Effects of Adrenergic Stimulation on Ventilation in Man

DONALD D. HEISTAD, ROBERT C. WHEELER, ALLYN L. MARK, PHILLIP G. SCHMID, and FRANCOIS M. ABBOUD

From the Cardiovascular Division, Department of Internal Medicine, University of Iowa College of Medicine, and Veterans Administration Hospital, Iowa City 52240, and U. S. Army Research Institute of Environmental Medicine, Natick, Massachusetts 01760

ABSTRACT The mechanism by which catecholamines affect ventilation in man is not known. Ventilatory responses to catecholamines were observed in normal subjects before and after adrenergic receptor blockade. Intravenous infusions of norepinephrine and isoproterenol caused significant increases in minute volume and decreases in end-tidal P_{CO_2} which were blocked by the administration of propranolol, a beta adrenergic receptor blocker. The hyperventilatory response to hypoxia was not altered by propranolol.

Intravenous infusion of phenylephrine caused a small but significant decrease in minute volume which was antagonized by phentolamine, an alpha adrenergic receptor blocker. Angiotensin, a nonadrenergic pressor agent, also decreased minute volume significantly.

100% oxygen was administered to suppress arterial chemoreceptors. Increases in minute volume and decreases in arterial P_{CO_2} in response to norepinephrine and isoproterenol were blocked by breathing 100% oxygen. The decrease in minute volume during phenylephrine was not altered by 100% oxygen.

The results indicate that: (*a*) beta adrenergic receptors mediate the hyperventilatory response to norepinephrine and isoproterenol but not to hypoxia. (*b*) the pressor agents phenylephrine and angiotensin decrease ventilation, and (*c*) suppression of chemoreceptors blocks the ventilatory response to norepinephrine and isoproterenol but not to phenylephrine. Implications concerning the interaction of adrenergic receptors and chemoreceptors with respect to the hyperventilatory response to catecholamines are discussed.

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INTRODUCTION

A report that catecholamines affect ventilation (2) was confirmed in man over 50 years ago (3). Epinephrine, norepinephrine and isoproterenol cause hyperventilation in man (4–6). In the present experiments, three studies were undertaken to examine systematically the mechanism by which catecholamines affect ventilation. In the first study, we tested the hypothesis that the stimulation of ventilation by catecholamines may be mediated by beta adrenergic receptors. In the second study, we examined the possibility that stimulation of alpha adrenergic receptors might suppress ventilation (7). Finally, it has been proposed (8, 9) that the stimulation of ventilation by catecholamines is mediated through arterial chemoreceptors. Therefore in the third study arterial chemoreceptors were suppressed by breathing 100% oxygen (10) to determine whether suppression of chemoreceptors attenuates the ventilatory effects of stimulation of beta adrenergic or alpha adrenergic receptors.

METHODS

23 healthy men and one woman, 19–25 yr of age, were studied. A venous catheter was inserted about 3 inches into the basilic vein and connected to a syringe for infusion of drugs.

First study. The effect of propranolol on the hyperventilatory response to norepinephrine, isoproterenol, and hypoxia was tested. 12 men were studied while sitting. The subjects breathed through a low resistance Rahn-Otis sampling valve. Expired gas was collected in plastic Douglas bags. The volume was measured and corrected to standard temperature and pressure. P_{O_2} and P_{CO_2} of the gas in the bags were measured with an IL Ultramicro gas analyzer (Instrumentation Laboratory, Inc., Lexington, Mass.) to allow calculation of oxygen consumption. P_{O_2} and P_{CO_2} were measured in alveolar gas samples. Arterial pressure was determined by auscultation and heart rate was counted from an electrocardiogram.

Measurements were made during i.v. infusions of norepinephrine and isoproterenol, while the subjects were

breathing room air and while they were breathing 10.5% oxygen in nitrogen. These interventions were repeated after i.v. injection of 8 mg of propranolol, followed by an additional 4 mg of propranolol injected 1 hr later. The order of the two infusions (norepinephrine and isoproterenol) and of the two gas mixtures (air and 10.5% oxygen) was reversed in alternate subjects.

