

Exercise-Induced Asthma

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Exercise has long been known to provoke a short attack of airways obstruction in asthmatics, and some 3 years ago we were able to review our own results and an extensive literature on this subject (4). Since then interest in exercise-induced asthma (EIA) has continued to flourish, and while a number of studies have merely confirmed earlier observations by more reliable methods, others have contributed substantially to our understanding of this very interesting phenomenon. It is the purpose of this article to briefly recapitulate the established facts about EIA and to review the more recent developments.

The pattern of the response of the asthmatic to exercise

Whatever the method of measuring the airway response to exercise in the asthmatic, the overall pattern is very similar to that shown in Fig. 1. During the initial part of exercise, there is moderate bronchodilation, but after 3 or 4 min mild bronchoconstriction usually becomes evident. The major increase in airways obstruction, however, only becomes apparent after stopping the exercise, and it reaches its maximum some 2 to 5 min after stopping. The changes in lung function can be expressed in terms of the percent rise during exercise and fall after exercise as in Fig. 1, or perhaps more accurately as the ratio of the post- to pre-exercise values (34).

The method of quantitating the exercise-induced changes is of some importance. Using the percentage changes, no

relationship has generally been observed between the pre-exercise level of lung function and the severity of EIA in children (42, 38), i.e., the children with better resting levels had greater absolute falls in lung function. In complete contrast, careful studies in adults have shown smaller changes in patients with better baseline values (25). This difference may depend on the type of patient studied. Of greater importance is the fact that the comparison between pre- and post-exercise values may be considerably modified when drugs which affect airway calibre are given before the test. As will be discussed later, atropine is a powerful bronchodilator, and the comparison between post-exercise lung function with either pre-drug pre-exercise or post-drug pre-exercise values may lead to entirely different conclusions. It is probably true that for comparative purposes, the closer the pre-exercise lung function in different studies, the more valid the conclusions about the changes induced by exercise.

The prevalence of EIA

It is becoming recognized that EIA is not, with very few exceptions, an isolated disorder in its own right, but rather just one method of provoking an attack in an asthmatic subject. The incidence of clear-cut EIA is not known for certain because so many factors influence its severity (24), and different studies have used different techniques. In children we found a greater than 10% fall in peak expiratory flow rate (PEFR) in some 90% of asthmatic children (21), while others

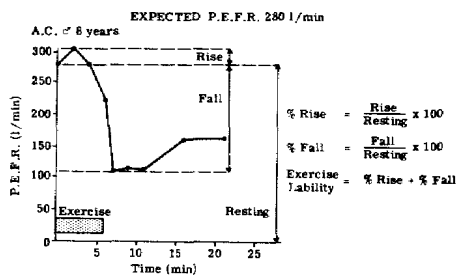


Fig. 1: Typical response to 6 min running of an asthmatic child showing one method of calculating indices of bronchial liability. (From ref. 24.)

have found responses in 60–70% of children (28, 15) using a 15–20% fall in forced expired volume in 1 sec (FEV_1) as their index of response. The higher estimate of incidence may be correct since it has been shown that a fall in PEFr greater than 10% is rarely seen in healthy children (9). Data on adults are less readily available except for one study of 21 subjects who showed an incidence of over 80% of abnormal changes in sensitive tests of lung function after exercise (25).

The exercise stimulus

Evidence continues to accumulate showing that the severity of EIA depends on the type of exercise, its intensity and duration. The greater asthmagenicity of running compared with other types of exercise, especially swimming (1, 18), agrees with clinical observations. More recent studies showed running to be more potent than walking in children (27), but in adults Miller et al. (34) found no difference between running and cycling, although only 11 of their subjects developed EIA. Comparing arm with leg exercise in children (4), we noted the potency of arm ergometer cranking compared with treadmill running at similar levels of oxygen consumption. In a study of 10 adults Strauss et al. (43) found that exhausting arm or leg pedaling both produced significant EIA, but non-exhausting leg cycling of similar intensity to the exhausting arm cranking produced less EIA. All this evidence suggests

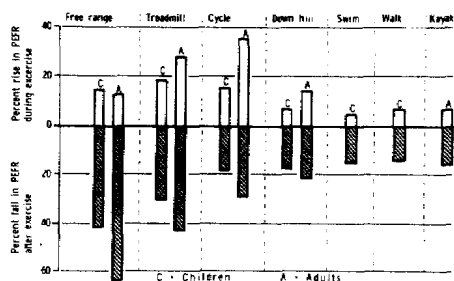


Fig. 2: The influence of the type of exercise on the response of asthmatic children and adults. Broncho-dilation during exercise is shown above the line and exercise-induced asthma below the line. The results were obtained from pooled data of a number of published studies in which subjects exercised at approximately 70–80% of their maximal working capacity. (From ref. 19.)

that the relationship between work load and muscle mass may influence the intensity of EIA, but would not readily explain the differences seen between running, swimming and kayak paddling (19), as summarized in Fig. 2.

