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Research Article

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A Critical Assessment of the Mechanism by which Hyperoxia Attenuates Exercise-Induced Asthma

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ABSTRACT Recent data demonstrate that the magnitude of the heat loss that occurs from the respiratory tract during exercise correlates with the degree of postexertional obstruction that develops in asthmatics. Respiratory heat loss relates directly to the minute ventilation and heat capacity of the inspired gas and inversely to its water content and temperature. Because it has been shown that inhaling 100% oxygen during exercise blunts the obstructive response, we wondered if this effect could be accounted for by differing values of heat exchange with air and oxygen breathing. To examine this question, we studied 10 asthmatics by measuring multiple aspects of pulmonary mechanics before and after four bouts of exhausting leg work during which the subjects inhaled either air or oxygen conditioned to provide widely differing thermal burdens on their airways. Under all inspired gas conditions, oxygen breathing produced significantly less obstruction than air. Minute ventilation was also significantly less with oxygen as was the total heat lost. As the latter fell, so did the magnitude of the postexercise obstruction. When the differences in ventilation and respiratory heat loss between air and oxygen were eliminated by eucapnic hyperventilation, the differences in the obstructive responses also disappeared. Thus, the effects of hyperoxia on exercise-induced asthma can be accounted for solely by alterations in heat exchange.

INTRODUCTION

A number of investigations into the nature of exercise-induced asthma have shown that it is possible to amplify (1) or attenuate (2–5) the severity of the postexertional bronchospasm that occurs by varying the temperature and (or) water content of the inspired air. Analysis of these observations in the context of the physics of heat exchange has demonstrated a quantitative relationship between the total amount of heat lost from the tracheobronchial tree during exertion, and the magnitude of the airway obstruction that develops (3, 6). The less heat lost, the less the response, and conversely the greater the loss, the greater the response. In the course of these studies, it was found that respiratory heat loss related directly to minute ventilation and the heat capacity of the inspired gas and inversely to its water content and temperature.

Recently Schiffman et al. (7) have found that the response to exercise can be reduced if asthmatics inspire 100% oxygen during the challenge. These authors speculated that the explanation for this phenomenon lay in the inhibitory action of oxygen on carotid body output, and concluded that a reflex initiated in the carotid bodies plays a role in exercise-induced asthma. However, because the thermodynamic properties of oxygen are slightly different than air, and because oxygen administration can alter the ventilatory requirements for a given exercise task, we wondered if the above effect could be accounted for by differing magnitudes of respiratory heat loss with oxygen and air breathing. We tested this hypothesis under precisely controlled experimental conditions of inspired temperature and humidity that were designed to place the subjects' airways under widely different thermal stresses. Our observations form the basis of this report.

METHODS

10 atopic individuals, 3 men and 7 women, (mean age = 24.3 ±2.1 yr SD) with reproducible exercise-induced asthma served as our subjects. All met the American Thoracic Society's definition of asthma (8) and none were smokers. None had used glucocorticoids or cromolyn sodium for at least 1 mo before these studies, and all refrained from taking any medication for at least 12 h before any study day. Informed consent was obtained from each participant.

Airway resistance and total lung capacity with its subdivisions were measured with a variable pressure plethysmo-

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graph that was serially interfaced to an analogue recorder (Electronics for Medicine, Inc., Pleasantville, N. Y.), and a minicomputer (Lab 8E, Digital Equipment Corp., Marlboro, Mass.) (9, 10). Resistance was converted to its reciprocal, conductance, and expressed as a conductance-volume ratio termed specific conductance (SGaw)[1] (11), four to five measurements of each variable were obtained and the mean computed. These data were considered acceptable if their coefficients of variation were 5% or less. Maximum forced exhalations were then performed in triplicate using a waterless spirometer (Electro Med, Searle Cardio-Pulmonary, Houston, Tex.). 1-s forced expiratory volumes (FEV_1) were computed by standard techniques. The subject's best effort, as defined by the curve with the largest forced vital capacity and FEV_1, was used for analysis.

Inspired gas temperature and water content were controlled by having the subjects breathe through a heat exchanger in series with a bubble humidifier as previously described (1–3, 6). This instrument was capable of producing temperatures between −20 and +120°C with water contents varying from 0 to full saturation at each temperature. Inspired gas temperature was continuously recorded in all experiments by a thermocouple situated in the airstream within the exchanger, 10 cm upstream from the mouth. Expired temperature was also continuously recorded with a second thermocouple that protruded 2.5 cm into the oral cavity through the mouthpiece. This thermocouple was shielded so as not to touch any mucosal surface. Expired gas was directed via a one-way valve into a Tissot spirometer so that tidal volume and minute ventilation ($\dot{V}_E$) could be recorded during the experiments in which the subjects performed exercise. A somewhat different configuration was employed for the eucapnic hyperventilation studies (discussed further in the text).

