

Exercise-induced bronchospasm, ventilation, and blood gases in asthmatic children

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Twelve atopic asthmatic children were subjected to indwelling brachial arterial catheterization and to bicycle ergometer exercise. Rest, exercise, and postexercise recovery measurements of blood gases and ventilation were performed on successive work load increases until tolerance or significant bronchospasm occurred. Six subjects developed significant bronchospasm, and this was shown to be reproducible at similar work intensities. These subjects revealed no correlative changes in blood gases or ventilation to coincide with onset of bronchospasm. They did show an increased alveolar-arterial oxygen difference at moderate exercise. The other 6 patients did not show significant bronchospasm, revealed similar blood gas-ventilation changes, and had alveolar-arterial oxygen changes similar to those of nonasthmatic subjects.

Exercise-induced bronchospasm (EIB) has been widely reported in patients with asthma.¹⁻³ Although bronchodilators may alleviate this phenomenon, EIB continues to be a management problem. The underlying pathophysiologic mechanisms of EIB have not been elucidated, although many hypotheses have been proposed.⁴⁻¹⁰ Children form a significant proportion of patients affected by EIB, but only a few physiologic studies have been done on this group.^{1-3, 11, 12, 13}

It was the purpose of this study to serially investigate atopic children with asymptomatic asthma during and following various intensities of exercise and

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Abbreviations used: EIB = exercise-induced bronchospasm; PEFR (liters per minute) = peak expiratory flow rate; $\dot{Q}$ = pulmonary vascular perfusion; R = respiratory exchange ratio; VE (liters per minute) = minute ventilation; $\dot{V}_{O_2}$ (milliliters per minute) = oxygen consumption; $\dot{V}_{CO_2}$ (milliliters per minute) = carbon dioxide production; P_{aCO_2} (millimeters of mercury) = arterial carbon dioxide tension; P_{ACO_2} (millimeters of mercury) = alveolar carbon dioxide tension; $P\bar{A}_{O_2}$ (millimeters of mercury) = "Ideal" alveolar oxygen tension; P_{aO_2} (millimeters of mercury) = arterial oxygen tension; pH = negative logarithm of H^+ concentration; HCO_3^- (milliequivalents per liter) = bicarbonate concentration—arterial; (A-a) P_{O_2} (millimeters of mercury) = alveolar-arterial oxygen difference; $\dot{V}_A$ (liters per minute) = alveolar ventilation.

to attempt to clarify the role of alveolar and arterial gas tensions and arterial acid-base changes in the induction of EIB.

METHODS

Subjects for this study were 12 children between 11 and 16 years of age with a diagnosis of atopic asthma from the pediatric allergy clinic of the UCLA Center for the Health Sciences and Harbor General Hospital (Table I). They did not require medication for bronchospasm at the time of testing. No attempt was made to select patients on the basis of a prior history of bronchospasm with exercise.

Before being studied, each patient was examined for wheezing at rest; none had detectable wheezing. Spirometry is difficult to obtain in children, therefore peak expiratory flow rates (PEFR) were obtained for each patient (Wright peak flowmeter No. 12466*),^{14, 15} with the best of three trials being recorded as the resting level. A 10 per cent decrease in PEFR has been shown and used as significant by several investigators. Thus, during the study a fall in PEFR greater than 10 per cent was considered to represent significant bronchospasm.^{3, 5, 11, 12} Again the best of three trials was recorded. The subjects who did not develop significant bronchospasm were considered to be a comparative (control) group for this study.

A polyethylene catheter (PE 160) was inserted percutaneously into a brachial artery under local anesthesia with the use of a Cournand needle and modified Seldinger technique as previously described.¹⁶ This allowed sampling of arterial blood during the test. A continuous electrocardiogram was taken at rest, during exercise, and throughout the postexercise period. This allowed for monitoring of heart rate and detection of cardiac arrhythmias.

