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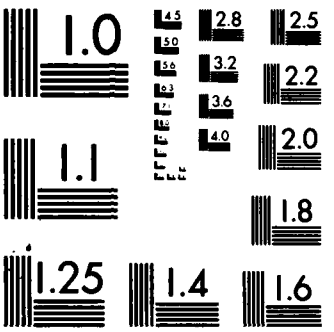

PULMONARY ADAPTATION TO HIGH ALTITUDE

ANNUAL PROGRESS REPORT - YEAR 05

Jerome A. Dempsey, Ph.D.

August 1982

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The work ~~accomplished during~~ year 05 of our contract was aimed at defining the limitations of the lung's gas exchange capabilities and those of the mechanical properties of the lung and chest wall during exercise in hypoxia, exploring the role of CO_2 (or alkalosis) in the genesis of periodic breathing during sleep in hypoxia and further exploration of the role of central nervous system neurotransmitter metabolism and cerebral acid production in ventilatory acclimatization to chronic hypoxia.

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The following major findings were obtained:

1. Failure of pulmonary gas exchange was quantified in healthy persons during heavy work at sea-level and the major potential causes were tested. Susceptibility of this arterial O_2 desaturation to even the mildest levels of acute hypoxia was documented and inter-individual susceptibility to this hypoxemia was based largely on the degree of hyperventilation.

2. The ventilatory response to heavy work in normoxia and especially in hypoxia showed significant limitations imposed by the mechanics of the lung and respiratory muscles.

3. Using gases of differing density and/or differing oxygenation it was shown that the ventilatory response to heavy work was determined as much or more by mechanical "constraints" as it was by the presence of chemical stimuli--or sensitivity to same. This importance of mechanical limitations was especially true in hypoxic environments.

4. Animal studies were initiated following the development of a number of methods designed to study the muscle metabolism of the exercising rat in varying environments. Preliminary studies show that the rat diaphragm undergoes anaerobic glycolysis during exercise to an extent which parallels (or may even exceed) that in limb skeletal muscle. A further effect of hypoxia was documented.

5. Final completion of a number of long-standing studies under this contract were documented pertaining to mechanisms for chronic ventilatory acclimatization to hypoxia. These included our studies of the role of supra-pontine influences (as studied in sleep) and brain acid-base regulation and neurotransmitter metabolism.

ANNUAL PROGRESS REPORT

Studies completed during contract year 05 were aimed at initial studies to define the limitations of the lung's gas exchange capabilities and those of the mechanical properties of the lung and chest wall during exercise in hypoxia, to explore the role of CO_2 (or respiratory alkalosis) in the genesis of periodic breathing during sleep in hypoxia, and to further examine the role of central nervous system neurotransmitter metabolism and cerebral acid production in ventilatory acclimatization to chronic hypoxia.

SUMMARY OF PROGRESS TO DATE

I. Exercise Gas Exchange

This ongoing study is now completed up to the point of thoroughly defining the effects of exercise in acute hypoxia (and normoxia) on pulmonary exchange of O_2 and CO_2, and quantitating the effects of changes in alveolar PO_2 on the regulation of arterial PO_2 in heavy work. (Preliminary results have been published and presented at national symposia [see Publications], and the full study is currently being prepared for submission to J. Appl. Physiol.). These data have also been used as the primary subject for discussion in a recent Annual Review of Physiology (Roussos, in press). To summarize major findings:

A. A significant arterial hypoxemia (-10 to -45 mmHg Pa_{O_2} or -5 to -12% Sa_{O_2}) occurred in more than one-half of subjects during heavy work. This most often occurred at extreme work loads in very fit subjects (> 4 l,min $\dot{V}O_2$) but was also evident in many susceptible subjects at lighter exercise loads (approx. 3 to 4 l,min $\dot{V}O_2$).

B. Studies using constant work loads with multiple arterial blood sampling showed that the hypoxemia occurred within 30 secs of the beginning of exercise and either worsened or was sustained as exercise time continued (up to 6 min).

C. The hypoxemia was worst in those subjects who hyperventilated the least, i.e. those who had the smallest exercise-induced decrements in $PaCO_2$ (-2 to -5 mmHg) and therefore the lowest alveolar PO_2 (<112 mmHg). Extremely wide A-a PO_2 differences (35 to 45 mmHg) were also found in these hypoxemic subjects.

D. Contrary to current ideas--and to what we have also observed during mild and moderate exercise--inter-individual differences in the response to heavy exercise bore no positive correlation to either the

level of measurable stimuli present (PaO_2, pHa or circulating norepinephrine) or to the resting ventilatory "responsiveness" to exogenous CO_2 or hypoxia. (Individual differences in mechanical constraints and compensatory responses to these constraints during these high ventilatory demands were probably more critical determinants of the ventilatory response—see below.)

E. Studies using helium breathing and varying F_IO_2 along with a computer analysis of $V_A:\dot{Q}_c$ maldistribution effects indicated that true alveolar shunt (i.e. $V_A:\dot{Q}_c = 0$) would have to be unreasonably large (>5% of $\dot{Q}_c$) to explain the hypoxemia as would any skewness in the $V_A:\dot{Q}_c$ distribution toward the lower end (<0.5 $V_A:\dot{Q}_c$). Thus an inadequate alveolar-capillary diffusion gradient in the face of extremely rapid capillary transit times and greatly desaturated mixed venous O_2 content was postulated as the primary cause of the hypoxemia, although our analysis of A-a PO_2 differences under varying levels of P_AO_2 could not detect this proposed diffusion limitation.

F. Acute hypoxia (reduced F_IO_2)--even at relatively mild levels (simulating 7,000 to 10,000 ft altitude)--commonly produced exercise-induced hypoxemia (PaO_2 approx. 35 to 45 mmHg). This occurred most markedly in those subjects who showed even slight hypoxemia (<15 mmHg decrease in PaO_2) in normoxia; and, as in normoxic air-breathing, the more sluggish the ventilatory response the greater the hypoxemia. Once again, as in normoxia (see D. above) chemoreceptor stimuli or responsiveness were not significant determinants of this hyperventilatory response to exercise in hypoxia.

In short, to our knowledge these data are the most comprehensive to date which clearly question the long-held premise that the reserve for gas exchange in the healthy lung is not threatened during exercise. When properly determined with multiple blood gas sampling and very careful validation procedures for blood gas measurements are used, these data demonstrate that significant and often severe exercise-induced hypoxemia does occur in the healthy lung. Most relevant to the purposes of this contract, the data also show marked effects of (even mild) ambient hypoxia on exercise gas exchange and have obvious implications for predicting susceptibility to hypoxemia--and perhaps even exercise limitation--in would-be sojourners to high altitudes.

II. Pulmonary and Chest Wall Mechanical Responses and Limitations in Exercise and Hypoxia.

A. Technique development. The impetus for this study comes from our findings (see above) that hyperventilation in heavy work was often "insufficient" to ensure constant arterial PO_2. This was a new aim under our contract last year; thus a considerable amount of time was spent in the initial 7 months developing and validating new techniques. For human studies we developed a measurement and computer analysis system for measurements of flow and volume and construction

of breath-by-breath flow-volume loops. Application of the "respitrace" inductance plethysmography system to exercise was also accomplished to measure the relative contribution of rib cage and abdomen to changes in tidal volume. More recently we have developed the use of esophageal and gastric pressure measurements to determine pulmonary mechanics and transdiaphragmatic pressures during exercise; and have begun development of a unique application of the helium rebreathing technique to determine FRC during exercise. To determine the effects of hypoxia and exercise on the metabolic status of respiratory muscles we developed an animal model in the exercising rat. To this end, we have developed and validated the following techniques: 1) In vivo freezing of diaphragm, intercostal and selected limb muscles using a freon "spray" technique which we adapted from our previous experience with freezing brain in vivo. This is ideal for study of high energy phosphates and metabolic acid production, because the technique simultaneously stops circulation as it freezes the tissue. Comparisons in the resting normoxic animal of the in vivo freezing with the more conventional biopsy technique has thus far shown higher glycogen and ATP levels and lower lactic acid concentrations in the diaphragm using the in vivo freezing technique. Further such comparisons in the exercising hypoxic animal are in progress. 2) An open, flow-through box system permitting simultaneous measurement of metabolic rate and anaerobic collection of arterial blood during exercise while the rat is exercising in various gaseous environments (see Table 1); and 3) Fluorometric assays of high energy phosphates in respiratory and limb muscles plus a variety of histochemical techniques to more fully describe the morphology of single muscle fibers in different portions of the muscle (the latter techniques were developed in collaboration with Dr. Robert Fitts, Marquette University).

III. Findings to Date Implicating a Role for the Lung and Chest Wall as Determinants of the Ventilatory response to Heavy Exercise.

A series of findings in exercising humans and rats strongly suggest a mechanical "constraint" imposed by the lung and chest wall on exercise ventilation. We illustrate and summarize the more relevant findings:

A. Humans

1. In heavy work in normoxia at minute ventilations greater than 100 l, min inspiratory and expiratory peak flow rates were often in excess of 5 l, sec; and were often in excess of 6 l,sec with further hyperventilation in hypxoia (Fig. 1). When breath-by-breath flow-volume loops were constructed of both the tidal breaths in moderately heavy and very heavy or maximum work and superimposed on the resting maximal flow-volume loop we observed that inspiratory and expiratory flows equaled or exceeded the maximum values over some portion of the flow:volume loop in normoxia (Fig. 2:A). With the augmented

hyperventilation in mild ambient hypoxia, this occurred even during submaximal exercise, especially during inspiration (Fig. 2:B).