In all experiments the inspired gases consisted of either compressed air or O_2 from cylinders. The water content of the gas exiting from the mouthpiece of the heat exchanger was physically measured by passing known volumes of gas through glass tubes containing anhydrous calcium sulfate and measuring the change in weight of the tube as previously described (2, 3, 6). Air or O_2 passed from cylinders directly through the exchanger without humidification contained <0.15 mg H_2O/liter and for the purposes of this study this value was considered to be zero.

In this first series of experiments we explored the effects of breathing air or O_2 at several temperatures and water contents. This was accomplished by having the subjects perform two bouts of exhausting leg work on a cycle ergometer while inhaling subfreezing dry air or O_2 in a random fashion. Each gas was inspired for 4 min before, during, and after exercise. Pulmonary mechanics were measured before and 5 min after cessation of work. Previous experience has demonstrated that this time interval coincides with the maximal response and this form of work provides reproducible results (1–3, 6, 12). After completion of the first study of the day, the subjects rested from 90 to 150 min to allow their pulmonary mechanics to return to preexercise levels. They then performed the same workload for the same duration while breathing the alternate gas at the same temperature and water content. The subjects were unaware of the gas that they were breathing during each part of the study. $\dot{V}_E$ and heart rates were measured continuously before and during exercise. The data from the last minute of the rest and exercise periods were analyzed.

[1] *Abbreviations used in this paper*: FEV_1, 1-s forced expiratory volumes; $PetCO_2$, end-tidal dioxide tensions; RHL, respiratory heat loss; RV, residual volume; SGaw, specific conductance; Te, expired gas temperature; Ti, inspired gas temperature; Ve, minute ventilation.

On another day the identical protocol was followed while the subjects inhaled air or O_2 conditioned to produce a lower thermal load on their airways. To precisely match the air and O_2 studies, and yet simulate usual ambient laboratory conditions of temperature and humidity (i.e., 26°C and 40%, respectively) the temperature of the water bath of the bubble humidifier was set at 9°C and maintained there to generate a water content of 8–9 mm H_2O/liter gas. The gas leaving the humidifier was then warmed to ≅26°C in the exchanger. Repeated measurements of the water content of the gas exiting the mouthpiece of the exchanger over a range of flows of 15–150 liters/min yielded a mean value of 8.7±0.3 mg H_2O/liter which was used in the calculation of respiratory heat loss. As before, the experimental sequence was randomized between air and O_2. The work loads were identical to those used on the 1st d and were kept constant for each study for each subject. The mean workload was 900±59 kilopond meters/min and the mean duration of exercise was 3.9±0.3 min.

Respiratory heat loss (RHL) was computed from the following formula:

$$RHL = \dot{V}_E[HC(Ti - Te) + HV(WCi - WCe)],$$

where $\dot{V}_E$ = minute ventilation in 4 min; HC, heat capacity of the gas (calories per liter); Ti = inspired gas temperature (degree Celsius); Te = expired gas temperature (degree Celsius); HV = latent heat of vaporization of water = 0.58 kcal/g; WCi = water content of inspired gas (milligrams H_2O per liter); WCe = water content of expired gas (milligrams H_2O per liter).

Because WCe is difficult to measure physically, we made the assumption that the expirate was fully saturated at Te. Numeric values for WCe were then obtained from standard saturation-temperature relationships (13). The heat capacity of air and O_2 was calculated from Bureau of Standards tables of the thermodynamic and transport properties of each gas (14). The values used were 0.311 and 0.313 cal/liter for air and O_2, respectively.

To evaluate if O_2 produced effects in addition to those on respiratory heat exchange, on a 3rd d we had five subjects perform eucapnic hyperventilation while they inhaled partially humidified air or O_2 through the heat exchanger in a random manner. In these experiments, $\dot{V}_E$ for O_2 and air breathing were precisely matched to each other at a level equivalent to that observed with exercise. The temperature and water contents of the inspired gases in this set of studies were identical to those of the ambient study described previously.

Eucapnic hyperventilation was accomplished by replacing the Tissot spirometer at the expiratory port of the exchanger with a 7-liter reservoir balloon that was being constantly evacuated at a controllable rate through a calibrated rotameter by a vacuum pump. The subjects were instructed to respire in such a way as to keep the reservoir filled. In this manner their expired $\dot{V}_E$ precisely matched the rate of emptying of the balloon, and $\dot{V}_E$ could be set at any desired level (6). End-tidal carbon dioxide tensions ($PetCO_2$) were continuously recorded at the mouth by a Beckman LB-2 analyzer (Beckman Instruments, Inc., Fullerton, Calif.) and displayed on the oscilloscope of the analogue recorder. At the inspiratory port of the exchanger, a mixing valve permitted us to supply sufficient CO_2 to keep $PetCO_2$ constant at resting eucapnic levels and thus avoid the bronchoconstrictive effects of hypocapnia (15). The period of time the subjects spent hyperventilating corresponded to the time spent performing exhausting leg work in the previous studies. As before, upon completion of each experiment, the subjects rested for at least 1.5 h while pulmonary mechanics returned to prehyperventilation levels before subsequent challenges were undertaken.