There have been a number of attempts to standardize the severity of the exercise in order to obtain a large and reproducible response. The studies of children running on a treadmill by Silverman & Anderson (39) showed increasing amounts of EIA with increasing duration of exercise up to 6 min, but not longer, and with increasing severity of work load up to about 60–80% of their predicted maximum oxygen consumption. This corresponded to a heart rate of about 180 per minute. A very similar conclusion was reached by Eggleston & Guerrant (15) who studied 48 subjects aged 8 to 36 years and suggested that the optimal test should produce a heart rate of about 90% of the predicted maximum heart rate based on age. Even with standardized tests, there is, however, a disconcertingly large variation in the response of the individual to repeated testing. For subjects whose tests are repeated within 1 to 4 weeks, the coefficient of variation appears to be about 20–30%, but rises to 50–60% for repeat testing at intervals of 1 to 4 months or longer (15, 39).

Remembering that the individual could easily vary by twice the coefficient of variation (i.e., two standard deviations), one might easily obtain a 50% difference in the severity of EIA to an identical test repeated within a week or so. The reason for this variability has not been satisfactorily determined but could, of course, be related to changes in bronchial lability induced by other methods, as seen recently in the response to methylcholine challenge after antigen-induced asthma (13).

The mechanisms of EIA

Since EIA is such a readily available model of asthma, great interest has developed in the physiological variables related to exercise which trigger the attack and in the pharmacological or neurological events leading directly to bronchoconstriction. The roles of hyperventilation, hypocapnia and acidosis, believed to be possible triggers, were reviewed by Anderson et al. (4), and none were thought to be clearly implicated. The recent studies of McFadden et al. (32) in eight asthmatic adults showed that neither isocapnic nor quite marked hypocapnic hyperventilation at rest (to simulate levels reached during exercise) provoked any real change in lung function. Giving CO_2 to asthmatics to breathe produces some bronchodilatation at rest and after exercise, but this appears to be a pharmacological effect and does not imply any role for hypocapnia in EIA (17).

One of the most interesting recent developments in this field has been the studies of the effect of humidity on EIA. Bar-Or et al. (5) studied a group of children who exercised on a treadmill in a climatic chamber at a temperature of 25–26°C and relative humidities of 25% and 90%. The mean fall in post-exercise maximum mid-expiratory flow rate (MMEF) was 26% in the drier climate and only 5% in the humid climate. This, of course, is in complete contrast to the generally held (but not substantiated) view that dry climates are good

for asthmatics. An identical conclusion was reached by Chen & Horton (12) who studied asthmatics exercising on a treadmill breathing air supplied at various combinations of temperature up to 37°C and humidity up to 100%. They showed a convincing relationship between the severity of EIA and the calculated amount of heat lost from the respiratory tract. It seems that receptors lying in the airway sensitive to water or heat loss might well trigger off the chain of events leading to asthma induced by running, but it remains to be seen if this mechanism can explain the different amounts of asthma following similar amounts of exercise of different types (Fig. 2). It could explain the relatively harmless nature of swimming, but not that of walking or kayak paddling in the laboratory.

Whatever the nature of the trigger there is accumulating evidence to suggest that the eventual bronchospasm is the result of the release of a stored chemical mediator(s). Thus Silverman & Andrea (40) showed that the drug sodium cromoglycate, which is not a bronchodilator but inhibits mediator release from mast cells, could inhibit EIA if given immediately before exercise but not if given immediately at the end of exercise. Furthermore, several studies have suggested that repeating exercise tests at short intervals diminishes the response (33, 11, 27). We have recently made a formal study of this refractory period following EIA (14) in asthmatic children. It was found that the severity of EIA in the second of a pair of exercise tests depended on the interval between the tests (Fig. 3) for tests of equal severity. When the severity of the first exercise period was varied to produce different amounts of EIA, the response in the second constant severity test of the pair was inversely related to the EIA produced by the first test (Fig. 4). We believe these results are compatible with the hypothesis that EIA is the result of the release of a stored mediator whose resynthesis takes an appreciable amount of time.

