THE PLACE OF PHYSICAL EXERCISE AND BRONCHODILATOR DRUGS IN THE ASSESSMENT OF THE ASTHMATIC CHILD

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Among the many factors that affect ventilatory function in the asthmatic subject, physical exercise and bronchodilator drugs are two of the more important. It has been shown that physical exercise has two distinct and opposite effects on ventilatory function depending upon the duration and level of exercise (Jones, Buston and Wharton, 1962). Providing the level is adequate, exercise lasting less than two minutes increases the forced expiratory volume in one second (F.E.V.), whereas exercise lasting eight to 10 minutes produces a fall of F.E.V. following and sometimes also during the exercise. In this paper we describe the clinical implications of these effects of exercise and their modification by bronchodilator drugs.

Methods

The forced expiratory volume was measured with a modified Gaensler spirometer which records the volume of gas expired in the first second of a forced expiration, excluding the first 100 ml. (Gaensler, 1951; McKerrow, McDermott and Gilson, 1960). The instrument was calibrated daily by the method described by McKerrow *et al.* All results were corrected to B.T.P.S. (body temperature and pressure, saturated with water vapour).

Exercise tests were performed by asking the child to run on a horizontal surface with the duration and level of exercise controlled as described below. After learning the technique of the forced expiratory volume test, at least three measurements were made before an exercise test, and measurements were made subsequently as described below.

We have found a bicycle ergometer an unsatisfactory means of demonstrating the two types of ventilatory response to exercise. An ergometer can be used for the short exercise test, but the response to prolonged exercise is unpredictable. This may be due to the unusual nature of the exercise causing muscular fatigue rather than breathlessness to become the limiting factor.

Drugs were given at variable intervals of time before

exercise. Isoprenaline sulphate 1% (Burroughs Wellcome preparation) was given as an aerosol using a Wright inhaler and an air flow rate of 8-9 litres per minute (Wright, 1958). The aerosol was fed into a face mask held close to the face. The substance was inhaled for one minute and for two subsequent half-minute periods during a total time of five minutes. Solutions of adrenaline and noradrenaline were made up from the solid substances (Burroughs Wellcome preparations) in strengths of 1% with added sodium metabisulphite. These preparations were used fresh and were inhaled in the same way as isoprenaline. Ephedrine hydrochloride (B.P.), choledyl (Allen and Hanbury Ltd.) and orthoxine (Upjohn Ltd.), were given in tablet form. Atropine sulphate (B.P.) was given subcutaneously. Changes of F.E.V. have been expressed both as percentages of the predicted normal and as percentages of the resting value because this method is more informative, especially when the F.E.V. is low.

All statements of statistical significance in the Tables refer to departures of the F.E.V. from values in the resting subject, which were produced by drugs and/or exercise.

Two types of exercise were carried out.

(1) **One Minute's Exercise.** The child is asked to run as fast as he can on a level surface for one minute. The F.E.V. is measured before and at one-minute intervals after the exercise.

(2) **Five to Ten Minutes' Exercise.** The child is asked to run or walk for a variable period of up to a maximum of 10 minutes. The details of the test are important if the characteristic effects on ventilatory function are to be obtained and if the test is to be carried out safely. The level and the duration of exercise are not fixed in advance, but are determined by the response to exercise as it proceeds. The level of exercise must be sufficient to produce moderate breathlessness, but at the same time should be below the maximum of which the child is capable. The test should not produce undue distress. The child is observed during the test and asked to run fast or slowly, or to walk, as indicated by the response to exercise. The F.E.V. is measured

TABLE 1
EFFECT OF ONE MINUTE'S EXERCISE ON F.E.V.
IN 34 SUBJECTS

	% N*	% R*
F.E.V. at rest	70 (17-88)	100
First post-exercise F.E.V. .. .	76 (29-106)	110 (88-171)
Peak F.E.V. .. .	80 (29-116) p < 0.001	116 (101-171)

