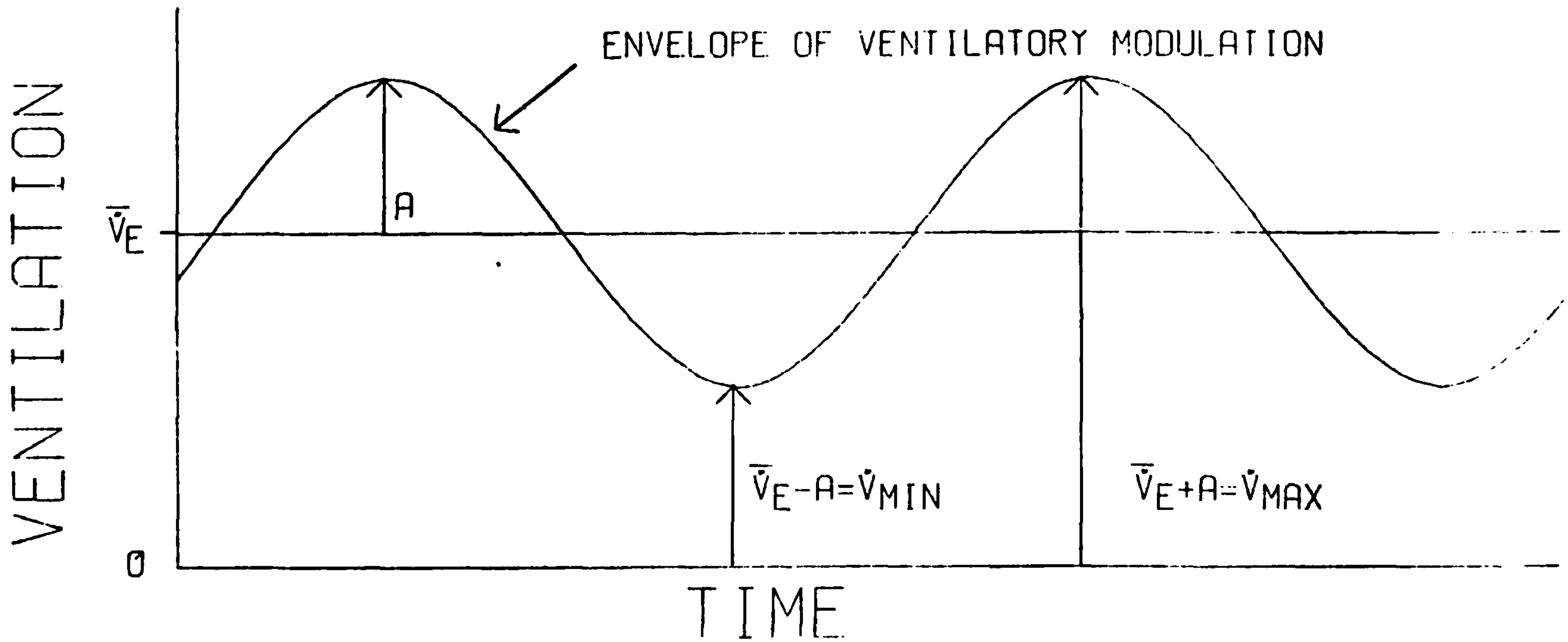
Figure 6

Effect of altitude on oscillation cycle time. All cycle times are corrected to a standard strength of M=1 using the relationships shown in Figure 5. Data are labelled according to subject number and experiment number.