The subjects breathed each gas mixture for 3–5 min before control measurements were made. *l*-norepinephrine bitartrate was infused at a dose of 5 μg/min (as the base) for 3 min and then at 10 μg/min for 3 min. Isoproterenol was infused at 1 μg/min for 3 min and then at 2 μg/min for 3 min. There was a 10 min rest period between each infusion to allow ventilation, blood pressure, and heart rate to return to control levels. Measurements were made for 2 min during the control period and during the last 2 min of infusion at each dose level of norepinephrine and isoproterenol.

Breathing 10.5% oxygen causes hyperventilation and hypocapnia. In this study, hypocapnia was prevented during the control period while breathing 10.5% oxygen by adding carbon dioxide to the inspired gas, as described previously (11). After the flow rate of carbon dioxide was adjusted during the control period it was not altered during the infusion of the drugs. The amount of expired gas removed by the CO_2 analyzer was constant throughout each study

TABLE I

Minute Ventilation in Response to i.v. Norepinephrine and Isoproterenol, before and after i.v. Propranolol

Subject	Before propranolol						After propranolol					
	Con*	NE_1	NE_2	Con	Iso_1	Iso_2	Con	NE_1	NE_2	Con	Iso_1	Iso_2
	liters/min			*liters/min*			*liters/min*			*liters/min*		
Minute ventilation during normoxia‡												
J. B.	5.31	6.47	8.30	5.55	8.24	8.97	5.06	5.25	5.06	5.31	5.73	6.04
R. A.	4.17	6.14	5.75	4.24	6.53	6.53	3.90	4.30	4.48	3.69	3.99	5.44
L. F.	4.88	5.28	5.95	5.50	7.18	9.10	5.74	6.63	6.11	5.53	6.17	5.40
R. R.	4.27	5.79	5.91	4.57	6.67	6.67	4.18	3.97	4.12	4.77	4.21	5.25
L. H.	6.47	6.81	6.93	6.21	7.75	7.60	4.99	5.58	5.84	5.29	5.52	5.49
M. B.	4.81	5.99	5.46	4.57	5.93	6.20	5.12	4.24	4.80	4.04	3.72	4.38
D. O.	5.90	7.31	7.34	6.16	7.15	7.39	5.66	6.17	5.66	6.56	6.50	6.88
A. B.	6.98	7.58	8.52	6.14	7.52	7.89	5.75	7.63	7.63	5.39	6.41	6.94
J. S.	6.39	6.93	7.17	7.11	7.99	10.01	6.14	6.62	6.59	5.46	6.86	7.01
E. W.	6.47	7.31	7.04	6.72	8.90	9.45	5.69	6.35	5.78	5.63	6.17	5.84
D. C.	6.07	6.39	6.10	5.63	9.11	8.82	5.38	5.97	5.91	6.76	7.25	7.90
D. B.	4.71	5.42	5.48	4.67	6.42	6.93	4.66	4.87	4.20	3.83	5.01	4.15
Mean	5.61	6.45	6.66	5.58	7.44	7.96	5.18	5.63	5.51	5.18	5.62	5.90
SE	0.29	0.21	0.30	0.26	0.28	0.36	0.19	0.32	0.29	0.27	0.33	0.32
Change from control		0.84	1.05		1.86	2.38		0.45	0.33		0.44	0.72
Minute ventilation during isocapnic hypoxia												
J. B.	12.26	13.85	15.19	12.93	17.14	—	12.20	12.20	12.93	12.69	12.39	13.24
R. A.	7.74	9.98	9.20	7.44	10.95	10.29	7.56	7.59	7.81	7.44	7.78	7.96
L. F.	9.16	8.55	9.13	8.49	9.83	12.09	8.15	8.76	8.46	9.22	10.38	9.68
R. R.	7.56	10.42	9.87	8.71	11.67	11.52	7.37	7.57	7.31	7.60	7.28	7.49
L. H.	11.50	13.49	13.56	11.27	13.39	16.90	12.79	11.63	12.38	11.80	12.04	13.02
M. B.	6.08	7.74	7.65	6.47	7.77	8.60	5.61	5.67	6.83	5.90	5.73	6.16
D. O.	8.81	10.19	10.46	7.18	9.44	10.61	11.50	11.50	11.44	10.57	10.57	10.36
A. B.	12.53	15.04	15.16	10.89	15.59	17.81	13.45	14.14	15.33	12.57	15.42	15.03
J. S.	10.14	11.61	13.20	10.77	12.41	11.96	11.40	11.07	12.87	11.85	11.70	12.93
E. W.	10.20	12.44	12.41	10.44	13.20	14.02	10.71	10.29	—	10.56	11.19	10.68
D. C.	11.96	13.07	13.49	11.71	12.77	14.19	11.33	10.87	11.66	11.07	11.66	12.59
D. B.	8.05	9.38	10.74	8.82	11.69	12.95	6.19	6.55	6.43	7.37	7.46	7.81
Mean	9.66	11.31	11.67	9.59	12.15	12.81	9.86	9.82	10.31	9.89	10.30	10.58
SE	0.60	0.66	0.72	0.58	0.75	0.84	0.78	0.74	0.91	0.67	0.79	0.81
Change from control		1.65	2.01		2.64	3.22		−0.04	0.45		0.41	0.69