Remembering the time course of events in

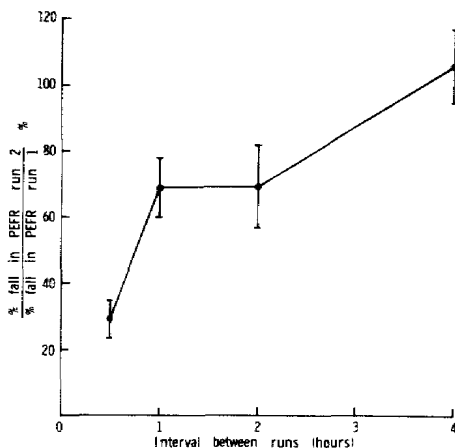


Fig. 3: The effect of the interval between pairs of exercise test of identical severity on the severity of EIA in the second test compared with the first. The reduction in EIA in the second test with short intervals between the pairs shows the refractory period. Mean of results in nine children with bars indicating ± 1 s.e.m. (From ref. 14.)

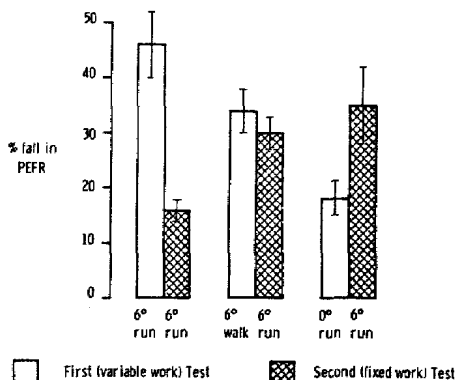


Fig. 4: Severity of EIA in each of paired exercise tests carried out 30 min apart. The first test was performed at different work rates, while the second test was always at the same work rate. The amount of EIA in the first test was proportional to the work rate, but that in the second test was inversely proportional to the EIA produced in the first test. (Redrawn from ref. 14.)

EIA and the evidence above about mediator release, a hypothetical model of the pathways involved has been constructed (21) and is shown in Fig. 5. The model suggests that

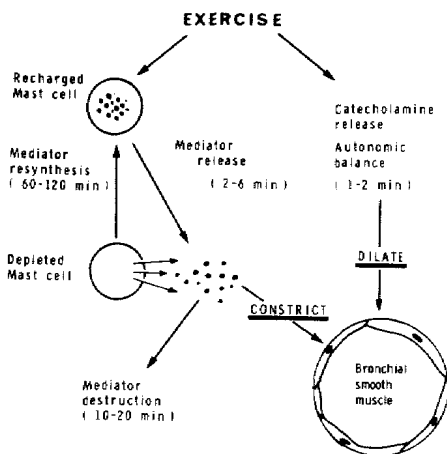


Fig. 5: Hypothetical pathways concerned in exercise-induced asthma. Exercise is envisaged as causing bronchoconstriction by the liberation of mediators from mast cells, and an opposing bronchodilation during the exercise period by the stimulation of the sympathetic nervous system. The time course of these events and of the destruction and resynthesis of mediator cause the sequence of events seen clinically, including the refractory period. (From ref. 21.)

during exercise there is both stimulation of mast cells to liberate stored mediators of bronchoconstriction and increased sympathetic drive which inhibits this constriction. In most cases the sympathetic effect predominates in the earlier part of exercise, and there is net bronchodilation. Once the patient stops exercising, the sympathetic drive falls off and the full constrictor effect takes over, which could account for the peak of EIA occurring some 2 to 3 min after stopping. Once the mast cells have been discharged, it takes an hour or two to resynthesize the transmitter, and this accounts for the refractory period described above. It is likely that the transmitter is itself actively destroyed at a relatively rapid rate so that if exercise is prolonged, virtually all the transmitter is inactivated while the sympathetic drive is still present, and then on stopping there is little or no EIA – i.e. the patient has “run through” his asthma (39).