Before each exercise period, the subjects sat quietly on a cycle ergometer for approximately 15 minutes so that steady-state resting measurements could be obtained. The exercise consisted of cycling at 60 r.p.m. (Lanooy Model cycle ergometer†) starting with a work rate of 25 watts for 6 minutes. Additional 6 minute 25 watt work increments were imposed until the subjects were unable to maintain the work rate because of either fatigue or shortness of breath. Between each work increment a 10 minute recovery period was allowed during which time PEFR measurements were obtained at 2 minute intervals.

During the test, the subjects breathed through a low-resistance modified Otis-McKerrow breathing valve‡ (dead space 175 ml.). Expired air was collected in meteorologic balloons during the sixth minute of each work period and was analyzed for mixed expired O₂ concentration within one minute of collection.§ Inspired and expired oxygen|| and carbon dioxide¶ concentrations were recorded continuously. The gas analyzers were calibrated with standard gases previously analyzed by the Scholander¹⁷ technique. Respiratory exchange ratio (R) was determined from end-tidal O₂ and CO₂ concentrations. Minute ventilation was obtained by integrating expired gas flow, measured with a pneumotachograph.¶ The system was shown to be linear through flow rates of 600 liters per minute. True O₂ difference was determined from mixed expired oxygen concentration and R from the nomogram of Dill and Folling.¹⁸ Oxygen consumption ($\dot{V}O_2$) was calculated from minute ventilation (STPD) and true O₂ difference for the sixth minute of each work period. Substituting arterial CO₂ tension (Pa_{CO₂}) for mean alveolar CO₂ tension (PA_{CO₂}), "Ideal" alveolar O₂ tension (P $\bar{A}O_2$) was calculated from the alveolar gas equation.¹⁹

Arterial blood samples were collected over several breaths before each work period, during

*The Monaghan Company, Denver, Colo.

†Lanooy Instrumentation Associates, New York, N. Y.

‡Modified Otis-McKerrow breathing valve, Collins Company, Cambridge, Mass.

§Model C-2, expanded scale O₂ analyzer, Beckman Instruments, Fullerton, Calif.

||Westinghouse O₂ analyzer, Model 209, Pittsburgh, Pa.

¶Model LB-1 CO₂ analyzer, Beckman Instrument Co., Palo Alto, Calif.

#Fleisch, Model 3, Instrumentation Associates, New York, N. Y.

TABLE I. Comparison of children studied for exercise-induced bronchospasm

Patient identification	Age	Sex	Weight (pounds)	Height (inches)	Resting PEFR	Predicted PEFR ³⁶ ± 2 standard deviations*
<i>Group A—children with significant bronchospasm after exercise†</i>						
1	16	Boy	130	63	380	300-525
2	12	Boy	75	57	250	300-375
3	11	Boy	65	53.5	285	250-325
4	14	Boy	170	70	340	350-575
5	14	Girl	135	63	370	300-525
6	15	Girl	139	63	345	300-525
Mean values ($\bar{x}$)	14		119	61.6		
<i>Group B—children without significant bronchospasm after exercise‡</i>						
7	14	Girl	109	60.5	270	225-450
8	15	Girl	106	65	335	325-575
9	16	Boy	130	68	400	350-575
10	12	Boy	52	52	340	175-325
11	16	Boy	195	70	450	350-575
12	13	Girl	85	62	260	275-500
Mean values ($\bar{x}$)	14		113	62.9		

*Ninety-five per cent confidence limits.

†Greater than 10 per cent decrease in PEFR after exercise.

‡Ten per cent or less decrease in PEFR after exercise.