* Con refers to control observations, NE_1 and NE_2 refer to infusions of 5 and 10 μg/min of norepinephrine, and Iso_1 and Iso_2 refer to infusions of 1 and 2 μg/min of isoproterenol.

‡ Changes in minute ventilation were not associated with a significant change in ventilatory rate (f): before norepinephrine, f was 13.5±0.7, and during the two doses of norepinephrine f averaged 14.2±0.6; before isoproterenol, f was 13.4±0.8, and during the two doses of isoproterenol f averaged 13.8±0.8.

and the expiratory minute volume was corrected to include this volume.

Statistical comparisons were made by analyses of variance (12).

Second study. The effect of phentolamine on the ventilatory response to phenylephrine was tested. 12 subjects were studied while lying supine. The brachial artery was cannulated with a polyethylene cannula (PE 90) and connected to a pressure transducer and to a syringe for obtaining blood samples. The subjects breathed through a Rudolph valve. In six subjects expiratory minute volume was measured as described above, and in six subjects expired gas was collected in a Tissot spirometer, which was adapted to allow continuous recording of volume.

Each subject was studied during an i.v. infusion of phenylephrine at 40 μg/min for 3 min and then at 80 μg/min for 3 min, while breathing room air and 100% oxygen. Observations were also made during i.v. infusion of phentolamine at a dose of 0.5 mg/min; after control measurements, the two doses of phenylephrine were infused while the infusion of phentolamine was continued. In order to determine the response to phentolamine, observations were made during an infusion of phentolamine at 0.5 mg/min for 10 min. The ventilatory effect of angiotensin, infused i.v. at 0.25 μg/min for 3 min and 0.5 μg/min for 3 min, was observed in six subjects. The order of the infusions was randomized.

Third study. The effect of breathing 100% oxygen on the ventilatory response to norepinephrine, isoproterenol, and phenylephrine was tested. Six subjects who had participated in the second part of the experiment were studied while lying supine. Measurements were similar to those in the second study.

Each subject was studied during an i.v. infusion of norepinephrine, isoproterenol, and phenylephrine, each drug being infused while breathing room air and 100% oxygen. The three drugs were infused as described above.