Figure A3

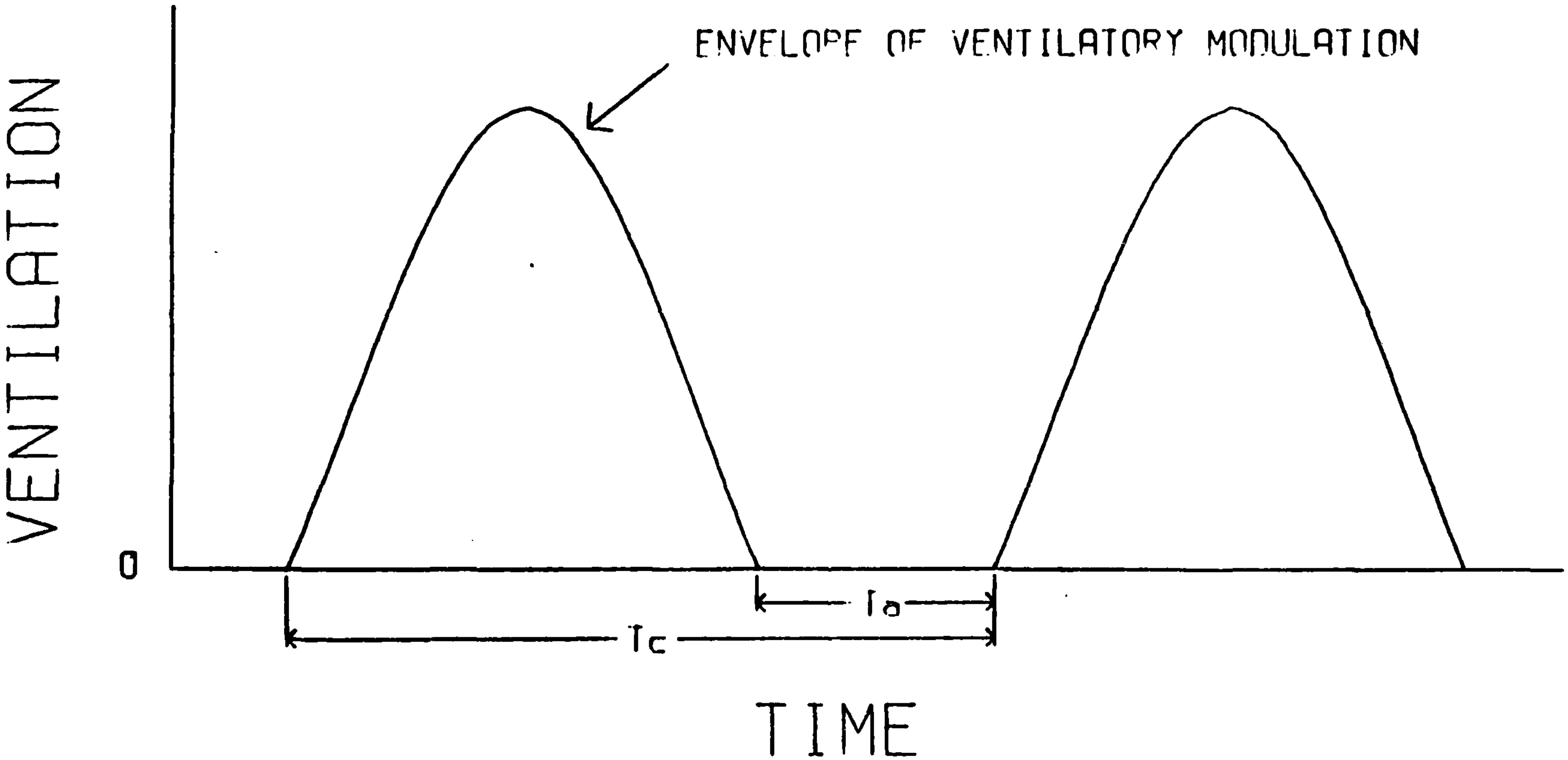
Relationship between our two definitions of the ventilatory strength index M, assuming sinusoidal modulation of ventilation. M from definintion (1) is the ordinate and M from definintion (2) is the abcissa. The dotted line is the line of identity.

FIG. A1



$$(1) \quad M = \frac{A}{\bar{\dot{V}}_E} = \frac{\bar{\dot{V}}_E + A - (\bar{\dot{V}}_E - A)}{\bar{\dot{V}}_E + A + (\bar{\dot{V}}_E - A)} = \frac{\dot{V}_{MAX} - \dot{V}_{MIN}}{\dot{V}_{MAX} + \dot{V}_{MIN}}$$