2. Over 50 trials of He:O_2 (.79 He: 21 O_2) breathing in 6 subjects were applied under various exercise conditions (Fig. 2C). Note that even though $\dot{V}_E$, f, and flow rates were substantially higher with helium, expiratory flow rates did not reach the maximum limits set by the resting flow-volume curve and those maximum values were achieved only during a portion of inspiration at maximum work.

Thus heavy exercise in normoxia and especially in hypoxia shows clear limitation to airflow--suggesting that dynamic compression of airways must have occurred during a significant portion of expiration and that the rate of shortening of inspiratory muscles was at or near maximum. That expiratory flow limitation was not evident with helium breathing suggests a relief of highly turbulent airway flow and reduction of the required pressure development for flow-resistive work. Hence, these data are revealing of a mechanical limitation of the lung and inspiratory muscles but need two further important types of information. First, the actual end-expiratory level (or FRC) during exercise is obviously critical to an evaluation of the flow-volume curve (see Fig. 1A-C). We have used (to date) only the conventional approach of assuming no exercise effect on total lung capacity and using the change in inspiratory capacity (rest to exercise) to define the FRC level. Our new helium equilibrium technique is needed to quantitate "real" FRC in exercise. Secondly, actual measurements of esophageal, transdiaphragmatic, and total system pressures are needed to determine the actual limits to development of inspiratory muscle force.

3. Taking the two sets of observations outlined above--even with their noted limitations--we hypothesized that these apparent mechanical constraints of the lung and chest wall would be an important determinant of the degree of hyperventilation achieved in heavy exercise. Thus we compared the effects of augmented chemical stimuli (decreased PaO_2, decreased pHa, and increased adrenergic amines) with the effects of mechanically "unloading" the system with helium breathing: An example of the results is shown in Table 2. Both He and low O_2 increased $\dot{V}_E$ (and lowered $PaCO_2$), but the effects of the mechanical "unloading" were usually greater (and never less) than the augmented chemical stimuli. In fact the increased tachypneic hyperventilation with helium breathing occurred and was sustained over 5-6 min of exercise <u>despite</u> a large decline in chemical stimuli (increased PaO_2 and pHa) which accompanied the initial hyperventilation of helium breathing. In moderate work of <2.5 l,min $\dot{V}O_2$ (not shown) where air flow was much less turbulent and no hyperventilation evident (breathing air) mechanical "unloading" usually had little or no effect on ventilatory response or blood gases: whereas increased chemical stimuli always produced a significant hyperventilation. The results in heavy work clearly implicate a critical role for mechanical "constraint" of the ventilatory response to heavy work. They are also inconsistent with two long-standing premises that: a) a substantial ventilatory

"reserve" exists in healthy subjects; and b) that chemical drive (i.e. metabolic acidosis in normoxia and arterial hypoxemia in hypoxia) and/or chemoreceptor sensitivity are the primary regulators of this hyperventilatory response. A critical next step in these studies is to determine inspiratory pressure development, the relative contribution of various respiratory muscle groups, and pulmonary mechanics under these same experimental conditions.

B. Animals

The exercising rat model was used to assess the metabolic status of the respiratory muscles. While much of this year was devoted to method development (see above) we have managed to obtain two sets of data thus far which describe the effects of heavy exercise in normoxia and hypoxia and the effects of hypoxia, per se (Table 3A and 3B). The major point to be made from the preliminary data is that--as we suspected from our human data--the respiratory muscles do show evidence of anaerobic glycolysis much in the same manner as that well established for working limb muscles. Note the glycogen depletion, lactate accumulation, and intracellular acidosis in the diaphragm during exercise; and these changes occurred to about the same extent in diaphragm as in gastrocnemius muscle. In hypoxia, even though exercise time was very short (<4 min vs 20-25 Min in normoxia at the same work load) there was also some evidence of ATP depletion. These data are currently being extended to eventually include a wide comparison of work loads combined with varying levels of ambient hypoxia.

IV. Ventilatory Control and Periodic Breathing in Hypoxic Sleep.

Substantial progress was made toward understanding the complex process of periodic breathing in hypoxic sleep in humans. Our computer analysis system provided a detailed profile of every breath taken in sleep, characterizing the distribution and magnitude of breath-by-breath differences in ventilatory timing and pattern. This analysis, along with the acid-base status of arterialized blood, was also applied in the waking state at rest and exercise from acute hypoxic exposure over 4 days and nights at 4300 m. Most relevant findings here are a series of studies which determined the role of CO_2 in the genesis of periodic breathing.

A. Apneic "threshold" to CO_2. First we determined the importance of the prevailing level of $PaCO_2$ to ventilatory control by applying positive pressure ventilation to waking and sleeping subjects over 3-4 min periods, measuring the change in $P_{ET}CO_2$, and then abruptly stopping this over-ventilation and observing its after-effects. These procedures were repeated in 4 subjects many times--awake and in NREM sleep, with hypoxic (F_IO_2 = .13) and normoxic backgrounds and over a wide range of PCO_2s from a maintained PCO_2 (at the spontaneous eupneic level) to -15 to 20 mmHg below eupnea. (Please note: The subjects wore a tight-fitting mask for these studies through which the positive pressure ventilation was applied. As might be expected, a very low success rate [<25%] was experienced in our attempts to maintain 3-4

mins of hypocapnia, repeatedly 10 to 15 times during a given night, without arousing the subject or changing sleep state.) While awake no consistent effects on post-hyperventilation apnea or breathing pattern were produced at any level of hypocapnia. During NREM sleep, we also saw no post-hyperventilation apnea if PCO_2 was held constant (via increased F_ICO_2) at the normal eupneic value (obtained just prior to the augmented ventilation). However, even the mildest levels of hypocapnia in NREM sleep produced significant post-hyperventilation apnea and disordered and variable breathing pattern. There are summarized in Fig. 3. Note that in both normoxic and hypoxic backgrounds apnea occurred when P_ACO_2 was reduced approximately 3 to 4 mmHg below the eupneic level (in NREM sleep) and that this "threshold" coincided in each case with the normal waking level of eupneic P_ACO_2 (40-41 mmHg at sea-level and 37 to 38 mmHg in hypoxia). We emphasize that extreme sensitivity of breathing rhythmicity to ΔP_ACO_2 in NREM sleep was demonstrated here only when the hypocapnia was generated by "passive" hyperventilation. The results in hypoxic-induced periodic breathing also show that this same sensitivity to hypocapnia exists even when the hyperventiltion is "actively induced" (see below).

B. Augmented CO_2 in hypoxia sleep (see Figs. 4A-F). During the first night at 4300 m simulated altitude, in NREM sleep the subjects were hypoxic, and moderately hypocapnic, and alkalotic and showed substantial periodic breathing with "breathing time" and "apneic time" usually close to 1:1 (Fig. 4A:B). If we added CO_2 via nasal flow and diluted with nitrogen so as to maintain SaO_2 at its normal (hypoxic) level, we were able to completely remove the periodic breathing as $PaCO_2$ rose only 1 to 3 mmHg and pHa fell only .01 to .02 units (Fig. 4C:D). This pronounced effect of very small increments in $PaCO_2$ was highly reproducible and reversible. Further (in 3 trials only to date), if we prevented the P_ACO_2 from falling in acute hypoxia we also prevented the development of periodic breathing (not shown). Acute hyperoxia (Fig. 4E) also removed periodic breathing; an effect which we also attribute to the small coincident rise in $PaCO_2$ (see Fig. 4:E).

Combining these two sets of studies (A and B) we feel confident in postulating that even very small reductions in P_ACO_2 become vital to the maintenance of normal rhythmic breathing in NREM sleep and must provide a substantial part of the explanation for periodic breathing in sleep in hypoxia. Indeed if one merely follows breath-by-breath changes in P_ACO_2 during sleep, transient apneic periods or prolongation of the post-expiratory pause is highly predictable from the magnitude of spontaneous breath-to-breath change in P_ACO_2. (It is of interest here that previous concepts have emphasized that the "response" to CO_2 changes are little if at all affected by the sleeping state. We confirm this concept--but only if one takes the conventional approach of increasing $PaCO_2$ (via increased F_ICO_2) and determining the usual CO_2 "response." It is, then, the small decrements in P_ACO_2 which are critical to rhythmic breathing.) Finally, it is of significance that periodic breathing was not evident during REM sleep stage in hypoxia, i.e. breathing continued to show its high degree of

variability during REM at high altitude as it did at sea-level with little effect of any superimposed pertubations such as hyperoxia or hypercapnia. During the acute stages of hypoxic exposure (Days 1-3) the quality ot sleep declines appreciably including a marked reduction in the time spent in REM stage sleep.

V. Role of CNS Metabolism in the Control of Chronic Ventilatory Acclimatization.

Several studies begun at various stages of this contract were completed this past year and are in press or in the process of being submitted for publication. We summarize the findings here: 1) Up to 80% depletion of CNS and carotid body norepinephrine and dopamine produced a moderate chronic hyperventilation in normoxic rats but was without significant effect on time-dependent ventilatory acclimatization to hypoxia. 2) Long-term ventilatory acclimatization to 4 days at 4300 m was identical in any sleep stage (NREM or REM) as it was during the waking state, suggesting that suprapontine influences on ventilatory control--as are presumably operative in wakefulness--were not requisite to the process of acclimatization. 3) Neither brain metabolic acid production or intracellular [H+] in brain stem or cortex of rats underwent appropriate changes to explain the time-course of ventilatory acclimatization (see Fig. 5). 4) In studies on the awake goat whose brain was perfused with varying degrees of alkalinity or acidity, the ventilatory response to specific carotid body stimulation was enhanced with CNS alkalinity and depressed with CNS acidity, i.e. chemoreceptor interaction showed "hypoaddition." The implications of this negative interaction to ventilatory control are obviously many--including further complications of any attempts to apply functional meaning to observed changes in systemic and/or cerebral fluid acid-base status in hypoxia.