TABLE II

*Alveolar P_{CO_2} and P_{O_2} in Response to i.v. Norepinephrine and Isoproterenol, before and after i.v. Propranolol**

	Before propranolol		After propranolol	
	P_{CO_2}	P_{O_2}	P_{CO_2}	P_{O_2}
	mm Hg		*mm Hg*	
During normoxia				
Control	38.8±0.6	104±1.4	36.7±0.8	106±1.8
NE_1	37.1±0.9	110±1.7	37.4±0.9	108±1.4
NE_2	34.4±0.8	113±1.6	36.6±1.0	111±2.2
Control	38.5±0.6	106±1.9	38.1±0.7	105±1.6
Iso_1	37.6±0.8	110±1.1	37.3±1.1	106±1.6
Iso_2	36.4±0.6	112±1.3	37.5±0.8	110±1.2
During isocapnic hypoxia				
Control	39.4±0.8	51±1.2	39.4±0.5	52±1.3
NE_1	37.0±0.8	52±1.2	38.7±0.5	51±1.3
NE_2	36.6±0.6	53±1.2	37.7±0.5	52±1.1
Control	40.3±0.5	48±1.1	39.0±0.5	51±1.1
Iso_1	38.7±0.6	51±1.1	39.4±0.5	50±1.2
Iso_2	37.5±0.6	52±1.2	38.8±0.6	51±1.3

* Values are mean of 12 subjects ±SE.

TABLE III

Analysis of Variance of Changes in Minute Volume in Response to Norepinephrine and Isoproterenol, before and after Propranolol, during Normoxia and Isocapnic Hypoxia

Source of variation	df	Mean square	F	P
Increase in minute volume before propranolol				
Subjects	11	1.05		
Oxygen*	1	16.56	18.22	<0.001
Drugs‡	1	30.16	33.19	<0.001
Drug dose	1	6.45	7.10	<0.01
Error	77	0.91		
Increase in minute volume before and after propranolol				
Subjects	11	1.70		
Propranolol§	1	114.45	181.67	<0.01
Oxygen	1	6.76	10.73	<0.01
Drugs	1	22.52	35.75	<0.01
Drug dose	1	7.01	11.13	<0.01
Error	163	0.63		

* Oxygen refers to variation among responses to drugs while breathing room air and 10.5% oxygen.

‡ Drug refers to difference between responses to norepinephrine and isoproterenol.

§ Propranolol refers to variation among responses to drugs before and after propranolol.

RESULTS

Effects of norepinephrine and isoproterenol

Normoxia. Expiratory minute volume increased during infusions of norepinephrine and isoproterenol while breathing room air (Table I). Changes in alveolar P_{CO_2} and P_{O_2} reflected the changes in minute ventilation (Table II). Respiratory frequency was not altered by norepinephrine or isoproterenol. Oxygen consumption was not altered by norepinephrine but was increased significantly ($P < 0.01$) by isoproterenol from 279±12 (mean ±SE) ml/min at rest to 332±16 during isoproterenol.

Hypoxia. While breathing 10.5% oxygen alveolar P_{O_2} decreased but P_{CO_2} was maintained despite hyperventilation by addition of CO_2 to the gas mixture (Table II). Hypoxia increased minute volume, and the hyperventilatory responses to norepinephrine and isoproterenol were greater during hypoxia than during normoxia (Tables I and III).

Propranolol. Changes in minute volume in response to norepinephrine and isoproterenol were significantly less after propranolol (Tables I and III). The increase in heart rate during isoproterenol was blocked by propranolol, indicating that propranolol effectively blocked beta adrenergic receptors. Before propranolol the heart rate increased from 72.0±2.9 at rest to 81.8±2.6 and

TABLE IV

Minute Ventilation in Response to i.v. Phenylephrine, before and during i.v. Phentolamine, and in Response to Angiotensin