Fig A2



$$M = \frac{T_c}{T_c - T_a} \qquad (2)$$

Figure A3

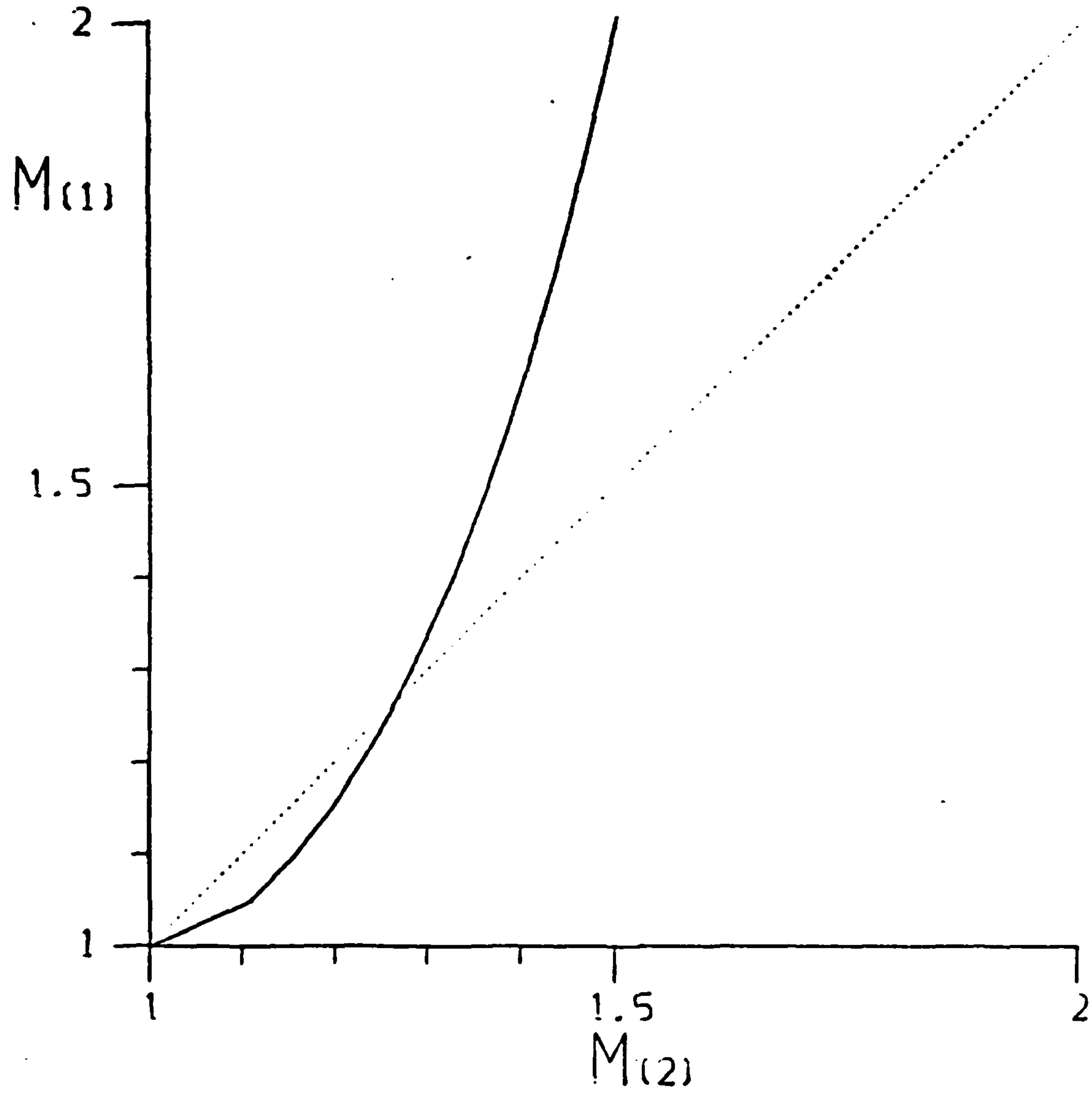