The data from the above experiments were analyzed by paired t tests and one and two factor analyses of variance.

RESULTS

The individual data on the effects of exercise on pulmonary mechanics while breathing air and O_2 at different temperatures and water contents are shown in Tables I through IV. In the cold studies the mean values for Ti and WCi were −11°C and 0, respectively, whereas in the ambient experiments Ti and WCi were 27°C and 8.7 mg H_2O/liter gas. There were no significant differences between air and O_2 for these variables. Equally, comparison of the absolute values for the base-line data for the three measures of mechanics for each of the four studies did not reveal any significant differences ($F < 1.0$ for every variable). Significant airway obstruction developed in each experiment as measured by base-line-response comparisons.

Comparison of the effects of breathing air and O_2 on the bronchospastic response to exercise under the different thermal loads employed is shown in Figs. 1 through 3. When cold air was inhaled during exercise, FEV_1 and SGaw decreased 39 and 60% from their base-line values, respectively, whereas residual volume (RV) increased 77% (Fig. 1). When O_2 at the same temperature and water content was inhaled, the magnitude of the response was reduced a small, but significant, amount. FEV_1 and SGaw now fell 32 and 50% from control, and RV only rose 68%. Reducing the thermal burden by heating and partially humidifying the inspirate produced the expected attenuation in response. Warm air produced only a 25% reduction in FEV_1 and a 48% fall in SGaw whereas RV increased 56%. These changes were significantly less than the cold air response by factorial analysis. Warm O_2 further attenuated the postexercise changes, again by a small, but statistically significant, amount. Under these experimental conditions, FEV_1 changed 16%, SGaw 37%, and RV 39%. This result was significantly less than that observed with cold O_2.

Fig. 2 displays the $\dot{V}_E$ and RHL data for each study. During exercise with cold air, $\dot{V}_E$ averaged 73 liters/min. With cold O_2, coincident with the reduction in the postexertional pulmonary mechanical response, $\dot{V}_E$ fell significantly to 67 liters/min. Increasing the temperature and water content of the inspirate had no effect upon the air-O_2 relationship. During cold air breathing, RHL averaged 1.92 kcal/min and fell significantly to 1.77 when cold O_2 was the inspired gas. Heating and partially humidifying the inspirate significantly reduced RHL, but the difference between air and O_2 remained.

Relating heat loss to the mechanical response gives the same general result observed in previous studies (3, 6); viz., large values for RHL are associated with large changes in lung function and small values with small changes (Fig. 3). More importantly, however, these data imply that O_2 exerts its effect on the postexercise bronchospastic response primarily by decreasing the quantity of heat lost. Obviously, if this were true, then elimination of the differences in heat exchange between air and O_2 should eliminate the differences in response. The data in Table V and Fig. 4 demonstrates that this is indeed what happens.

Table V gives the individual data for the studies in

TABLE I
Bronchospastic Response after the Inhalation of Dry Subfreezing Air

Subject	Ti	Te	$\dot{V}_E$	RHL	FEV_1		SGaw		RV	
					B	R	B	R	B	R
	°C	°C	liters/min	kcal/min	liters		liters/s/cm H_2O/liter		liters	
1	−12.0	25.0	90.6	2.26	3.45	1.73	0.20	0.05	1.57	2.53
2	−12.0	26.0	68.1	1.76	2.89	1.63	0.14	0.04	1.49	2.75
3	−11.0	27.0	70.3	1.88	2.61	1.80	0.15	0.03	2.20	2.86
4	−8.0	28.0	80.2	2.16	2.34	1.83	0.15	0.07	1.20	2.16
5	−13.0	27.0	57.2	1.57	1.75	0.79	0.11	0.04	1.36	3.71
6	−12.5	28.5	77.9	2.26	3.38	2.39	0.15	0.06	2.02	3.22
7	−12.5	26.0	60.4	1.60	2.53	2.06	0.20	0.14	0.84	1.29
8	−10.0	26.0	49.8	1.26	1.32	0.53	0.06	0.03	2.01	3.63
9	−6.0	27.0	101.8	2.58	3.41	2.54	0.16	0.07	1.20	2.07
10	−11.5	25.0	73.7	1.83	1.80	0.85	0.07	0.03	3.38	5.90
Mean	−10.9	26.6	73.0	1.92	2.55	1.62	0.14	0.06	1.73	3.01
SD	2.3	1.2	15.6	0.40	0.75	0.68	0.05	0.03	0.72	1.25
P	—	—	—	—	<0.001		<0.001		<0.001	

B, base line; R, the postexercise response.
The P values were derived from base-line-response comparisons.

