EFFECT OF HYPERCAPNIA UPON VENTILATORY RESPONSES IN PORCUPINES AND WOODCHCUKS: RODENT CHARACTERISTIC OR BURROWER'S ADAPTATION?

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A special tribute, one that is not normally found in a paper such as this, goes to the young men and coaching staff of the Frenchtown High School football team. Because of their special kind of courage and excellence I was able to make it through the long hours. Thankyou!

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ABSTRACT

The purpose of this experiment was to compare the ventilatory response to acute environmental hypercapnia in the woodchuck and in a nonfossorial control: the porcupine.

Respiratory measurements of tidal volume (V_T), breath frequency (f), inspiratory (T_I) and expiratory (T_E) times were made using the barometric method while the animals breathed normoxic room air (20% O_2) or hypercapnic (5% CO_2) gases.

The woodchuck's ventilatory response to hypercapnic environmental conditions is significantly different from that of the porcupine in both the degree and pattern. These differences may reflect genetic adaptation to its semi-fossorial habitat.

INTRODUCTION

Living in a burrow provides protection from predators and climatic extremes. This unique advantage has resulted in its wide spread use by a great number of species. Diffusion through the soil is the essential mechanism of gas exchange in burrows but this may not be adequate in the burrows of most endotherms to avoid large gradients of respiratory gases. Insufficient gas exchange would involve an elevation of CO_2 gas concentrations in the burrow accompanied by a reduction in burrow O_2 concentrations [18].

The problem for a burrow-dwelling mammal is the chronic hypercapnia found to exist within the burrow. Physiological adjustments are necessary to avoid inordinate amounts of energy expenditure in respiratory work. While avoiding this work the animal must still allow for adequate levels of oxygen to be delivered to its tissues.

Ventilatory responses to CO_2 appear to be reduced in fossorial mammals, but too often many of the species that were studied were

rodents whose ventilatory responses were compared to those of man [5]. A study of the white rat demonstrated a CO_2 ventilatory response significantly lower than that of man [1]. Is this significant difference due to a rodent's characteristic or a burrower's adaptation? This question raises some doubts concerning the credibility of comparing the ventilatory CO_2 responses of burrowing rodents to primates. To answer the question requires finding a non-fossorial rodent such as the porcupine and comparing it to a fossorial rodent of similar size, the woodchuck.

The respiratory cycle of an animal involves the interaction of respiratory "drive" and mechanics. Respiratory drive is related to the chemical stimuli, such as carbon dioxide, that the animal might be subjected to. Some studies have shown that the respiratory frequency and tidal volume selected by an animal should achieve the best gas exchange for the least expenditure of energy (Mead, 1960) [15]. The efficiency of gas exchange depends a great deal upon good distribution of ventilation. Inspiratory and expiratory flow rates may be responsible for sufficient distribution of ventilation. Tidal

volume and frequency, and its components --inspiratory and expiratory durations-- vary due to mechanics and the interplay of central and peripheral chemoreceptors.

Understanding the control of the components of each breath is essential to an understanding of the control of total ventilation. One simplified model states that the duration of each phase is limited by the switching on and off of medullary inspiratory neurons [13]. The tidal volume (V_T), becomes a function of "inspiratory drive" and inspiratory time (T_I). During the inspiratory phase inhibitory volume feedback information is sent to the medulla by afferent pulmonary stretch receptors and intercostal muscle fiber spindles to terminate inspiration. Hypercapnia inhibits pulmonary stretch receptor activity and may thereby prolong inspiration or terminate it at higher volumes. CO_2 also increases "inspiratory drive" (V_T/T_I) by stimulating central chemoreceptors, and may shorten expiratory time through its effects on peripheral chemoreceptors [12].

An animals passive expiration is driven by the potential energy stored during the inspiratory phase and its duration depends upon the

resistant features of the lung. Resting expiration is not restricted to passive relaxation, but may be delayed by laryngeal and diaphragmatic "braking" mechanisms [6]. Species who demonstrate expiratory durations greater than passive expiratory times achieve "expiratory braking" by adduction of the vocal cords that will increase laryngeal resistance and by post-inspiratory diaphragmatic activity. Chemical stimulation from carbon dioxide can reduce expiratory braking. Decreased braking occurs through increased activity of the posterior cricoarytenoid (PCA) muscle which abducts the vocal cords and this decreased resistance induces a reduction in expiration duration [2].

The reduced expiratory time (T_E) response to carbon dioxide stimulation seems to be determined by intact carotid bodies in dogs [7]. Removal of the carotid bodies leads to a prolonged period of expiration. This raises the question whether or not two species with different CO_2 sensitivities demonstrate different patterns of respiratory timing. Boggs and Tenney (1984), showed that the ratio of T_E/T_{Tot} (i.e. expiratory time to total breath time), is an

interspecifac constant among 11 species of mammals within the size range of mouse to horse.[6].

Conditions of normoxia and hypercapnia will be used to indirectly test Bowes's theory that peripheral CO_2 sensitivity regulates duration of expiration. Subjecting each species to hypercapnia will also help to answer the question whether lower sensitivity to CO_2 is a rodent characteristic or a burrower's adaptation.

The purpose of this study was to compare the ventilatory response to acute hypercapnia in the woodchuck and a non-fossorial control, the porcupine. Examination of the results may provide answers to the following questions confronted in this study:

1) Is a low CO2 ventilatory response due to a rodent characteristic or a burrower's adaptation?

2) Whether or not two species with different CO2-sensitivity demonstrate different patterns of respiratory timing?

The results obtained may point to those adaptations selected to be most beneficial for existence of a fossorial mammal in the hypercapnic environment of a burrow. These results may confirm existing theories about the role of CO_2 in the control of expiratory time.

LITERATURE REVIEW

Burrow dwelling species are often exposed to an environment of hypercapnia within their burrows. These species seem to have adapted to hypercapnic conditions. In several fossorial and semi-fossorial mammals, the ventilatory response to CO_2 has been well documented and has shown a clear reduction in CO_2 sensitivity compared to non-burrowing mammals [5]. The greatest reduction in CO_2-sensitivity was demonstrated by the burrowing mole rat [1].