VI. Publications Relevant to Contract No. DAMD 17-77-C-7006, Contract Year 05 (October 1, 1981 to July 1, 1982)

A. MANUSCRIPTS PUBLISHED OR IN PRESS

1. Dempsey, J., P. Hanson, D. Pegelow, A. Claremont and J. Rankin. "Limitations to exercise capacity and endurance: pulmonary system." Can. J. Appl. Spt. Sci., 7(1):4-13, 1982 (Symposium Proceedings on Limiting Factors in Exercise, Toronto, Canada, October 1981).

2. Dempsey, J.A. and H.V. Forster. "Mediation of ventilatory adaptations." Phys. Rev., 62(1): 262-346, 1982. *(see footnote)

* This invited review includes a synthesis of many of the findings we have obtained under the auspices of USA RDC contracts, beginning in 1967 in collaboration with Principal Investigator Dr. Robert Grover

3. Dempsey, J.A. "Relative significance of HbO_2 dissociation curve shifts, in exercise and in chronic hypoxia." The Physiologist, 25: 89-90, 1982. (Symposium on Blood Oxygen Affinity as a Factor in Tissue Oxygen Delivery, APS Fall Mtg., Cincinnati, October 1981).

4. Dempsey, J.A., A. Berssenbrugge, T. Musch, and J. Skatrud. "The lung: hypoxia, acid-base changes, and the control of breathing." Sem. Resp. Med., 3(2):76-79, 1981.

5. Mitchell, G.S., C.A. Smith, L.C. Jameson, E.H. Vidruk, and J.A. Dempsey. "Ventilatory control in goats following serotonin depletion with p-Chlorophenylalanine (PCPA)." (in press)

6. Hanson, P., A. Claremont, J. Dempsey, and W. Reddan. "Determinants and consequences of ventilatory responses to competitive endurance running." J. Appl. Physiol., 52: 615-623, 1982.

7. Forster, H.V., and J. Dempsey. "Ventilatory adaptations." Lung Biology in Health and Disease: Regulation of Breathing. Part II, edited by T.F. Hornbein. Vol. 17. Marcel Dekker, Inc., NY: 1981.

B. ABSTRACTS

1. Skatrud, J. and J. Dempsey. "Effect of sleep on ventilatory response to alkalosis in humans." Fed. Proc., 41(4):4866, 1982.

2. Smith, C.A., L.C. Jameson, G.S. Mitchell, T.I. Musch and J.A. Dempsey. "Central-peripheral chemoreceptor interactions in the awake, CSF-perfused goat." Fed. Proc., 41(4):4872, 1982.

3. Jameson, L.C., C.A. Smith and J.A. Dempsey. "A method for cisterna magna perfusion of synthetic CSF in the awake goat." Fed. Proc., 41(4):4873, 1982.

4. Berssenbrugge, A., J. Dempsey, J. Skatrud and P. Wilson. "The effect of CO_2 on human periodic breathing (PB) during sleep in hypoxia." Fed. Proc., 41(4):6475, 1982.

5. Musch, T.I., J.A. Dempsey, C.A. Smith, N.T. Bateman and G.S. Mitchell. "Effects of severity of chronic hypoxia on brain metabolic acid production and pH_i." Fed. Proc., 41(5):8301, 1982.

6. Mitchell, G.S., C.A. Smith, L.C. Jameson, E.H. Vidruk, and J.A. Dempsey. "Ventilatory control in goats following serotonin depletion with p-Chlorophenylalanine (PCPA)." Fed. Proc., 41(5):8304, 1982.

7. Dempsey, J., P. Hanson, D. Pegelow, and R. Fregosi. "Mechanical vs chemical determinants of hyperventilation in heavy exercise." Med. Sci. Sports Exer., 14(2): 131, 1982.

C. UNPUBLISHED PRESENTATIONS AT NATIONAL MEETINGS

1. Dempsey, J. "Pulmonary response to exercise in health." Presented at the Symposium on Industrial Disability, American College of Chest Physicians, San Francisco, October 1981.

2. Dempsey, J.A. "Ventilatory control in changing 'states'--exercise, sleep, and chronic exercise." International Symposium--Central Neural Production of Periodic Respiratory Movements, April, 1982, Lake Bluff, IL, J.L. Feldman (ed.).

3. Berssenbrugge, A., J. Demsey, and J. Skatrud. "Genesis of periodic breathing during sleep at high altitude." To be prsented at APS symposium on High Altitude Adaptation, San Diego, October 1982.

VII. Military Significance

Our contract work is aimed at a better understanding of two physiologic problems occurring in hypoxic environments which clearly effect the well-being and performance capabilities of the human sojourner at high altitudes. These problems are periodic breathing during sleep leading to loss of quality sleep and the resulting daytime hypersomnelence and fatigue; and the regulation of the ventilatory response and pulmonary gas exchange during exercise in hypoxia which are key determinants of exercise performance.

Our work on periodic breathing during hypoxic sleep provides the first comprehensive, quantitative description of this problem. This past year's work has provided, we think, important insights into this phenomenon--in the form of the critical level of CO_2 required to maintain rhythmic breathing during sleep and explains the effect of acute oxygen therapy on relieving periodic breathing in sleep.

Exercise capacity as determined by the pulmonary system in hypoxia and the debilitating symptoms of dyspnea which accompany exercise in hypoxia have been the subjects of our investigations. Our work has detailed the critical limitations to oxygen transport presented by the failure of the lung's gas exchange and ventilatory control system and chest wall mechanics to respond adequately and/or efficiently to heavy work in hypoxic environments. Further, the baseline work in normoxic environments clearly shows the susceptibility of some healthy individuals to these problems during exercise, thereby providing a basis for prediction of problems with high altitude exercise from measurements made at sea-level.

VIII. Facilities and Personnel

The only changes made in this past year were a further updating and application of our computer system to analysis of sleep and exercise data in humans and animals. In personnel we began collaboration with Dr. Robert Fitts, Marquette University, for assistance with our studies in skeletal muscle.

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TABLE 1
Effects of Mild and Moderate Steady-State Exercise on Arterial Blood Gases and Acid-Base Status in Rats
(N=8 - normoxia; 10 mins per workload)

	Rest	11 meters/min	16 meters/min
PaO_2 (mmHg)	*(6) 88.85±4.90	(8) 89.27±5.10	91.38±6.83
$PaCO_2$ (mmHg)	(6) 38.55±1.30	(8) 31.40±3.90	28.56±2.24
pHa	(6) 7.40±0.01	(8) 7.39±0.06	7.37±0.05
$[HCO_3^-]$ (meq/ℓ)	(6) 23.00±1.34	(8) 18.30±2.45	16.10±3.00
Lactate (nMol/ℓ)	(6) 0.58±0.11	(8) 0.99±0.32	1.14±0.42
HCT (%)	(6) 35.00±2.76	(8) 36.50±2.20	38.00±1.90
$Temp_{Rect}$ (°C)	(6) 38.60±0.80	(8) 38.75±0.66	39.02±0.53

* (n)

TABLE 2

Mechanical Constraint vs Chemical Drive as Determinants of the Ventilatory Response to Heavy Exercise ($\dot{V}O_2$ = 3.8 ℓ,min)

	.21 O_2:N_2	.18 O_2:N_2	.21 O_2:He	
"DETERMINANTS"				
pH	7.34	7.24	7.37	
PaO_2	55	47	69	mmHg
Norep.	15x	24x	12x	Rest
Insp. Flow	5.6	5.9	7.4	ℓ,sec
Reynolds No.*	13,000	14,000	5,000	
"RESPONSE"				
$PaCO_2$	38.0	34.0	30.0	mmHg
$\dot{V}_E$	112	126	145	ℓ,min
f/min	52	56	69	

* Reynolds No. determined for third generation airways

= Density x Velocity x $\frac{\text{Diameter}}{\text{Viscosity}}$. Reynolds No. > 2,000 usually indicate beginning of turbulent flow.