TABLE II

Bronchospastic Response after the Inhalation of Dry Subfreezing Oxygen

Subject	Ti	Te	$\dot{V}_E$	RHL	FEV_1		SGaw		RV	
					B	R	B	R	B	R
	°C	°C	*liters/min*	*kcal/min*	*liters*		*liters/s/cm H_2O/liter*		*liters*	
1	−13.0	25.0	89.3	2.26	3.17	2.08	0.18	0.05	1.54	2.40
2	−12.0	27.0	56.5	1.54	2.73	1.73	0.12	0.04	1.66	2.80
3	−12.0	26.0	67.0	1.74	2.76	2.13	0.13	0.08	2.26	2.69
4	−8.0	28.0	68.5	1.86	2.45	1.98	0.15	0.11	1.23	1.96
5	−12.0	27.0	56.2	1.53	2.01	0.98	0.13	0.05	1.29	2.94
6	−10.0	28.0	79.4	2.20	3.45	2.61	0.16	0.08	2.18	3.25
7	−12.5	26.0	60.4	1.60	2.54	2.28	0.22	0.15	0.84	1.31
8	−10.0	26.5	38.8	1.00	1.52	0.76	0.09	0.05	2.04	3.48
9	−5.0	27.0	93.3	2.33	3.44	2.83	0.16	0.08	1.15	1.80
10	−12.5	26.5	60.3	1.62	1.72	0.74	0.09	0.04	2.33	5.00
Mean	−10.7	26.7	67.0	1.77	2.58	1.81	0.14	0.07	1.65	2.76
SD	2.5	0.9	16.5	0.41	0.68	0.75	0.04	0.04	0.53	1.03
P	—	—	—	—	<0.001		<0.001		<0.001	

B, base line, R, the postexercise response.
The *P* values were derived from base-line-response comparisons.

which the subjects hyperventilated to identical levels while breathing air or O_2. In these experiments the only independent variable was the slight difference in the heat capacities of the two gases which should produce negligible effects upon RHL. There were no significant between-gas differences for Ti, Te, $\dot{V}_E$, RHL, $PetCO_2$, WCi (the latter was kept at 8.7 mg/liter for both gases), or any of the base-line values for the measures of pulmonary mechanics. Base-line-response comparisons of the tabular data reveal that this challenge resulted in significant airway obstruction, and the values for $PetCO_2$ during the last minute of hyperventilation demonstrate that hypocapnia was not the cause.

Fig. 4 contrasts the consequences of exercise and eucapnic hyperventilation in this group of subjects. It can be readily appreciated that hyperpnea produced changes in pulmonary mechanics that equaled or exceeded those seen with physical exertion and that the

TABLE III

Bronchospastic Response after the Inhalation of Warm Air Containing 8.7 mg H_2O/liter

Subject	Ti	Te	$\dot{V}_E$	RHL	FEV_1		SGaw		RV	
					B	R	B	R	B	R
	°C	°C	*liters/min*	*kcal/min*	*liters*		*liters/s/cm H_2O/liter*		*liters*	
1	27.0	34.0	90.5	1.72	3.63	2.40	0.23	0.08	1.29	1.87
2	27.5	34.0	68.9	1.30	2.84	1.75	0.12	0.04	1.46	2.68
3	27.5	34.0	74.5	1.40	3.14	2.56	0.17	0.10	1.45	2.12
4	26.5	33.5	80.0	1.51	2.21	1.93	0.17	0.11	1.07	2.10
5	26.5	34.5	65.8	1.30	2.41	1.95	0.21	0.12	1.08	1.50
6	26.5	32.5	81.2	1.38	3.15	2.36	0.16	0.07	2.06	3.09
7	25.0	32.5	66.9	1.16	2.51	2.36	0.21	0.15	0.89	1.35
8	26.5	33.0	53.9	0.95	1.24	0.88	0.09	0.05	1.94	2.82
9	26.5	32.0	104.0	1.68	3.39	3.01	0.13	0.05	1.03	1.61
10	27.5	34.0	70.6	1.33	2.12	1.02	0.10	0.05	1.96	2.82
Mean	26.7	33.4	75.8	1.37	2.66	2.02	0.16	0.08	1.42	2.20
SD	0.8	0.8	14.2	0.23	0.71	0.67	0.05	0.04	0.43	0.62
P	—	—	—	—	<0.001		<0.001		<0.001	

B, base line; R, the postexercise response.
The *P* values were derived from base-line-response comparisons.