The site of constriction in EIA

It is likely that the airway narrowing which occurs in EIA must be mechanical rather than inflammatory, since it is so readily and rapidly reversed, but the site of this narrowing is not certain. The changes in crude tests of lung function such as the PEF_R and FEV₁ implicate gross changes in larger airways, but changes in lung recoil pressure or closure of lung units could also be involved (20). In a group of children Benatar & Konig (6) found that EIA caused similar and significant changes in both crude and sensitive tests of lung function, but of particular interest was an increase in residual volume, fall in flow rates in the terminal part of the flow-volume curve and a decrease in the slope of the curve, which they felt indicated closure of some lung units. Similar conclusions were reached by Freedman et al. (20) in a study of adults with EIA, but they also noted a substantial increase in total lung capacity in some subjects with a parallel shift of the pressure-volume curve to the left suggesting decreased elastic recoil, closure of lung units and widespread airway narrowing.

When a mixture of oxygen and helium is breathed instead of air, the density of the mixture is less, and if the predominant site of resistance to flow is in airways with a small total cross-sectional area (i.e. the central airways) maximum flow rates will be higher with O₂/He than air. Using this technique to study EIA, it has been found that children and some adults showed increased density dependence of flow during EIA which probably means that the predominant site of airways obstruction is in the larger, central airways (6, 31). Other adults, however, show a fall in density dependence of flow with EIA suggesting small airways as the primary site of obstruction. Furthermore, McFadden et al. (31) noted that the subjects with the predominantly small airway response were helped by pre-treatment with sodium cromoglycate but not by the anti-cholinergic drug SCH 1000, while those with the large airway response were more likely to be

helped by SCH 1000. They suggested that chemical mediators might be affecting small airways in EIA while the effect on large airways was reflexly mediated through the vagus. In summary, it seems likely that both large and small airways are involved in EIA to a varying degree in different subjects, and this might account for some of the differences in response to drugs, such as atropine, which have been observed.

The influence of drugs on EIA

EIA can be prevented or substantially reduced by a number of different drugs, and a study of their action has been of some importance in understanding EIA. The general pattern of response to four agents used to treat asthma is shown in Fig. 6. In this illustration, the results have been deliberately expressed in terms of the percentage of expected normal lung function in order to emphasize the effects of the drugs given before the exercise as well as the exercise effect itself. The sympathomimetic, cholinergic and methyl xanthine drugs all caused an elevation in baseline lung function, and only sodium cromoglycate caused no shift because it is not a broncho-

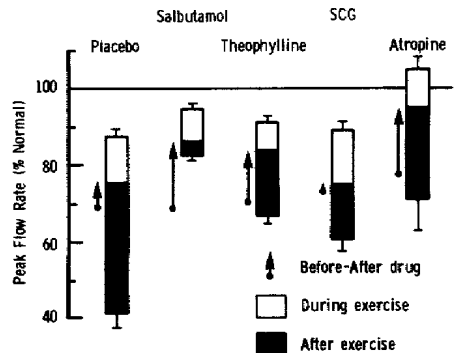


Fig. 6: The effect of drugs on exercise-induced asthma with values being expressed as percentage of the expected peak flow rate. The arrow indicates the bronchodilatation due to the administration of the drug occurring at rest before the exercise test. All values are the mean of 15 children, apart from the atropine group in which there were seven children. The bars indicate 1 s.e.m. (From ref. 4.)

dilator. For this reason, it is only possible to be confident that sodium cromoglycate partially inhibited EIA since the drug and placebo tests started from the same baseline. The effect of the other drugs is more difficult to define and is largely a question of semantics. Clearly, the post-exercise PEFR never fell as low as it did with placebo, but the fall from the elevated baseline was quite clear in the case of theophylline and atropine. There were also individual differences in response with a major degree of inhibition of EIA noted in all subjects with salbutamol, and significant inhibition in 75% with theophylline and sodium cromoglycate, and in 60% with atropine (23).

The exact role of anticholinergic agents in provoked asthma remains uncertain despite continuing work in this field. Thus the study by Borut et al. (8) showed that both atropine and SCH 1000 were powerful bronchodilators at rest, but some constriction from the elevated baseline still occurred after exercise similar to that shown in Fig. 6. Chan-Yeung (10) found that SCH 1000 inhibited EIA without showing much initial bronchodilator effect, which is rather difficult to understand. In relation to antigen-induced asthma, most recent work suggests that after allowing for its initial bronchodilator effect, neither atropine nor SCH 1000 cause significant inhibition (30, 16). In view of the results of McFadden et al. (31), it is possible that the observed differences are due to intersubject differences in the site of airways obstruction.