TABLE 3A

Effects of Heavy Exercise in Normoxia (80% Max $\dot{V}O_2$)(28 m/min, 10% gd., N=7) on Metabolic Acids, High Energy Phosphates, and Intracellular pH in Rat Diaphragm and Gastrocnemius Muscle

		Glycogen mg/g w.w.	Lactate mM/kg w.w.	Pyruvate mM/kg w.w.	ATP mM/kg w.w.	ADP mM/kg w.w.	AMP mM/kg w.w.	CP mM/kg w.w.	Creatine mM/Kg w.w.	Lac. / Pyr.	ATP / ADP	Intracellular pH *
Diaphragm												
REST	$\bar{x}$	2.4	1.963	.90	6.23	.507	.942	14.71	6.856	2.775	13.6	7.06±11
	S.D.	1.1	.93	.48	1.5	.18	.19	3.37	1.8	1.8	6.4	
MAX EX.	$\bar{x}$	1.22	8.06	1.3	5.86	.5703	1.358	9.63	7.83	6.34	10.98	6.82±.24
	S.D.	.62	2.64	.267	.55	.144	.79	3.34	1.73	1.7	3.5	
Gastrocnemius												
REST	$\bar{x}$	3.65	2.715	1.12	7.3	.662	1.24	12.97	5.7	2.58	12.22	7.10±.16
	S.D.	1.9	1.13	.406	1.8	.26	.46	2.26	1.5	1.3	4.53	
MAX EX.	$\bar{x}$	.89	11.15	.954	5.58	.43	.98	9.31	7.33	13.6	14.7	6.97±.17
	S.D.	.64	4.6	.52	1.44	.18	.33	2.01	2.3	7.3	6.3	

* Intracellular pH determined by CPK equilibrium technique

$pH_i = -\log K'_{CK} + \log K$; where $K'_{CK} = \frac{CR \cdot ATP}{CP \cdot ADP} + \log K = 12.1 \times 10^{-7}$

TABLE 3B

Effects of Heavy Exercise in Hypoxia (F_IO_2=.12)
(28 m/min, 10% Grade, 2 to 5 mins) on Metabolic Acids, High
Energy Phsophates, and Intracellular pH in Rat Diaphragm and Gastrocnemius Muscle

	Lactate	Glycogen	ATP	CP
Rest Hypoxia				
Diaphragm	1.01 ±.35	2.02 ±.72	2.92 ±.44	10.6 ±1.9
Gastrocnemius	2.50 ±.51	2.22 ±.71	5.03 ±.79	9.7 ±2.3
Exercise Hypoxia				
Diaphragm	2.6 ±1.1	1.32 ±.30	2.37 ±.5	7.0 ±5.0
Gastrocnemius	3.36 ±1.12	1.78 ±.21	4.83 ±.57	12.7 ±1.0

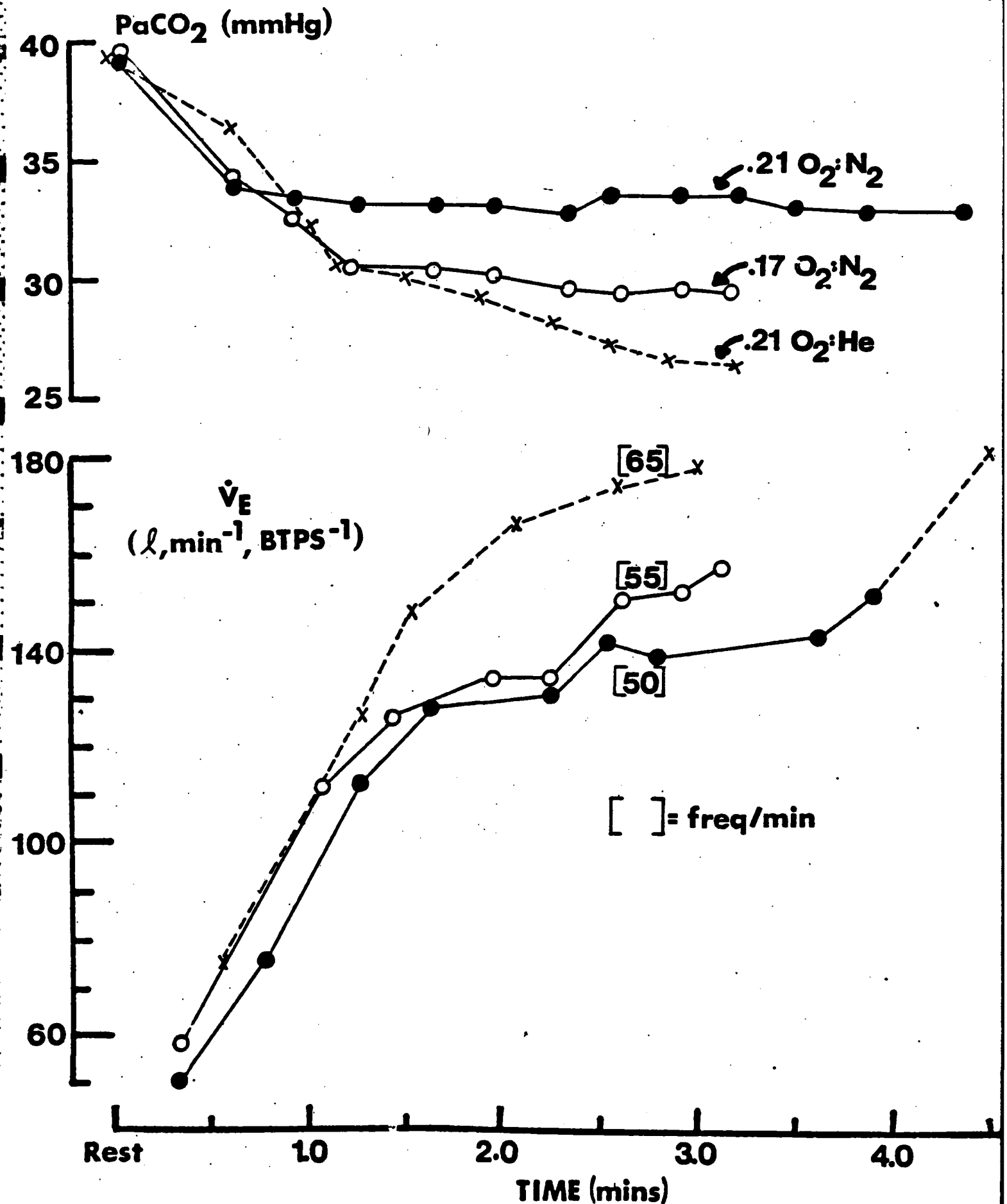


Fig. 1. Effects of increased chemical drive via reduced F_IO_2 (decreased PaO_2 and pHa) vs mechanically unloading the system with helium breathing in normoxia (also see Table 2).

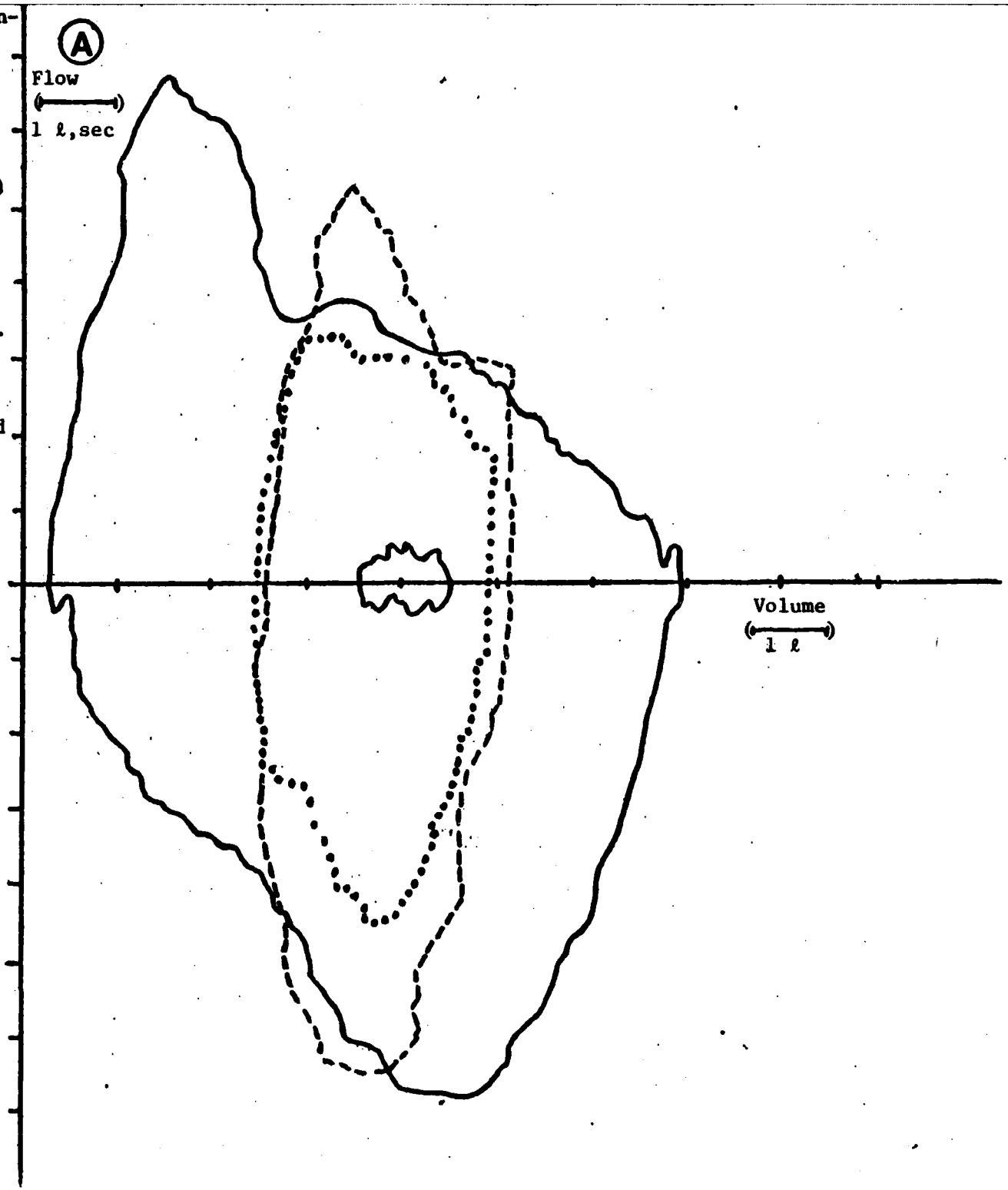


Fig. 2:A. Flow:volume relationship during exercise in normoxia. Shown are the loops for resting tidal volume and for maximum flow:volume at rest (———). The loops achieved during tidal breathing in moderately heavy exercise (••••••) (70% Max $\dot{V}O_2$) and very heavy exercise (90-100% Max $\dot{V}O_2$) (---) are superimposed. Note that both inspiratory and expiratory flows exceed the maximum in very heavy exercise. The increase in FRC (i.e. end-expiratory level) is only an estimate using conventional techniques and must be verified using some direct method (see text).

