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Research Article

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Hyperoxic Attenuation of Exercise-Induced Bronchospasm in Asthmatics

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ABSTRACT To investigate the mechanism of exercise-induced bronchospasm, we measured specific airway conductance before and after exercise in 7 healthy normals, 12 asthmatics with intact carotid bodies, and 5 asthmatics who had had bilateral carotid body resection. The subjects breathed either air or oxygen (randomly assigned) during cycle ergometer exercise. Post-exercise bronchodilation was the usual pattern in normals, whereas post-exercise bronchospasm occurred in all asthmatics who breathed air during exercise. Oxygen breathing during exercise markedly attenuated the post-exercise bronchospasm in those asthmatics with intact carotid bodies, but had no significant effect in those without carotid bodies. The attenuation of the bronchospasm with oxygen occurred with either incremental or constant load exercise of high intensity. The degree of attenuation did not correlate significantly with changes in end-tidal P_{CO_2}, maximum work rate, maximum exercise ventilation, or maximum heart rate. These studies indicate that oxygen attenuates exercise-induced bronchospasm in asthmatics through its action on the carotid bodies.

INTRODUCTION

Post-exercise bronchospasm is a common occurrence in asthmatic subjects. Hypocapnia (1, 2), metabolic acidosis (3), hypoxemia (4), stimulation of mechanical or irritant receptors in the airways (1, 2), and altered sympathetic response (4) have all been implicated as causative mediators but none have been proven to be.

Because lactic acid reaches its peak after the cessation of heavy exercise (3), the carotid bodies, which are known to be the primary respiratory chemoreceptors responsive to acute changes in arterial H^+ (5), would receive additional stimuli secondary to the acidemia. Because stimulation of the carotid bodies is capable of producing bronchoconstriction (4), we considered that exercise-induced bronchospasm might be partially mediated via the carotid bodies (by H^+ stimulation). We attempted to determine if the carotid bodies could be playing a role in exercise-induced bronchospasm by measuring specific airway conductance before and after exercise, during which either air or 100% oxygen was breached, because hyperoxia can attenuate carotid body responsiveness in man (6). We studied control and asthmatic subjects as well as a group of asthmatic subjects who had, several years before, undergone carotid body resection. These studies provide evidence that the carotid bodies play a role in exercise-induced bronchospasm.

METHODS

We studied 7 healthy adults without history of lung disease, 12 asthmatic subjects with symptomatic exercise-induced bronchospasm, and 5 asthmatic subjects who had had bilateral carotid body resection at least 5 yr before (Table I). Only one patient in the latter group, subject 20, had symptomatic asthma. All gave informed consent before the studies.

All subjects were instructed not to drink coffee or take other stimulants for at least 2 h, and to take no medication for at least 4 h before the testing. Only the four following subjects were currently on medication. Subject 8 employed a metered isoetharine inhaler, but had not used it for several days. Subjects 9, 10, and 20 each took 200 mg of aminophylline, or 200 mg of oxtriphylline orally three or four times daily plus 2.5 mg of terbutaline sulfate or 20 mg of metaproterenol three or four times daily, but in no case within 9 h of study. No subjects used disodium cromoglycate, corticosteroids, or long acting theophyllines.

We used specific airway conductance, measured in a constant volume plethysmograph, as described by DuBois et al. (7) to estimate the degree of bronchospasm, because we, and others have found it to be a more sensitive index of exercise-induced bronchospasm than the 1-s vital capacity or the maximal midexpiratory flow rate (8). The subjects exercised on a cycle ergometer at ≅60 rpm at 18–20°C while

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TABLE I

*Identifying Data and Selected Values in Three Groups of Subjects Performing Incremental Exercises**