TABLE II. Peak expiratory flow rates following 6 minute exercise periods on two separate

Patient	Resting PEFR*	Post exercise peak							
		25 Watts (minutes)					50 Watts		
		1	3	5	7	9	1	3	5
1	380	365	365	330	330	345	350	365	280
	390	370	375	360	365	370	360	370	340
2	250	240	230	240	235	240	230	240	270
	250	245	240	235	280	240	240	240	260
3	285	285	275	260	270	270	260	285	190
	310	300	310	290	285	290	240	200	175
5	370	360	350	355	—	335	260		
	360	350	340	345	—	330	280		
8	335						330	335	330
	460						450	470	450
10	340	350	340	—	335	330	350	335	335
	420	440	420	—	415	420	400	400	380
11	460	440	430	440	420	420	450	460	440
	450	440	435	440	420	410	445	450	440
12	260	240	235	250	250	285	290	250	255
	360	360	375	360	360	360	360	355	360

*Separate trials, within ninety-five per cent confidence limits of normal (see Table I) for Cases with resting PEFR lower than that predicted in at least one trial.

the sixth minute of exercise, and every 2 minutes during the recovery periods. The blood samples were analyzed for pH, PaCO_2 , and (HCO_3^-) by the Astrup technique* and for PaO_2 with a Clark-Severinghaus electrode† at a temperature of 37° C.

The children reported in this study were divided into two groups: (1) those who exhibited greater than 10 per cent decrease in postexercise PEFR as compared to resting levels (Group A) and (2) those who had 10 per cent or less decrease in postexercise PEFR (Group B). Both groups had comparable values of PEFR at rest (Table I).

RESULTS

In Table II and Fig. 1 the changes in PEFR occurring after exercise at different work intensities are shown for the 8 patients who were tested twice. Together with 2 children who were tested only once, a total of 6 children who did develop EIB revealed up to 10 per cent differences for one or two work rates. However, they then showed an immediate drop in PEFR as the work rate was increased further (Fig. 1). This rapid fall in PEFR at a specific work rate varied between subjects and appears to be related to the relative work intensity. This phenomenon was re-evaluated on 2 different days in 8 of 12 subjects and found to be reproducible (Table II, Fig. 1), i.e., similar changes in PEFR occurred after the same work load on both occasions.

Mean resting values of PaO_2 appeared to be higher for the non-EIB group (B); however, the difference between the groups became less distinct as the work rate was increased. At the 25 watt work load a decrease in PaO_2 in Group

*Astrup Micro Equipment, Radiometer, Copenhagen, Denmark.

†Beckman O_2 microelectrode and Model 160 gas analyzer.

occasions with cycle ergometer in children depicted in Table I.

expiratory flow rates											
(minutes)		75 Watts (minutes)					100 Watts (minutes)				
7	9	1	3	5	7	9	1	3	5	7	9
310	225										
320	275										
290	290	256	225	240	—	225	250	185			
270	270	260	240	250	230	225	250	175			
330	340						340	335	330	340	340
430	440	460	440	460	440	440	440	460	430	430	450
340	345	350	335	340	350	350					
390	410	400	395	420	420	400	420	410	415	395	415
410	450	440	430	440	425	430	450	460	440	430	420
—	430	450	440	445	430	410	450	440	435	430	420
240	245	235	235	235	250	265					
340	360	360	330	330	350	360					

1, 3, 5, 8, and 11. In Case 10 the resting PEFR is better than predicted, but Cases 2 and 12 re-