TABLE IV

Bronchospastic Response after the Inhalation of Warm Oxygen Containing 8.7 mg H_2O/liter

Subject	Ti	Te	$\dot{V}_E$	RHL	FEV_1		SGaw		RV	
					B	R	B	R	B	R
	°C	°C	*liters/min*	*kcal/min*	*liters*		*liters/s/cm H_2O/liter*		*liters*	
1	27.5	34.0	70.6	1.33	3.61	3.17	0.21	0.13	1.53	1.80
2	27.5	35.0	63.7	1.29	2.67	1.93	0.13	0.05	1.61	2.39
3	27.5	34.0	64.8	1.22	3.05	2.54	0.15	0.09	1.59	2.32
4	27.0	33.5	71.2	1.30	2.22	2.04	0.15	0.11	1.16	1.82
5	27.0	34.0	58.8	1.12	2.57	2.25	0.21	0.13	1.16	1.60
6	27.0	32.5	71.7	1.20	3.69	3.00	0.18	0.11	1.54	2.24
7	25.0	32.0	60.1	1.10	2.54	2.46	0.21	0.16	0.89	1.20
8	27.5	33.0	48.1	0.85	0.97	0.79	0.06	0.04	2.22	2.98
9	26.5	32.0	95.2	1.54	3.36	3.11	0.15	0.09	1.07	1.49
10	27.5	33.5	64.5	1.17	2.19	1.53	0.10	0.07	2.03	2.50
Mean	27.0	33.4	66.9	1.21	2.69	2.28	0.16	0.10	1.48	2.03
SD	0.8	1.0	12.2	0.18	0.81	0.75	0.05	0.04	0.42	0.54
P	—	—	—	—	<0.001		<0.001		<0.001	

B, baseline; R, the post-exercise response.

The *P* values were derived from base-line-response comparisons.

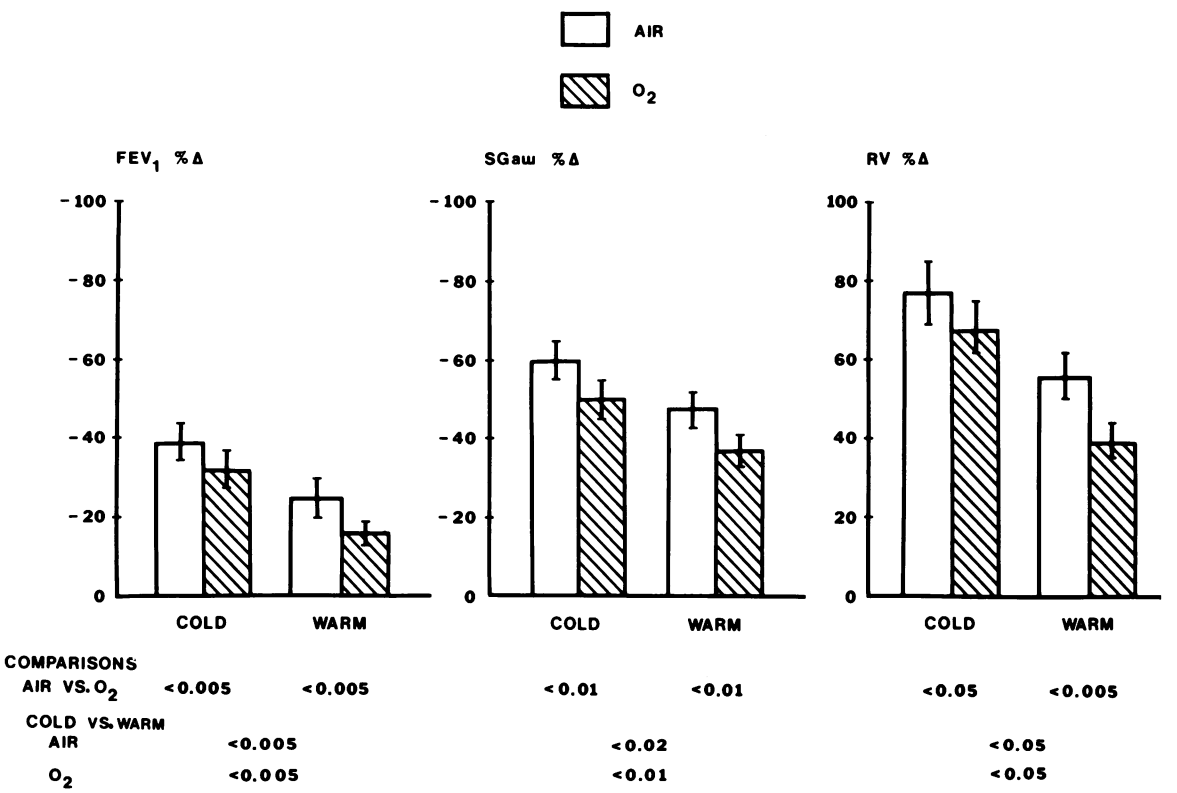

FIGURE 1 Comparison of the effects of air and oxygen breathing on the bronchospastic response to exercise under differing thermal loads. The heights of the bars represent mean values and the brackets 1 SE. The notations cold and warm refer to the subfreezing and room temperature experiments, respectively. The open and hatched bars represent air and oxygen studies, respectively. FEV_1 %Δ = the percentage change in FEV_1 is computed from base-line-response comparisons.