The reduced CO_2-sensitivity of burrowing mammals is reflected by low resting ventilation, low arterial PO_2 and high arterial PCO_2. The mole rat's respiratory frequency is 60% of predicted values and its ventilation is 70% of predicted values based on body size [1]. The arterial PO_2 values of 60-75 Torr are much lower than the normal mammalian values of 90-95 Torr, and the $PaCO_2$ values of 45-53 Torr are greater than the normal value of

35-40 Torr [5]. These mammals demonstrated a reduction in normoxic ventilation with an elevation of $PaCO_2$ and a drop in PaO_2. A reduction of ventilatory response to CO_2 may represent an effort towards energy conservation. Increased ventilation would only be a futile effort to eliminate CO_2 when CO_2 levels of the burrow are so elevated.

Hypercapnia has been found to be a powerful respiratory stimulus. Every mammalian species will respond to elevated CO_2 levels by increasing their minute ventilation (V), but by varying amounts depending upon their relative CO_2-sensitivity. Burrow-dwelling mammals who are chronically exposed to CO_2 stimulus tend to show a reduced ventilatory response to carbon dioxide [5].

Carbon dioxide produces a powerful stimulus during respiration because both the peripheral and central chemoreceptors work in the same direction; to increase ventilation [16].

Carbon dioxide stimuli are responded to primarily by central chemoreceptors. These primary receptors involved with minute-by-minute ventilatory control are found near the ventral surface of the medulla. Encompassed by brain extracellular fluid, central chemoreceptors respond to changes in H+ concentrations. An elevation of [H+] or dissolved CO_2 will stimulate ventilation while a drop will inhibit it [21].

Peripheral chemoreceptors also respond to carbon dioxide, but their response has less of an impact (e.g. if an individual is exposed to a CO_2 mixture, less than 20% of the ventilatory response is due to peripheral chemoreceptors) [21]. Peripheral chemoreceptors are important because they respond much more rapidly than central chemoreceptors in adapting ventilation to changes in PCO_2 [21].

Peripheral chemoreceptors are found in the carotid bodies of the common carotid arteries, and in the aortic bodies above and below the aortic arch. A study done by Beek et al., (1984) found that the peripheral chemoreceptors play a role in the frequency response to hypercapnia by decreasing the period of expiration [20]. The

importance of the carotid body lies in its ability to influence both phases of the respiratory cycle. This influence is felt through an alteration of inspiratory time, while producing an independent change in expiratory duration [6,11].

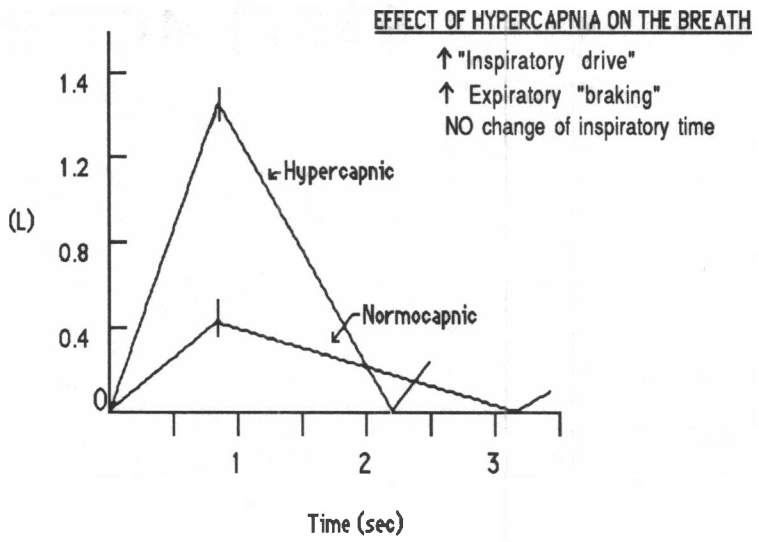

Figure 1. Effect of Hypercapnia upon inspiratory and expiratory timing. Hypercapnia augments inspiratory and expiratory flow, without changing inspiratory timing. Adapted from Remmers, (1976).

Hypercapnia initiates characteristic changes in ventilation: tidal volume (V_T) increases while expiration time (T_E) decreases. Yet, there is little change in inspiratory time (T_I) [17]. All of these qualities contribute to the effect CO_2 posesses to increase the volume and inspiratory flow more than the rate of inspiration [14]. The expiratory phase is substantially shortened during hypercapnic conditions (Fig. 1). If CO_2 stimulus were intensified, active contractions of expiratory muscles would occur and expiration would be further abbreviated [13]. This will help create a more rapid lung volume collapse and so will initiate an earlier inspiratory phase [17].

Within the past twenty years there has been an expanded effort to fully appreciate the regulatory process involved with breathing. These efforts have been advanced through analytical studies concerned with the control of the two pulmonary phases; inspiration and expiration. Breathing, in its simplest form, is a

series of "events" coinciding with the change between inspiration and expiration. These events involve the inspiratory neurons of the medulla which are turned on and off in an "all-or-nothing" event [22]. A simplified model of the "switching" process was proposed by J. E. Remmers, in 1976, (Fig. 2) [17]. The duration of each phase is based upon a theory that breathing is controlled by neural phase switching [6].

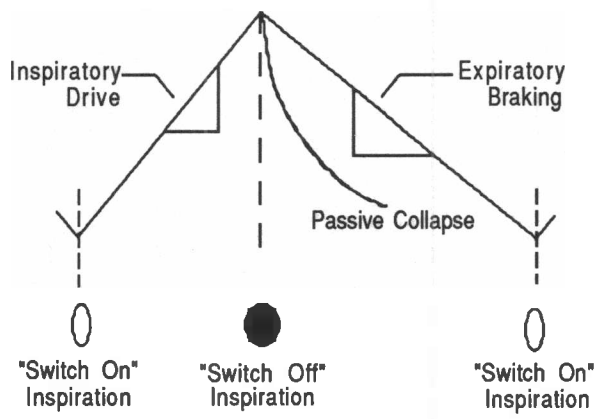

Figure 2. Remmer's Single Breath Model.
Breathing components are shown for a single, ideal breath. Vertical dashed lines represent phase transition coinciding with the switching on or off of inspiratory neurons. The slope of the diagram, during inspiration, demonstrates "inspiratory drive". The expiratory slope demonstrates the retarding action of expiratory braking mechanisms. Adapted from Remmers, (1976).