Subject No.	Age	Sex	Ht‡	TGV		SGaw		Max work rate		Max heart rate		Max $\dot{V}_E$	
				A	O_2	A	O_2	A	O_2	A	O_2	A	O_2
			cm	*liters*		*liters/cm H_2O/s*		*W*		*per min*		*liters/min*	
Normals													
1	27	M	178	3.7	3.2	0.26	0.26	210	225	159	161	96	124
2	39	M	183	4.7	4.3	0.13	0.16	180	165	164	164	72‡	—
3	31	F	174	2.8	3.3	0.26	0.23	180	180	164	160	60	56
4	33	M	178	3.2	3.5	0.20	0.19	240	225	170	168	103	87
5	28	F	160	2.4	2.3	0.23	0.27	135	135	184	176	78	58
6	29	M	183	3.9	4.0	0.22	0.22	180	195	172	172	84	104
7	36	M	185	4.4	4.6	0.27	0.20	285	285	192‡	—	198	150
Mean±SD				3.6	3.6	0.22	0.22	201	201	169	167	103	100
				±0.8	±0.7	±0.03	±0.02	±45	±50	±8	±6	±36	±30
Asthmatics													
8	19	M	178	4.8	4.1	0.10	0.09	165	165	169	165	73	70
9	26	F	152	4.1	3.6	0.09	0.09	90	90	183	163	51	52
10	25	F	161	3.3	4.3	0.15	0.09	120	120	180	161	58	52
11	34	M	185	5.2	3.8	0.14	0.17	240	240	184	180	163	120
12	30	M	183	4.3	4.4	0.22	0.12	225	240	165	169	126	120
13	25	M	180	4.0	3.6	0.15	0.13	210	210	184	180	97	100
14	32	M	168	3.3	2.6	0.19	0.26	195	180	180	172	98	82
15	26	M	178	3.5	3.8	0.42	0.25	165	180	176	199	84	73
16	27	F	157	2.7	2.5	0.11	0.19	135	135	180	171	76	93
17	27	M	145	3.2	3.2	0.17	0.15	150	180	161	172	66	92
18	35	M	168	3.6	3.5	0.19	0.13	195	210	158	162	99	87
19	27	M	183	3.8	3.5	0.16	0.13	210	210	184	184	136	128
Mean±SD				3.8	3.6	0.17	0.15	175	180	175	173	94	89
				±0.7	±0.6	±0.08	±0.04	±43	±45	±9	±11	±32	±24
Asthmatics with bilateral carotid body resection													
20	36	F	174	6.6	4.0	0.03	0.06	60	75	145	148	32	38
21	45	M	183	5.6	4.0	0.15	0.17	120	180	161	165	34	41
22	21	F	173	3.5	3.4	0.19	0.14	135	150	178	184	34	45
23	18	M	192	4.4	5.2	0.12	0.14	210	210	184	188	50	52
24	47	M	180	6.6	6.2	0.06	0.08	75	90	117	117	30	41
Mean±SD				5.3	4.8	0.11	0.12	120	141	157	160	36	43
				±1.2	±1.0	±0.04	±0.03	±53	±52	±24	±26	±7	±5

Abbreviations used in this table: Ht, height; TGV, thoracic gas volume; A, subject breathed air during exercise; O_2, subject breathed 100% oxygen during exercise; SGaw, specific conductance of the airways; $\dot{V}_E$, expired ventilation.

* All air and oxygen values were compared by *t* test. No significant differences were found.

‡ Unpaired value excluded from mean.

breathing air or 100% oxygen from an Otis-McKerrow breathing valve. Either compressed air or oxygen from cylinders was partially humidified by passing it through a 5-liter Plexiglas (Rohm and Hass Co., Philadelphia, Pa.) chamber with water at room temperature, providing a surface area of 900 cm^2, and then into two 6-liter reservoir bags connected to the Otis-McKerrow valve intake. The P_{H_2O} ranged from 14.5 to 17.5 mm Hg at this point, but was most likely further humidified to a P_{H_2O} of ≅20 mm Hg by the moisture in the breathing valve. The humidification procedure was, therefore, identical for the various inspirates and hence, subject-to-subject and trial-to-trial variability would be random and small. End-tidal P_{CO_2} (LB-2 Beckman Instruments, Inc., Fullerton, Calif.) was measured for each breath from the mouthpiece. Expired flow was continuously measured with a Fleisch No. 3 pneumotachograph and Statham PM-97 differential pressure transducer (Statham Instruments, Inc., Oxnard, Calif.). This signal was used to derive tidal volume by integration, breathing frequency, and also minute ventilation. Heart rate was measured continuously from the R-R interval of the electrocardiogram, using a Beckman heart rate coupler. All of these measurements were displayed on a Beckman Type R dynograph recorder.

