

Current Concepts of Exercise-Induced Asthma

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In 1975 when a major review of this subject was published (2) the study of exercise-induced asthma (EIA) was generally confined to the research laboratory, where it was considered to be a "useful model of asthma". Since that time exercise has become well established as a provocation test for the diagnosis and assessment of asthma.

Exercise-induced asthma has been defined as a reduction in peak expiratory flow rate (PEFR) or forced expiratory volume in 1 sec (FEV₁) after exercise of 10% or more of the pre-exercise value (6, 58). When 6–10 min of strenuous exercise is performed under ambient laboratory conditions the incidence of EIA is generally reported to be 70–80% of the clinically recognised asthmatic population (50, 76). In patients with moderate to severe EIA, the airways obstruction induced by exercise is accompanied by hyperinflation and arterial hypoxemia, making it undesirable for many to take part in regular physical activity. It is for this reason that an understanding of the prevention and treatment of EIA with pharmacological agents is essential in the management of patients with asthma.

There have been many studies on the irritant effects of pharmacological agents and these have recently been reviewed (6). Beta-sympathomimetic agents when delivered as aerosols and inhaled sodium cromoglycate (SCG) are now well recognised as the best

prophylactic drugs for EIA. Studies of other medications less commonly used in the treatment of asthma have provided insight into possible mechanisms of EIA and some of these will be discussed in detail.

In earlier studies, the nature, intensity, and duration of exercise were shown to be important factors affecting the magnitude of the airway response to exercise (1, 76). In 1976 Weinstein and his colleagues (90) reported the beneficial effect of inhaling humidified air during exercise. Since that time the temperature and water content of the inspired air have both been recognised as vital determinants of the asthmatic response to exercise. The studies of Chen & Horton (30) and Strauss and his colleagues (83, 84), clearly demonstrated that EIA could be blocked when the inspired air was conditioned to body temperature and fully saturated with water vapour, and enhanced when cold dry air was inhaled. There is now a general consensus that airway cooling is important as an initiating stimulus in EIA (9, 30, 35). More recently it has been suggested that water loss *per se* may also be important by acting as a hypertonic stimulus (9, 37) but more studies are required to confirm this hypothesis.

The beneficial effect of many drugs with anti-allergic properties, particularly SCG, has led to the theory that mast cell derived mediators, potentially capable of inducing smooth muscle contraction, are released in response to airway

cooling or water loss. There is now some direct evidence to support this contention as some patients have an increase in plasma histamine in response to exercise (8, 20, 45). In addition, a neutrophil chemotactic-like factor has been measured in the serum of asthmatics at a time when exercise has induced an attack of asthma (54). There are other substances which have been implicated in EIA which do not arise from mast cells such as noradrenaline, which is released during exercise. Noradrenaline may cause bronchial smooth muscle contraction by acting on alpha-receptors which, in turn, may be activated as a result of airway cooling.

The following review examines the manner in which EIA has been diagnosed and assessed in the laboratory, the drugs used for its prevention and some of the possible mechanisms by which it occurs.

Which measurement is best?

The identification of abnormal bronchial reactivity and its severity in response to exercise is determined by the method used to measure changes in airways resistance. The availability and simplicity of instruments for measuring PEFR and FEV_1 has led to their use in documenting the incidence and severity of EIA. However, there are other advantages which favour these measurements. Peak expiratory flow rate and FEV_1 are more reproducible than measurements such as specific conductance (SGaw), flow rate at 50% of the vital capacity ($\dot{V}_{50}$) and the forced expiratory flow in the middle half of the vital capacity (FEF_{25-75}) (12). Unlike $\dot{V}_{50}$ and FEF_{25-75} , PEFR and FEV_1 are not dependent on a prolonged and complete expiration so that measurements may be made at frequent intervals both during and after exercise. The changes in PEFR and FEV_1 in response to exercise correlate well with changes in FEF_{25-75} and $\dot{V}_{50}$ (4, 12) and have been well documented in the normal population. Measurements of SGaw, $\dot{V}_{50}$ and FEF_{25-75} have frequently been cited as "more sensitive" for the detection of EIA because the changes are greater compared with the changes in PEFR and FEV_1 . However, this concept of sensitivity tends to

ignore the fact that normal non-asthmatic subjects also have greater changes in these indices. In our laboratory, we define an abnormal response to exercise as a reduction in flow rates, volumes or conductance (expressed as a percentage of the pre-exercise level) greater than the mean plus 2 SD of the reduction observed in normal non-asthmatics performing an exercise challenge under the same conditions. Thus for the percent reduction in SGaw to be regarded as abnormal (i.e. in the asthmatic range) a value of 50% or more is required, for PEFR the reduction need only be 10%.