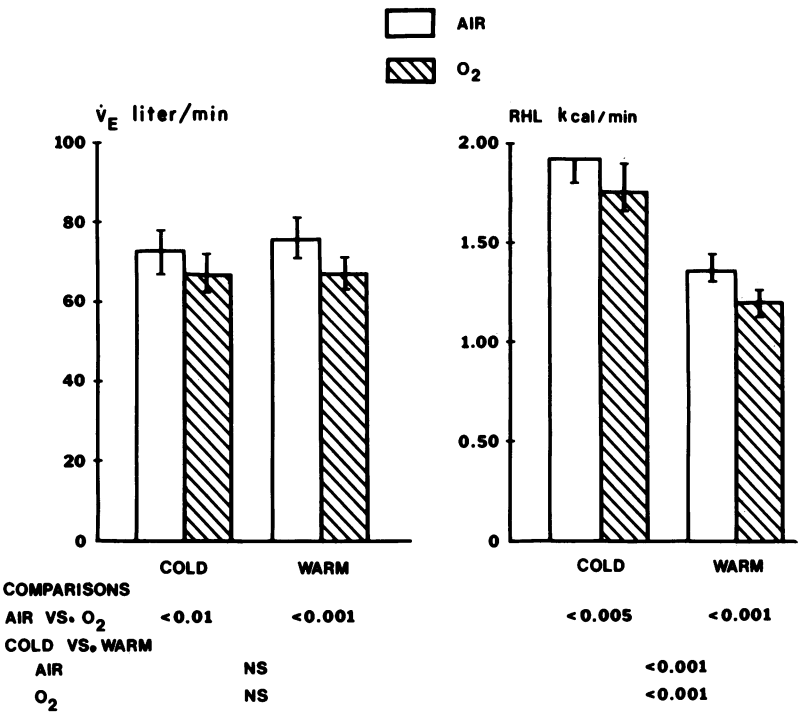

FIGURE 2 Comparison of the effects of air and oxygen on $\dot{V}_E$ and RHL. The format is identical to Fig. 1.

effects of O_2 disappeared when the differences in $\dot{V}_E$ and RHL between air and O_2 were eliminated.

DISCUSSION

The results of this study demonstrate that when oxygen, instead of air, is inhaled during exercise, the magnitude of the airway obstruction that develops in asthmatic subjects is reduced a small, but significant, amount. The mechanism for this effect is related to the fact that during oxygen breathing, the ventilatory requirements for a fixed exercise task are diminished (Fig. 2). As $\dot{V}_E$ falls, so does the quantity of heat lost (Fig. 2), and as this is lowered, so is the subsequent bronchospastic response (Fig. 3). The data in Fig. 4 and Table V strongly argue that this sequence is cause and effect, for when the differences in $\dot{V}_E$ and RHL between air and oxygen breathing were eliminated by having the subjects hyperventilate to identical levels on both gases, the differences in the mechanical responses between the two gases also disappeared.

To establish the validity of the latter point, it is necessary to consider the relationship between voluntary hyperventilation and the hyperpnea of exercise. In the past, attempts have been made to compare or contrast these two stimuli and the results have been inconsistent from study to study, thus generating considerable controversy (16–20). Recently, we have systematically reexamined the bronchoconstrictor effects of these two forms of increased ventilation in the context of the principles governing respiratory heat loss (6). As in the present study, we have been able to dem-

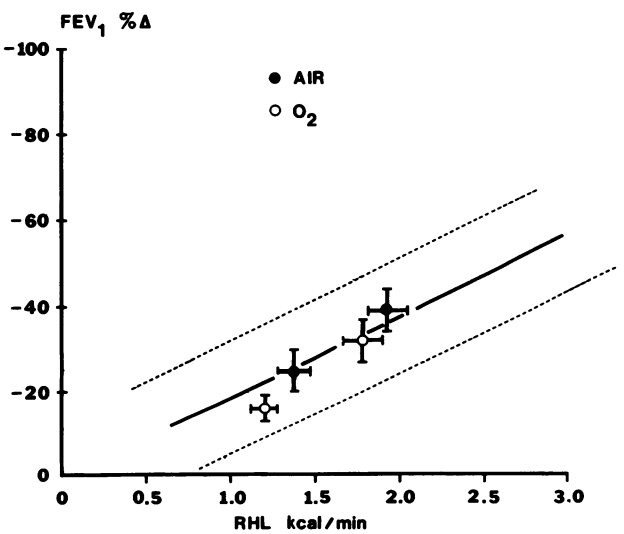

FIGURE 3 Comparison of the quantities of heat lost from the respiratory tract during exercise with air and oxygen breathing and the degree of obstruction that developed. The data points are mean values and the brackets 1 SE. The solid and broken lines represent the mean and 2 SE of the estimate of the relationship between heat loss and the fall in FEV_1 found previously (3).