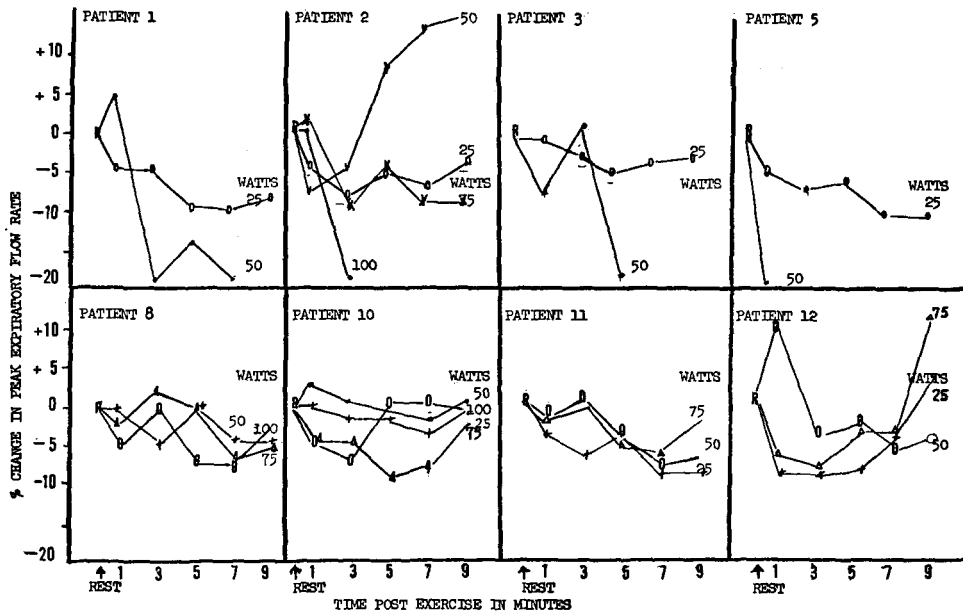


FIG. 1. Per cent change in peak expiratory flow rate with time after various work loads on 8 asthmatic children (same patients depicted as reproducible in Table II). Significant PEFR changes occur in 1 to 5 minutes in Patients 1, 2, 3, and 5 at work intensities which vary from patient to patient. Only 10 per cent PEFR changes occur in asthmatic Patients 8, 10, 11, and 12 without exercise-induced bronchospasm regardless of work intensity.

TABLE III. Mean blood gas determination during sixth minute of measured cycle ergometer work rates of atopic asthmatic children

Work load	Number	Group	Blood gases (Mean values $\pm$ standard errors [in parentheses] of the mean)			
			pH	(HCO ₃) (mEq/L.)	PaO ₂ (mm. Hg)	Paco ₂ (mm. Hg)
Rest	6	A	7.37 (± 0.019)	20.0 ($\pm .76$)	81 (± 3.6)	37 (± 3.1)
	6	B	7.40 (± 0.027)	19.8 ($\pm .98$)	93 (± 5.0)	33 (± 3.1)
25 Watt	4	A	7.33 ($\pm .04$)	20.3 ($\pm .57$)	75 (± 0.6)	38 (± 4.0)
	4	B	7.39 (± 0.006)	20.3 ($\pm .6$)	95 (± 2.4)	36 (± 1.4)
50 Watt	6	A	7.35 (± 0.020)	18.2 (± 0.5)	82 (± 2.3)	35 (± 1.7)
	6	B	7.38 (± 0.008)	18.5 (± 1.3)	96 (± 2.4)	33 (± 2.7)
75 Watt	4	A	7.34 (± 0.030)	17.6 ($\pm .43$)	84 (± 3.2)	37 (± 3.5)
	4	B	7.37 (± 0.009)	18.5 (± 1.6)	97 (± 3.5)	34 (± 2.6)
100 Watt	4	A	7.32 (± 0.020)	15.3 (± 0.6)	91 (± 3.5)	35 (± 2.0)
	2	B	7.34 (± 0.103)	17.6 (± 1.7)	92 (± 4.4)	34 (± 3.9)

Group A—children with significant bronchospasm after exercise; Group B—children without significant bronchospasm after exercise.

A was primarily the result of one patient's initial response pattern. Other arterial blood gas and acid-base measurements (Table III) were not significantly different between the two groups at any equivalent work rate, nor were there any abnormalities which correlated with the onset of bronchospasm. Hyperventi-

