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### Research Article

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The results indicate that peripheral chemoreceptor reflex responses to hypoxia are preserved in subjects in whom sympathetic nervous responses are impaired. However, the central nervous depression of ventilation by hypoxia is enhanced simultaneously. The inordinate central depression is attributed to the inability of the dysautonomic subjects and goats to maintain systemic blood pressure and, consequently, cerebral blood flow during hypoxia, thereby aggravating [...]

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# The Effects of Abnormal Sympathetic Nervous Function upon the Ventilatory Response to Hypoxia

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**ABSTRACT** The ventilatory response to hypoxia was studied in two groups of subjects with abnormal sympathetic nervous control: (a) human subjects with familial dysautonomia (Riley-Day syndrome), and (b) unanesthetized goats treated with an alpha-adrenergic blocking agent (phenoxybenzamine). The ventilatory response to hypoxia was evaluated in two ways: (a) from the slope of the relationship between ventilation and alveolar  $P_{CO_2}$  ( $\dot{V}_E$ - $P_{ACO_2}$  slope) during the rebreathing of hypoxic and hyperoxic gases, and (b) from the change in ventilation produced when hypoxia was abruptly relieved.

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during hypoxia, thereby aggravating central nervous hypoxia.

## INTRODUCTION

The normal ventilatory response to hypoxia requires not only the proper sensing of the hypoxic stimulus by the peripheral chemoreceptors, but also the integration of the nervous output from the peripheral chemoreceptors with other neural and chemical stimuli that converge upon the central nervous system. The role of the sympathetic nervous system in this complicated interplay is not settled. Studies involving the infusion of norepinephrine in human subjects have suggested that the sympathetic nervous system may modulate the ventilatory response to acute hypoxia by controlling blood flow through the carotid body; i.e., diminished flow would elicit an increased chemoreceptor response (1). However, observations on an isolated peripheral chemoreceptor (carotid body) have not been corroborative; i.e., the expected decrease in the nervous discharge of the chemoreceptor to hypoxia after sympatholytic agents were applied did not occur (2).

In the present study, a different approach to the problem was used. The ventilatory response to acute hypoxia was examined in two groups of subjects with impaired sympathetic nervous function: (a) patients with familial dysautonomia (Riley-Day syndrome), a congenital disease in which the outstanding feature is dysfunction of the sympathetic nervous system, and (b) unanesthetized goats which had been subjected to alphaadrenergic blockade with phenoxybenzamine.

Since the experience of others had indicated that even a few minutes of moderate hypoxia may produce syncope and convulsions in patients with familial dysautonomia (3), the steady-state techniques that are usually used to study the regulation of ventilation in human subjects were not used in the present study. Instead, transient-state methods were developed so that the ventilatory

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TABLE I  
Description of Subjects

Subject	Age	Height	Weight	Vital Capacity		Maximum voluntary ventilation		SaO <sub>2</sub>	Paco <sub>2</sub>	Ventilation
				liters	% predicted	liters/min	% predicted			
Familial dysautonomia										
G. R.	17	169	51	2.34	55	83	67	95	36	5.63
S. H.	9	126	24	1.22	52	20	47	93	48	4.31
H. R.	24	178	61	2.60	56	67	61	92	45	6.19
M. H.	14	149	37	2.10	78	52	65	98	43	5.57
S. A.	20	158	38	2.16	74	55	60	94	44	5.19
B. Z.	14	142	33	2.22	92	68	89	93	44	5.01
Controls										
E. N.	18	173	64	4.90	98	160	92	96	41	5.86
E. R.	29	181	86	5.68	110	200	180	97	39	8.86
N. L.	20	152	45	4.30	108	155	116	98	36	6.01
A. H.	21	180	80	5.94	120	185	95	95	37	7.21
H. Z.	12	148	40	3.01	118	92	111	97	41	5.28
A. E.	10	138	30	2.95	135	86	121	96	40	4.55

responses could be tested during brief exposures to hypoxia. These methods are described in the next section. During the course of the study the transient-state methods also proved to have an added advantage over the steady-state methods in that they made possible a more precise distinction between the abnormal ventilatory response due to diminished chemoreceptor activity and the abnormal ventilatory response due to other mechanisms, e.g., depression of the central nervous system during severe hypoxia.

## METHODS

### Human subjects

Six human subjects with familial dysautonomia were studied. Their ages varied from 9 to 27 yr. Six normal subjects of approximately the same age served as controls. Descriptive data and the results of pulmonary function studies for both patients and control subjects are listed in Table I.

Two different transient-state methods were used to assess the effects of hypoxia upon the ventilation of these subjects: a rebreathing method and an open circuit method.

#### REBREATHING METHOD

*Effect of hypoxia on the ventilatory response to progressive hypercapnia.* In these studies, the ventilatory response to hypoxia was assessed by comparing the responses to progressive hypercapnia with and without progressive hypoxia. The principle of this approach is presented in a subsequent section (see Principles of Methods). The rebreathing method was used for two reasons: (a) so that the time of exposure to the test gas could be short, and (b) because by comparing the ventilatory response to progressive hypercapnia, per se, with the response to progressive hypercapnia plus hypoxia, such influences as mechanical limitation of the

thoracic cage could be minimized as determinants of the response. The results were analyzed by plotting the ventilation versus the alveolar Pco<sub>2</sub> during rebreathing at 15-sec intervals. Since the relationship between ventilation and alveolar Pco<sub>2</sub> became linear within 2 min of the start of rebreathing, the linear portion of this response curve was used to characterize the relationship. The ventilatory response to hypoxia was taken as the ratio of the slope of the ventilation-Pco<sub>2</sub> line during hypoxia to the slope of this line during nonhypoxic rebreathing.

The subjects were seated and breathed through a low resistance, unidirectional valve. The inspiratory and expiratory ports of the valve were connected to a 9 liter spirometer (Collins) which was filled to one-third capacity with the test gas mixture. The total volume of the rebreathing circuit was 10 liters. Each subject rebreathed 100% O<sub>2</sub> for one period and a mixture of 12% O<sub>2</sub> in N<sub>2</sub> for another. Rebreathing continued for at least 1.5 min after the CO<sub>2</sub> in the spirometer had equilibrated with alveolar gas (ie. after the inspired and expired Pco<sub>2</sub> were equal). The total rebreathing time was approximately 5 min.

Ventilation was recorded using a circular potentiometer mounted on the spirometer. The electrical signal of the potentiometer was proportional to the excursion of the spirometer bell. Gas was continuously sampled at the mouth-piece and analyzed for Pco<sub>2</sub> using an infrared analyzer (Beckman Instruments, Inc., Fullerton, Calif.) which was calibrated with known gas mixtures saturated with water vapor prior to each study. End-tidal Pco<sub>2</sub> was assumed to be equal to alveolar Pco<sub>2</sub>. Arterial O<sub>2</sub> saturation was recorded using an ear oximeter (Waters X350). Since previous experience had shown that patients with familial dysautonomia became very emotionally upset by both the prospect and performance of an arterial puncture, no attempt was made to calibrate the oximeter in vivo, i.e., by using arterial blood samples of these subjects. Instead, the oximeter was repeatedly checked for stability and calibrated on other patients; for the calibration, the oximeter value for O<sub>2</sub> saturation was compared with that of arterial blood drawn

simultaneously and analyzed manometrically by the method of Van Slyke and Neill.