*N = predicted normal F.E.V.
*R = resting F.E.V. before exercise.

after five minutes of exercise. If it is below the resting level, exercise is discontinued and a post-exercise fall of the F.E.V. may be expected to follow. This is recorded by measuring the F.E.V. at one-minute intervals, commencing immediately after exercise. Similarly, if excessive breathlessness and wheezing are observed at any time during exercise, it should be stopped because ventilatory function which has diminished as a result of the exercise is likely to continue to fall. If the F.E.V. at five minutes is at or above the resting level, exercise should be continued for a further three to five minutes, and if the level of exercise has been adequate a post-exercise fall of F.E.V. will occur. Frequent interruption of exercise for the purpose of measuring the F.E.V. should be avoided because this will prevent the post-exercise fall occurring in a number of subjects.

The subjects examined were children in hospital

recovering from an acute exacerbation of asthma or residing at a special school for asthmatics. All had a long history of chest trouble and had been examined by consultant paediatricians and diagnosed as suffering from asthma according to the commonly accepted criteria.

Results

One Minute's Exercise. The effect of exercise of one minute's duration was examined in 34 subjects (Table 1). An increase of F.E.V. occurred in all, although in the majority it was small. The peak value was reached in 24 subjects during the first minute and in the remainder, one to five minutes after exercise. Twenty returned to their resting value within five minutes and in the remainder it varied from six to over 39 minutes.

Five to Ten Minutes' Exercise. The main features of the response to this form of exercise have been reported already (Jones *et al.*, 1962) and only additional features of clinical interest are described here. When the level of exercise is low, the F.E.V. increases slightly during the exercise and soon returns to the resting level afterwards (subject G.G., Fig. 1). With a higher level of exercise the majority of asthmatics show an increase of the F.E.V. during the exercise. At the end, the F.E.V. is frequently near the resting level, and a post-exercise fall occurs during the next five minutes. The resting level is usually reached again within 10 to 15 minutes (subject C.H., Fig. 1), but it may

FIG. 1.—Repeated measurements of F.E.V. in four subjects to show changes in ventilatory function during and after exercise. The first reading is the resting value.

TABLE 2
EFFECT OF 5-10 MINUTES' EXERCISE ON F.E.V.

No. of Subjects	47 (Whole group)		10 (Subgroup within predicted normal range)	
	% N	% R	% N	% R
F.E.V. at rest	69 (22-108)	100	91 (88-108)	100
First post-exercise F.E.V.	56 (17-105)	87 (25-165)	73 (37-105)	74 (42-100)
Lowest F.E.V. after exercise	39 (14-87) $p < 0.001$	53 (18-88)	56 (16-87) $p < 0.001$	56 (18-83)

take considerably longer. Other subjects have a greater tendency to bronchoconstriction and in these the F.E.V. falls below the resting level during exercise and a further fall occurs following exercise. In these the return to normal tends to be slower (subjects W.B. and D.L., Fig. 1). These falls of ventilatory function are more striking when the resting level is 70-80% of predicted normal than when it is lower. The results of 50 such tests are summarized in Table 2.

Post-exercise Fall of F.E.V. A post-exercise fall occurred in all but three subjects. Excluding these, the mean F.E.V. at rest was 69% of predicted normal. Immediately after exercise the F.E.V. was below the resting level in 30, above it in eight and at the resting level in seven. In all 47 it subsequently fell during the next one to eight minutes to a mean of 53% of the resting value.

In 10 the F.E.V. at rest was within the predicted normal range and it might be expected that they would have a nearer to normal ventilatory response to exercise than the remainder of the group. Yet the post-exercise fall to a mean of 56% of the resting value (range 18-83%) was just as great as for the group as a whole (mean 53%, range 18-88%).