Towards the end of the inspiratory phase pulmonary stretch receptors initiate suppressive volume feedback information that will be sent to the medulla and eventually begin the "switching off" of the inspiratory phase [19].

Expiration , unlike inspiration, is not an "all-or-nothing" event but instead depends on constant neural feedback. Dependency upon constant neural feedback allows for its variation in duration. Shorter periods of expiration are associated with an earlier "switching on" of inspiration while longer periods delay the switching process.[8]

Expiration can take place passively or may be prolonged through braking mechanisms (Fig. 2). Expiratory airflow may also be effected by the recruitment of expiratory muscles so that the time of expiration will be less than that of passive collapse. The path the expiratory phase follows, depends greatly on the present condition of the mammal (i.e. excitability, temperature, health, etc.), and its own environment (i.e. hypercapnic,hypoxic or normoxic conditions).

Passive expiratory collapse occurs through the potential

energy stored during the previous inspiratory phase. Passive expiration is contingent on a number of factors; inspiratory time (T_I), end-expiratory lung volume , upper airway resistance and airway CO_2 concentrations [6]. Other factors involved are lung and chest wall compliance and the initial length of the respiratory muscles [9].

Quiet expiration is usually not restricted to passive collapse but may be prolonged through the influence of laryngeal and diaphragmatic braking mechanisms. These braking mechanisms involve inspiratory muscle activity early during the expiratory phase and resistances in the upper airways by adduction of the vocal cords [9,13,18]. Braking mechanisms were extensively studied by Gautier et al., (1973) in both humans and cats [9].

Expiratory braking mechanisms provide advantages necessary to minimize energy expenditures. Energy is expended with each trans-pulmonary pressure swing. If the energy expenditures accompaning pressure swings are to become more efficient the fixed resistance of the tracheobronchial tree must be comparable

with working rather than resting ventilation [13]. The laryngeal braking mechanism is more than adequate to fulfill this role. Flow resistance becomes augmented within the relaxed larynx but this resistance can be rapidly decreased to much lower levels by the posterior cricoarytenoid (PCA) muscles opening the glottis involving negligible costs in energy [13].

Hypercapnia has the ability to minimize expiratory braking mechanisms through stimulation of the PCA muscle. Increased PCA muscle activity results in vocal cord abduction that decreases laryngeal resistance. Studies done by Dixon et al., (1974) showed that hypercapnic ventilation created an increase in activation of PCA muscles resulting in abduction of the vocal cords [3].

MATERIALS AND METHODS

Species

The data were collected from two different animal species: the woodchuck (*Marmota monax*) and the porcupine (*Erithizon dorsatum*).

The group of woodchucks used was comprised of eight adult woodchucks (mean weight = 5.36 $\pm$ 1 kg) obtained from Pennsylvania and Virginia. The woodchucks were held in captivity for at least 2 months prior to this study and maintained on woodchuck chow (large pellets), fresh apples and carrots.

Because time did not allow for capture of porcupines, comparative physiological studies were done between the present work on woodchucks and data obtained on porcupines in an early phase of this study at Dartmouth Medical School (in press). To allow for comparison the same methods and guidelines were observed.

Ventilatory Measurements

Ventilatory measurements were made from recordings obtained by the barometric method of Drorbaugh and Fenn [10].

Measurements were made of respiratory frequency (f) and tidal volume (V_T). From these recordings inspiratory (T_I) and expiratory (T_E) times, and minute ventilation (V) were later calculated. This technique measures the pressure changes produced within a sealed plethysmograph by the expansion of inspired gas volumes as they flow from the cooler ambient environment into the warmer airways and lungs of the animal. The sealed plethysmograph was a whole-body plethysmograph made of plexiglass. The major advantage to this approach is that it allows for ventilatory measurement of an nonanesthetized, unrestrained small animal.

The animals were put through several training periods prior to being subjected to experimentation. At the time of the study, the animals were placed in the plethysmograph breathing room air (normoxic) and given sufficient time to acclimatize to the plethysmograph apparatus.

The pressure changes within the 26.2-liter chamber representing tidal volume (V_T) were measured with a model DP45-16 differential pressure transducer and were recorded with a

Gould Recorder model 2400 polygraph at a paper speed of 10 mm/sec. Prior to an experimental run, barometric pressure was measured. Chamber temperature was also monitored continuously during the experiment. Chamber temperature averaged 26.4 ^{0}C and varied no more than $\pm$ .3 ^{0}C over the course of the experiment. Body temperature was measured using a YSI Tele-Thermometer with a YSI series 400 probe and was found to be 37.4 ^{0}C $\pm$ .5^{0}C. A series of calibration volumes of 3cc were regularly introduced into the chamber during ventilatory measurements.

While studying ventilatory responses to hypercapnia, the animals were exposed to approximately 5% CO_2 mixed on line with air. Mixture of CO_2 with air was accomplished through the use of flow rotameters. Fractional concentrations of CO_2 flowing into and out of the plethysmograph were measured by an open circuit method. Fractional CO_2 was monitored with the aid of an Applied Electrochemistry model CD-3A CO_2 analyzer. Air samples drawn through the CO_2 analyzer were dried using Drierite.

Data Analysis

The study involved situations of hypercapnia and normoxia. The animals were exposed to test gases for an interval of 40 to 60 min. long. Recordings of subsequent breathing patterns were made during normal, quiet breathing. Simultaneous measurements of tidal volume (V_T) and respiratory frequency (f) were made during several 2 min. intervals with the plexiglass box sealed. These simultaneous measurements were recorded using the Gould Recorder model 2400.