Blood pressure was recorded at 30-sec intervals using an arm cuff and a mercury sphygmomanometer. The heart rate was calculated from pulses recorded in the oximeter trace. Ventilation, alveolar  $PCO_2$ , and arterial  $O_2$  saturation were continuously recorded using an oscilloscopic recorder (Electronics for Medicine, Inc., White Plains, N. Y.). Each re-breathing test was repeated after a 10 min interval and the average of the two results was used for analysis.

#### OPEN CIRCUIT METHOD

*Response to the abrupt induction and relief of hypoxia.* An open circuit system with a low resistance, unidirectional respiratory valve was used. The humidified inspired gases were contained in separate, 100-liter, neoprene bags which were housed in a rigid, airtight box. A valving system was arranged so that each subject could breathe room air, a low  $O_2$  mixture, and 100%  $O_2$ , in sequence, without being aware that the composition of the inspired gas had been changed. The procedure was as follows. The seated subject breathed room air until the ventilation and the end-tidal  $PCO_2$  were steady for 2 min. The valve was then turned surreptitiously so that the chosen hypoxic gas mixture was substituted for room air as the inspired gas mixture. By experience, it was found that in order to achieve comparable levels of arterial hypoxemia during the run, the dysautonomics had to breathe a mixture of 12%  $O_2$  in  $N_2$ , whereas the normal subjects had to breathe a mixture of 9-11%  $O_2$  in  $N_2$ . At the end of breathing the low  $O_2$  mixture for 3 min, the valve was again turned so that the subjects could breathe 100%  $O_2$ ; this gas was breathed for an additional 3 min. Each sequence was done in triplicate, allowing 10 min between tests. Ventilation was monitored using a spirometer which recorded changes in the volume of the rigid box. Alveolar  $PCO_2$ , arterial  $O_2$  saturation, and heart rate were recorded as indicated above.

#### Unanesthetized goats

These studies were done in order to determine whether blockade of the vasoconstrictor response to hypoxia in an animal that was otherwise intact would result in a "dysautonomic" pattern of ventilatory response to hypoxia. Therefore, both the re-breathing and open circuit tests were carried out in five intact, unanesthetized female goats before and after alpha-adrenergic blockade with phenoxybenzamine. In addition, the use of the animals made it possible to test the steady-state responses to acute hypoxia after sympathetic blockade; as indicated above, these methods were considered to be too hazardous to use in the dysautonomic subjects. Each goat was trained for several weeks to wear a mask fitted with a low resistance, unidirectional valve. On the day prior to study, an indwelling cannula was placed in one femoral artery using local lidocaine anesthesia, so that blood pressure could be measured and arterial blood could be sampled at will during the study, without disturbing the goat. Blood pressure was measured using Statham P23Db transducers (Statham Instruments, Inc., Oxnard, Calif.). The pH and  $PCO_2$  of the arterial blood was determined using a glass and modified Severinghaus electrode, respectively; the  $PO_2$  was measured with a modified Clark electrode (Instrumentation Laboratory, Inc., Lexington, Mass.).

#### REBREATHING STUDIES

*Effect of hypoxia on the ventilatory response to progressive hypercapnia.* The re-breathing studies were carried out,

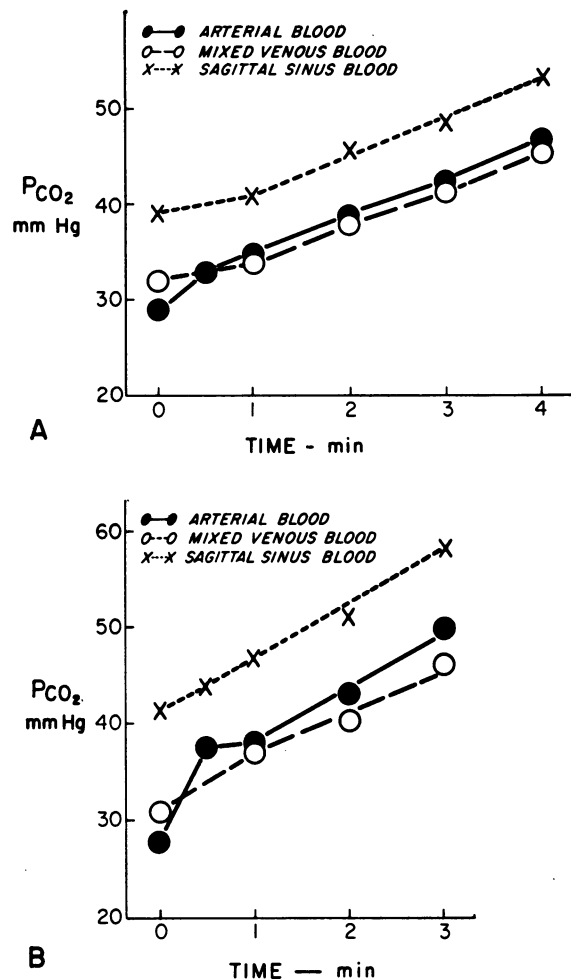


FIGURE 1 Rise of arterial, mixed venous, and cerebral venous (sagittal sinus)  $PCO_2$  during apneic oxygenation (A) and asphyxia (B) in an anesthetized and paralyzed dog. In (A) arterial  $O_2$  saturation was maintained above 98%. In (B) it fell from 94% to 40%. Within 1 min arterial and mixed venous  $PCO_2$  values became nearly equal and thereafter  $PCO_2$  at all three sampling sites rose linearly with respect to time, and at equal rates.

in duplicate, before and 1 hr after 5 mg/kg phenoxybenzamine had been administered by slow (15 min) intravenous infusion. Since the goal of the study in goats was to simulate the dysautonomic pattern of the patients by impairing alpha-adrenergic function, no attempt was made to achieve complete pharmacologic blockade of the alpha-adrenergic receptors.

The protocols for the re-breathing studies were the same as those used in the human studies except that 10%  $O_2$  in  $N_2$  rather than 12%  $O_2$  was used as the inspired hypoxic gas mixture. The use of the more hypoxic mixture widened the difference between the hypoxic and hyperoxic ventilatory responses to  $CO_2$  during the control periods of re-breathing. For re-breathing, the circuit was arranged so that the inspiratory and expiratory ports of the unidirectional breathing valve were connected to a 13 liter rubber bag, half

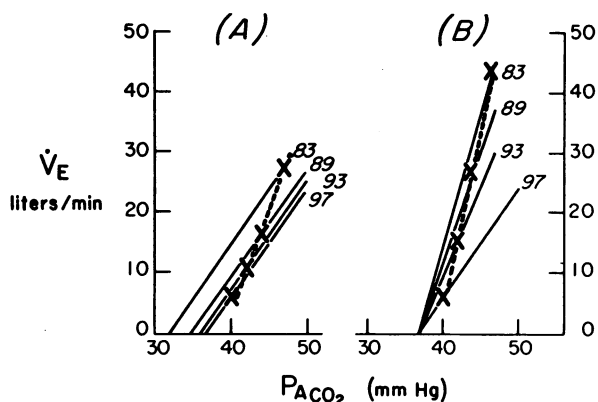


FIGURE 2 Predicted  $\dot{V}_E$ - $P_{ACO_2}$  relationships during progressive hypoxia and hypercapnia for two different models of chemical control of breathing. In (A) the additive model of Gray (6) has been plotted assuming a resting  $\dot{V}_E$  of 6 liters/min at  $P_{ACO_2} = 40$  and using  $SaO_2$  rather than  $PaO_2$  as the parameter. In (B) the multiplicative model of Lloyd, Jukes, and Cunningham (7) for normal subjects has been plotted using  $SaO_2$  as the parameter. For comparative purposes the slopes of the isoxic lines in (B) have been reduced by a uniform factor so that the euoxic  $\dot{V}_E$ - $P_{ACO_2}$  slopes ( $SaO_2 = 97$ ) in both (A) and (B) are equal. The broken lines indicate the predicted  $\dot{V}_E$ - $P_{ACO_2}$  relationship when  $SaO_2$  falls 2% for each mm Hg rise in  $P_{ACO_2}$ . The figure illustrates that both models predict a linear  $\dot{V}_E$ - $P_{ACO_2}$  relationship for combined progressive hypoxia and hypercapnia.