TABLE V

Comparison of the Effects of Eucapnic Hyperventilation While Breathing Air and Oxygen

Subject	Ti	Te	$\dot{V}_E$	RHL	$PetCO_2$	FEV_1		SGaw		RV	
						B	R	B	R	B	R
	°C	°C	*liters/min*	*kcal/min*		*liters*		*liters/s/cm H_2O/liter*		*liters*	
Air											
2	26.0	30.0	70.3	0.97	37.8	3.21	2.12	0.16	0.04	1.64	2.14
6	26.0	32.0	83.6	1.37	37.3	3.59	2.74	0.21	0.11	1.49	2.25
8	25.5	33.0	43.9	0.79	39.6	1.72	1.42	0.12	0.06	1.22	2.46
9	26.3	31.0	94.6	1.46	34.1	3.08	2.00	0.13	0.04	1.05	2.40
10	26.0	29.0	63.1	0.79	39.6	2.17	1.11	0.11	0.05	1.39	2.22
Mean	26.0	31.0	71.0	1.08	37.7	2.75	1.88	0.15	0.06	1.36	2.29
SD	0.3	1.6	19.5	0.3	2.3	0.78	0.64	0.04	0.01	0.23	0.13
P	—	—	—	—	—	<0.005		<0.005		<0.005	
Oxygen											
2	27.0	30.0	70.0	0.95	38.1	3.07	2.17	0.14	0.03	1.54	2.29
6	25.0	32.5	85.7	1.50	36.1	3.93	3.13	0.19	0.12	1.55	2.00
8	25.5	32.5	43.8	0.76	38.0	1.54	1.23	0.10	0.05	1.57	2.70
9	26.3	31.0	94.9	1.43	36.9	3.31	2.39	0.16	0.05	0.93	2.40
10	25.0	30.0	64.1	0.91	38.0	2.08	1.18	0.11	0.04	2.20	3.12
Mean	25.8	31.2	71.7	1.11	37.4	2.79	2.02	0.14	0.06	1.56	2.50
SD	0.9	1.3	19.8	0.3	0.9	0.96	0.82	0.04	0.04	0.45	0.43
P	—	—	—	—	—	<0.005		<0.005		<0.01	

B, base line; R, the postexercise response.

The *P* values were obtained from base-line-response comparisons.

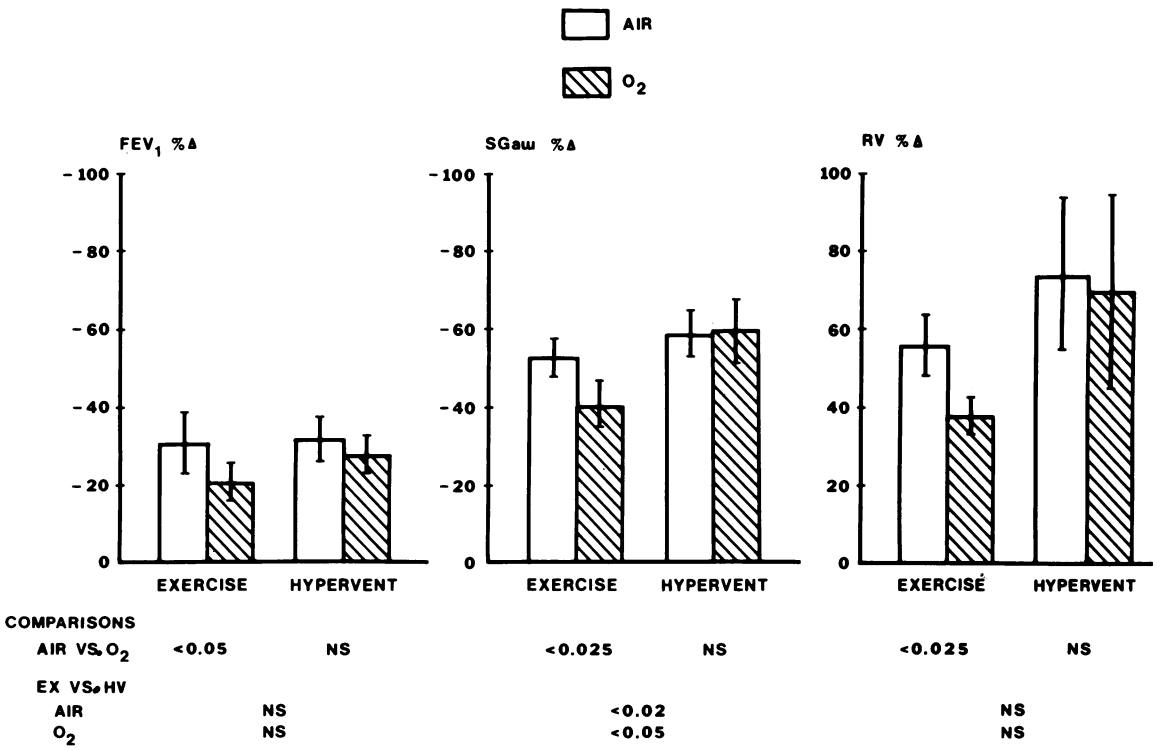

FIGURE 4 Comparison of the effects of exercise and eucapnic hyperventilation (hypervent) while breathing air and oxygen. The format is identical to Fig. 1.

onstrate that there is no difference in the obstructive response that develops after equivalent degrees of increased ventilation, whether induced by exercise or voluntarily when inspired water content and temperature and end-tidal $PetCO_2$ values are matched (6). In effect, exercise serves as an asthmogenic stimulus only through imposing a thermal burden on the airways that is in direct proportion to the level of $\dot{V}_E$ achieved and the water content and temperature differences between inspired and expired gas. Thus, when thermal loads are matched so that equivalent degrees of RHL occur, irrespective of gas mixture breathed or the manner by which ventilation is increased, equivalent degrees of airway obstruction develop.