A post-exercise fall of F.E.V. is so constant in the asthmatic that a failure to demonstrate it should lead to a reconsideration of the diagnosis or of the technique of the test. Failure may occur if the level of exercise is too low, which was probably so in two of the three subjects who did not show a fall, or if the exercise is interrupted repeatedly to measure the F.E.V. as happened in the third subject, or if an unsuitable form of exercise is used, such as a bicycle ergometer.

Return to Resting Level. Although the F.E.V. begins to rise within 10 minutes of the end of exercise, the time taken to reach the resting value varies considerably (Table 3). It can be seen that

the 10 subjects with relatively normal ventilatory function at rest did not return to their resting levels more rapidly than those with greater impairment of ventilatory function.

In a few subjects the F.E.V. rose above the resting level following the post-exercise fall. Thirty-one children were observed for periods of up to one and a half hours after exercise. In 25 the F.E.V. rose towards the resting level but never exceeded it. In the remainder it rose within an hour of the end of exercise to from 5 to 42% above the resting value and then remained stable or fell slowly towards the resting value during the remainder of the observation period.

Modification of Exercise Effects by Bronchodilator Drugs. Broadly speaking, bronchodilator drugs modify the effects of exercise on ventilatory function in two ways. Exercise lasting less than two minutes preceded by such a drug produces a greater increase of F.E.V. than exercise alone, and the post-exercise fall produced by five to 10 minutes of exercise is reduced or abolished. These actions of the sympathomimetic drugs, adrenaline, noradrenaline, isoprenaline and methoxyphenamine have been examined; so also have the actions of choline theophyllinate and atropine sulphate.

The combined action of drugs and exercise on ventilation has a more prolonged effect than that

TABLE 3
TIME TO RESTING F.E.V. AFTER FIVE TO 10 MINUTES' EXERCISE

Time After End of Exercise (min.)	No. of Subjects	
	47 (Whole group)	10 (Subgroup within predicted N. range)
< 15	12	1
15-30	11	4
30-60	15	2
60+	9	3

TABLE 4
ISOPRENALINE AND ONE MINUTE'S EXERCISE

No. of subjects	6		6	
	< 5 min.		10-23 min.	
Interval between drug and exercise	% N	% R	% N	% R
F.E.V. at rest	54 (17-97)	100	67 (33-95)	100
Highest F.E.V. after drug	67 (25-104) $p = 0.001-0.002$	140 (91-205)	81 (47-105) $p = 0.001-0.002$	132 (103-194)
Highest F.E.V. after drug and exercise	75 (33-108) $p < 0.001$	162 (105-236)	87 (55-111) $p < 0.001$	141 (100-205)

of either form of exercise above. Therefore, we have examined the trend of the F.E.V. throughout the day in the subject at rest and also the effect of drugs in the resting subject as controls for the action of drugs plus exercise. These results will be mentioned only where relevant, since this paper is primarily concerned with the effects of exercise. In general about 50% of subjects examined at rest showed an upward trend during the day. This was usually of the order of 5-15% of the resting value over a period of six hours. In a few, much larger increases occurred, but these did not exceed 50% of the changes produced by drugs and occurred over a longer period than the drug effects.

Isoprenaline Sulphate and Exercise. One minute's exercise produced an increase of F.E.V. when performed after bronchodilatation with isoprenaline and the increase was rather greater when the interval between drug and exercise was five minutes or less (Table 4). The time to the peak increase was shorter

than it was when the drug was given alone. In 10 subjects the peak was at 15 minutes (range three to 43 minutes). The peak after drug plus exercise was reached almost at once. The effect of exercise, therefore, is to produce a higher, earlier peak. The duration of the increase was longer than after exercise alone but was very variable, extending from five minutes to over an hour.

Isoprenaline effectively prevented the post-exercise fall of the F.E.V. when the interval between drug and five to 10 minutes' exercise was less than five minutes (Table 5). Using this short interval the post-exercise fall was prevented in all the eight subjects examined (Table 6), the lowest F.E.V. following exercise being actually higher than the resting value ($p = 0.002$). A Wright inhaler was used for this investigation as described above.