filled with the test gas mixture (either 100%  $O_2$  or a mixture of 10%  $O_2$  in  $N_2$ ). Ventilation was recorded using a pneumotachygraph in the inspired line; a Rahn-Otis type end-tidal gas sampler was used to collect end-tidal ("alveolar") gas which was continuously sampled and analyzed for  $PCO_2$  (infrared analyzer, Godart) and  $PO_2$  (paramagnetic analyzer, Beckman).

#### OPEN CIRCUIT STUDIES

**Abrupt induction and relief of hypoxia.** The open circuit method for assessing the ventilatory response of the goats to transient hypoxia, before and after phenoxybenzamine administration, was the same as that outlined above for the human studies. As in the rebreathing studies on goats, the initial inspired hypoxic mixture contained 10%  $O_2$  in  $N_2$  both before and after phenoxybenzamine was administered. Each study was done in duplicate. The ventilation, alveolar  $PCO_2$  and  $PO_2$  were recorded as above.

#### STEADY-STATE RESPONSES TO HYPOXIA AND HYPERCAPNIA

The effect of alpha-adrenergic blockade was also determined in goats using steady-state tests of the ventilatory response to both hypoxia and hypercapnia. The response to hypercapnia was tested by having goats breathe mixtures of 3, 5, and 7%  $CO_2$  in air; the response to hypoxia was tested by using an inspired mixture containing 8%  $O_2$  in  $N_2$ ; and the response to combined hypoxia and hypercapnia was tested by using a mixture containing 8%  $O_2$  plus 5%  $CO_2$  in  $N_2$ . Each gas mixture was administered until a steady ventilation was reached (8–10 min), whereupon an arterial blood sample was drawn for blood gas analysis. These studies were repeated 1 hr after the administration of 2

mg/kg of phenoxybenzamine intravenously. This quantity was less than that used in the transient-state studies (see above) since, in each of four goats, the breathing of 8%  $O_2$  in  $N_2$  after pretreatment with 5 mg/kg of phenoxybenzamine caused severe hypotension and inability to stand up in the pen.

#### PRINCIPLES OF METHODS

Two important assumptions are inherent in the use of the ratio of the slopes of the ventilation- $P_{ACO_2}$  lines during hypoxic and nonhypoxic rebreathing as an index of ventilatory response to hypoxia: (a) that the rate of increase in alveolar  $P_{CO_2}$  during rebreathing is a good measure of the rate of increase of  $P_{CO_2}$  at both the peripheral and central chemoreceptors; and (b) that the progressive hypoxemia which results from the rebreathing of an hypoxic gas mixture will increase the slope but not distort the linearity of the ventilation-alveolar  $P_{CO_2}$  relationship.

Fowle and Campbell have shown (4) that once alveolar and mixed venous  $P_{CO_2}$  values equilibrate during rebreathing, the two values remain equal as  $CO_2$  tensions rise in the closed system. In order to determine whether, in the closed system, used in the present experiments, the rate of rise of  $P_{CO_2}$  in mixed venous blood is equal to that in arterial and cerebral venous blood, i.e. at the peripheral and central chemoreceptors, respectively (5), we made additional observations on six anesthetized and paralyzed dogs: the technique of apneic oxygenation was used to simulate rebreathing of an oxygen-rich mixture; asphyxia was used to simulate the rebreathing of an hypoxic gas mixture. The results, shown in Fig. 1, illustrate that, in both experiments, within 1 min, the rates at which  $CO_2$  tensions increased in mixed venous, arterial, and sagittal sinus (cerebral venous) blood were the same.

In order to determine the nature of the ventilation-alveolar  $P_{CO_2}$  relationship during rebreathing of an hypoxic gas, we applied data obtained in the present study to two alternative models that have been proposed to account for the interaction of hypoxia and hypercapnia as ventilatory stimuli. In Fig. 2A is shown the model proposed by Gray (6), according to which hypoxia and hypercapnia act as independent, additive stimuli. Fig. 2B illustrates the multiplicative model of Lloyd, Jukes, and Cunningham (7), by which the response to a given degree of hypoxia increases with increasing values of alveolar  $P_{CO_2}$ . The broken line in each figure was based on data from the present study indicating that during the rebreathing of an hypoxic gas there was, on the average, a 1 mm Hg rise in alveolar  $P_{CO_2}$  for each 2% fall in arterial  $O_2$  saturation. It may be seen that, under these conditions, for either model of the combined influence of hypoxia and  $CO_2$  on breathing, the predicted relationship between ventilation and alveolar  $P_{CO_2}$  during progressive hypoxemia is approximately linear. This prediction was borne out in the present study.

#### RESULTS

##### Human subjects

Table I lists the pertinent clinical features and the results of the pulmonary function studies in the human subjects. In all but one dysautonomic subject the values for maximal voluntary ventilation and vital capacity were abnormally low. In addition, two subjects (S.H.

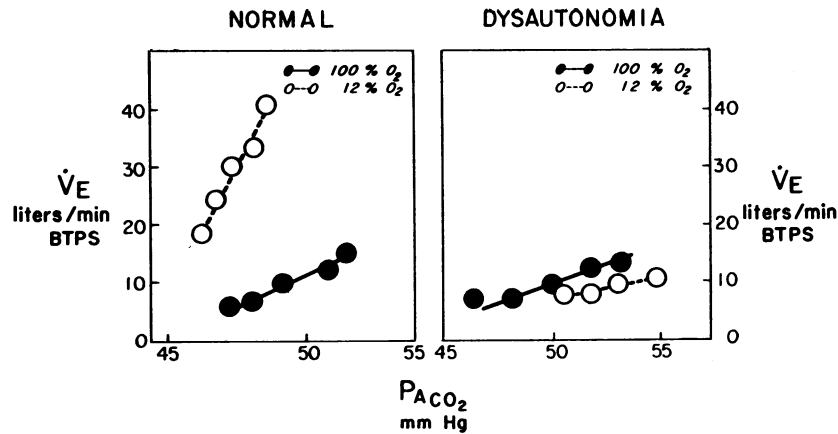


FIGURE 3 Relationship between ventilation and alveolar  $P_{CO_2}$  during the rebreathing of 100% and 12% oxygen by a normal (N. L.) and a dysautonomic subject (S. A.) Data from the first 2 min of rebreathing are not included. Arterial  $O_2$  saturation was above 95% at the beginning of each study and remained above this level during 100%  $O_2$  rebreathing. Oxygen saturation fell to 84% in the normal subject and 81% in the dysautonomic at the end of rebreathing of 12%  $O_2$ . The increase in ventilation per unit rise in  $P_{ACO_2}$  was similar in the two subjects during 100%  $O_2$  rebreathing. However, the progressive hypoxemia during 12%  $O_2$  rebreathing was associated with a fourfold increase of ventilation per unit  $P_{ACO_2}$  in the normal but a 50% decrease in the dysautonomic subject.