Two protocols were used to study the effect of air and 100% O_2 breathing during exercise on specific airway conductance (Fig. 1). Protocol I consisted of two incremental exercise tests (one with air and one with O_2 as the inspirate) in which the work rate was increased 15 W every minute until exhaustion. Each exercise test was

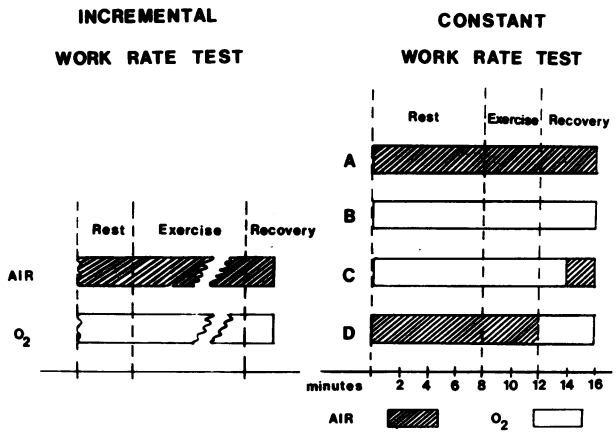

FIGURE 1 Diagram of the exercise protocols. Protocol I (left) was an incremental test to the subjects' maxima while breathing air or O_2. Protocol II (right) consisted of exercising at a constant load with four different patterns of air and O_2 breathing. The order of studies was randomized in both protocols.

performed on a separate day or, in a few cases, after a rest of 4 h, with the order of the air or oxygen tests randomly assigned.

Protocol II consisted of four constant load exercise studies performed on 4 additional days. Before exercise, the subjects sat quietly on a cycle ergometer and breathed either air (studies A and D) or oxygen (studies B and C) for at least 8 min. On signal, they cycled at a work rate that was 90% of the maximum attained in protocol I during air breathing. At the end of 4 min, the subjects stopped cycling and remained seated for an additional 4 min while continuing to breathe through the same mouthpiece. In study A, the subjects breathed air throughout this 16-min period. In study B, the subjects breathed oxygen throughout. In study C, subjects breathed oxygen throughout, until 2 min after exercise when the inspired gas was switched to air, whereas in study D, the subjects breathed air during the pre-exercise and exercise periods but were switched to oxygen breathing for the first 4 min of the post-exercise period.

The 7 normal and all 12 asthmatic subjects, and the 5 additional asthmatic subjects who had had their carotid bodies removed, performed protocol I. Only 7 of the 12 asthmatic subjects were studied using protocol II. The reduction in number of subjects studied in protocol II was due to the unavailability of some subjects to perform both protocols.

Specific airway conductance was measured before exercise and at 3, 5, 8, 10, 15, 25, and 35 min after exercise in protocol I, and at 5, 9, 13, 17, 21, 25, and 29 min after exercise in protocol II. Subjects were seated on a chair just outside the body of the plethysmograph during the time intervals between measurements. Paired *t* tests were used for statistical analysis unless otherwise stated.

RESULTS

Protocol I. Pre-exercise specific airway conductance was not significantly different before air or O_2 breathing in either the normal or asthma groups (Table I). After air breathing exercise, the asthmatic group developed significant bronchoconstriction with the maximum drop in specific airway conductance occurring at an average of 5 min after cessation of exercise (Fig. 2). However, different subjects had their maximum drop in specific conductance at different times after exercise (Tables II and III). Breathing oxygen during exercise and the first 2 min of recovery resulted in a significant attenuation of the post-exercise decrease in specific airway conductance (Fig. 2) at all seven measurement points during the 35-min period after exercise in the asthmatic group. Four of the asthmatic subjects with exercise-induced bronchospasm were able to attain a higher work rate when breathing oxygen, (subjects 12, 15, 17, 18; Table I). Yet, compared to the air breathing study, all four of these subjects had a smaller decrease in specific airway conductance after exercise.