In a similar investigation seven subjects were tested using a 'medihaler'* containing isoprenaline,

* Riker Laboratories Ltd.

TABLE 5
RELATION BETWEEN POST-EXERCISE FALL OF F.E.V. AND INTERVAL BETWEEN DRUG
AND FIVE TO 10 MINUTES' EXERCISE

Subject	F.E.V. at Rest (litres)	Lowest Post-exercise F.E.V. (litres)		Interval Between Drug and Exercise (min.)
		Isoprenaline Before Exercise	No Isoprenaline	
1	2.05 2.05	2.14 1.46	0.64	5 54
2	0.91 0.91	1.31 0.81	0.89	3 65
3	1.75 1.40	1.81 0.89	0.45	4 62
4	1.10 1.33	1.38 0.50	0.30	3 22
5	1.74	1.74	1.00	34

TABLE 6

ISOPRENALINE FOLLOWED WITHIN FIVE MINUTES BY FIVE TO 10 MINUTES' EXERCISE IN EIGHT SUBJECTS

	% N	% R
F.E.V. at rest	63 (43-101)	100
Highest F.E.V. after drug only ..	84 (61-98)	124 (97-148)
Lowest F.E.V. after drug and exercise	80 (62-102) p = 0.002	117 (100-143)
Lowest F.E.V. after exercise only	34 (10-62) p < 0.001	42 (18-69)

and four inhalations were given as the standard dose. In three subjects the fall was completely prevented, in two partly prevented and in two it was not prevented at all. This result was considered to be due to inadequate dosage.

Oral isoprenaline in a dosage of 0.6-0.7 mg./kg. was much less consistent in its effect. Out of 10 subjects examined it partly or completely prevented the fall in only six. Although the interval between drug and exercise was varied from 24 to 57 minutes this did not seem to affect the results materially.

Adrenaline and Noradrenaline. A small number of subjects were examined using adrenaline and noradrenaline in order to compare the effectiveness of these drugs with isoprenaline (Table 7). Adrenaline prevented the post-exercise fall completely in three subjects and partly in two. Noradrenaline was only partially effective in all the four subjects examined. The interval between drug and exercise for these experiments was two minutes.

Ephedrine Hydrochloride. The effect of one minute's exercise following ephedrine was similar

TABLE 8

EPHEDRINE HYDROCHLORIDE, 0.8-1 mg./kg., FOLLOWED BY ONE MINUTE'S EXERCISE IN NINE SUBJECTS

	% N	% R
F.E.V. at rest	56 (28-94)	100
Highest F.E.V. after drug only ..	68 (41-108) p < 0.001	126 (100-174)
Highest F.E.V. after drug and exercise	75 (45-111) p < 0.001	141 (114-189)

to the effect of exercise after isoprenaline (Table 8). Exercise was given one to three hours after the drug (mean two hours), but the response was not closely related to this interval. In seven subjects given ephedrine alone, the peak effect was reached in one to five hours (mean two and three-quarter hours), so that the drug should have been maximally effective at the time of the exercise. The peak after exercise was reached within two minutes and, as in the case of isoprenaline, was sustained for a variable period usually longer than with exercise alone.

Ephedrine effectively prevented the post-exercise fall in the majority of subjects (Table 9). The fall was completely prevented in 12, partly prevented in six, and in two the drug did not materially influence the effect of the exercise. The interval between drug and exercise was varied from 20 to 200 minutes in an attempt to find out the most effective interval. This appeared to be between one and two and a half hours, but effectiveness was not so closely related to the interval between drug and exercise as in the case of isoprenaline. In seven subjects given the drug alone the peak increase was at two and three-quarter hours (range one to five hours), so that the