One of the more interesting recent observations in relation to EIA concerns the relative efficacy of orally administered and inhaled bronchodilators in preventing the attack. Anderson and her colleagues, in a number of studies, showed that while aerosol salbutamol or fenoterol clearly prevented EIA, oral salbutamol, terbutaline, metaproterenol or theophylline had relatively little effect, even though they produced bronchodilatation at rest (2, 3, 35, 37). In a related study, Hertz et al. (26) looked at the effect of sympathomimetic drugs given long enough

before exercise for their bronchodilator effect to have worn off, and in three out of 11 subjects they found that EIA was still inhibited. Both groups have suggested that sympathomimetic agents may inhibit EIA by mechanisms other than a direct effect on bronchial smooth muscle, and Anderson et al. (2) proposed the interesting idea that the aerosol drugs might reach bronchial mast cells and have a cromoglycate-like effect. The implication is that orally administered agents do not reach these mast cells in sufficient concentration to block mediator release. One might also speculate whether similar considerations explain the failure so far to produce a really effective orally active cromoglycate-like compound. For clinical purposes, it is obviously best to advise the use of an aerosol bronchodilator to prevent EIA.

Is exercise testing of clinical value in asthma?

It has been very tempting to assume that because exercise provokes an attack of asthma closely resembling clinical attacks in some respects, extrapolation can be made from EIA to clinical asthma. Unfortunately, there are some important differences between clinical asthma and EIA which have led many to conclude that different mechanisms might be involved in the brief type of asthma provoked by exercise and the more prolonged and troublesome asthma seen clinically.

There can be little doubt of the clinical value of exercise testing as an aid to diagnosis in cases where this is not clear, as, for example, in children who present at the clinic between attacks with no clinical or physiological abnormality. As discussed above, a very high proportion of asthmatics will have a positive response to exercise not seen in other conditions. The same probably applies to adults, although there are obvious problems about exercise testing in older subjects. What is less certain is whether or not the response to exercise reflects clinical

severity of asthma. In the studies of asthmatic children by Silverman (38) which we reviewed (4), there was no clear correlation between the severity of EIA and the severity of the asthma as judged by recent symptoms, asthma diary scores or home recording of PEFr over the preceding month. Moreover, Silverman et al. (41) found no improvement in EIA in a group of asthmatic children under treatment which considerably improved their clinical and physiological condition. On the other hand, Haynes et al. (25) noticed a greater degree of abnormality in several tests of lung function after exercise in adults with more abnormal resting values, but commented, that because of the variance, it would be difficult to predict the behaviour of a given individual.

EIA seemed at first to be an ideal model for studying the action of drugs used to treat asthma, since many of them can be shown to block EIA quite effectively (Fig. 6). It was soon realized that the correlation between the effect of a drug in blocking EIA and its clinical value to the individual patient was either poor or non-existent. Thus, Godfrey et al. (22) in a long-term follow-up of children treated with sodium cromoglycate found that EIA was effectively blocked in many children who were not controlled clinically, and vice versa. Most studies of the efficacy of steroids in EIA have shown them to have little effect in the majority of subjects (29) despite their very obvious clinical usefulness. In a recent study, Pollock et al. (36) showed that high-dose theophylline therapy could inhibit EIA and that the effect was related to the blood level achieved. However, Bierman et al. (7) compared the inhibition of EIA by high-dose theophylline with its clinical effect, and, although it inhibited EIA to some degree in most children, they did not find a correlation with clinical efficacy. At the present time one must draw the conclusion that EIA is not a reliable model of clinical asthma on which to test the relative efficacy of drugs used to control the usual type of clinical asthma. However, many people, especially children, are specifically bothered by EIA

itself which may be severely curtailing their everyday activities. In these patients, exercise testing with and without different drugs can be very informative.

For the individual patient, exercise testing thus seems to be chiefly of value in diagnosis where this is uncertain, and for determining the efficacy of drugs used specifically to control the symptoms of EIA where these are prominent. In the wider sphere, EIA is undoubtedly contributing to a better understanding of pathophysiological processes in asthma, and also to an understanding of the epidemiology of the disease and its relationship to bronchial lability.

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