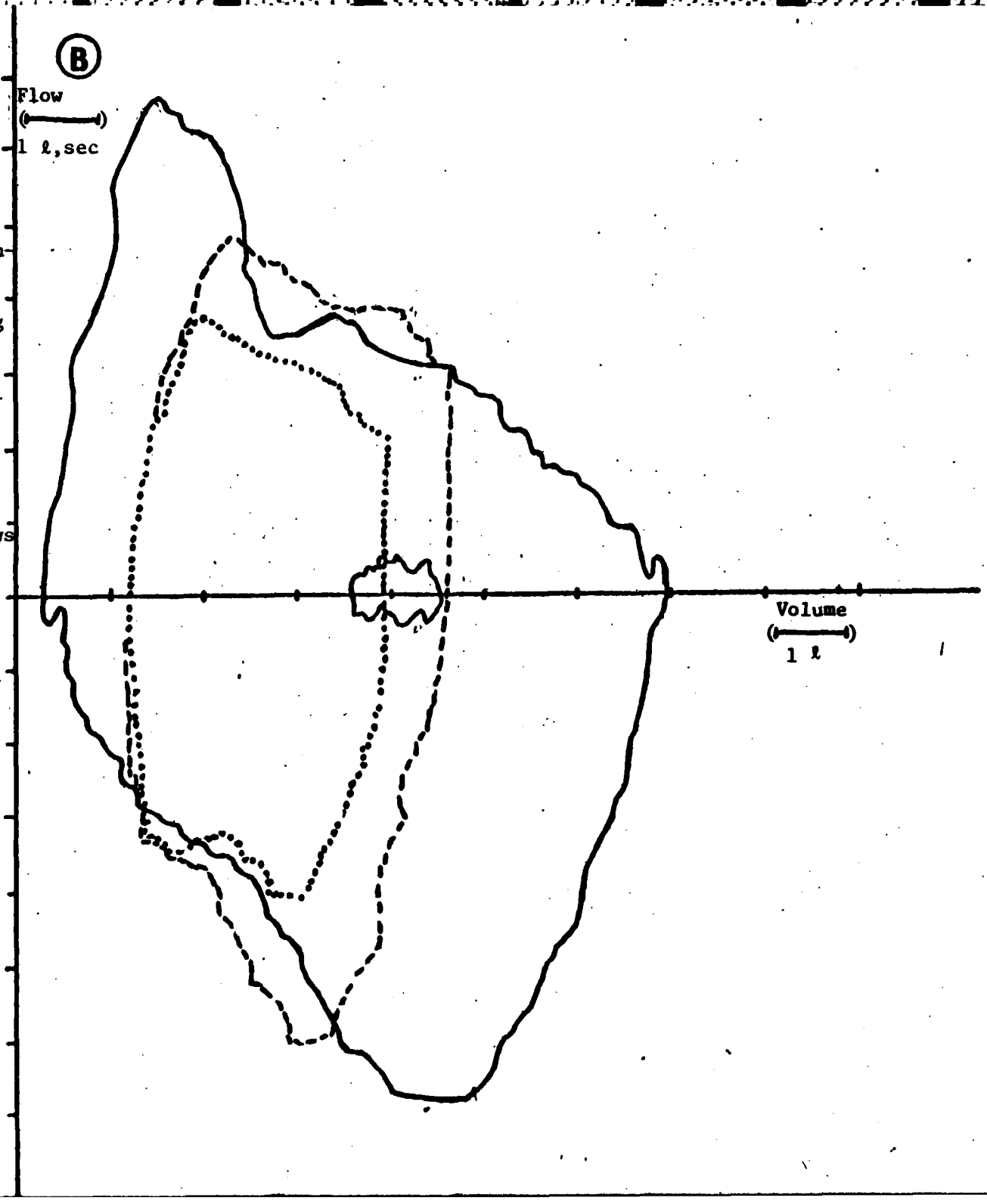


Fig. 2:B. Flow:volume relationship during exercise in mild ambient hypoxia (F_IO_2=.17). Shown are the loops for resting tidal volume and for maximum flow:volume at rest (——). The loops achieved during tidal breathing in moderately heavy exercise (••••) (70% Max $\dot{V}O_2$) and very heavy exercise (90-100% Max $\dot{V}O_2$)(---) are superimposed. Note that both inspiratory and expiratory flows exceed the maximum in very heavy exercise. However, with the augmented hyperventilation of hypoxia, these excessive flows occur even in moderately heavy exercise.

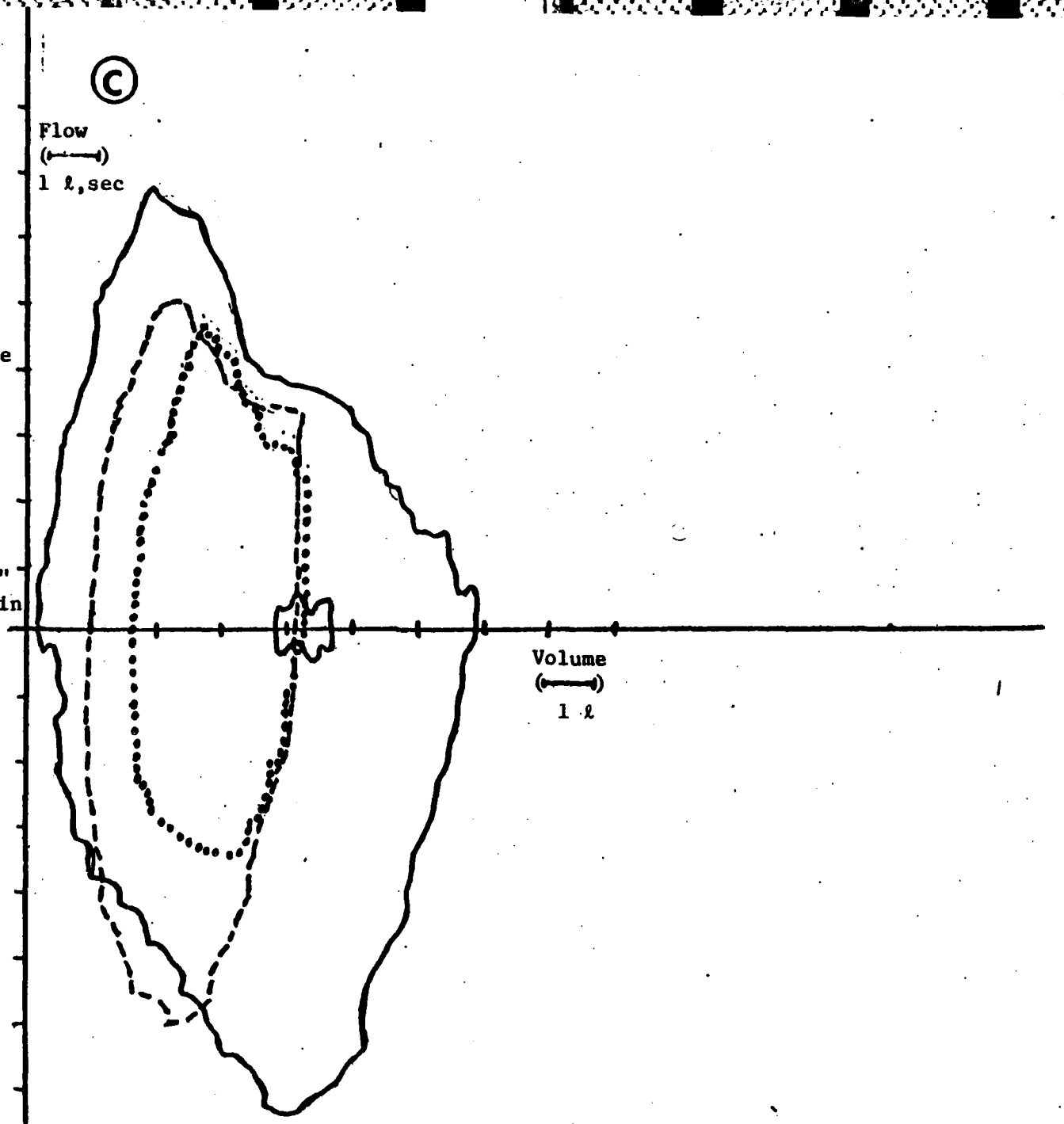


Fig. 2:C. Flow:volume relationship during exercise in normoxia, with helium breathing (.21 O_2:.79 H_e). Shown are the loops for resting tidal volume and for maximum flow: volume at rest (——). The loops achieved during tidal breathing in moderately heavy exercise (•••) (70% Max $\dot{V}O_2$) and very heavy exercise (90-100% Max $\dot{V}O_2$)(---) are superimposed. Note that "unloading" the pulmonary system resulted in expiratory flow not exceeding maximum limits even in heavy exercise (although inspiratory flow exceeded the maximum limit in very heavy exercise).