Another criticism of the use of PEFR and FEV_1 has been that these measurements are too insensitive to detect changes in small airways and therefore they are not always adequate for determining the site of action of drugs. Further there has been some concern about tests which require a deep inspiration for determining changes in airway calibre in response to a bronchoconstrictor stimulus (61). This is particularly important in normal subjects, who may overcome the bronchoconstrictor effect of methacholine merely by taking a maximal inspiration prior to a PEFR or FEV_1 manoeuvre. This may be the reason that the change in SGaw after exercise in normals is greater than changes in PEFR or FEV_1 . In patients with moderate to severe asthma the effect of a deep breath is minimal (61). However in mild asthmatics it is possible that, as with normal subjects, the constrictor response is missed as a result of a deep inspiration and abnormality may be better detected by use of measurements of SGaw. The practice of recording the highest of three values for PEFR or FEV_1 in the post-exercise period, may underestimate the incidence of EIA in patients with mild asthma. However, as few patients complain of symptoms of asthma when the PEFR or FEV_1 falls less than 20% after exercise, these measurements are more than adequate for the clinical management of EIA.

From the point of view of research and documentation of EIA, measurements reflecting both large and small airways calibre should be made and interpreted in the light of the responses in normal non-asthmatic subjects. Small breath tests may provide useful information in

assessment of both normal subjects and mild asthmatics.

Which index is best?

The diagnosis and severity of EIA is usually made using the percent fall index (% fall). This index is defined as the reduction in flow rates (e.g. PEFR) or volumes (e.g. FEV₁) after exercise expressed as a percentage of the value measured immediately prior to challenge. Since the normal non-asthmatic population exhibits a mean percent fall + 2 SD in PEFR of 10% or less, a value of 10% fall or more is now generally accepted as diagnostic of EIA when PEFR or FEV₁ are measured. A fall of 25% or more is considered severe enough to require prophylactic therapy (6).

There are other indices which have been used to assess the airway response to exercise, the Jones lability index (JLI) (48) and the exercise lability index (ELI) (76). More recently the ELI has been referred to as the top-bottom index (TBI) (26). The ELI (or TBI) is calculated by adding the rise in flow rates or volumes in response to exercise, expressed as a percentage

of the pre-challenge level, (percent rise) and the percent fall. Thus these indices give a measurement of the overall bronchial lability either in response to exercise alone (ELI & TBI) or exercise and bronchodilator drugs (JLI) and are therefore excellent to characterize bronchial reactivity. It is perhaps unfortunate that many investigators have neither measured nor reported, the changes in flow rates that may have been observed during exercise. The opportunity to obtain an index of overall bronchial lability makes exercise a superior test for bronchial reactivity compared with the methacholine and histamine inhalational challenges which assess reactivity only by a decrease in flow rates or volumes. However, the JLI, ELI or TBI should not be used for the assessment of the severity of EIA, because the initial bronchodilatation induced by exercise is not specific to asthma (34, 51).

A comparison of the percent fall index and the ELI (% rise plus % fall) is made in Fig. 1 for the effects of drugs and repeated exercise challenge. It can be readily observed that an overall reduction in ELI may be indicative of drug efficacy. However, the use of ELI tends to

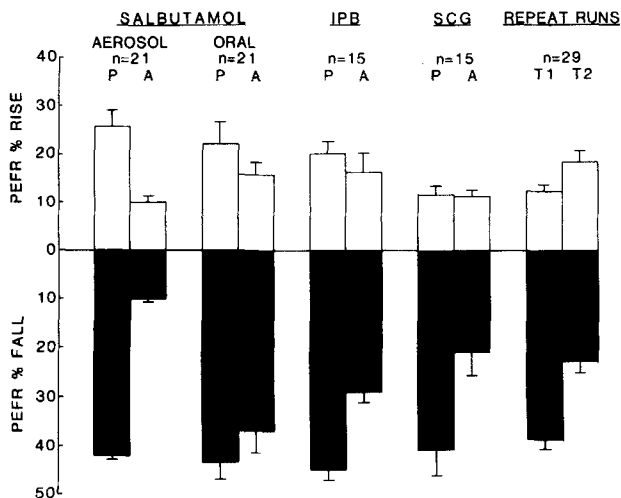


Fig. 1. The mean + 1 SEM increase in peak expiratory flow rate (PEFR) in response to exercise expressed as a percentage of the pre-exercise value (% rise) and the mean + 1 SEM fall in PEFR after exercise expressed as a percentage of the pre-exercise value (% fall) in 80 asthmatics. Fifty-one patients exercised after a placebo (P) and an active drug (A). Twenty-one of these patients exercised after 200 µg (aerosol) and 4 mg (oral) of salbutamol. Ipratropium bromide (IPB) in a dose of 80 µg was given 15 min prior to exercise as was sodium cromoglycate (SCG) in a dose of 2 mg by metered dose inhaler. Twenty-nine patients exercised on two occasions 40 min apart (T1, T2). The exercise lability index is the % rise plus the % fall.

detract from the effect of a drug on the post-exercise fall and the significance of refractoriness with repeated exercise challenge. This is particularly the case when an agent such as SCG, which has no effect on the resting level of lung function, is used, or when exercise is repeated at a lower initial level of FEV_1 or PEFr.