TABLE II  
Response to Rebreathing 100% and 12% Oxygen

Subject	100% $O_2$					12% $O_2$					Arterial $O_2$ saturation, end %
	Ventilation- $P_{ACO_2}$ response slope	Heart rate		Blood pressure		Ventilation- $P_{ACO_2}$ response slope	Heart rate		Blood pressure		
		Start	End	Start	End		Start	End	Start	End	
	liters/min/ mm Hg/m <sup>2</sup>	beats/min		mm Hg		liters/min/ mm Hg/m <sup>2</sup>	beats/min		mm Hg		
Dysautonomia											
G. R.	0.90	86	92	96/74	90/72	0.19	97	85	120/76	82/40	80
S. H.	0.95	78	80	118/74	120/70	0.63	97	92	120/76	60/30	85
H. R.	1.10	92	98	136/82	130/78	0.85	86	78	128/72	112/58	81
M. H.	0.97	86	80	94/70	100/70	0.10	92	86	90/70	75/50	83
S. A.	0.72	96	94	102/68	110/70	0.20	97	85	122/74	62/36	85
B. Z.	0.50	100	100	126/80	122/72	0.18	118	118	134/80	100/30	85
Mean	0.84	90	91	112/75	112/72	0.36	97	90	119/75	81/40	83
Controls											
E. N.	2.30	75	85	124/80	126/78	3.25	76	88	124/72	130/88	80
E. R.	1.10	78	84	—	—	2.73	68	92	—	—	84
N. L.	1.56	86	94	130/84	136/82	4.43	99	120	124/84	150/88	79
A. H.	0.73	72	78	108/80	110/84	2.65	66	84	112/78	126/94	84
H. Z.	0.69	86	90	106/72	118/76	2.36	87	124	110/70	120/80	87
A. E.	1.86	80	80	100/76	100/68	3.72	93	120	90/70	100/72	82
Mean	1.38	79	86	115/78	118/78	3.19	82	105	112/75	121/84	83

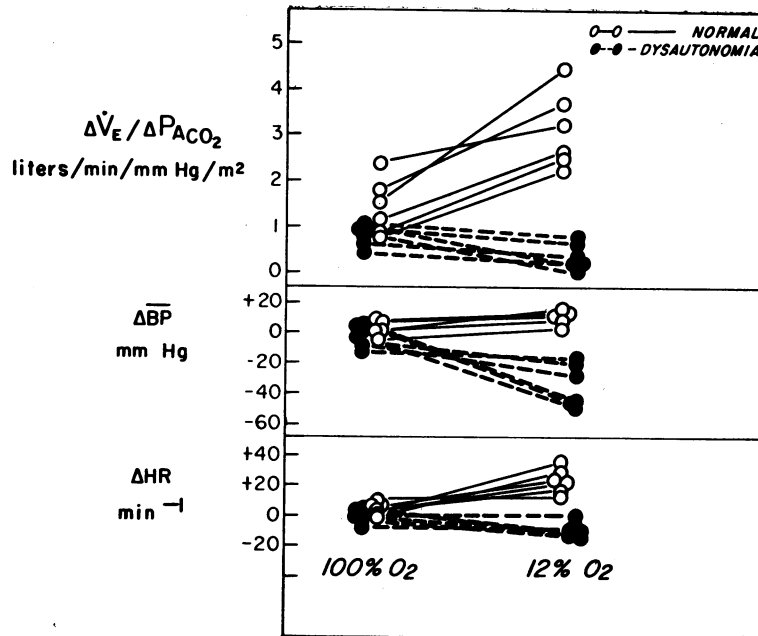


FIGURE 4 Ventilatory and cardiovascular responses to the rebreathing of 100% and 12% oxygen by six dysautonomic and six normal subjects. Left hand points: 100% O<sub>2</sub>; right hand points: 12% O<sub>2</sub>. Upper panel: ventilatory response to CO<sub>2</sub> expressed as increase in ventilation per mm Hg increase in P<sub>A<sub>CO<sub>2</sub></sub> normalized for body surface area. Middle panel: each point represents the change in mean systemic blood pressure from the beginning to the end of a rebreathing period. Lower panel: each point represents the change in heart rate from the beginning to the end of a rebreathing period. In contrast to control subjects, rebreathing 12% O<sub>2</sub> by dysautonomia subjects resulted in a lower ventilatory response to CO<sub>2</sub> than during 100% rebreathing, bradycardia, and a substantial fall in systemic blood pressure.</sub>

and H.R.) had borderline abnormalities in arterial O<sub>2</sub> saturation and alveolar P<sub>CO<sub>2</sub></sub> at rest.

#### REBREATHING METHOD

*Effect of hypoxia on the ventilatory response to progressive hypercapnia.* The response of one control subject and of one dysautonomic subject, matched with respect to age and height, are shown in Fig. 3. Both subjects had a similar ventilatory response to hypercapnia during rebreathing when 100% O<sub>2</sub> was the starting gas. However, the responses were quite different when the hypoxic mixture was used. When the control subject rebreathed 12% O<sub>2</sub>, the increase in ventilation per unit increase in alveolar P<sub>CO<sub>2</sub></sub> was four times as great as when 100% O<sub>2</sub> was rebreathed. In contrast, the dysautonomic subject had less of an increase in ventilation per unit increase in alveolar P<sub>CO<sub>2</sub></sub> while rebreathing 12% O<sub>2</sub> than while rebreathing 100% O<sub>2</sub>.

Table II lists the results obtained in the rebreathing studies. Each value is the average of two consecutive, identical runs. Duplicate values always agreed within 25%. The average variability, which was the same in

both groups of subjects, was 12%. The ventilatory response of the dysautonomic subjects to hypercapnia (expressed by the slope of the ventilation-CO<sub>2</sub> response line) was only about two-thirds that of the control subjects. However, the striking difference between the two groups was the blunting effect of hypoxia (rebreathing 12% O<sub>2</sub>) on the ventilatory response to CO<sub>2</sub> in the dysautonomic subjects as compared to the enhancement of the ventilatory response to CO<sub>2</sub> by hypoxia in the control subjects. Thus, the ventilatory response of the control subjects to CO<sub>2</sub> more than doubled during hypoxia as compared to hyperoxia whereas that of the dysautonomic subjects were halved. This difference occurred even though the degree of hypoxia, indicated by the average arterial O<sub>2</sub> saturation at the end of the rebreathing period, was approximately the same in both groups (average of 83 ± 1.5% sd).

The two groups were similar with respect to changes in heart rate and in blood pressure while rebreathing 100% O<sub>2</sub> but differed during the rebreathing of 12% O<sub>2</sub> (Table II). In the dysautonomic subjects, rebreathing of 12% O<sub>2</sub> was associated with a decrease of approxi-

mately 10% in heart rate and of 40% in blood pressure; the same procedure in the control subjects elicited a 25% increase in heart rate and a 10% increase in blood pressure. The differences between the two groups with respect to the responses of the blood pressure and

heart rate to 12% O<sub>2</sub> rebreathing were statistically significant ( $P < 0.05$ ).