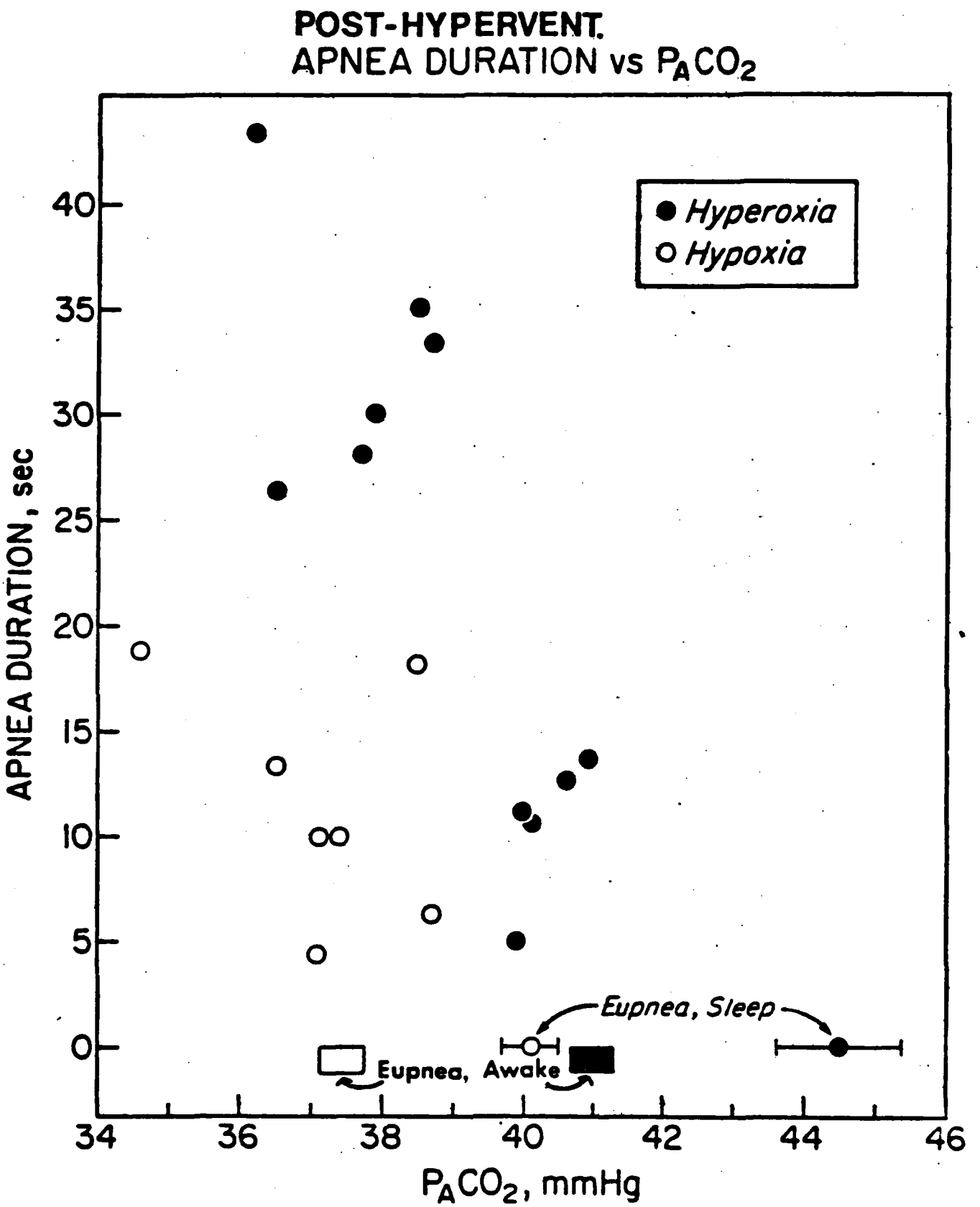


Fig. 3. Compilation of data obtained with positive pressure hyperventilation (for 3-4 min periods) during NREM sleep in normoxia and acute hypoxia ($F_IO_2 \sim .12$, $SaO_2 \sim 80\%$). Normoxia. Note, the P_ACO_2 obtained during spontaneous eupnea increases from 41 mmHg while awake to 44.5 mmHg coincident with the hypoventilation of NREM sleep. Post-hyperventilation apnea ensued when P_ACO_2 was lowered just to that P_ACO_2 obtained while awake. Hypoxia. P_ACO_2 also rose from awake to asleep (37.5 to 40 mmHg) and apnea occurred when P_ACO_2 was lowered to the awake P_ACO_2 value. Increased $\dot{V}_E$ alone, by positive pressure ventilation at iso-PCO_2, did not cause apnea; nor did post-hyperventilation apnea occur while awake at any decrease in P_ACO_2 (not shown).

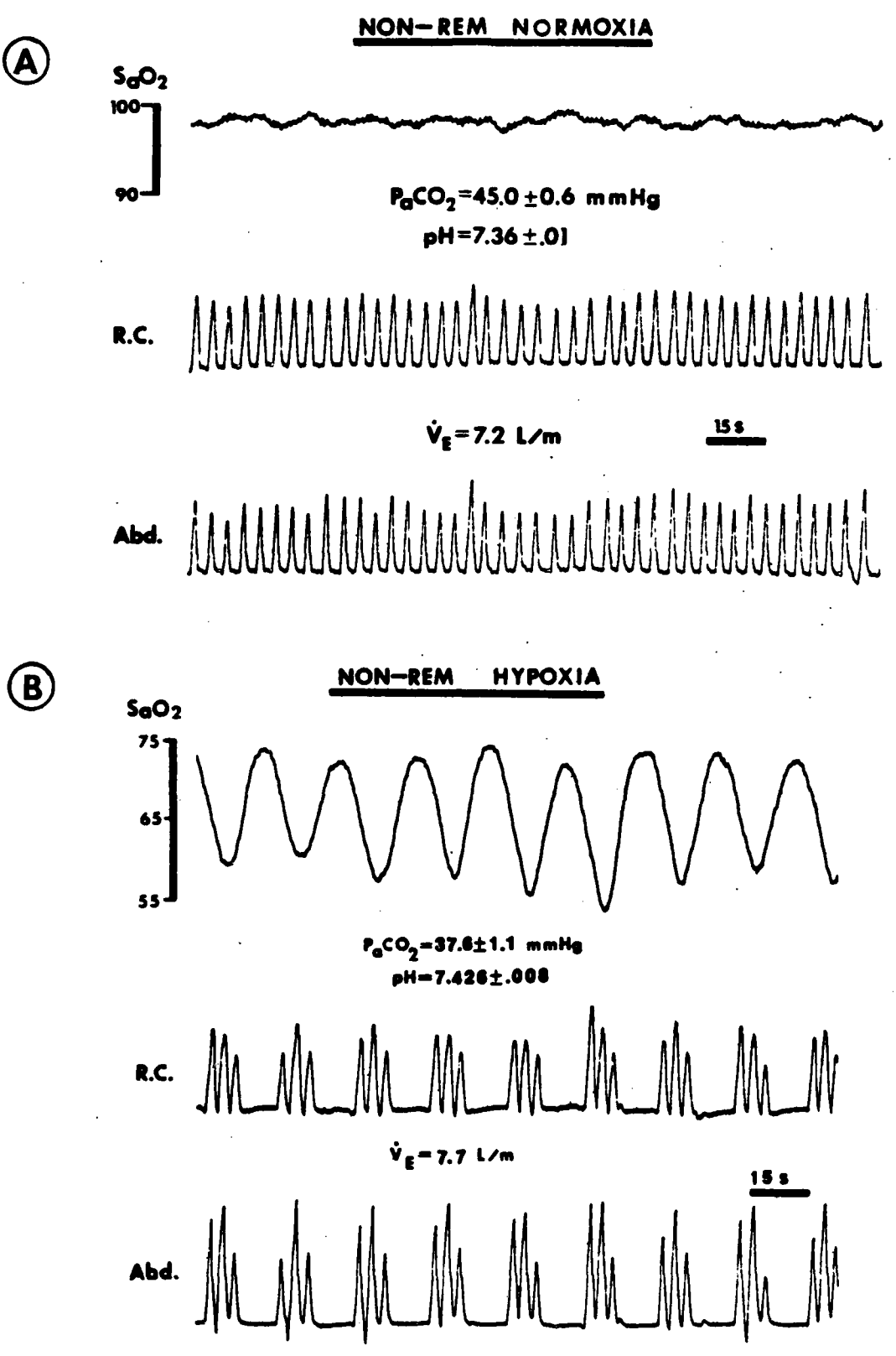


Fig. 4 A:B. Comparison of rhythmic breathing during NREM sleep at sea-level vs the periodic breathing during the first few hours at 4300 m. At 4300 m the time spent in apnea vs "breathing time" was about 1:1; whereas at sea-level no apneas (>5 secs) were observed.