Under the above conditions, tidal volume (V_T) was calculated by using the equations presented by Bartlett and Tenney (Table 1)[4]. Both respiratory frequency (f), which was taken directly from the recording, and the calculated V_T value were used to determine minute ventilation (V) [Minute Ventilation(ml/min) = V_T(ml) X f(min^{-1})]. Inspiratory (T_I) and expiratory (T_E) respiratory times (sec.) and total respiratory cycle time (T_{Tot}) were obtained by direct measurement of the polygraph recordings.

To better compare the two species, V_T and V were expressed per 100g of body weight. Also, the ventilatory response of each animal to hypercapnia was expressed as a change from 20% O_2 and 0.03% CO_2 (normoxic/normocapnic values). Ventilatory responses were compared between species by analysis of variation and multiple comparisons.

Table 1.

Plethysmographic calculation of V_T

FORMULA FOR CALCULATION OF TIDAL VOLUME
USING THE BAROMETRIC METHOD.

$$V_T = \frac{P_T}{P_K} \times V_K \times \frac{T_R (P_B - P_C)}{T_R (P_B - P_C) - T_C (P_B - P_R)}$$

P_K = calibration of pressure deflection

P_T = breath pressure deflection

V_K = calibration volume (3cc)

P_B = barometric pressure

P_C = water vapor pressure at chamber temp.

P_R = water vapor pressure at body temp.

T_R = body temp. (Kelvin)

T_C = chamber temp. (Kelvin)

RESULTS

Normoxic group

Ventilation in porcupines and woodchucks breathing 20% O_2 and 0.03% CO_2 differed in several ways (Table 2). Breath frequency (f) was found to be somewhat lower in the porcupine (28.11 breaths/min) than in the woodchuck (38.17 breaths/min), but V_T/100g was found to be similar for both species (.57 vs. .50 ml/100g). The net result, because of a lower breathing frequency, was a lower V/100g in the porcupine compared to that of the woodchuck's.

TABLE 2. Ventilatory measurements in porcupine and woodchuck breathing 20% O_2.

	n	V_T, ml·100 g^{-1}	f, breaths · min^{-1}	V, ml· min^{-1} ·100 g^{-1}
PORCUPINE	4	0.57 ± 0.03	28.11 ± 1.83	15.62 ± 1.21
WOODCHUCK	8	0.50 ± 0.04	38.17 ± 2.08	17.34 ± 0.89
		(P < .04)	(P < .09)	(P < .03)

Values are means ± standard error. V_T, tidal volume; f, breathing frequency; V, minute ventilation.

Breathing patterns were also different in terms of respiratory cycle timing (Table 3). Both T_I and T_E were longer in the porcupine than those associated with the woodchuck.

TABLE 3. Respiratory timing and airlow rates in porcupines and woodchucks breathing 20% O_2 .

	n	T_I , sec.	T_E, sec.	V_T/T_I ml·sec^{-1}	T_I/T_T	T_E/T_{Tot}
PORCUPINE	4	.99 ± .08	1.32 ± .07	38.30 ± 2.53	.42 ± .01	.58 ± .01
WOODCHUCK	8	.45 ± .01	1.21 ± .07	60.07 ± 2.63	.29 ± .01	.71 ± .01
		(P < .22)	(P < .03)	(P < .14)	(P < .12)	(P < .06)

Values are means ± standard error. T_I , inspiratory time; T_E , expiratory time; V_T/T_I mean airflow; T_I/T_T duty cycle; T_E/T_{Tot} , ratio of expiratory time to total respiratory time.

Hypercapnic group

The ventilatory responses to acute exposure to a 5% CO_2 (hypercapnic) environment also differed between species. The porcupine increased its breath frequency (f) in response to hypercapnia while the woodchuck showed a decrease in its breath

frequency (Fig. 3). Both species demonstrated an increase in tidal volume (V_T); though the porcupine's own response was much greater (Fig. 4). Because both the f and V_T were increased in response to hypercapnia, the porcupine's increase in minute ventilation ($V=V_T$ X f) was much greater than the woodchuck's (Fig. 5). Although the woodchuck increased its minute ventilation in response to the hypercapnia, it was accomplished solely through an increase of V_T since it decreased its own breathing frequency (Fig. 3 , 4).

The change in ventilatory patterns between the porcupine and woodchuck were again different. In response to hypercapnia the porcupine's T_I decreased from control levels (Fig. 6), but its T_E remained relatively unchanged (Fig. 7). The woodchuck showed large increases in both T_I and T_E in response to hypercapnia (Fig.6,7). However, even with the decreases in T_I and T_E, the porcupine showed a much greater mean airflow rate change (V_T/T_I) than the woodchuck (Fig. 8).

