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Plasma catecholamines during exercise-induced bronchoconstriction in bronchial asthma

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ABSTRACT Plasma levels of adrenaline and noradrenaline during and after submaximal exercise in patients with bronchial asthma were investigated. Three groups were studied comprising 10 patients with exercise-induced bronchoconstriction (EIB), 10 asthmatic patients without EIB and four normal control subjects. Plasma catecholamines were measured at rest, at the end of exercise, and five and 15 minutes after exercise. Changes in airway resistance were assessed by measuring peak expiratory flow rate. Significant differences in catecholamine levels between reacting and non-reacting patients were found. In 10 patients developing EIB adrenaline and noradrenaline levels had risen significantly by the end of exercise and remained elevated up to the fifth minute of recovery. The rise in catecholamine levels in non-reacting asthmatics was insignificant. In control subjects noradrenaline had increased significantly by the end of exercise.

Despite many years of investigation some aspects of exercise-induced bronchoconstriction (EIB) remain unclear. Its mechanism is not yet known nor are the reasons for its appearance after completion of exercise rather than during it. It is well known that plasma catecholamine levels increase during physical exercise.[1] A rise in noradrenaline level depends on the work performed in relation to the maximal oxygen uptake.[2 3] Adrenaline level rises only at a very high workload.[4 5]

Adrenaline is one of the most potent endogenous bronchodilators. Noradrenaline induces a constriction of bronchial smooth muscle. Respective levels and reciprocal relations between adrenaline and noradrenaline during and after physical exercise in patients with bronchial asthma may influence the time of onset and the course of EIB.

The aim of this study was to investigate the changes in catecholamine levels during and after exercise in asthmatic patients with and without EIB.

Methods

Twenty patients with atopic asthma were studied. The diagnosis was based on history, positive skin tests, and eosinophilia in the blood or sputum. The patients were divided into two groups according to their response to exercise. The first group comprised 10 patients developing EIB. The second contained asthmatics without EIB. Four healthy members of the medical staff made up the control group. In order to avoid a large range of physical performance between subjects, an age of 39 years was taken as an upper limit for admission to the study.

It was noted in general that patients with EIB had more severe asthma than non-reactors. Their mean basal PEFR was lower, they were using more drugs, two of them were on continuous steroids therapy and they were physically less fit. Non-reactors were on intermittent beta-adrenergic stimulating drugs only. The majority of this group were students regularly performing sporting activity.

Exercise tests were done in a sitting position on a bicycle ergometer. A steady-state submaximal exercise of 10 minutes was performed by each subject, the workload being individually adjusted during preparatory tests to achieve a steady heart rate ranging between 80–90% of predicted maximal heart rate.[6] Peak expiratory flow rate was measured in the sitting position at rest and at one, five, and 15 minutes after the completion of exercise using a Wright peak flow meter. Patients in whom the PEFR fell

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by more than 20% of the resting value were placed in the EIB group.

The investigations were performed in the morning at a room temperature of around 20°C. All medications were withdrawn eight hours before testing. Patients were familiar with the procedure as preparatory exercising was performed in the same surroundings and supervised by the same people. Each subject rested for half an hour in a supine position before the initial resting venous blood sample from a previously sited cannula was taken. Consecutive blood samples were taken at the tenth minute of exercise and at five and 15 minutes after the end of exercise.

The blood was put into heparinised polyethylene tubes containing sodium pyrosulphide, immediately centrifuged and the serum frozen. Adrenaline and noradrenaline levels were determined by the fluorimetric method of Anton and Sayre,[7] the laboratory normal values for noradrenaline being $0{\cdot}94 \pm 1{\cdot}04$ μg/l and for adrenaline $0{\cdot}35 \pm 0{\cdot}09$ μg/l. The error of the method is $\pm 0{\cdot}02$ μg/l, recovery for adrenaline being 72% and that of noradrenaline 77·2%.

Blood pressure measurements and ECG, lead V_5, were recorded every two minutes during exercise. Statistical analysis of the data made use of paired *t* testing, correlation coefficients, and multifactorial regressions.

Results

Mean age and heart rate at rest and on exercise (also expressed as a percentage of predicted maximal heart rate) are shown in table 1. Exercise tolerance was lowest in patients with EIB and highest in control subjects. The scatter of exercise heart rate in each group was small averaging 88–89% of the maximal predicted heart rate.[6]

Table 2 shows change in PEFR and catecholamine levels at rest, on exercise, and after exercise in patients developing bronchospasm. Peak expiratory flow rate was lowest five minutes after completing exercise. The mean fall in PEFR at that time was 39% ($p<0{\cdot}001$). There was a significant increase in catecholamine levels on exercise. Noradrenaline rose from $0{\cdot}88 \pm 0{\cdot}21$ μg/l to $1{\cdot}32 \pm 0{\cdot}40$ μg/l ($p<0{\cdot}001$). Five minutes after exercise these levels decreased but remained significantly higher than at rest ($p<0{\cdot}05$). Fifteen minutes after exercise they returned to the initial values.