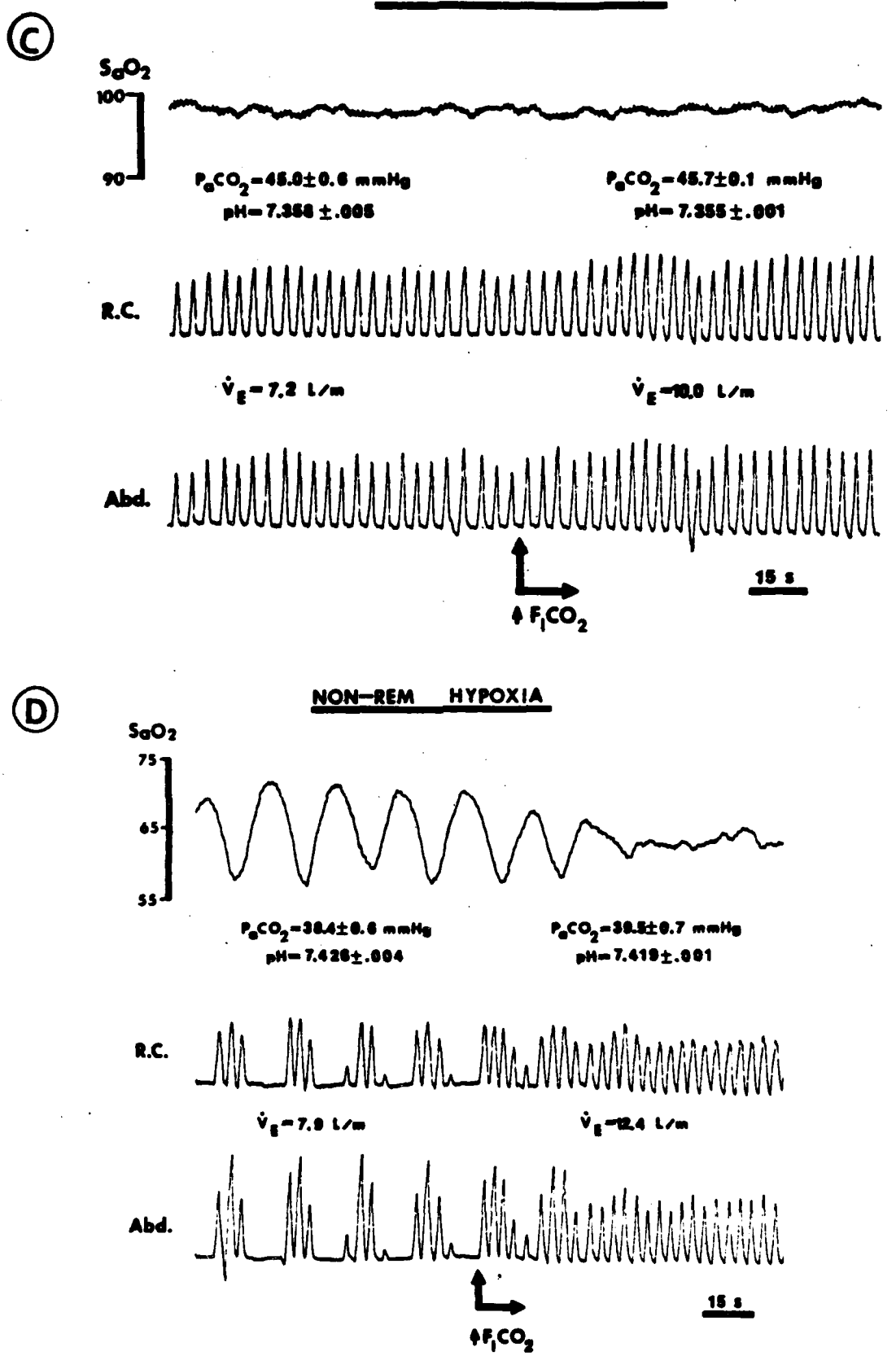


Fig. 4 C:D. Effects of changes in $PaCO_2$--administered by nasal flow--on breathing pattern in NREM sleep. Note, at sea-level, augmenting F_ICO_2 simply increased $\dot{V}_E$ and Vt in a normal fashion without changing pattern. At 4300 m, ↑F_ICO_2 and ↑$PaCO_2$ by <1-2 mmHg rapidly changed the periodic pattern to rhythmic. When CO_2 via nasal flow was abruptly stopped (not shown) the pattern immediately reverted back to a periodic one. Similarly, if $PaCO_2$ was prevented from falling during induction of hypoxia, periodic breathing was prevented (not shown).

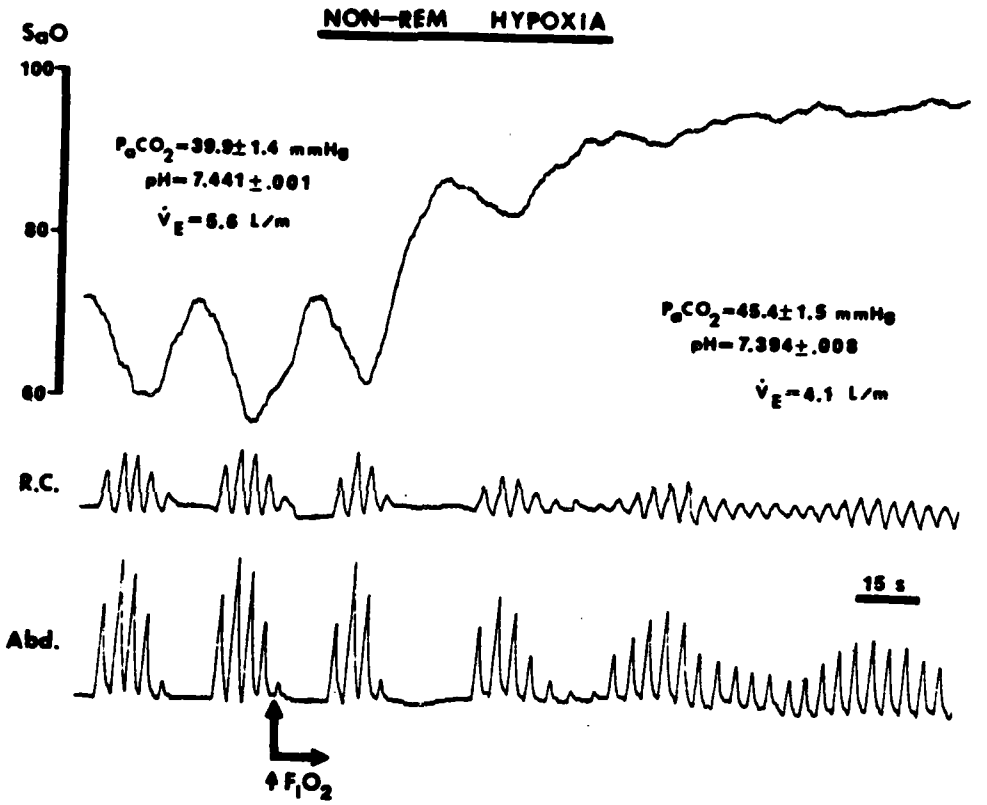


Fig. 4:E. Effects of ↑F_IO_2 (and therefore ↑ SaO_2) on periodic breathing at 4300 m. Note that ↑FIO2 causes both ↑ SaO2 and a ventilatory depression (∿ +5 mmHg $PaCO_2$). When SaO_2 is > 90% disordered breathing was still evident and did not become regular until a later time when a hypoventilation was realized. Thus while we cannot rule out a role for alleviation of cerebral hypoxia in the genesis of periodic breathing in hypoxia, the data do implicate a major role for hypocapnia (as in Fig. 4:D) in these effects of hyperoxia.

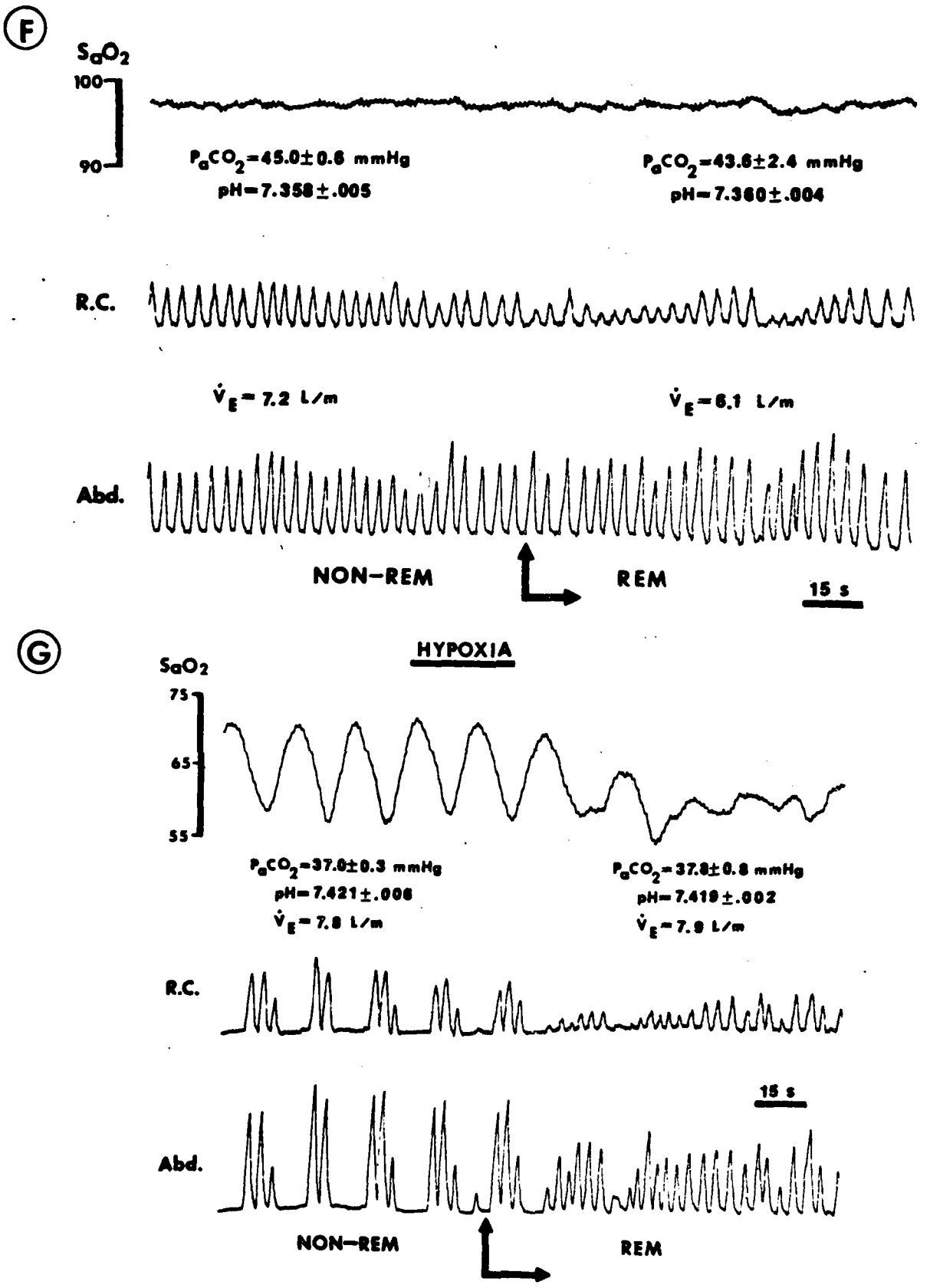


Fig. 4 F:G. Effects of sleep stage on breathing pattern at sea-level and at 4300 m. At sea-level breathing was rhythmic in all NREM sleep stages (I-IV) and converted to an unstable, variable pattern in REM, but with no apnea periods. At 4300 m the periodic pattern was obtained in all NREM sleep stages, but never in REM sleep, where the pattern was identical to that in sea-level REM. Imposing $\uparrow F_ICO_2$ or hyperoxia during REM had little effect on breathing pattern or its distribution during REM sleep at either altitude (not shown).