After exercise, the control group demonstrated a mild increase in specific airway conductance, whether air or oxygen was breathed during exercise, with no significant differences attributable to the type of gas inhaled (Fig. 2).

If all subjects reached the same work rate while on air and O_2, it would be expected that, as a group, maximum minute ventilation and maximum heart rate might be higher and end-tidal carbon dioxide tension lower while breathing air during the final minute of exercise. Because all subjects exercised to their maximum, and four asthmatics were able to attain higher work rates while exercising with O_2 as the inspirate, there was no significant difference between maximum minute ventilation or maximum heart rate during the last minute of exercise for the air and O_2 studies. While end-tidal P_{CO_2} was found to be significantly lower during the last minute of exercise during the air breathing study, there was no

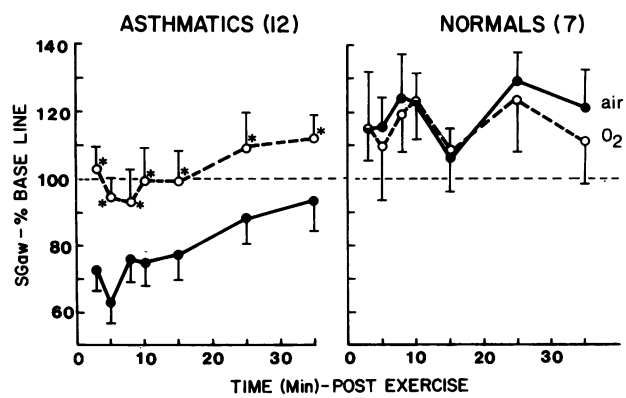

FIGURE 2 Changes in specific airway conductance (SGaw) after a maximal incremental exercise test in 12 asthmatic and 7 normal subjects. The base-line value for each subject (i.e., 100%) is the pre-exercise level. The vertical lines represent one SE. The change in post-exercise specific airway conductance was significantly less (asterisks indicate $P < 0.05$) with the O_2 administration in the asthmatic group at each measured time.

TABLE II
Post-Exercise Specific Conductance, Percent of Control Protocol I (Air)

Subject No.	Time, *min*	Post exercise 3	5	8	10	15	25	35
Normal								
1		96	112	88	115	88	119	100
2		108	123	123	115	100	115	108
3		142	123	185	165	165	165	163
4		121	80	150	140	111	159	157
5		122	148	100	113	83	113	122
6		132	145	123	105	102	118	123
7		80	81	100	104	96	111	80
Mean		114.4	116.0	124.1	122.4	106.4	128.6	121.9
±SEM		8.1	10.4	12.8	8.4	10.4	8.7	11.3
Asthmatics								
8		66	67	81	103	102	98	158
9		38	26	44	41	42	55	62
10		55	50	53	49	65	73	100
11		67	56	121	121	121	121	132
12		89	70	75	89	75	107	82
13		60	61	58	87	87	113	113
14		126	84	74	68	79	68	68
15		83	64	117	88	98	100	62
16		84	84	85	88	56	65	85
17		79	85	73	55	56	127	100
18		79	58	74	79	95	79	95
19		55	55	59	52	41	49	58
Mean		73.4	63.3	76.2	68.3	76.4	87.9	92.9
±SEM		6.4	4.9	6.7	7.1	7.3	7.6	8.8
Asthmatics with bilateral carotid body resection								
20		113	106	106	87	71	52	103
21		93	90	87	87	90	107	97
22		97	95	79	89	87	105	129
23		80	80	74	90	98	84	107
24		84	72	72	67	51	54	54
Mean		93.4	88.6	83.6	84.0	79.4	80.4	98.0
±SEM		58	5.9	6.2	4.3	8.3	11.9	12.3

significant correlation between the magnitude of decrease in specific airway conduction and the magnitude of the reduction in end-tidal P_{CO_2} during air and O_2 breathing.

The asthmatics with resected carotid bodies showed a different response from those with intact carotid bodies. The former had a decrease in airway conductance which was unaffected by oxygen, and which also was smaller and delayed (Fig. 3 and Tables II and III).