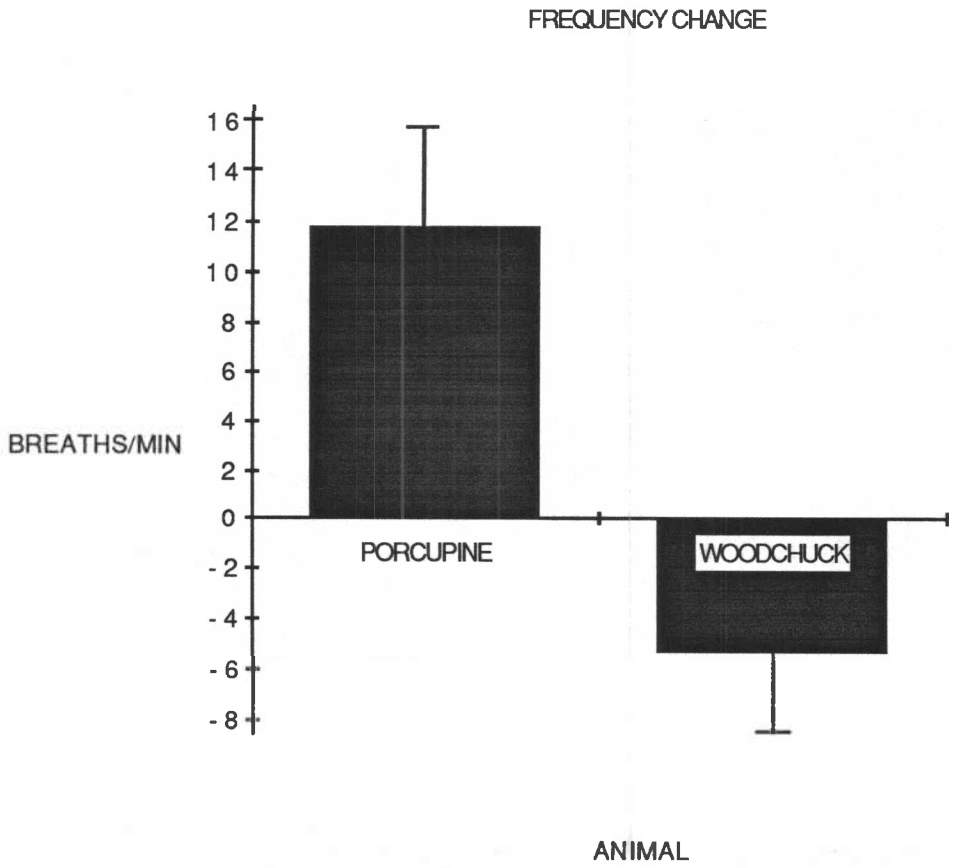

Figure 3. Comparison of frequency changes in the porcupine and woodchuck in responseto hypercapnic gas mixture (5% Carbon Dioxide). $P < .17$.

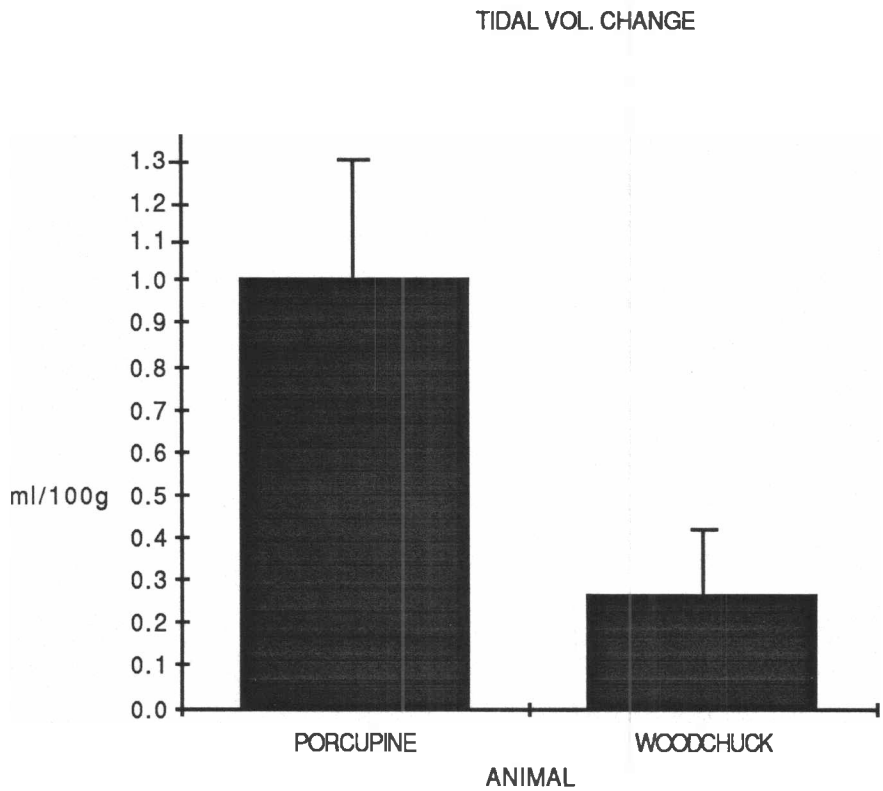

Figure 4. Comparison of Tidal Volume changes of porcupine and woodchuck in response to hypercapnic gas mixture (5% Carbon Dioxide). $P < .003$.

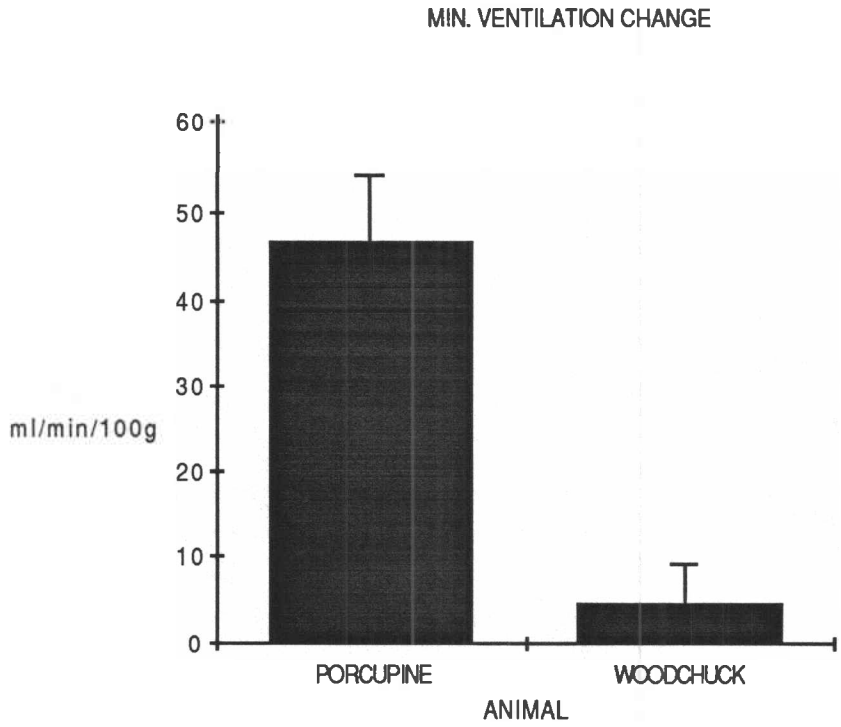

Figure 5. Comparison of Minute Ventilation Change of porcupine and woodchuck in response to hypercapnic gas mixture (5% Carbon Dioxide). $P < .001$.