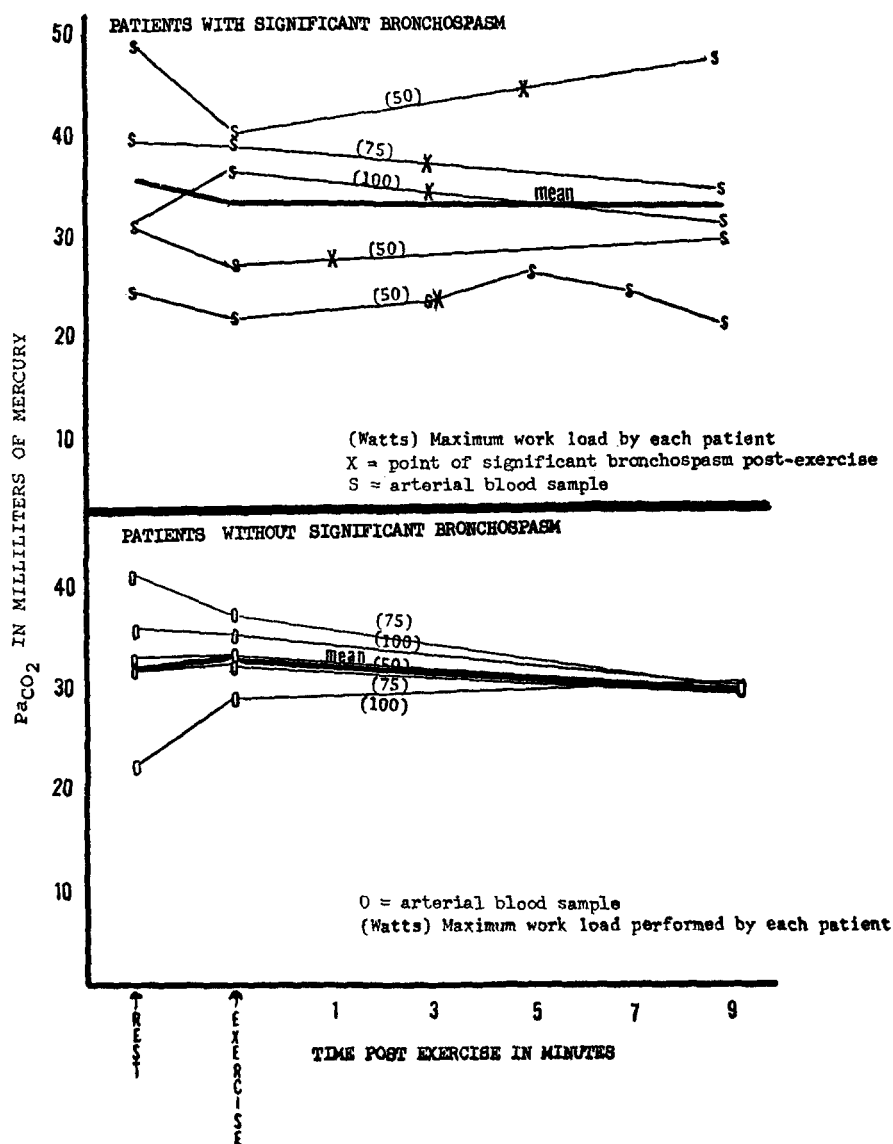


FIG. 2. Alterations in PaCO_2 in pre-exercise, exercise, and postexercise periods in children with and without significant bronchospasm. Patients with bronchospasm in top graph (Group A). Patients without bronchospasm in bottom graph (Group B). There is no significant difference between the two groups. The mean values for the children are shown by the heavy line.

lation noted in one patient disappeared with increasing exercise rates. The pH and (HCO_3^-) decreased at the higher work rates (Table III) in which lactic acidosis was presumably occurring and respiratory compensation was only partial.