Although the percent fall index has been the most widely used guide to the severity of EIA there is some criticism of its use when comparing responses between patients with varying degrees of airways obstruction at rest (22). For example, two patients with comparable predicted values for FEV_1 may have the same fall in FEV_1 , expressed as a percentage of the pre-exercise value, yet have different values for FEV_1 , prior to exercise. Whether the severity of EIA is similar in these two subjects remains difficult to answer!

It has been argued that the airway response to a variety of stimuli will be greater when the airways have abnormal tone prior to challenge, and less when bronchodilatation is present (22, 86). This would appear to be the case for the manner in which the data are illustrated in Fig. 2. However, we have not been able to demonstrate a correlation between the percent fall index for either PEFr or FEV_1 and the resting

level of airways obstruction (Fig. 3a). This observation of a bronchoconstrictor response to exercise being independent of the size of the airways prior to challenge has been emphasized by others (58). The lack of correlation may be related to the bronchodilatation observed during exercise which is greater in the presence of airways obstruction (Fig. 2). Not unexpectedly there is a significant correlation between the lowest values recorded after exercise and the resting level of airways obstruction when both are expressed as a percentage of the predicted value (Fig. 3b). However, it is difficult to use this type of analysis for the documentation of EIA, particularly when comparing responses to exercise within a population or in response to drugs which induce bronchodilatation at rest (6).

Although the severity of EIA appears to be independent of bronchomotor tone at rest the incidence is not (12, 58). In 313 children of whom 187 had normal lung function at rest (i.e. PEFr greater than 80% of predicted) the incidence of EIA was 71%. By contrast the incidence of EIA was 86% in the 126 asthmatics who had airways obstruction at rest. The distribution of severity of EIA (as judged by the percent fall index) was not different between the two groups (12). In fact the lower incidence

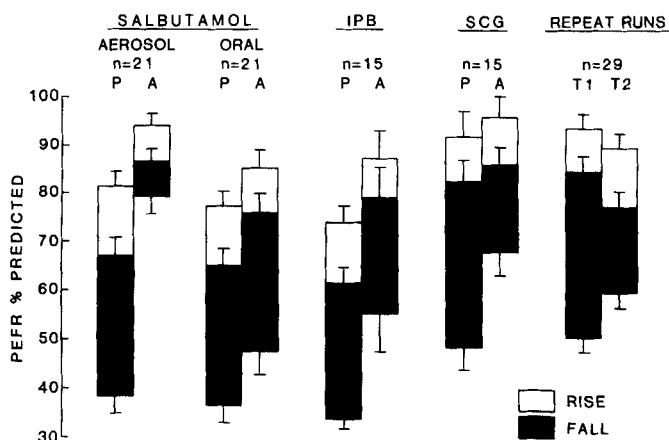


Fig. 2. The mean $\pm$ or -1 SEM values for PEFr expressed as a percentage of the predicted value at rest (white bar), during exercise (black bar) and after exercise (black bar). The resting levels are taken after administration of the placebo or active drug and immediately prior to exercise. Rise in PEFr was measured by taking the highest value for PEFr during exercise and the fall, using the lowest value recorded after exercise.