TABLE 7

ADRENALINE AND NORADRENALINE FOLLOWED WITHIN FIVE MINUTES BY FIVE TO 10 MINUTES' EXERCISE

Drug	Adrenaline		Noradrenaline	
	5		4	
No. of subjects	% N	% R	% N	% R
F.E.V. at rest	85 (64-97)	100	91 (68-113)	100
Lowest F.E.V. after drug and exercise	79 (55-106) p > 0.1	91 (80-109)	70 (44-83) p = 0.001-0.002	66 (30-92)
Lowest F.E.V. after exercise only	25 (14-46) p < 0.001	30 (18-48)	20 (14-26) p < 0.001	25 (18-35)

TABLE 9
EPHEDRINE HYDROCHLORIDE, 0.8-1.0 mg./kg., FOLLOWED
BY FIVE TO 10 MINUTES' EXERCISE IN 20 SUBJECTS

	% N	% R
F.E.V. at rest	69 (26-99)	100
Highest F.E.V. after drug only ..	82 (43-112)	123 (100-160)
Lowest F.E.V. after drug and exercise	65 (17-104) $p > 0.1$	94 (32-125)
Lowest F.E.V. after exercise only	44 (15-87) $p < 0.001$	57 (20-85)

most effective interval was rather shorter than the time to the peak action of the drug.

Methoxyphenamine Hydrochloride. The action of this sympathomimetic drug appeared to be comparable with that of ephedrine (Table 10). It completely prevented the post-exercise fall in four subjects, partly prevented it in two and failed to prevent it in one subject. It appeared to be most effective when given one to two and a half hours before exercise, which was when the drug acting alone was found to exert its maximum effect on the F.E.V. In seven subjects given the drug alone, the peak increase was at two hours and 10 minutes (range one to four hours).

Choline Theophyllinate. The post-exercise fall of F.E.V. was prevented in six subjects, partly prevented in two and was not influenced at all in one subject (Table 10). The interval between drug and exercise was varied from 40 minutes to three and a half hours with a mean of two and a half hours.

Again there was no clear relation between the interval and effectiveness but one and a half to two and a half hours seemed to be the most satisfactory interval. The time to peak increase of the F.E.V. in eight subjects given the drug only was 91 minutes (range 24-190 minutes). Exercise is best given, therefore, when the drug is producing its maximum effect.

Atropine Sulphate. This drug was relatively ineffective (Table 10). It completely prevented the fall in two subjects, partly prevented it in two and failed to prevent it in two subjects. The interval between drug and exercise was varied from 12 to 26 minutes. The action of atropine alone was only examined in two subjects and the peak effect was achieved in 20 minutes and 30 minutes.

Discussion

The characteristic effects of exercise on ventilatory function have three clinical implications worthy of consideration. First, we have found them to be of diagnostic value. The increase of ventilatory function with brief exercise and decrease with five to 10 minutes' exercise is a very constant finding and demonstrates the essentially labile state of the bronchi in asthma. By contrast, our experience of other conditions such as bronchitis, bronchiectasis and the normal subject are that these effects of exercise are small or absent. We have come to regard them as highly specific for asthma.

Secondly, they are of value in the assessment of the asthmatic. They are of greatest help in the subject with a history suggestive of asthma, with no abnormal clinical signs on examination and ventilatory function at rest within predicted normal

TABLE 10
DRUGS AND FIVE TO 10 MINUTES' EXERCISE

	Methoxyphenamine		Choline Theophyllinate		Atropine Sulphate	
No. of subjects	7		8		6	
	% N	% R	% N	% R	% N	% R
F.E.V. at rest	77 (47-103)	100	49 (21-84)	100	76 (20-106)	100
Highest F.E.V. after drug only ..	85 (56-108)	111 (102-120)	64 (31-95)	159 (100-308)	82 (24-115)	108 (103-113)
Lowest F.E.V. after drug and exercise ..	81 (50-107) $p > 0.1$	82 (23-117)	52 (14-93) $p > 0.1$	123 (47-333)	52 (18-105) $p = 0.05-0.1$	69 (21-104)
Lowest F.E.V. after exercise only ..	40 (15-69) $p < 0.001$	48 (25-76)	35 (15-63) $p = 0.002$	80 (48-132)	25 (14-47) $p = 0.002$	41 (16-111)
Dose	7-9 mg./kg.		7-9 mg./kg.		0.01-0.03 mg./kg.	