Table 1 *Age and heart rate at rest and on exercise in three studied groups. Mean, standard deviations, and range are shown*

	Age (*yr*)	*Heart rate beats/min*		
		Rest	*Exercise*	*% of predicted maximal*
Group 1	26·7 ± 6·5	74 ± 10	174 ± 10	88 ± 4
	17–37	60–92	156–185	82–94
Group 2	24·6 ± 6·7	81 ± 9	177 ± 4	89 ± 4
	17–38	60–96	174–186	84–98
Control Subjects	31·5 ± 6·4	73 ± 7	172 ± 8	89 ± 4
	26–38	64–82	163–178	84–94

Table 3 shows the above-mentioned parameters in asthmatic patients without EIB. There was a small statistically insignificant increase in PEFR after exercise in this group. There was also a small statistically insignificant rise in catecholamine levels at the end of exercise. On recovery these levels had returned to resting values.

Table 4 shows changes in PEFR and catecholamine levels induced by exercise in the control subjects. Noradrenaline level rose from $1{\cdot}15 \pm 0{\cdot}23$ μg/l at rest to $1{\cdot}43 \pm 0{\cdot}27$ μg/l on exercise ($p<0{\cdot}01$) and fell rapidly to resting levels on recovery.

There was no correlation between catecholamine levels at rest, on exercise, or on recovery except between resting values in the group with EIB ($r=0{\cdot}84$) and in the tenth minute of exercise in normal subjects ($r=0{\cdot}9$). No correlations were observed in any group between PEFR and adrenaline or noradrenaline separately or together.

Discussion

The study has shown that there were substantial differences in catecholamine levels in asthmatic subjects submitted to physical exercise depending on whether EIB was present or not. Thus an increase in catecholamine levels on exercise and early in the post-exercise phase was found in patients reacting with EIB but no significant change was observed in patients not developing EIB.

Our findings on catecholamine levels in patients with EIB are consistent with previous reports.[8-10] Although these authors also found increased catecholamine levels during and immediately after exercise they doubt that this rise plays a role in the development of EIB. Their opinion is based on the observation that the changes in catecholamine levels in asthmatic patients do not differ from those seen in normal controls,[8-10] and that they found no correlation between catecholamine levels and increased airway resistance.[9 10]

We have not found a paper comparing catecholamine levels in asthmatic patients with and

Table 2 *Plasma catecholamine and peak expiratory flow (PEFR) values in 10 asthmatic patients developing exercise-induced bronchoconstriction*

Patient	*Sex*	*PEFR l/min*					*Catecholamine µg/l*							
		Initial	*% of predicted*	*After exercise*			*Initial*		*End of exercise*		*5 min after exercise*		*15 min after exercise*	
				1 min	*5 min*	*15 min*	*A*	*NA*	*A*	*NA*	*A*	*NA*	*A*	*NA*
1	M	270	45	340	235	210	0·42	0·93	0·56	1·31	0·56	1·04	0·35	0·93
2	M	285	46	150	125	125	0·35	0·82	0·60	1·12	0·61	1·16	0·24	0·81
3	F	375	91	360	260	280	0·47	1·38	0·47	2·22	0·39	0·87	0·33	0·59
4	F	420	99	335	235	210	0·25	0·53	0·44	1·15	0·37	0·92	0·31	0·66
5	F	370	84	285	220	215	0·28	0·85	0·34	1·01	0·26	0·87	0·20	0·55
6	M	370	62	355	185	170	0·32	0·83	0·46	1·25	0·41	1·18	0·29	1·11
7	M	540	84	460	375	425	0·29	0·73	0·46	0·78	0·45	1·21	0·35	1·13
8	F	390	89	300	150	195	0·29	0·87	0·75	1·68	0·30	1·01	0·38	0·92
9	M	365	73	430	330	380	0·35	0·98	0·52	1·51	0·44	1·24	0·32	1·17
10	F	390	93	340	265	285	0·37	0·85	0·60	1·14	0·57	1·34	0·21	0·81
Mean		387·5	76·60	335·5	238·0	249·5	0·34	0·88	0·52	1·32	0·44	1·08	0·30	0·87
Standard deviation		78	4·32	84	76	94	0·07	0·21	0·11	0·40	0·12	0·17	0·06	0·22
p					<0·001	<0·001			<0·001	<0·001	<0·05	<0·05	NS	NS

p values concern difference between initial and respective value of studied variable.
NS = not significant (p > 0·05). A = adrenaline, NA = noradrenaline.