The mean PaCO_2 values at rest, during exercise, and in the tenth minute of

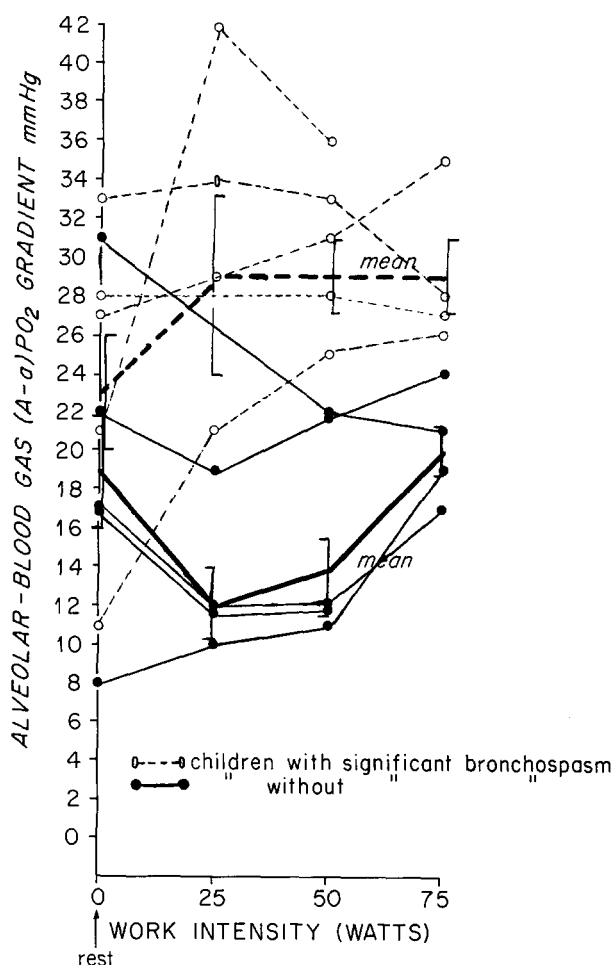


Fig. 3. Differences in alveolar blood gas oxygen during the fifth minute of exercise at various work intensities in asthmatic children with and without bronchospasm after exercise. There are significant changes between the groups at moderate work intensity but not at rest; standard errors of the means are shown.

the recovery period were similar in both groups. The development of bronchospasm in the recovery phase was therefore not apparently related to the PaCO_2 changes (Fig. 2). There were no significant differences in PaCO_2 during the exercise or recovery periods for the two groups.

Analysis of the $(A-a)\text{Po}_2$ difference revealed different responses between Groups A and B to exercise (Fig. 3). Group B showed an initial decrease in the $(A-a)\text{Po}_2$ at the mild exercise levels; in contrast, Group A increased the initial $(A-a)\text{Po}_2$ at the lowest work rates.

The metabolic and ventilatory responses (Table IV) to graded exercise were normal. In both groups, at submaximal loads, $\dot{V}\text{O}_2$, $\dot{V}\text{CO}_2$, R, and the ratio between minute ventilation ($\dot{V}\text{E}$) to $\dot{V}\text{CO}_2$ ($\dot{V}\text{E}/\dot{V}\text{CO}_2$) suggested a normal work efficiency and ventilatory response to exercise. In Group B, the $\dot{V}\text{O}_2$ was the