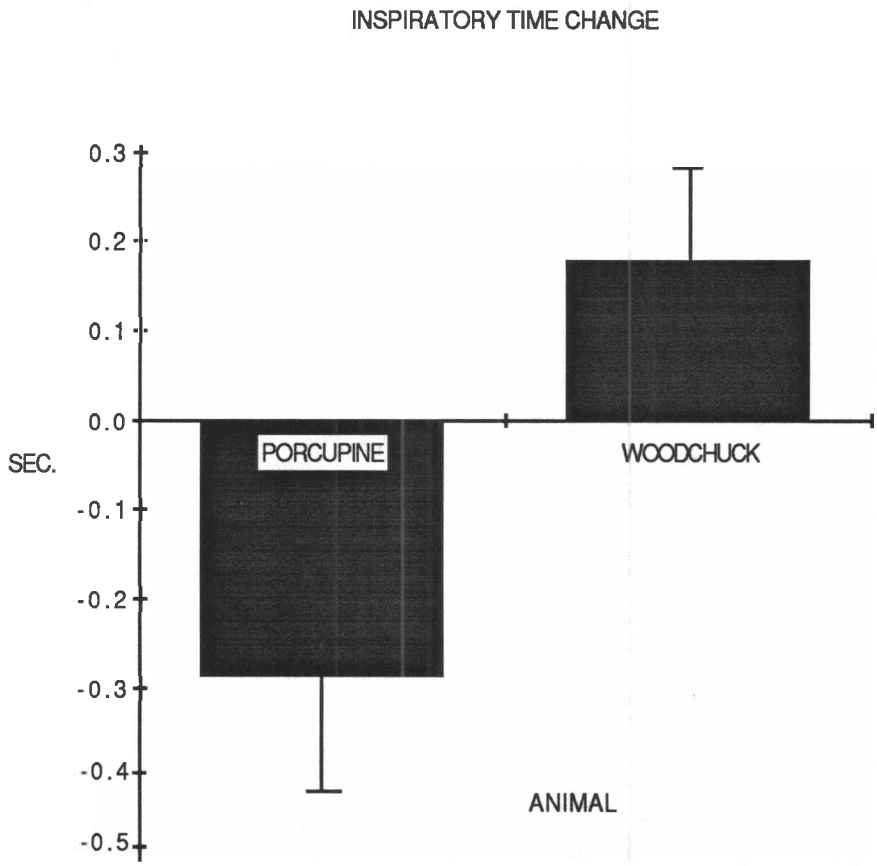

Figure 6. Comparison of Inspiratory time changes of porcupine and woodchuck in response hypercapnic gas mixture (5% Carbon Dioxide).

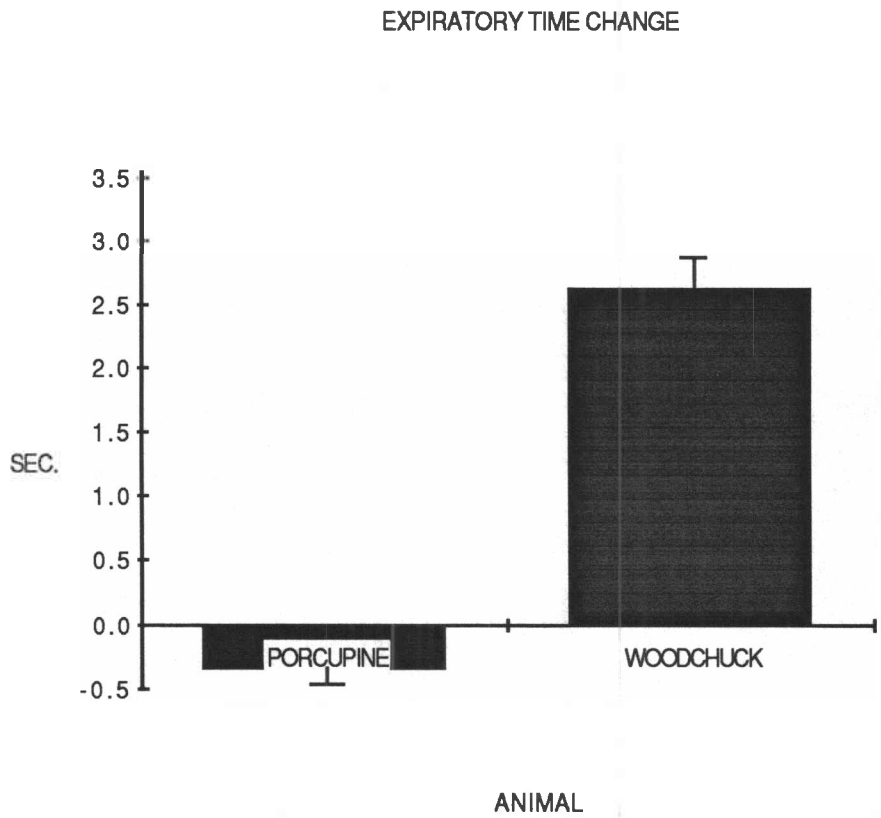

Figure 7. Expiratory time changes of porcupine and woodchuck in response to hypercapnic gax mixture (5% Carbon Dioxide).