FIG. 5

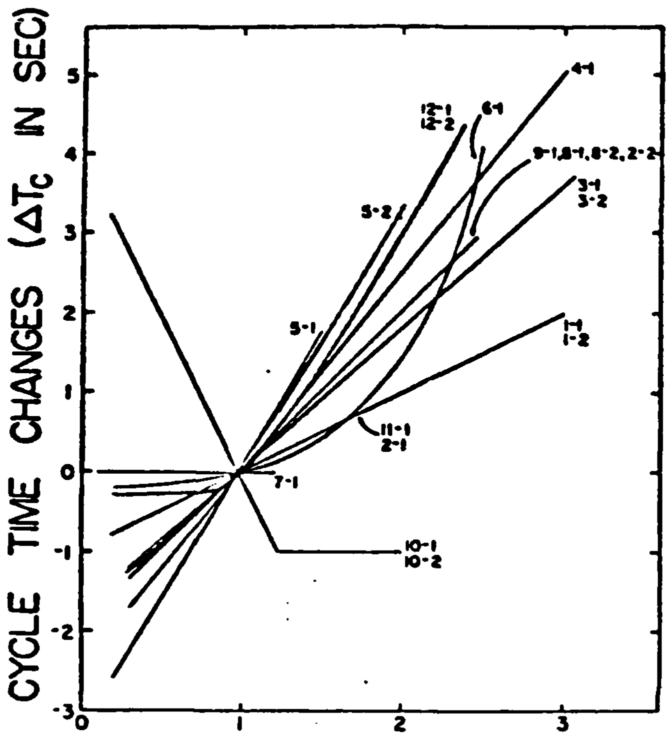
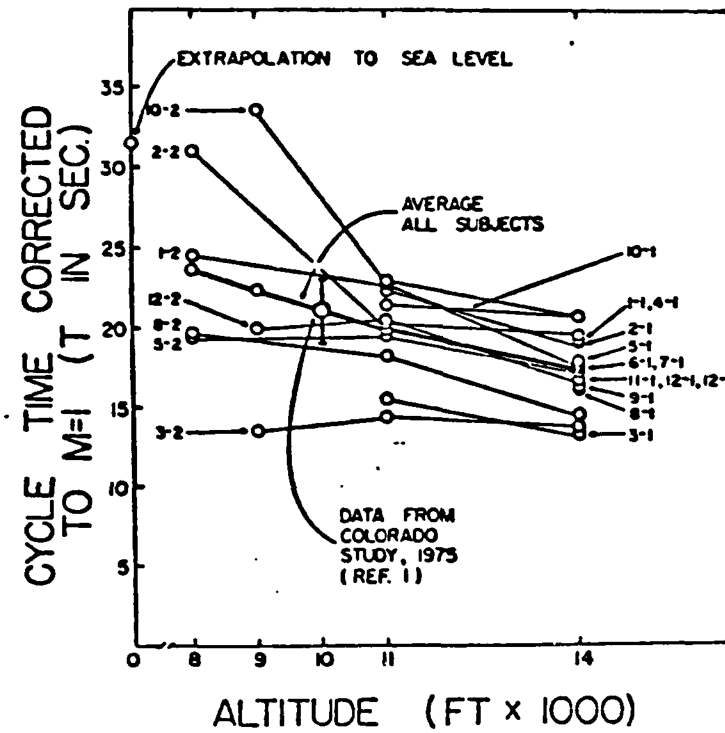