The results of the rebreathing studies are summarized in Fig. 4. The depression, rather than enhancement, of the ventilatory response to CO<sub>2</sub>, the fall in systemic blood pressure and the failure of heart rate to increase in the dysautonomic subjects during 12% O<sub>2</sub> rebreathing are clearly different from normal and suggest that both the respiratory and circulatory reflex responses to hypoxia are deficient in dysautonomic subjects.

*Ventilatory response to abrupt induction and relief of hypoxia.* The possibility that the dysautonomic subjects had an abnormally diminished reflex respiratory response to hypoxia was examined more critically by abruptly exposing subjects to 100% O<sub>2</sub> after transient exposure to 12% O<sub>2</sub> in N<sub>2</sub>. As may be seen in the record illustrated in Fig. 5, the effect upon ventilation of abruptly relieving approximately the same levels of hypoxemia (about 80% O<sub>2</sub> saturation) was strikingly different in the control and dysautonomic subjects. In the control subjects, exposure to 100% O<sub>2</sub> effected a moderate decrease in ventilation (40% of the room air value); in the dysautonomic subject, breathing stopped completely as soon as the O<sub>2</sub> saturation increased sharply to 100%, and remained arrested for about 25 sec. In four of the six dysautonomic subjects, this apneic response (no breath for at least 10 sec) occurred in each of three trials; the longest apneic period was 56 sec. In two others, apnea occurred in one of the three trials; in the other two trials, external stimuli, e.g. noise in the room, seemed to interrupt the apneic period which ordinarily followed the relief of hypoxemia. Apnea was not observed in control subjects.

The average responses to induction and relief of hypoxia are summarized in Fig. 6. The data in this figure are averages for all trials; each point was calculated for the 30 sec period preceding the time indicated. By 1.5 min of breathing the hypoxic gas mixtures, both groups had increased their ventilation, the controls to a significantly greater degree ( $P < 0.05$ ). But, as hypoxia continued, ventilation decreased to prehypoxic levels in the dysautonomic group. Upon abrupt relief of hypoxia, the ventilation of both groups fell to below prehypoxia levels. On the average, the ventilation of the dysautonomics during the first 30 sec of 100% O<sub>2</sub> breathing was 30% of the prehypoxic value, whereas that of the control group was 75% of the prehypoxic ventilation. This difference is statistically significant ( $P < 0.01$ ). In both groups, the ventilation returned to prehypoxic levels after 3 min of O<sub>2</sub> breathing. The arterial O<sub>2</sub> saturations in the two groups were approximately the same since they were deliberately matched by the experimental procedure. On the other hand, the changes in alveolar Pco<sub>2</sub> were reciprocally related to the changes in ventila-

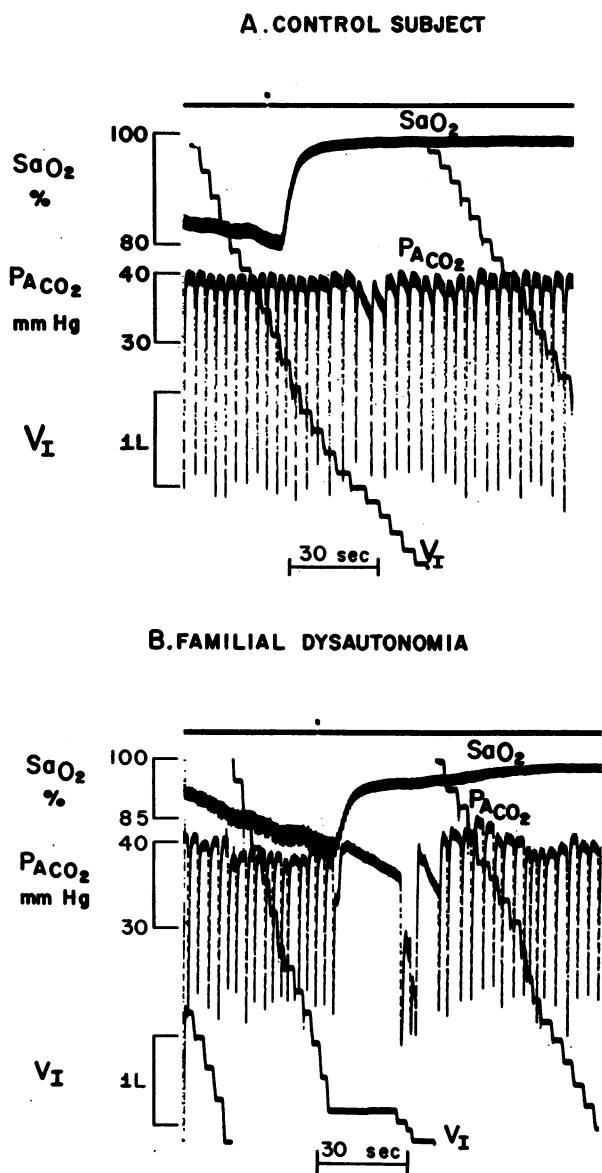


FIGURE 5 Records illustrating the ventilatory response to a sudden change of inspired gas from one with reduced O<sub>2</sub> content to 100% O<sub>2</sub>. Upper trace: arterial O<sub>2</sub> saturation recorded with an ear oximeter. Low trace: end-tidal Pco<sub>2</sub>. Diagonal line: each step represents inspired tidal volume. The normal subject (A) responded to a sudden increase in arterial O<sub>2</sub> saturation with a decrease in tidal volume of approximately 50%. The dysautonomic subject (B) ceased breathing coincident with the sharp rise in SaO<sub>2</sub> and remained apneic for 24 seconds.



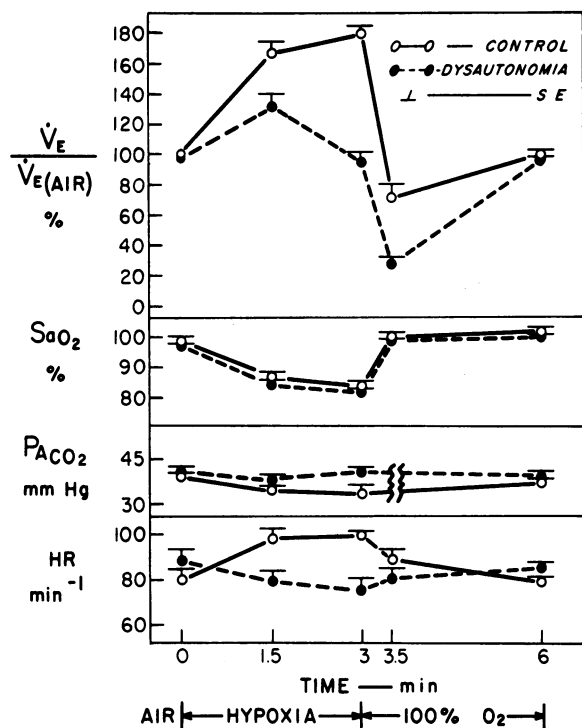


FIGURE 6 Summary of the responses to breathing air, an hypoxic gas mixture and 100% O<sub>2</sub> in sequence for 3-min periods in six normal and six dysautonomic subjects. Each point represents an average value of the variable for the 30-sec period preceding the time indicated on the horizontal axis, and is the mean of all 18 (three trials in each subject) observations. From above: ventilation expressed as a percentage of that breathing room air; arterial O<sub>2</sub> saturation determined with an ear oximeter; alveolar (end-tidal) P<sub>CO<sub>2</sub></sub> and heart rate. As SaO<sub>2</sub> fell during 3 min of hypoxia, normals exhibited a sustained increase in ventilation whereas dysautonomics only increased ventilation transiently. Nevertheless, abrupt relief of hypoxemia produced a marked fall in ventilation in the dysautonomic as well as the control group, indicating the presence of chemoreceptor drive throughout the entire hypoxic period. In contrast to the increase in heart rate in the normal subjects, patients with dysautonomia developed a bradycardia during hypoxia.

tion. The heart rate during transient hypoxia differed in the two groups: in the control subjects, the heart rate increased during hypoxia, averaging approximately 20% more than during air breathing; conversely, in the dysautonomic subjects, the heart rate decreased by 20% during hypoxia.