Protocol II. Oxygen breathing attenuated exercise-induced bronchospasm in the group of seven asthmatics who performed the constant high intensity work for 4 min (Fig. 4 and Table IV). When O_2 was breathed throughout the exercise and for 4 min of recovery (study B), specific airway conductance was significantly greater than the comparable air breathing study (study A) for six of the seven measurement times. Also, in the study in which O_2 was breathed during exercise, but for only 2 min of recovery (study C), the specific airway conductance was significantly greater than in study A at five of the seven times. In study D, the air breathing exercise was followed by O_2 breathing for the first 4 min of recovery. This produced an intermediate response of post-exercise specific airway conductance, not significantly different from studies A, B, or C.

When oxygen, rather than air, was breathed during the constant work rate test, minute ventilation was significantly lower and end-tidal P_{CO_2} significantly

TABLE III

Post-Exercise Specific Conductance, Percent of Control Protocol I (Oxygen)

Subject No.	Time, *min*	Post exercise 3	5	8	10	15	25	35
Normal								
1		158	142	150	142	115	112	81
2		137	144	94	113	100	125	87
3		164	130	196	196	138	187	164
4		90	90	132	142	126	163	118
5		81	93	100	81	104	93	100
6		82	82	82	81	85	96	81
7		100	108	121	146	90	85	150
Mean		116.0	139.3	125.0	128.7	108.3	123.0	111.6
±SEM		13.6	12.7	14.8	15.4	7.2	14.6	12.8
Asthmatics								
8		99	106	99	101	110	134	108
9		55	63	55	69	76	80	104
10		89	67	56	52	59	56	58
11		116	116	116	129	123	148	142
12		100	117	167	150	142	108	154
13		65	85	75	73	77	138	119
14		115	92	62	73	112	150	85
15		144	100	108	140	140	104	122
16		102	70	70	70	98	70	83
17		113	113	107	107	100	127	120
18		123	123	131	139	131	108	119
19		108	78	77	92	65	92	121
Mean		102.4	94.2	93.6	99.6	102.8	109.6	111.3
±SEM		7.0	5.9	13.6	9.1	8.3	8.9	7.8
Asthmatics with bilateral carotid body resection								
20		100	122	94	73	75	53	95
21		97	85	85	85	91	100	100
22		107	86	79	82	88	111	114
23		79	68	71	89	82	100	104
24		92	79	86	79	59	47	45
Mean		95.0	88.0	83.0	81.6	79.0	82.2	91.8
±SEM		4.7	9.1	3.8	2.7	5.7	13.3	12.1

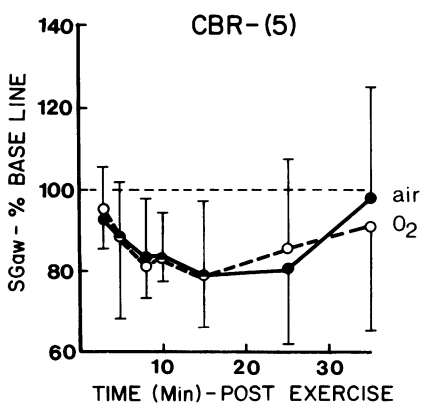

FIGURE 3 Changes in specific airway conductance (SGaw) after maximal incremental exercise in five asthmatics with bilateral carotid body resection. Definition of axes and vertical lines are the same as Fig. 2. Post-exercise changes in specific airway conductance are similar whether air or O_2 was breathed.

higher during the last minute of exercise ($P < 0.05$) (Table V). However, there were no significant correlations between post-exercise changes in specific airway conductance and maximum exercise ventilation, maximum heart rate, or end-tidal P_{CO_2} at the end of exercise or at 1 min after exercise.

Additionally, four asthmatic subjects, numbers 9, 10, 13, and 16, had specific airway conductance measured on a separate day before and after sitting quietly on a cycle ergometer for a duration equivalent to that of an exercise study. The specific conductance remained unaltered.