Subject	Before phentolamine			During phentolamine					
	Con*	P_1	P_2	Con	P_1	P_2	Con	A_1	A_2
	liters/min			*liters/min*			*liters/min*		
R. S.	4.38	4.33	4.60	5.23	5.27	5.27	—	—	—
K. V.	5.41	5.18	4.96	6.04	5.77	6.00	—	—	—
J. G.	5.59	5.10	4.20	5.19	5.12	4.93	—	—	—
W. C.	4.97	4.97	4.95	5.06	5.82	4.53	—	—	—
J. M.	7.40	4.75	5.74	7.89	7.28	6.69	—	—	—
P. A.	4.75	4.22	4.28	5.32	5.25	4.60	—	—	—
P. T.	4.40	3.76	3.40	4.70	3.63	5.20	5.05	5.00	3.90
R. R.	7.53	5.96	6.58	6.55	6.62	6.20	6.82	6.70	6.01
L. B.	6.67	5.75	5.93	5.42	5.13	4.51	5.49	4.98	5.18
S. B.	6.15	5.65	6.55	7.49	7.61	7.52	7.81	7.23	7.46
P. J.	6.18	5.55	5.52	5.82	6.28	6.45	6.05	5.35	5.00
R. L.	8.07	7.67	7.95	7.40	7.47	7.40	7.80	7.50	7.10
Mean	5.95	5.24	5.38	6.00	5.93	5.77	6.50	6.12	5.77
SE	0.36	0.28	0.36	0.30	0.33	0.31	0.47	0.46	0.54
Change from control		−0.71	−0.57		−0.07	−0.23		−0.38	−0.73

* Con refers to control observations, P_1 and P_2 refer to infusions of 40 and 80 μg/min of phenylephrine, and A_1 and A_2 refer to infusions of 0.25 and 0.5 μg/min of angiotensin.

107.4±3.9 during 1 and 2 μg/min of isoproterenol ($P < 0.001$). After propranolol, heart rate was 60.3±2.7 at rest, and 60.8±2.8 and 62.2±2.6 during 1 and 2 μg/min of isoproterenol ($P > 0.05$). In contrast, propranolol did not alter the hyperventilatory response to hypoxia (Table I) nor did it alter the increase in heart rate during hypoxia. Before propranolol heart rate increased from 72.3±2.9 during normoxia to 87.4±3.0 during hypoxia. After propranolol heart rate increased from 60.3±2.6 during normoxia to 73.6±2.3 during hypoxia.

TABLE V

Analysis of Variance of Changes in Minute Volume and Arterial P_{CO_2} in Response to Phenylephrine, before and during Phentolamine

Source of variation	df	Mean square	F	P
Decrease in minute volume during phenylephrine				
Subjects	11	0.79		
Phentolamine*	1	2.38	11.81	<0.002
Phenylephrine dose	1	0.01	0.05	NS‡
Error	33	0.20		
Change in arterial P_{CO_2} during phenylephrine				
Subjects	11	3.63		
Phentolamine	1	0.01	0.01	NS
Phenylephrine dose	1	0.21	0.11	NS
Error	33	1.93		

* Phentolamine refers to variation among responses to phenylephrine before and during phentolamine.

‡ NS indicates not statistically significant ($P > 0.05$).

Effects of phenylephrine and angiotensin

Phenylephrine decreased expiratory minute volume (Table IV). Phentolamine blocked this effect of phenylephrine (Tables IV and V). Phentolamine alone did not alter expiratory minute volume. The dose of phentolamine was effective in blocking the pressor effect of phenylephrine. Before phentolamine mean arterial pressure increased from 91.3±2.9 mm Hg at rest to 98.5±3.8 and 105.1±4.3 during infusions of 40 and 80 μg/min of phenylephrine. During infusion of phentolamine, resting arterial pressure was 90.7±3.3, and 89.3±3.4 and 90.1±3.1 during 40 and 80 μg/min of phenylephrine.

Angiotensin also decreased expiratory minute volume (Table IV). Mean arterial pressure increased from 89.2±1.5 mm Hg at rest to 100.3±5.4 and 111.2±5.1 during 0.25 and 0.5 μg/min of angiotensin, respectively.