The initial increase in ventilation during 12% O<sub>2</sub> breathing, and the profound decrease in ventilation when hypoxia was abruptly relieved, indicate that a reflex ventilatory response to hypoxia must have been present in the dysautonomic subjects. Moreover, the pattern of ventilatory changes, during and after hypoxia, suggests that there are two components to the ventila-

tory response of the dysautonomic subject to hypoxia: (a) a stimulation of ventilation, which starts promptly with the start of hypoxia and falls off within seconds after arterial hypoxemia is relieved; and (b) a depression of ventilation, which either starts or reaches its peak effect more slowly and persists for a longer time (as much as 1-min) after arterial hypoxemia has been relieved.

### Unanesthetized goats

The studies performed on goats were done to determine whether normal animals would manifest a "dysautonomic" ventilatory response to hypoxia after alpha-adrenergic blockade.

### REBREATHING

*Effect of hypoxia on the ventilatory response to progressive hypercapnia.* The results of the rebreathing studies are shown in Fig. 7. Before phenoxybenzamine, rebreathing 100% O<sub>2</sub> was associated with a ventilatory response to CO<sub>2</sub> of 0.02 liters/min per mm Hg per kg; the corresponding value for rebreathing 10% O<sub>2</sub> was 0.045. Thus, the ventilatory response in the goat to hypoxic rebreathing was 50% greater than to the hyperoxic rebreathing. The systemic arterial blood pressure increased in every animal during rebreathing, but the increase was less during the hyperoxic rebreathing (average of 5 mm Hg) than during hypoxic rebreathing (26 mm Hg). The increase in heart rate was twice as great during the hypoxic rebreathing (average increase of 38 beats per minute) than during the hyperoxic rebreathing (average increase of 19/min).

Phenoxybenzamine did not modify either the ventilatory response to CO<sub>2</sub> or the changes in blood pressure and heart rate during hyperoxic rebreathing. However, after phenoxybenzamine, the increase in ventilatory response to CO<sub>2</sub> during hypoxia no longer occurred. Also during hypoxic rebreathing, the mean blood pressure decreased so that it was 35 mm Hg less than it was during hypoxic rebreathing in the control period. On the other hand, a similar increase in heart rate occurred after phenoxybenzamine as before (average of 52/min). Thus, with respect to ventilation and blood pressure, unanesthetized goats which had been subjected to partial alpha-adrenergic blockade by phenoxybenzamine responded to the rebreathing of an hypoxic gas mixture in a manner similar to that of human subjects with familial dysautonomia.

### OPEN CIRCUIT

*Ventilatory response to abrupt induction and relief of hypoxia.* The ventilatory and circulatory responses to 3 min of hypoxia (open circuit) before and after phenoxybenzamine administration are shown in Fig. 8.

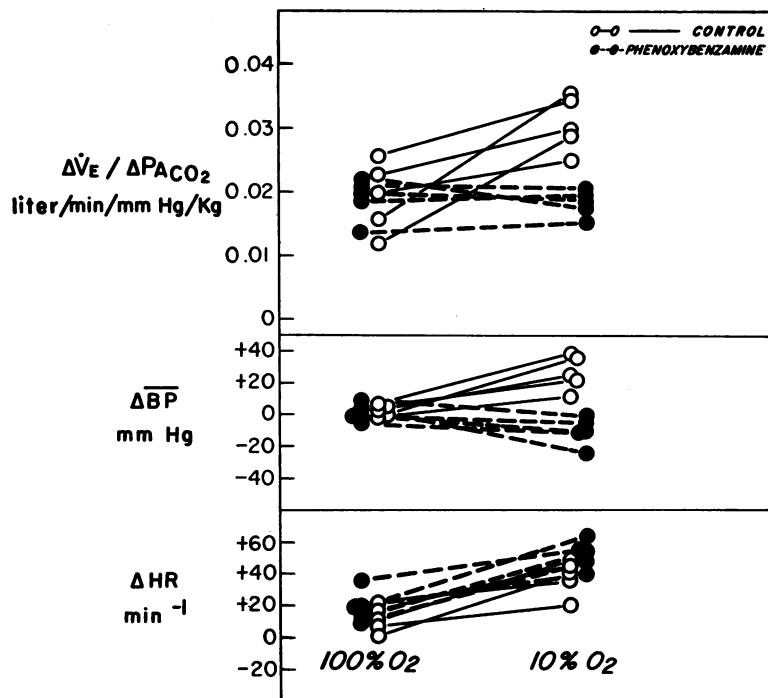


FIGURE 7 Ventilatory and cardiovascular responses to the rebreathing of 100% (left) and 10% (right) O<sub>2</sub> before and after administration of phenoxybenzamine to five goats. Upper panel: ventilatory response to CO<sub>2</sub> expressed as increase in ventilation per mm Hg increase in P<sub>A</sub>CO<sub>2</sub>, normalized for body weight. Middle panel: change in mean systemic blood pressure from beginning to end of a rebreathing period. Lower panel: change in heart rate from beginning to end of rebreathing period. Phenoxybenzamine treatment did not alter the ventilatory or cardiovascular response to 100% O<sub>2</sub> rebreathing, but did abolish the enhancement of ventilatory response to CO<sub>2</sub> and systemic pressor effect of 10% O<sub>2</sub> rebreathing. Note similarity between phenoxybenzamine-treated animals and dysautonomic humans (Fig. 4).

Before blockade, the breathing of 10% O<sub>2</sub> for 3 min resulted in a sustained increase in ventilation reaching 140% of the room air value; concomitantly, the alveolar P<sub>CO<sub>2</sub></sub> decreased from 35 to 28 mm Hg, the alveolar P<sub>O<sub>2</sub></sub> decreased from 86 to 35 mm Hg, the mean systemic arterial blood pressure increased from 93 to 104 mm Hg, and the heart rate increased from 95 to 125 beats per min.

After phenoxybenzamine (5 mg/kg intravenously), the response to 3 min of hypoxia changed in three ways. First, the mean systemic blood pressure decreased from an average control value of 83 mm Hg during air breathing to 68 mm Hg during hypoxia; this decrease was gradual and uniform over the 3 min period. Second, after phenoxybenzamine, the ventilation during the first 90 sec of hypoxia was greater than during air breathing. However, this increase in ventilation was not sustained so that ventilation was only 116% of the room air value by the end of 3 min of hypoxia. Finally,

the ventilation upon relief of hypoxia was significantly less ( $P < 0.01$ ) following treatment with phenoxybenzamine: 25% as compared to 85% of the prehypoxic level of ventilation. Three of the five animals that had received phenoxybenzamine became apneic within 5 sec after abrupt relief of hypoxia.