The observed attenuation of the postexertional bronchospastic response after oxygen breathing is qualitatively similar to the recent findings of Schiffman and colleagues (7); however, the discrepancies between the air-oxygen responses were less in the present study. To account for the large differences between the two gases, and for the fact that oxygen breathing seemed to have no effect in subjects without carotid bodies, these authors postulated that the increase in hydrogen ion concentration that occurs with exercise on air interacted positively with existing levels of arterial oxygen tensions in stimulating the carotid bodies which then reflexly increased airway resistance via vagal efferents. Producing hyperoxia then either abolished this interaction or diminished it so that there was less vagal activity.

It is difficult to assess the validity of the afferent or efferent components of this hypothesis since insufficient data in support of either were provided. However, based upon the following considerations, it is probable that neither one is correct. First, it is well established that not all patients with exercise-induced asthma have a reflex component to their disease (17, 21, 22). Second, even in those patients who do, prevention of the increase in circulating hydrogen ion concentration that occurs with exercise has no effect upon the response (12). Third, in the current study, the differences on the responses to air and oxygen breathing were eliminated by hyperventilation during which $\dot{V}_E$ and RHL for each gas were matched. More importantly, however, hyperventilation, with its low level of physical work and consequently hydrogen ion, evoked the identical degree of airway obstruction as did cycle ergometry with its exhausting work and high hydrogen ion concentrations. Fourth, in the Schiffman study (7) the smaller postexercise changes in the patients with carotid body resections, and their apparent lack of response to oxygen, cannot be taken as *a priori* evidence that the carotid bodies are involved in exercise-induced asthma. The reason for the absolute and relative responses in this population is the low level of $\dot{V}_E$ they achieved with exercise. In these subjects, $\dot{V}_E$ on air averaged only 36 compared with 96 liters/min in the other asthmatics. Based upon our previous experiences with the relationship between $\dot{V}_E$, RHL and the degree of airway obstruction (6), if the inspired gas were at ambient room temperature and near full saturation with water at a $\dot{V}_E$ of 40 liters/min, we would have expected the maximum reduction in SGaw to have been only ≈20%. This degree of obstruction is exactly what was found in the subjects without carotid bodies.

Given the above information, it seems extremely unlikely that the carotid bodies play any major role in the production of postexercise asthma. Nonetheless, the differences in the two studies with respect to the size of the oxygen effect must be explained. Careful examination of the methods employed to condition inspired gases in the study of Schiffman et al. (7) provides some clue. These authors passed dry gases from cylinders into plexiglass chambers where they were said to be partially humidified. From here the inspirate entered a reservoir and then the patient through a mixing valve. Based upon the information provided, it seems that the authors assumed the water in the humidifier to be at room temperature and did not physically measure it. This is unfortunate because as gas began to flow through the humidifying chamber, its large surface area would cause evaporate cooling of the contents to occur unless an external source of heat was supplied to prevent it. The higher the flow rates, the greater the initial evaporative losses will be, and the lower the temperature of the chamber and its contents will become. As water temperature falls, its vapor pressure falls, and consequently inspired water content falls (13). These effects may or may not be large (depending upon such factors as the amount of water in the chamber, its initial and final temperatures and the flow rate of the gas) but they are systematic and can lead to considerable variation in inspired gas conditions on a day-to-day basis as room temperature changes. More relevant to our study is the fact that when this information is coupled with the observation that $\dot{V}_E$ during air breathing was greater than that of oxygen, it becomes possible that the water content of the oxygen not only varied from trial to trial but also may have been systematically higher than that of air. If this were so, then under these circumstances the effects of oxygen could have varied considerably from subject to subject, and the air-oxygen differences postexercise would have been larger than the ones we recorded simply because the greater quantity of water in the oxygen would have reduced RHL by some amount in addition to that produced by the decrease in $\dot{V}_E$.

In summary, the effect of oxygen breathing on the bronchospastic response of asthmatics to exercise can be explained completely by a reduction in the quantity of heat lost from the respiratory tract. If carotid body stimulation interacts at all with the response, the data

from the present study suggest that it does so in a 'fine tune' fashion. Acid end products of metabolism generated during exercise may stimulate these organs to cause an increase in $\dot{V}_E$, and thus may worsen the degree of obstruction by increasing RHL. However, this is an 'add on' effect, not an initiating event.

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