FIG. 6



I. KRONAUER ET AL PSYCHOLOGIST: 19, 259, 1976.

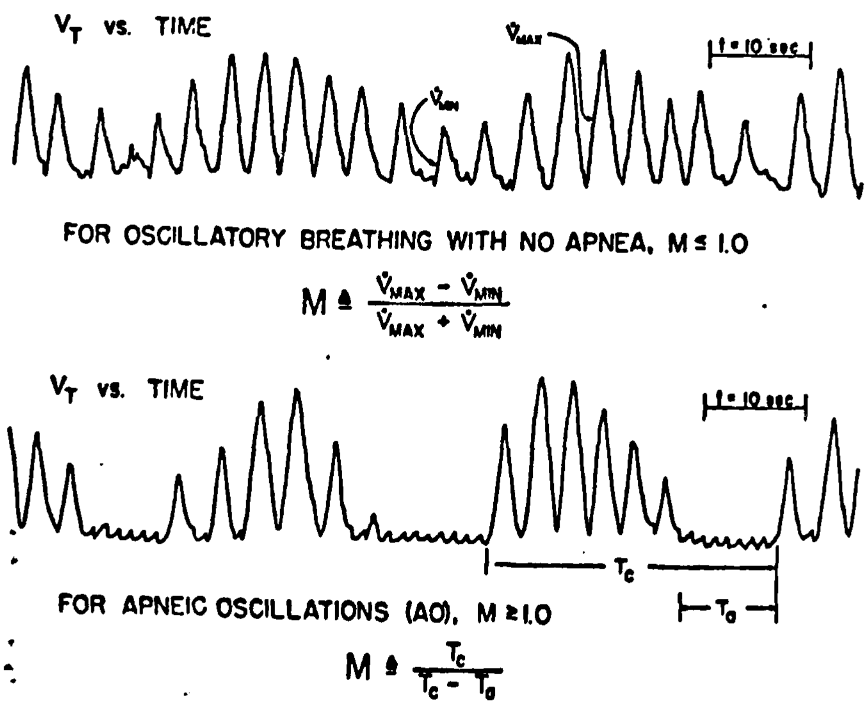
TABLE I

REPRODUCIBILITY OF AVERAGE CYCLE TIME (CORRECTED TO M=1)

SUBJECT NUMBER	1	2	3	5	8	10	12
14000 FEET							
T_c (SECONDS) SERIES 1	19.2	19.0	12.9	17.6	16.7	20.4	16.5
T_c (SECONDS) SERIES 2	17.4	19.6	13.5	16.8	14.2	20.4	16.5
% DIFFERENCE	10%	3%	5%	5%	18%	0%	0%
MEAN % DIFFERENCE = 6%							
11000 FEET							
T_c (SECONDS) SERIES 1		22.2	13			21.2	
T_c (SECONDS) SERIES 2		19.9	14.2			22.7	
% DIFFERENCE		11%	8%			7%	
MEAN % DIFFERENCE = 9%							

FIG. 1

DEFINITION
OF VENTILATORY OSCILLATION (VO) STRENGTH INDEX, M



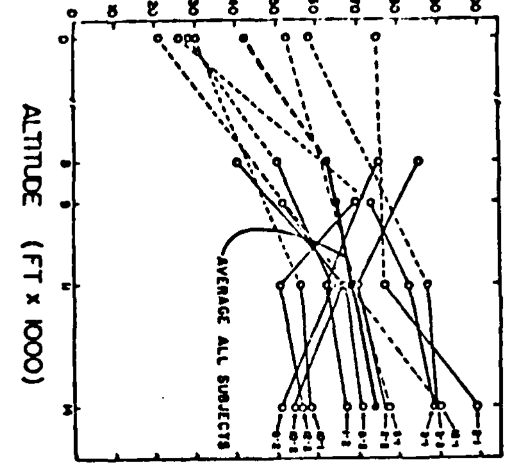


FIG. 2

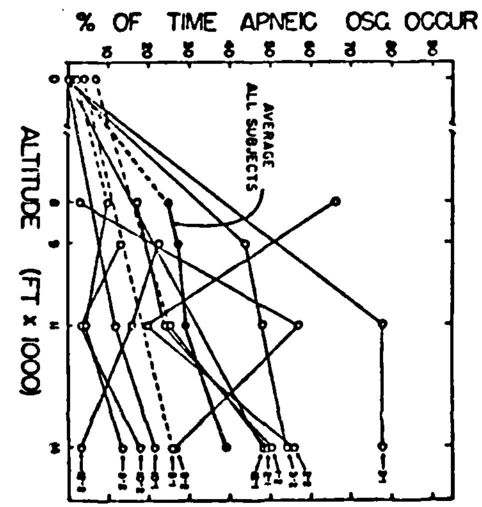


FIG 3

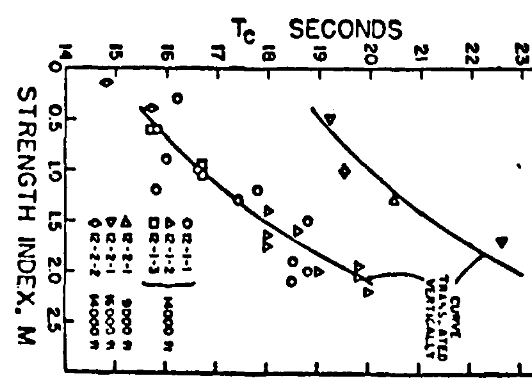


FIG. 4

4 -

DT