TABLE IV
Post-Exercise Specific Conductance Protocol II

Subject No.	Time, *min*	Post exercise 5	9	13	17	21	25	29
Study A								
8		69	48	48	57	58	62	63
9		91	72	65	95	96	109	111
10		60	55	38	26	40	71	69
12		85	76	63	130	93	98	118
13		67	61	54	91	106	106	98
15		88	82	80	48	39	68	62
16		86	65	107	120	73	65	98
Mean		78.0	65.6	65.0	81.0	72.1	82.5	88.4
±SEM		4.5	4.5	8.6	14.6	10.3	7.8	8.8
Study B								
8		105	80	95	86	112	112	112
9		103	94	80	94	94	113	127
10		65	83	84	81	111	69	75
12		95	102	80	88	102	113	95
13		121	82	75	82	124	114	163
15		91	89	76	104	98	104	91
16		133	151	131	122	212	229	142
Mean		101.7	97.3	88.7	93.9	121.9	122.0	115.0
±SEM		8.3	9.4	7.5	5.6	15.5	18.8	11.7
Study C								
8		121	92	87	102	137	116	111
9		90	83	97	90	100	103	100
10		50	47	50	49	53	56	64
12		281	211	172	219	159	219	398
13		75	66	75	88	84	91	94
15		77	75	86	84	73	82	86
16		—	141	109	177	171	271	224
Mean		115.7	102.1	96.6	115.6	111.0	134.0	153.9
+SEM		34.4	21.2	14.4	22.6	17.1	30.0	45.1
Study D								
8		57	64	48	92	92	109	163
9		57	43	47	57	61	72	68
10		71	99	101	56	57	59	67
12		155	189	233	175	185	209	240
13		56	41	41	38	62	81	88
15		87	87	87	85	104	91	126
16		82	76	69	63	77	80	109
Mean		80.0	85.6	89.4	80.9	105.4	100.1	123.0
±SEM		13.3	19.0	25.4	17.1	22.3	19.1	23.3

DISCUSSION

Bronchial asthma is a disease that shows a wide clinical spectrum, with multiple causative factors and a great deal of variability in responsiveness. Conflict in the literature over mechanisms of exercise-induced bronchospasm in asthmatics may reflect the variety of mechanisms that interact in this syndrome.

We found that O_2 attenuates the post-exercise bronchospasm that occurs in asthmatics with intact carotid bodies. This attenuation did not correlate significantly with the differences in end-tidal P_{CO_2}, maximum exercise ventilation or maximum heart rate in the air and O_2-breathing exercise studies. Four subjects actually attained higher work rates, minute ventilation and heart rate while breathing O_2 in protocol I than during exercise while breathing air. Yet, they still developed less bronchospasm after

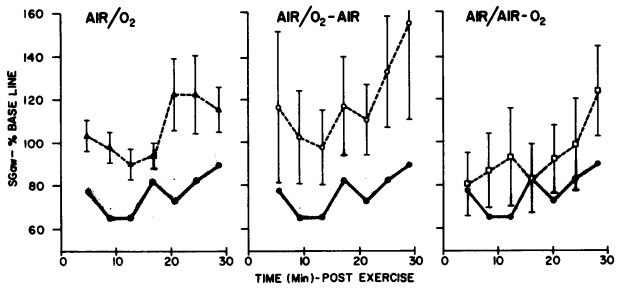

FIGURE 4 Change in specific airway conductance (SGaw) after four constant load exercise tests in seven asthmatic subjects. The protocol for the four studies is diagrammed in Fig. 1. (Left-studies A and B; center-studies A and C; right-studies A and D.) Values and vertical lines are defined in the legend of Fig. 2. The shaded area includes one SE of study A values.

O_2-breathing exercise. Thus, in agreement with the findings of McFadden et al. (9) exercise-induced bronchospasm was not significantly correlated with end-tidal P_{CO_2} or magnitude of ventilation.