limits or only slightly impaired. In this group, five to 10 minutes' exercise reveals a striking fall of the F.E.V., thus demonstrating marked impairment of ventilatory function despite normal findings at rest. In addition, one minute's exercise, especially when combined with isoprenaline nearly always produces a small increase of F.E.V. When the resting value is low, a fall of the F.E.V. can be demonstrated, but is of less value. In this group isoprenaline and one minute's exercise demonstrates the presence of bronchoconstriction more effectively.

Thirdly, the response to five to 10 minutes' exercise has therapeutic implications. Exercise tolerance may be surprisingly poor despite few or no physical signs and relatively good ventilatory function at rest. This is because exercise tolerance is not determined by the level of ventilatory function at rest, but by the level to which it falls on exercise. A suitable bronchodilator drug given an appropriate interval of time beforehand may greatly improve exercise tolerance by preventing bronchoconstriction during exercise.

The bronchodilator action of brief exercise and a drug may prove to have therapeutic value. We have found the combined effect of isoprenaline and exercise a useful means of producing rapid, maximum bronchodilatation before postural drainage and coughing when there is associated infection. This régime also prevents the fall of F.E.V. which commonly occurs during postural drainage and coughing and it thereby improves the efficiency of the procedure.

It follows from the evidence presented that prolonged continuous exercise is unsuitable for the asthmatic, even if the level is such as not to make him unduly breathless. On the other hand, ball games in which the exercise is in the form of short bouts is a suitable form of exercise. In our experience this form of exercise usually produces an increase of F.E.V. both during and after a game, but in subjects with a marked post-exercise fall ventilatory function may decrease considerably during a game despite the intermittent nature of the exercise. It is in these subjects that a drug such as ephedrine given one to two hours beforehand may be of value.

This paper is not primarily concerned with the causes of the changes in ventilatory function with exercise. The increase of F.E.V. with short exercise has been considered to be due to a fall in airways resistance associated with an increase in the rate of inspiration and/or an increase of lung blood volume (Capel and Smart, 1959). However, release of adrenaline during exercise (Lewis and Morton, 1954) remains a possible cause since it has been

shown (Jones *et al.*, 1962) that the phenomenon is virtually abolished after maximum bronchodilatation with an isoprenaline aerosol.

The bronchoconstriction occurring at a later stage of the exercise must be caused by a factor operating in an opposing fashion. It may be due, for example, to the response of an abnormal bronchial tree to muscle metabolites released during exercise. Although the numbers examined are too small to allow of definite conclusions, the preventive effect of sympathomimetic drugs in order of potency on present evidence is isoprenaline—adrenaline—noradrenaline, and this is the order of their potency as bronchodilator agents in the resting asthmatic subject. It is also their order of potency as inhibitors of smooth muscle in the rabbit under experimental conditions (Furchgott, 1959). Atropine is distinctly less effective and this too is in line with previous clinical observations that blocking of parasympathomimetic activity with atropine does not abolish all bronchoconstriction.

Summary

Exercise of one minute's duration produces an increase of ventilatory function in the asthmatic child as measured by the forced expiratory volume test. Exercise of five to 10 minutes' duration produces a decrease of ventilatory function. These effects are considered to be due to bronchodilatation and bronchoconstriction respectively.

The action of bronchodilator drugs on these ventilatory effects of exercise has been examined. When bronchodilatation is produced by a drug, a further increase of the F.E.V. follows one minute's exercise. Bronchodilator drugs partly or completely prevent the fall of F.E.V. following five to ten minutes' exercise. The diagnostic and therapeutic implications of these effects of drugs and exercise on ventilation are discussed.

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