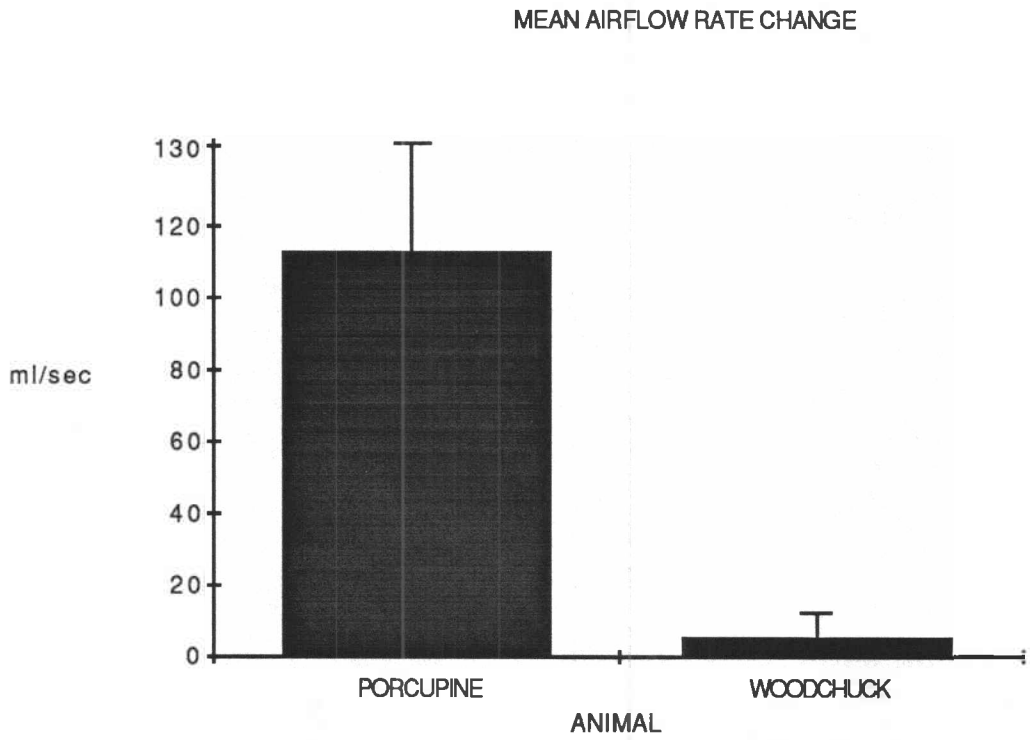

Figure 8. Mean Airflow Rate Change of porcupine and woodchuck in response to hypercapnic gas mixture (5% Carbon Dioxide). $P < .001$.

DISCUSSION

This study reveals differences in the ventilatory responses and breathing patterns between the porcupine and woodchuck exposed to hypercapnic conditions. These differences may reflect adaptations that might facilitate the woodchuck in its semi-fossorial environment.

This experiment has demonstrated that respiratory timing and V_T responses of the two mammalian species are significantly different ($P < .001$). The porcupine responded to hypercapnia by increasing its respiratory rate, while also increasing its tidal volume and minute ventilation. The porcupine's increase in respiration was a result of a decrease in both T_I and T_E. As a result, the increase of mean airflow (V_T/T_I) was the product of an increase in V_T and a reduction in T_I. The woodchuck responded to acute hypercapnia by decreasing its respiratory rate showing little

change in tidal volume and minute ventilation. The decrease of respiratory rate in response to hypercapnia seems characteristic of burrowing animals. Increased ventilation would not aid in the elimination of CO_2 that is found so abundantly within a burrow, but would only increase respiratory work.

The changes in T_I, T_E and mean airflow (V_T/T_I) were significantly different between the two species ($P < .001$). As noted before, the porcupine increased both V_T and respiratory rate in response to a hypercapnic environment. The rate increase in the porcupine was due to a decrease in both T_E and T_I. Therefore, the increase in V_T/T_I was due to an increase of V_T while T_I decreased. The woodchuck, in response to hypercapnia, increased V_T without an increase in respiratory rate. Thus the increase in mean airflow rate (V_T/T_I) was mostly the product of volume and not respiratory timing changes.

These data clearly point out that the woodchuck is less

sensitive to CO_2 that the porcupine. This then answers the first question of this study--that a low CO_2 ventilatory response is due to a burrower's adaptation to a chronic hypercapnic environment and is not characteristic of rodents in general (Fig. 9,[5]). The porcupine's response is simular to that of man (Fig. 9).

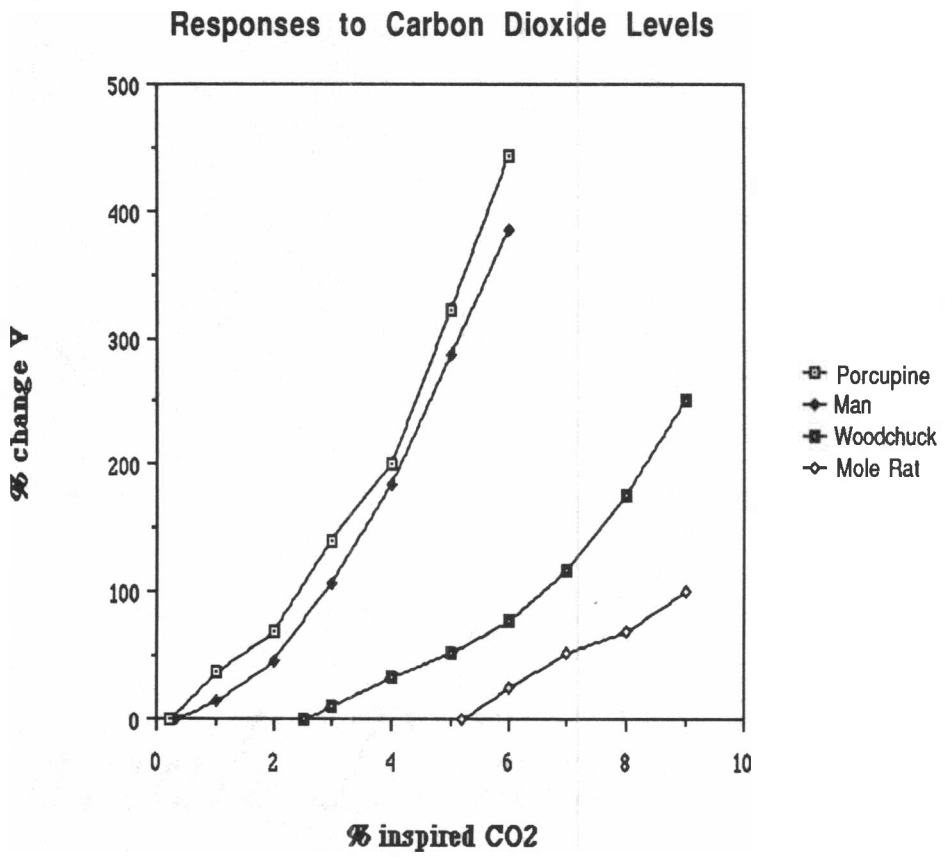

Figure 9. Ventilatory responses to inspired carbon dioxide by the fully fossorial mole rat, semi-fossorial woodchuck, and by the non-fossorial man and porcupine.