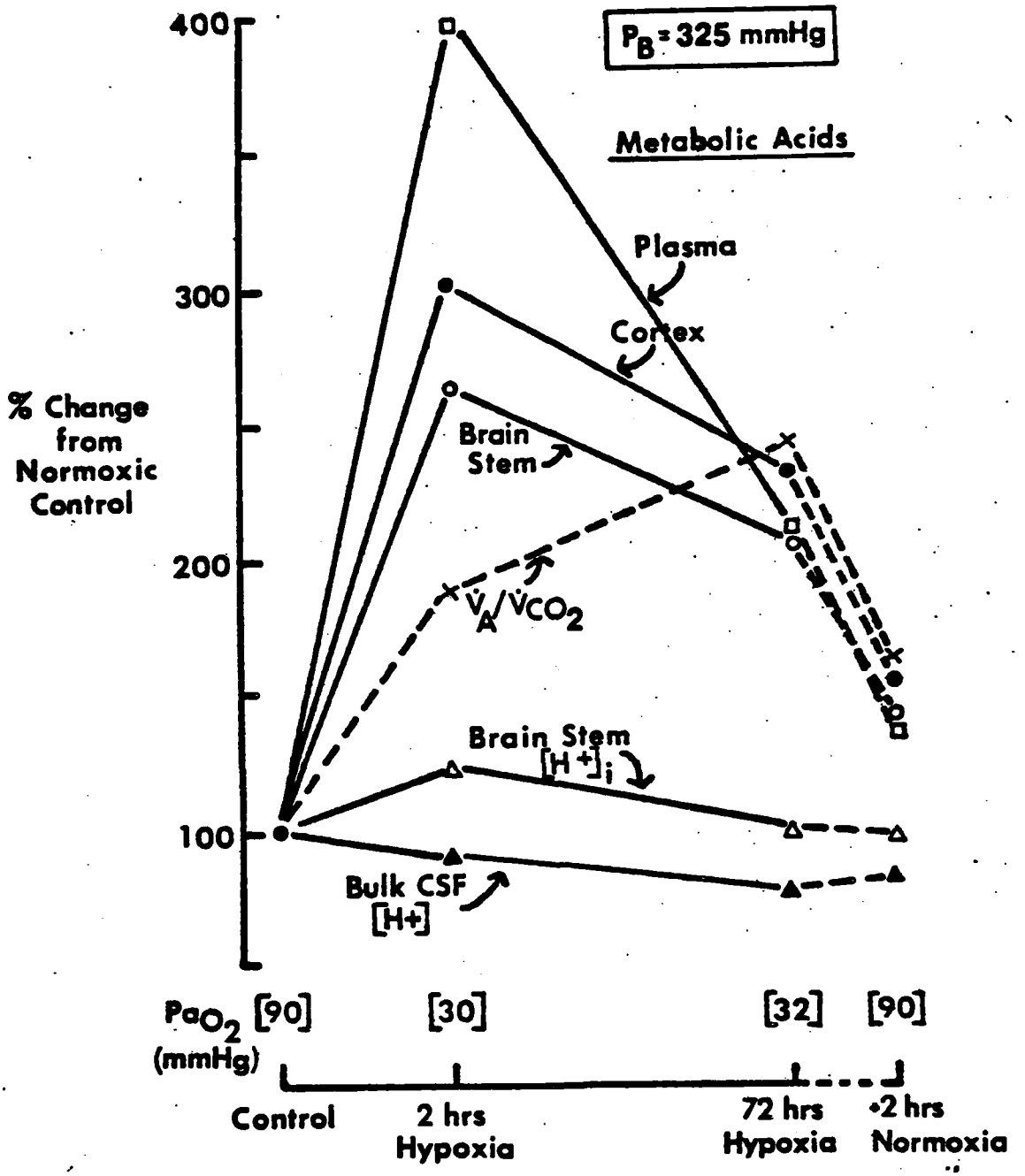
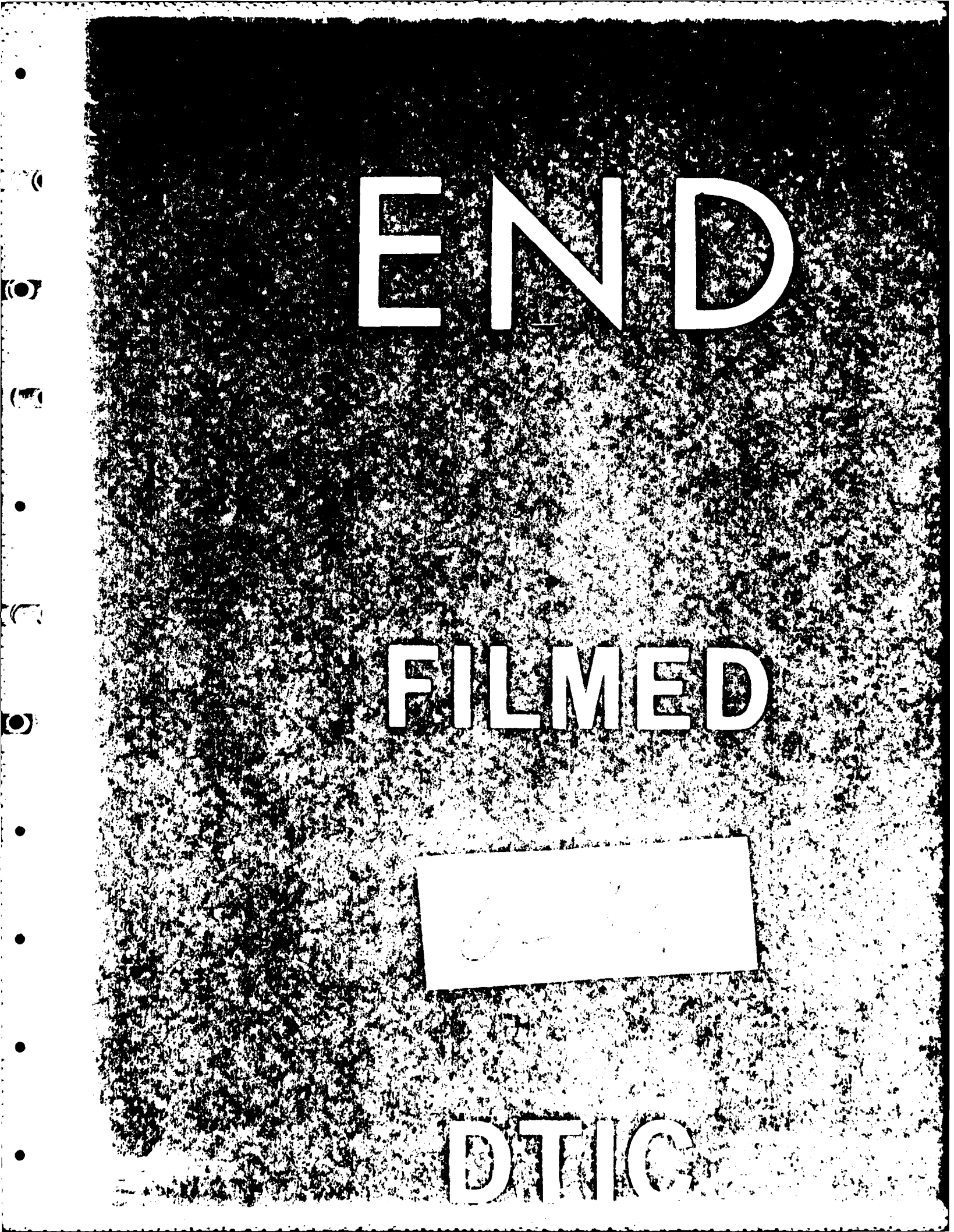


Fig. 5. An example from our rat studies of the complex profile of brain intra- and extra-cellular fluid acid-base status during acclimatization to very high altitude (>6000 m). Most striking is the degree of adaptability of brain tissue to this severe hypoxemia (PaO_2 28-31 mmHg) as metabolic acid production (mainly lactic acid production) and intracellular acidosis peaks at 2 hours of hypoxia but returns to or toward normoxic control over 3 days at high altitude. A similar trend, without the severity of derangement in acute hypoxia, was seen at 4300 m (not shown). The time-course of ventilatory acclimatization ($\Delta V_A/\dot{V}CO_2$ or $\Delta PaCO_2$) shows no positive relationship with these acid-base changes.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