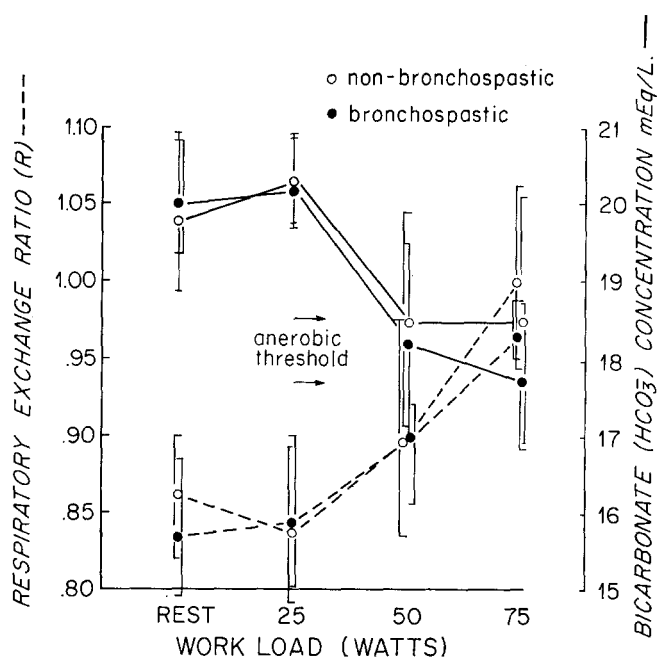


FIG. 4. Respiratory exchange rate (R) and bicarbonate concentration (HCO_3^-) during the fifth minute of each work intensity on the cycle ergometer. The rise in bicarbonate and fall in R beyond 25 watts is comparable (anaerobic threshold) in both bronchospastic and nonbronchospastic postexercise asthmatic children. Standard errors of the means for both groups are shown at each work rate.

same as that for normal subjects. However at the highest exercise loads, the $\dot{V}\text{O}_2$ was greater than normal for Group A subjects,²⁰ suggesting a high O_2 cost of breathing at high ventilations in the subjects.

In Fig. 4 we have related changes in R and (HCO_3^-) during graded exercise. It may be seen that R showed a sharp increase at the same work rate that (HCO_3^-) revealed a sharp decrease. This point, the anaerobic threshold,²¹ was the same for both groups, suggesting that the children are of similar levels of fitness. EIB was therefore not related to differences in anaerobic threshold.

DISCUSSION

The usefulness of the cycle ergometer for studying EIB in children has been previously described.^{1, 3, 22-25} In addition to reproducibility, acceptability, and adaptation by children, an important feature is that the cycle ergometer offers a test system not dependent upon the patient's weight; thus, the exact work load is known and work intensity can be determined.

Induction of bronchospasm in this study appears to be related to intensity of exercise (Fig. 1). Significant bronchospasm established by PEFR^{14, 15, 22} occurred at different work rates for different children and was unrelated to age, sex, or resting asthmatic state. Those children who did not develop a significant

TABLE IV. Mean gas exchange data during sixth minute of measured cycle ergometer work rates for atopic asthmatic children

Work Load	Number	Group	Gas exchange (Mean values $\pm$ standard errors [in parentheses])			
			$\dot{V}O_2$ (ml./min.)	$\dot{V}CO_2$ (ml./min.)	R (end tidal)	$\dot{V}E/\dot{V}CO_2$
Rest	6	A	273 ($\pm$ 24)	234 ($\pm$ 24)	0.86 ($\pm$ 0.04)	43.46 ($\pm$ 2.30)
	6	B	240 ($\pm$ 19)	199 ($\pm$ 27)	0.83 ($\pm$ 0.04)	37.40 ($\pm$ 1.80)
25 Watt	4	A	806 ($\pm$ 74)	678 ($\pm$ 123)	0.83 ($\pm$ 0.05)	31.13 ($\pm$ 3.07)
	4	B	577 ($\pm$ 9)	487 ($\pm$ 44)	0.84 ($\pm$ 0.06)	32.00 ($\pm$ 0.97)
50 Watt	6	A	1,235 ($\pm$ 125)	1,146 ($\pm$ 126)	0.90 ($\pm$ 0.04)	31.40 ($\pm$ 1.99)
	6	B	947 ($\pm$ 93)	818 ($\pm$ 44)	0.89 ($\pm$ 0.02)	28.70 ($\pm$ 0.80)
75 Watt	4	A	1,419 ($\pm$ 140)	1,448 ($\pm$ 242)	1.00 ($\pm$ 0.06)	26.77 ($\pm$ 3.39)
	4	B	1,268 ($\pm$ 29)	1,217 ($\pm$ 38)	0.96 ($\pm$ 0.02)	29.50 ($\pm$ 1.30)
100 Watt	4	A	2,157 ($\pm$ 472)	2,672 ($\pm$ 503)	0.99 ($\pm$ 0.07)	27.00 ($\pm$ 2.70)
	2	B	1,827 ($\pm$ 120)	1,675 ($\pm$ 19)	0.98 ($\pm$ 0.03)	28.30 ($\pm$ 1.10)

Group A—children with significant bronchospasm after exercise; Group B—children without significant bronchospasm after exercise.

fall in PEFR could work to their maximal exercise levels with some even showing improvement in postexercise PEFR.