Effects of breathing 100% oxygen on responses to norepinephrine, isoproterenol, and phenylephrine

Increases in minute volume and decreases in alveolar and arterial P_{CO_2} in response to norepinephrine and isoproterenol during normoxia (Tables I, II, and VI) were blocked by breathing 100% oxygen (Tables VI and VII). The small decrease in minute volume during phenylephrine was similar while breathing room air and 100% oxygen (Tables VI and VII).

TABLE VI

Minute Ventilation and Arterial P_{CO_2} in Response to i.v. Norepinephrine, Isoproterenol, and Phenylephrine during Normoxia and while Breathing 100% Oxygen

	Normoxia		100% oxygen	
	Vent.	P_{CO_2}	Vent.	P_{CO_2}
	liters/min	*mm Hg*	*liters/min*	*mm Hg*
Norepinephrine (n=6)				
Control	5.41±0.18	40.0±1.4	5.53±0.26	37.9±1.2
NE_1	6.43±0.44	37.7±1.7	5.44±0.11	37.8±1.3
NE_2	6.48±0.40	35.6±1.0	5.67±0.28	37.0±1.4
Isoproterenol (n=6)				
Control	4.91±0.33	40.7±1.0	6.14±0.51	36.1±1.7
Iso_1	7.01±0.46	38.1±1.1	5.98±0.26	37.6±1.6
Iso_2	7.32±0.48	37.8±1.1	6.46±0.37	39.0±1.3
Phenylephrine (n=12)				
Control	5.95±0.36	40.5±0.8	6.52±0.40	39.7±1.3
$Phenyl_1$	5.24±0.28	41.1±0.8	5.66±0.32	39.5±1.2
$Phenyl_2$	5.38±0.36	40.4±1.0	5.75±0.32	40.3±1.0

DISCUSSION

These studies indicate that norepinephrine and isoproterenol stimulate ventilation in man. Propranolol, which blocks beta adrenergic receptors, suppressed this increase in ventilation. The attenuation of the ventilatory response to norepinephrine and isoproterenol by propranolol is not a nonspecific depression, as indicated by the preservation of the ventilatory response to hypoxia after propranolol. Studies in animals (13) have also shown that the response to hypoxia is preserved after propranolol.

The metabolic effect of catecholamines, and its possible relationship to stimulation of ventilation, has received little attention (14). The increase in metabolism during infusion of catecholamines (15) causes an increase in carbon dioxide production which might account for the increase in ventilation. In this study, however, the increased metabolism must not be the primary mechanism for the hyperventilation. Norepinephrine caused hyperventilation without detectable change in metabolism during the periods of infusions. In addition, the arterial P_{CO_2} decreased significantly in response to the catecholamines; we would expect the P_{CO_2} to increase slightly or remain unchanged if the hyperventilation were a response to increased carbon dioxide production.

Since stimulation of beta adrenergic receptors increased ventilation we considered the possibility that stimulation of alpha adrenergic receptors might suppress ventilation. The findings with phenylephrine tend to support this possibility. It is also possible that the rise in arterial pressure per se may have depressed ventilation (16) since angiotensin, which causes a pressor response by activating nonadrenergic receptors (17), also depressed ventilation.

The study also suggests that arterial chemoreceptors are involved in the ventilatory response to norepinephrine and isoproterenol but not to phenylephrine. Breathing 100% oxygen, which suppresses arterial chemoreceptors (10), abolished the hyperventilatory response to catecholamines but did not alter the depression of ventilation by phenylephrine. The role of arterial chemoreceptors in the ventilatory effects of norepinephrine and epinephrine was demonstrated in the cat (8) by the finding that the rate of discharge from the carotid body increases during infusions of catecholamines, and that section of carotid sinus and aortic nerves prevents the increase in ventilation in response to catecholamines.