This study also answered the second question--that two species with different CO_2-sensitivities demonstrate different patterns of respiratory timing. Table 3 shows the woodchuck tends to have a longer T_E/T_{Tot} on air than the porcupine (.71 vs. .58). The burrowing woodchuck has also been shown to be less sensitive to CO_2 because of its lower breathing frequency, tidal volume and minute ventilation under acute hypercapnic conditions. Also, there is a significant difference between woodchuck and porcupine's mean airflow rate change ($P < .001$). The woodchuck's much lower mean airflow rate change is important because V_T/T_I is an index of the "inspiratory drive" from the central chemoreceptors. So the results show that the woodchuck experiences less of a stimulus from carbon dioxide both centrally and peripherally than does the porcupine.

In conclusion, the semi-fossorial woodchuck possesses ventilatory characteristics of a burrowing rodent necessary for adaptation to a chronically hypercapnic environment such as its burrow.

LITERATURE CITED

[1] Arieli, R. and A. Ar ,(1979). Ventilation of a fossorial mammal (Spalax ehrenbergi) in hypoxic and hypercapnic conditions. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 47: 1011-1017.

[2] Bartlett, D. Jr., (1980). Effects of vagal afferents on laryngeal responses to hypercapnia and hypoxia.

[3] Bartlett, D. Jr., S. L. Knuth and K. V. Knuth, (1981). Effects of Pulmonary Stretch Receptor blockade on laryngeal responses to hyper-capnia. Respiration Physiology. 45:67-77. North-Holland Publishing Co., Amsterdam.

[4] Bartlett, D. Jr., and S. W. Tenney, (1970). Control of Breathing in Experimental Anemia. Resp. Physiol. 10:384-395.

[5] Boggs, D. F., D. C. Kilgore, Jr. and G. F. Birchard, (1984). Respiratory Physiology of Burrowing Mammals and Birds. Comparative Biochemistry and Physiology. Vol 77A,No. 1, pp 1-7. Pergamon Press, New York.

[6] Boggs, D. F. and S. M. Tenney, (1984). Scaling Respiratory Pattern and Respiratory Drive. Resp. Phys. 58: 245-251.

[7] Bowes, Glenn, S. M. Andrey, L. F. Kozar and E. A. Phillipson, (1982). Role of theCarotid Chemoreceptors in regulation of Inspiratory Onset.J. Appl. Physiol.: Respirat. Environ. Exercise Physiology. 52(4): 863-868. Amer. Physiol. Society.

[8] Cunningham, D. J., and W. N. Gardner, (1972). The relation between tidal volume and inspiratory and expiratory times during steady state CO2 inhalation in man. J. Physiol.(London) 227:50-51.

[9] Cunningham, D. J., and W. N. Gardner, (1977). A Quantitative Description of thePattern of Breathing During Steady-state CO_2 inhalation in man, with special emphasis on Expiration. J. Physiol.(London). 272, pp. 613-632. .

[10] Drorbaugh, J. E. and W. O. Fenn, (1955). A barometric method for measuring ventilation in new born infants. Pediatrics 16:81-87.

[11] Eldridge, F., (1976). Expiratory Effects of Brief Carotid Sinus Nerve and Carotid Body Stimulations. Respiration Physiol. 26:395-410. North-Holland Publishing Co., Amsterdam.

[12] Gardner, W. N. Analysis of Breathing Patterns in Man. Bulletin of Physiol. Path. Resp. 11:78-80. (1975)

[13] Gautier, H., J. E. Remmers and D. Bartlett, Jr., (1973). Control of the duration of Expiration. Respir. Physiol. 18:205-221. North-Holland Publishing Co., Amsterdam.

[14] Hey, E. N., B. B. Lloyd, D. J. C. Cunningham, M. C. M. Jukes and D. P. G. Balton, (1966). Effects of various respiratory stimuli on the depth and frequency of breathing in man. Respir. Physiol. 1:193-205. North-Holland Publishing Co., Amsterdam.

[15] Mead, J., (1960). Control of Respiratory frequency. J. Appl. Physiol. 15: 325-336.

[16] Mills, Allan. Respiratory Physiology. Raven Press, New York. (1981) p. 145.

[17] Remmers, J. E. Analysis of Ventilatory Response. Chest, 70:1, July 1976 Supplement. pp 134-137.

[18] Remmers, J. E. and D. Bartlett, Jr., (1977). Reflex Conrol of Expiratory Airflow and Duration. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 42(1): 80-87.

[19] Sheldon, M. I., and G. J. Franklin, (1982). Evidence for Pulmonary CO_2 Chemosensitivity: Effects on ventilation. J. Appl. Physiol. 52(5): 1192-1187.

[20] Speck, D. F., and C. L. Webber, Jr., (1985). Effect of hypoxic, hyperoxic or hypercapnic ventilation on ispiratory termination in the cat. Respiration Physiology 60: 205-215. North-Holland Publishing Co., Amsterdam..

[21] West, J. B. Respiratory Physiology. Williams and Wilkens Pub. Co., Baltimore (1979). p. 158.

[22] Wilson, K. J., and D. L. Kilgore, Jr., (1978). The effect of locomotion and design on the diffusion of respiratory gases in mammal burrows. J. Theor. Biol. 71: 73-101.