Numerous investigators have associated bronchospasm with hypoxemia and respiratory alkalosis,^{4, 6, 8, 26, 27} increased hydrogen ion concentration,^{6, 9} hypocapnia,^{4, 5, 29, 30, 32, 37} low plasma bicarbonate,⁸ and reflex mechanisms.²⁸⁻³² It was apparent in this study that the initiation of EIB was not related to specific changes in P_{aCO_2} (Fig. 2, Table III), as EIB was induced at work rates in which no changes in P_{aCO_2} were noted. In contrast to a recent report³⁷ suggesting hyperventilation as a cause of postexercise hypocapnia, dyspnea, and bronchospasm, there was no significant difference in P_{aCO_2} between the two groups, either during exercise or in the postexercise periods. Also, from Tables III and IV and Fig. 4, it is clear there was no correlation between any acid-base or P_{aCO_2} changes with EIB.

Both groups revealed normal $\dot{V}E$ and metabolic rates at lower work intensities (Table IV). However, a higher O_2 uptake than normal was noted in Group A at the higher work intensities (Table IV). Conceivably, increased airway resistance would cause secondary increased work of breathing which would manifest itself most strikingly at higher levels of $\dot{V}E$. This seems to be more accentuated in the children with significant bronchospasm and can be seen in the abnormal (A-a) P_{O_2} difference in Group A patients.

An observation which appears to differentiate the two groups of patients is the (A-a) P_{O_2} difference (Fig. 3). A decreased (A-a) P_{O_2} with moderate exercise has been observed by Hesser and Matell³³ and Whipp and Wasserman³⁴ in normal subjects. This decreased (A-a) P_{O_2} with moderate exercise was followed by a secondary increase at higher work intensities,³⁴ as in the case of Group B (Fig. 3). Proposed explanations of these changes are given by Whipp and Wasserman.³⁴ Apparently under conditions of rest, the effect of gravity results in a relative under perfusion ($\dot{Q}$) to the lung apices. At the same time there is

greater alveolar ventilation ($\dot{V}_A$) at the lung bases due to transpulmonary pressure changes or structural differences. A decreased $(A-a)Po_2$ with moderate exercise is probably secondary to increased $\dot{Q}$ in the apices relative to the $\dot{V}_A$. The $\dot{V}_A/\dot{Q}$ ratio therefore becomes more even with moderate exercise. At high work intensities a low mixed venous Po_2 in shunted blood and an inadequate oxygen diffusion are proposed as partially accounting for secondary $(A-a)Po_2$ increases.

In our groups (Fig. 2), the children with less than a 10 per cent decrease in postexercise PEFR revealed $(A-a)Po_2$ changes similar to those of normal adults, as described by Whipp and Wasserman.³⁴ However, the children who developed EIB showed an immediate increase in $(A-a)Po_2$ at moderate exercise rather than a decrease. These abnormally high values were sustained. The group with bronchospasm appears to have a factor which may limit O_2 transport during even light and moderate exercise intensities. It may also be inferred that the distribution of $\dot{V}_A/\dot{Q}$ over the lung becomes more uneven in this group with light exercise rather than improving as suggested for the normal groups.³⁵ It is noted that this $(A-a)Po_2$ is our only finding that discriminates between the two groups at moderate exercise intensities. Further investigations need to be carried out on this important point.

CONCLUSIONS

We have observed a decrease in peak expiratory flow rate induced by exercise in some children with atopic asthma. The results suggest that this phenomenon is related to exercise intensity. EIB appeared not to be related to acid-base or hyperventilation changes. However, $(A-a)Po_2$ differences at rest and with moderate exercise were abnormally increased in the group with EIB. This was most likely caused by $\dot{V}_A/\dot{Q}$ unevenness. It was not possible to determine if this abnormality in arterial O_2 is the cause or the result of bronchospasm.

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