Thus, alpha-adrenergic blockade altered the ventilatory response of unanesthetized goats to transient hypoxia so that it resembled that of human subjects with dysautonomia in two aspects: (a) the inability to maintain a sustained increase in ventilation during hypoxia, and (b) the marked fall in ventilation below room air values upon sudden relief of hypoxia.

*Steady-state studies.* The results of the steady-state studies of ventilatory response to hypoxia and hypercapnia are listed in Table III. The untreated, unanesthetized goats had ventilatory responses to CO<sub>2</sub> which averaged 0.03 liters/mm Hg per kg. The response to breathing a mixture of 8% O<sub>2</sub> in N<sub>2</sub> was an increase in ventilation

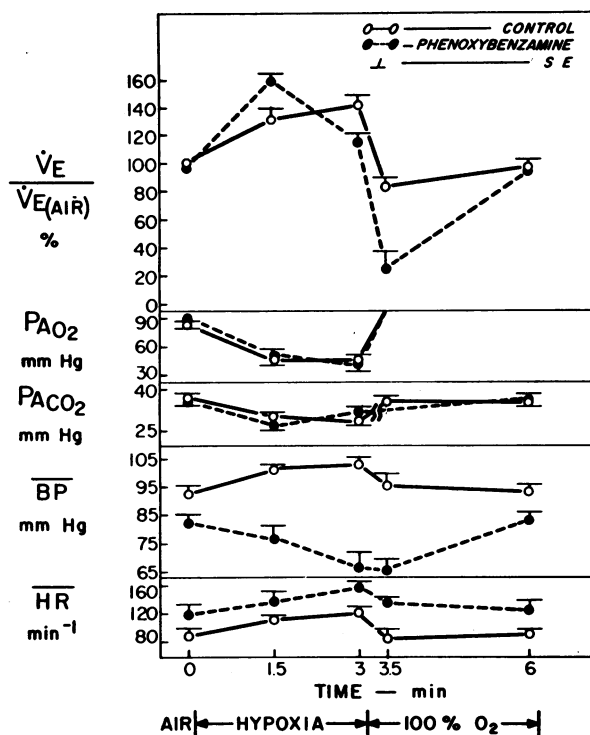


FIGURE 8 Summary of the responses of five goats to breathing air, 10% O<sub>2</sub>, and 100% O<sub>2</sub> in sequence before and after administration of phenoxybenzamine. Each point represents the mean value for the 30-sec period preceding the time indicated on the horizontal axis and is an average of duplicate studies in all animals. From above, ventilation expressed as a percentage of the room air value; alveolar P<sub>O</sub><sub>2</sub>, alveolar P<sub>CO</sub><sub>2</sub>; mean systemic blood pressure and heart rate. Administration of phenoxybenzamine did not impair the initial ventilatory response to hypoxia but did render the animals unable to sustain this response for 3 min. The fall in ventilation upon abrupt relief of hypoxia was at least as great following phenoxybenzamine administration as in the control state, indicating a maintenance of arterial chemoreceptor drive despite the preceding fall in ventilation. Phenoxybenzamine caused hypotension to occur during hypoxia but did not alter the heart rate response. Note similarity to dysautonomic humans (Fig. 6).

to 192% of the room air value. A combination of hypoxia and hypercapnia (8% O<sub>2</sub> plus 5% CO<sub>2</sub> in N<sub>2</sub>) increased the ventilation to 348% of the room air value. The administration of a relatively small amount of phenoxybenzamine (2 mg/kg) had no effect upon the ventilatory response to either hypercapnia or hypoxia, per se; nor did this dose of phenoxybenzamine affect blood pressure while breathing room air or a gas mixture which was either high in CO<sub>2</sub> or low in O<sub>2</sub>. However, when the treated animals were exposed to the combination of hypoxia and hypercapnia, blood pressure fell precipitously within 6–8 min and apnea occurred in each of the five animals. Table IV lists the blood pressures

and the arterial blood gases at the point of apnea. Of interest is that at the apneic point, the degrees of hypoxia and of hypercapnia were no greater than when each stimulus had been applied separately (Table III). Thus, by administering relatively small quantities of phenoxybenzamine, it was possible to achieve a state in which the ventilatory and circulatory responses to either CO<sub>2</sub>-enriched or O<sub>2</sub>-poor gases were unaltered, but the breathing of combined hypoxic and hypercapnic mixtures caused systemic hypotension and depression of ventilation. The studies suggest, therefore, that the abnormal ventilatory responses to hypoxia in the goats treated with phenoxybenzamine were a consequence of the concomitant hypotension rather than a primary effect of the drug, upon either the chemoreceptors or the respiratory center.

## DISCUSSION

*The ventilatory response to hypoxia in familial dysautonomia.* There were three main features of the ventilatory response to hypoxia in the patients with familial dysautonomia: (a) during rebreathing, hypoxia decreased the ventilatory response to progressive hypercapnia instead of increasing it as in normal subjects; (b) in contrast to the sustained hyperventilation which normal subjects showed while breathing an hypoxic (CO<sub>2</sub>-free) gas mixture, the dysautonomic patients manifested only a fleeting, initial hyperventilation; and (c) apnea followed sudden relief of hypoxemia in all of the dysautonomic subjects whereas normal subjects had only a 40% decrease in ventilation. In addition, the dysautonomic subjects developed bradycardia during hypoxia and both bradycardia and hypotension during combined hypoxia and hypercapnia.

These abnormal ventilatory responses may be interpreted in terms of the established effects of systemic hypoxia upon the regulation of ventilation. Two opposing effects are involved in normal subjects. Most apparent is the reflex hyperventilation that follows stimulation of the peripheral arterial chemoreceptors; this hyperventilation begins within 5 seconds of the fall in arterial P<sub>O</sub><sub>2</sub> and subsides just as rapidly when hypoxia is relieved (8, 9). More difficult to demonstrate in the normal subject is the depressant effect which hypoxia exerts on the central system since this is ordinarily obscured by the stimulation of ventilation originating from the peripheral chemoreceptors. However, this depressant effect on ventilation can be demonstrated in subjects in whom the peripheral chemoreceptor response to hypoxia is blunted, e.g., as in native residents of high altitudes (10). A similar depressant effect of central nervous system hypoxia upon ventilation has also been demonstrated in unanesthetized dogs and goats in which the peripheral chemoreceptors have been denervated (11–13) and in

TABLE III  
Effects of Phenoxybenzamine on the Ventilatory Response to Steady-State Hypoxia and Hypercapnia

Goat		Room air			CO <sub>2</sub> response slope	8% O <sub>2</sub>			8% O <sub>2</sub> + 5% CO <sub>2</sub>		
		Ventila- tion	Paco <sub>2</sub> *	PaO <sub>2</sub> †		ṠR‡	Paco <sub>2</sub>	PaO <sub>2</sub>	ṠR	Paco <sub>2</sub>	PaO <sub>2</sub>
		liters/ min	mm Hg	mm Hg		%	mm Hg	mm Hg	%	mm Hg	mm Hg
1	Control	2.4	36	89	0.8	208	25	33	395	41	54
	Phenox	3.3	31	93	1.2	367	18	41	—	—	—
2	Control	7.0	30	95	0.8	192	23	40	306	45	52
	Phenox	6.8	32	91	1.0	174	25	37	—	—	—
3	Control	2.8	36	79	1.0	243	19	35	467	40	56
	Phenox	3.2	33	85	0.8	337	16	45	—	—	—
4	Control	3.5	34	83	0.6	137	27	38	275	46	49
	Phenox	3.5	34	85	0.5	139	26	41	—	—	—
5	Control	3.0	38	79	0.9	183	21	47	295	43	51
	Phenox	3.5	39	81	0.9	212	23	41	—	—	—
Mean	Control	3.8	35	85	0.82	193	23	39	348	43	52
	Phenox	4.1	34	87	0.88	246	22	41	—	—	—

\* Paco<sub>2</sub> = partial pressure of CO<sub>2</sub> in arterial blood.