It is well known that vagally mediated reflexes may play a role in bronchoconstriction (4, 10), as atropine can block exercise-induced bronchospasm (11, 12). In addition, Nadel and Widdicombe (4, 13) showed that carotid body stimulation induced airway constriction in dogs that could be abolished by sectioning the vagus or glossopharyngeal nerves. Hornbein and Roos (14), measuring integrated carotid sinus nerve activity in cats, showed that H^+ is the pre-eminent chemical stimulator of the carotid body whose effect could be modified by O_2 tension. Hall et al. (15) also showed that increasing arterial oxygen tension in cats decreased carotid chemoreceptor discharge. Wasserman et al. (5) showed that human subjects whose carotid bodies had been surgically removed failed to show respiratory compensation for the metabolic acidosis of exercise. Because carotid body stimulation may cause changes in the mechanical properties of the lung (13), and because bronchospasm peaks after completion of strenuous exercise when H^+ levels are greatest, the factors are present that might account for bronchospasm induced by carotid body stimulation. Although hypoxia, itself, can induce bronchospasm (4, 13), it is unlikely to be the trigger, as patients with exercise-induced bronchospasm frequently are not hypoxic (2, 3). Owing to the inhibitory action of oxygen on carotid body output, it follows that oxygen attenuated bronchospasm in the asthmatic subjects might be accounted for by decreasing carotid body discharge. The studies done on the asthmatics who had their carotid bodies removed (Fig. 3) support this concept.

Strauss et al. (16) were unable to block exercise-induced bronchospasm in six asthmatic subjects with bicarbonate infusion or to produce bronchospasm in five resting asthmatics with intravenous infusion of sodium lactate. Both of these experiments would have alkalinized the patient and presumably would have reduced afferent neural drive to expired ventilation from the carotid bodies. However, high inspired O_2 has been shown in man to abolish the ventilatory effects of high CO_2-H^+ attributable to the carotid bodies. A similar effect has not been demonstrated with alkalinization of the blood. Hence, the high O_2 experiments may inhibit carotid body mediated effects of exercise more completely than the $NaHCO_3$ infusions and, therefore, account for the differences between the results of our study and those of Strauss et al. (16). In addition, as these investigators did not infuse lactate during exercise, we cannot be certain that the combination of exercise (during which the contribution of the carotid bodies to ventilation is significantly greater than at rest

TABLE V
Effect of O_2 Breathing on Ventilation and P_{CO_2} during Constant Load High Intensity Exercise

Subject No.	Ventilation, last minute of exercise			End-tidal P_{CO_2}, last minute of exercise		
	Room air*	100%*	Δ	Room air*	100%*	Δ
	liters/min§			*mm Hg*		
8	61.0	57.5	3.5	46.0	52.5	6.5
9	54.5	55.0	−0.5	32.0	31.0	−1.0
10	63.5	58.0	5.5	36.0	41.0	5.0
12	88.0	84.0	4.0	34.0	37.5	3.5
13	115.5	99.5	16.0	32.5	35.0	2.5
15	68.0	64.0	4.0	40.0	43.5	3.5
16	84.0	79.0	5.0	30.5	30.5	0.0
Mean±SEM	76.4±8.0	71.0±6.4	5.4±1.9‡	35.9±2.1	38.7±2.9	2.9±1.0‡

* Average of two studies.
‡ Significantly different from zero ($P < 0.05$).
§ Ambient temperature and pressure, saturated.

[17, 18]) and the high lactate would not induce bronchospasm in those patients. However, in our study, high O_2 did reduce exercise-induced bronchospasm markedly and we believe it likely that this was, in large part, consequent to the attenuation of carotid body responsiveness. Strauss et al. (19) also found that the water vapor content in the inspired air of their asthmatics, during exercise, affected the magnitude of exercise-induced asthma. They were able to block exercise-induced asthma by saturating the inspired air with water at body temperature. In our study, both the air and O_2 were saturated with water vapor by the same technique to obviate variations in water vapor pressure from confounding the results.

As oxygen attenuated the bronchospasm in all 12 asthmatics (and prevented it in some), but had no effect on those asthmatics who had undergone bilateral carotid body resection, we conclude that exercise-induced bronchospasm in the asthmatic is multifactorial in origin, and that carotid body stimulation, possibly by H^+, plays a role in mediating at least part of this phenomenon in susceptible individuals.

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