Table 3 *Plasma catecholamine and peak expiratory flow (PEFR) values in 10 asthmatic patients not developing exercise-induced bronchoconstriction*

Patient	*Sex*	*PEFR l/min*					*Catecholamine µg/l*							
		Initial	*% of predicted*	*After exercise*			*Initial*		*End of exercise*		*5 min after exercise*		*15 min after exercise*	
				1 min	*5 min*	*15 min*	*A*	*NA*	*A*	*NA*	*A*	*NA*	*A*	*NA*
1	M	415	72	460	360	355	0·81	1·56	0·52	1·25	0·56	1·09	0·49	0·98
2	M	385	63	420	365	400	0·40	1·27	0·44	1·04	0·26	1·27	0·20	0·74
3	M	580	91	660	590	590	0·32	0·83	0·36	1·07	0·26	0·87	0·24	0·87
4	F	420	105	430	400	410	0·28	1·04	0·35	1·14	0·29	1·03	0·24	1·00
5	M	530	89	580	535	510	0·31	0·83	0·36	0·99	0·23	0·72	0·29	1·04
6	M	570	93	585	550	570	0·29	0·66	0·41	1·29	0·42	1·15	0·24	0·81
7	F	430	100	460	440	430	0·28	0·89	0·52	1·40	0·51	1·00	0·28	0·71
8	M	460	72	410	425	440	0·41	0·87	0·30	0·87	0·79	1·00	0·28	0·67
9	M	470	71	525	485	480	0·32	0·81	0·51	1·00	0·49	1·20	0·29	0·90
10	M	425	65	480	470	465	0·32	1·19	0·54	1·71	0·65	1·30	0·52	1·14
Mean		468·5	82·1	501·0	462·0	465·0	0·38	1·00	0·43	1·18	0·45	1·06	0·31	0·89
Standard deviation		68	15	84	79	75	0·16	0·27	0·09	0·25	0·19	0·18	0·11	0·15
p				NS	NS	NS			NS	NS	NS	NS	NS	NS

Notes and abbreviations as in table 2.

Table 4 *Plasma catecholamine and peak expiratory flow (PEFR) values in four healthy men subjected to submaximal physical exercise*

Number	*PEFR l/min*					*Catecholamine µg/l*							
	Initial	*% of predicted*	*After exercise*			*Initial*		*End of exercise*		*5 min after exercise*		*15 min after exercise*	
			1 min	*5 min*	*15 min*	*A*	*NA*	*A*	*NA*	*A*	*NA*	*A*	*NA*
1	600	103	585	520	570	0·44	1·01	0·40	1·50	0·33	1·08	0·22	0·69
2	540	87	540	535	540	0·36	1·08	0·40	1·27	0·37	1·04	0·33	0·69
3	680	113	670	620	620	0·23	1·01	0·33	1·18	0·26	1·00	0·23	0·82
4	560	89	585	550	555	0·41	1·48	0·51	1·78	0·36	1·19	0·24	0·99
Mean	595·0	98	595·0	556·3	571·3	0·36	1·15	0·41	1·43	0·33	1·08	0·26	0·80
Standard deviation	62	12·3	54	44·2	34·7	0·09	0·23	0·07	0·27	0·05	0·08	0·05	0·14
p								NS	<0·01	NS	NS	NS	NS

Notes and abbreviations as in table 2.

without EIB. The difference in catecholamine levels between these two groups suggests that an increased noradrenaline level on exercise and in the early post-exercise period may play a role in the mechanism of EIB. Perhaps this occurs as a result of sensitisation of receptors in smooth muscle. Another possibility would be a summation effect of noradrenaline and the actual mediator of bronchoconstriction.

In a previous study[11] we have found indirect evidence that histamine is a probable mediator of EIB. Our hypothesis was subsequently supported by Anderson *et al* who found an increase in blood histamine level during EIB.[12] In a recent study Radomyski *et al*[13] also found that whole blood histamine in eight asthmatic patients developing EIB increased from a resting level of $64 \pm 24{\cdot}4$ μg/l to 75 ± 21 μg/l at the end of submaximal exercise ($p < 0{\cdot}05$).

There is some evidence that alpha receptor blockade prevents histamine-induced bronchoconstriction,[14 15] or protects asthmatic patients against EIB.[16 17] Here one might assume that noradrenaline released during exercise stimulates alpha receptors in the bronchial smooth muscles sensitising them to the histamine.

The significant increase in adrenaline levels in patients with EIB not seen in normal controls may have resulted from mental stress. These patients were submitted to at least one preparatory test after which they developed severe bronchospasm which was not reversed for 15 minutes. Anticipation of the same unpleasant sensation may have caused the increase in adrenaline level.

It is difficult to explain why in non-reacting asthmatic patients the noradrenaline level on exercise did not increase significantly as was seen in reactors and control subjects, particularly as the relative heart rates were similar in all three groups. Non-reacting subjects did not receive any treatment that could interfere with catecholamine release or with the rate of elimination of noradrenaline from the circulation. McDermott *et al*[18] have found that catecholamine release during exercise was higher in older men (mean age 46·8 years) than in younger ones (mean age 25·3 years). Although our non-reacting subjects were younger than reactors and control subjects, the intergroup age differences were probably too small to be responsible for the differences in noradrenaline release.

Apart from being younger the non-reacting subjects also regularly performed physical exercise, whereas the reactors and control subjects led a sedentary life. Davies[19] has shown that the prediction of maximal oxygen uptake from heart rate can be a source of important underestimation. It might be assumed that in spite of the same relative heart rate as the other groups, non-reacting patients were working at lower relative oxygen consumption. Were this the case it may have accounted for the lower noradrenaline increase on exercise.

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