† PaO<sub>2</sub> = partial pressure of O<sub>2</sub> in arterial blood.

‡ ṠR = observed ventilation/room air ventilation × 100.

anesthetized dogs in which the arterial chemoreceptor and cerebral circulations were separated (14). The studies on the chemodenervated dogs (11) also demonstrated that depression of ventilation due to hypoxia of the central nervous system is manifest only after a minute or more of arterial hypoxemia and may persist for as long as 1 min after relief of cerebral hypoxia. However, despite the consistency in dog, goat, and man, there does appear to be a species difference since Chalmers, Korner, and White failed to demonstrate a decrease in ventilation during systemic hypoxia in rabbits, although arterial hypotension was present, after both carotid sinus and aortic nerves had been cut (15).

When considered in the light of the above observations by others, the present data suggest that patients with familial dysautonomia have a normal peripheral chemoreceptor response to hypoxia but an inordinate central depression of ventilation by hypoxia. Such a combination would account for the prompt increase in ventilation (stimulation of peripheral chemoreceptors) upon breathing 12% O<sub>2</sub> followed by the decrease in ventilation to control levels (central nervous depression) as the hypoxia is continued. The apnea that followed abrupt relief of hypoxia in the dysautonomic subjects therefore appears to be a consequence of cessation of the hypoxic drive from the peripheral chemoreceptors at a time when hypoxia had dulled the central nervous re-

spiratory centers to their usual stimuli (e.g. hydrogen ions, carbon dioxide tension).

The abnormal circulatory response of the dysautonomic subjects to hypoxia suggested a mechanism by which the sympathetic nervous system could be involved in the inordinate depression of the ventilatory response. It is generally accepted that the sympathetic nervous system plays an important role in the reflex tachycardia and redistribution of blood flow occurring during hypoxia so that blood flow to the brain and heart is favored because of vasoconstriction elsewhere (16). Also, when sympathetic activity is diminished by administration of sympatholytic drugs, systemic arterial blood pressure falls during hypoxia (17). Since recent studies indicate that

TABLE IV  
Blood Pressure and Blood Gases at Apnea

Goat	Systemic blood pressure		Arterial blood gases at apnea	
	Air	At apnea	Pco <sub>2</sub>	Po <sub>2</sub>
	mm Hg		mm Hg	mm Hg
1	108/80	60/35	46	38
2	125/85	50/30	44	36
3	125/75	60/30	46	48
4	120/74	80/60	30	41
5	100/50	70/50	45	30

autoregulation of the cerebral vasculature (maintenance of constant blood flow over a wide range of arterial blood pressures) is abolished by hypoxia (18, 19), systemic hypotension during hypoxia must decrease cerebral blood flow relative to normal subjects with equivalent arterial hypoxemia. In the dysautonomic subjects of the present study, hypoxia during rebreathing was associated with a marked decrease in systemic arterial blood pressure and bradycardia, suggesting that the excessively depressed ventilatory response which they manifested was probably attributable to a decrease in cerebral blood flow which, in turn, intensified the hypoxia of the cerebral tissues. However, since cerebral blood flow was not measured in these studies, the alternative possibility remains that the brains of the dysautonomia subjects were unusually sensitive to the depressant effects of hypoxia. That this possibility is unlikely is suggested by the ability to reproduce the phenomenon in normal goats after treatment with phenoxybenzamine. In addition, inordinate sensitivity to the ventilatory depressant effects of central nervous hypoxia has never, to our knowledge, been reported in either animal or man.

The present study may be relevant to previous studies in which it was not possible to distinguish between impairment of the sympathetic nervous function and impairment of the baroreceptors as the basis for the inadequate cardiovascular response of dysautonomic subjects to tilting (20). In the present studies, the inappropriate cardiovascular response to hypoxia clearly seemed to be related to sympathetic nervous, rather than to chemoreceptor dysfunction since the use of transient stimuli showed that the ventilatory response to peripheral chemoreceptor stimulation, per se, was largely intact.

*The animal model.* The studies done in unanesthetized goats indicate that after alpha-adrenergic blockade, the ventilatory responses of the goats resembled those of the dysautonomic patients in several major respects: (a) the breathing of a (CO<sub>2</sub>-free) low O<sub>2</sub> gas mixture was followed by an initial increase in ventilation which was not sustained; subsequently, when hypoxia was relieved, a profound ventilatory depression ensued; (b) during rebreathing the ventilatory response to hypoxia was abolished; (c) in a variety of studies, i.e. open circuit, rebreathing, and steady-state, systemic hypotension invariably accompanied the depression of ventilation in the phenoxybenzamine-treated goats. The similarity between the abnormal ventilatory responses of the dysautonomic patients and the goats treated with phenoxybenzamine supports the idea that the inordinate depression of ventilation produced by hypoxia in subjects with familial dysautonomia is related to an inadequate cardiovascular response to hypoxia.

*The role of the sympathetic nervous system in the ventilatory response to hypoxia.* The results of the present

study are consistent with the observations of Biscoe and Purves (21) which indicate that an increase in sympathetic nervous discharge to the carotid bodies is not involved in the response of the peripheral chemoreceptors to hypoxia at rest. However, the present data provide no evidence concerning the suggestion made by others that heightened activity of the sympathetic nervous system, such as may occur during exercise, increases the response of peripheral chemoreceptors to hypoxia (1).

*Previous studies.* A study of the ventilatory response to hypoxia and hypercapnia in familial dysautonomia was carried out previously by Filler, Smith, Stone, and Dancis (3). Their dysautonomic subjects hyperventilated as much as the controls while breathing 12% O<sub>2</sub>, but they had lower levels of arterial O<sub>2</sub> saturation, and, despite the hyperventilation, the arterial P<sub>CO<sub>2</sub></sub> was virtually the same during air and hypoxic breathing. In addition, three of the six subjects experienced syncope or a grand mal seizure. Although systemic arterial blood pressures were not recorded, the coincidence of hyperventilation with an unchanged arterial P<sub>CO<sub>2</sub></sub> and a marked fall in O<sub>2</sub> saturation is consistent with the occurrence of systemic and pulmonary arterial hypotension and therefore an increased physiological dead space (22). Thus, the findings of Filler et al. are consistent with those of the present study in that, after prolonged hypoxia, the ventilatory response to this stimulus was blunted, probably in association with systemic hypotension.

The relationship of the results of the present study to other disturbances of the autonomic nervous system in man is unknown. For example, the ventilatory responses to acute hypoxia and hypercapnia have not yet been tested in neurological disorders, such as idiopathic postural hypotension, or in patients whose sympathetic nervous activity has been modified either by surgical or pharmacologic means. Similarly, the effects of abnormal circulatory responses to hypoxia upon regulation of ventilation have not been investigated in patients with severe hypoxemia of different causes and durations.

#### ACKNOWLEDGMENTS

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