TABLE VII

Analysis of Variance of Changes in Minute Volume and Arterial P_{CO_2} in Response to Norepinephrine, Isoproterenol, and Phenylephrine while Breathing Room Air and 100% Oxygen

Source of variation	df	Mean square	F	P
Responses to norepinephrine and isoproterenol				
Increase in minute volume				
Subjects	5	0.61		
Oxygen*	1	30.74	42.87	<0.001
Drug‡	1	4.91	6.85	<0.01
Drug dose	1	0.87	1.21	NS§
Error	15	0.72		
Decrease in arterial P_{CO_2}				
Subjects	5	6.88		
Oxygen	1	182.91	77.06	<0.001
Drug	1	33.17	13.97	<0.001
Drug dose	1	2.57	1.08	NS
Error	15	2.37		
Responses to phenylephrine				
Change in minute volume				
Subjects	11	2.05		
Oxygen	1	0.33	1.74	NS
Phenylephrine dose	1	0.19	0.99	NS
Error	33	0.19		
Change in arterial P_{CO_2}				
Subjects	11	3.90		
Oxygen	1	1.40	0.64	NS
Phenylephrine dose	1	0.69	0.78	NS
Error	33	2.17		

* Oxygen refers to variation among responses while breathing room air and 100% oxygen.

‡ Drug refers to difference between responses to norepinephrine and isoproterenol.

§ NS indicates not statistically significant ($P>0.05$).

Injection of norepinephrine into the internal carotid artery beyond the carotid chemoreceptors produces a slight increase in ventilation in man (18). We cannot exclude the possibility that norepinephrine may stimulate ventilation in part by a direct effect on the respiratory center. It is also possible that injection of norepinephrine into the internal carotid artery may increase efferent nerve traffic to the carotid chemoreceptors, similar to the effect noted in response to epinephrine in cats (19). The efferent nerve traffic might then influence chemoreceptor discharge (20) to produce hyperventilation. This reflex pathway, although initiated in the central nervous system, would nevertheless be susceptible to suppression while breathing 100% oxygen, because of the mediation through carotid chemoreceptors.

It appears therefore from this work and that of others (21) that norepinephrine and isoproterenol activate chemoreceptors in man. This study indicates in addition that the activation of chemoreceptors by the catecholamines is dependent on a mechanism involving beta adrenergic receptors. In contrast the activation of chemoreceptors by hypoxia does not involve a beta adrenergic mechanism. It is also evident from this work that the same doses of catecholamines produce a greater hyperventilatory response when the chemoreceptors are already activated by hypoxia. Cunningham, Hey, Patrick, and Lloyd have reported (21) that an infusion of norepinephrine increases the ventilatory response to hypoxia. There appears to be a synergistic response when chemoreceptors are activated simultaneously through a beta adrenergic mechanism by the catecholamines and through a nonadrenergic mechanism by hypoxia.

One might speculate on the nature of this beta adrenergic mechanism in light of recent work concerning chemoreceptor physiology. It has been observed that there are two types of cells in the carotid body, type I and type II cells (22). Type I cells contain abundant stores of catecholamines (23), and are surrounded by type II cells, which appear to be, or enclose, the chemoreceptor sensors (20). Type I cells are influenced by efferent excitatory and depressant nerve impulses (19, 20, 24) and the activity of these cells may modify afferent nerve traffic originating in the type II cells (20). The release of neurotransmitter from the type I cells may have a modulating influence on afferent nerve traffic by an effect on distribution of blood flow (25) or on oxygen consumption of the carotid body (26). The neurotransmitter may also sensitize chemoreceptors to other stimuli. Catecholamines are known to sensitize frog mechanoreceptors (27) and mammalian muscle spindles (28) so that sensitization of chemoreceptors would not be a unique action. We would suggest that exogenous norepinephrine and isoproterenol as administered in this study may stimulate ventilation by activating the same adrenergic receptor mechanism in the carotid body as the one affected by efferent nerves to the type I cells of the carotid body, and that this mechanism may activate the chemoreceptors or sensitize them to hypoxia. We recognize the speculative nature of this discussion, since the function of type I and type II cells is not certain, but it seems reasonable to conclude that activation of an adrenergic mechanism which may be related to the type I cell may influence chemoreceptor activity which may be structurally related to the type II cell.

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