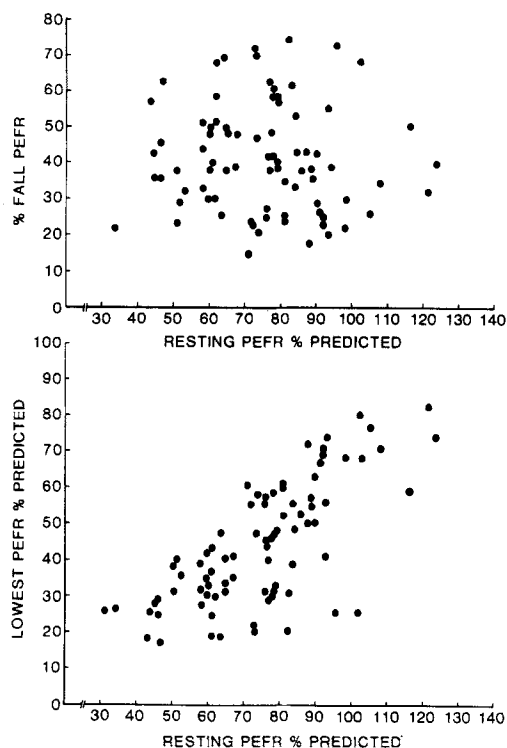


Fig. 3. a) Individual values for the percent fall in PEFR for the 80 patients described in Fig. 1 in relation to the pre-exercise value of PEFR expressed as a percentage of predicted ($r = -0.007$, NS). b) The lowest PEFR recorded after exercise expressed as a percentage of the predicted value in relation to the PEFR recorded prior to exercise expressed as a percentage of predicted in the same patients ($r = 0.60$, $P < 0.001$). The values were measured in the presence of placebo in 51 patients and after the initial run in 29 patients.

of EIA reported by others (16, 29) may be explained by the mild nature of the asthma in their subjects.

Prophylactic therapy with pharmacological agents is usually only required in patients with a reduction in PEFR or FEV_1 greater than 25% of the pre-exercise level (6). In this situation, the effect of a drug is usually compared with a placebo in the same individual. It would seem that the percent fall index is still the best index available for determining drug efficacy, providing that the reproducibility of the response without the drug is taken into account (6, 41).

Drugs which prevent EIA

The beta-sympathomimetic agents delivered as aerosols in the clinically recommended dose have been shown to inhibit or totally prevent EIA in 90% of patients (6). In addition to their relaxant effect on bronchial smooth muscle their mode of action in preventing EIA is thought to result from an inhibitory effect on mediator release from mast cells lying superficially in the bronchial mucosa (3). Because beta-sympathomimetics induce bronchodilation in addition to their preventative action they must be considered the drug of choice in patients who have airways obstruction at rest. The superiority of the aerosol route of administration of these agents is thought to be related to the concentration of the drug in the airways. This concept is based on the observation that the bronchodilating effect of a beta-sympathomimetic lasts longer than its inhibitory effect on EIA (3, 74). Since the events triggered by either airway cooling or osmotic changes due to water loss are most likely to occur superficially in the bronchial mucosa, it does not seem surprising that many drugs delivered as aerosols are effective in preventing EIA!

The superiority of the aerosol route of administration compared with the oral route has been described for both the beta-sympathomimetics and sodium cromoglycate (4, 33, 53) (Figs. 1, 2). Although there is a recent study showing that oral salbutamol in a dose of 0.15 mg kg^{-1} is as effective as aerosol $200 \text{ } \mu\text{g}$ salbutamol in children (39), the doses used and the time required for the oral form to take effect make patient compliance unlikely (25).

There are important clinical reasons for choosing the aerosol route for delivery of pharmacological agents. Firstly, aerosols have a rapid onset of action for either inducing bronchodilation and/or for preventing EIA. Secondly, the effective dose of a drug, delivered as an aerosol, is considerably less, so that tachycardia and skeletal muscle tremor are not commonly observed with the beta-sympathomimetics. Further, oral agents containing theophylline may induce nausea in a significant proportion of patients. Finally, aerosols are deliver-

ed directly to the respiratory tract and unlike tablets are not dependent on gastrointestinal absorption which may be variable throughout a day.

The mode of delivery of an aerosol may also be important. Sodium cromoglycate delivered from a conventional spinhaler in a dose of 20 mg has been shown to be effective in 60–70% of asthmatics. However, if this same drug is delivered from a metered dose inhaler (MDI) in a much lower dose of 2–4 mg (Fig. 4) the efficacy may be as high as 90% of patients (75). The apparent superiority of SCG delivered from an MDI may be due to the size of the particles entering the respiratory tract. Although both the spinhaler and MDI deliver the same particle

size, the particles from the powder probably increase in size after inhalation due to the hygroscopic nature of SCG (80). It is possible that the particles from the MDI reach further into the lung than the powder and for this reason they are more effective in preventing EIA.

There have been some interesting observations on the effect of the anticholinergic agent ipratropium bromide (IPB) in EIA. Several studies report an all or none effect with this drug (6, 56, 87). This is well illustrated in Fig. 4 for a group of 15 patients, nine of whom had no protection afforded by IPB and six of whom were entirely protected. Although a dose-dependent relationship has been demonstrated for IPB (43) the dose used in the study of McFadden et al. (56) was shown to be sufficient to block the response to inhaled methacholine. McFadden and his co workers (56) observed that patients who had airflow limitation primarily in the large airways were responsive to IPB. This is not unexpected since it is these airways which are predominantly under vagal control. Thomson et al. (87) have proposed that mediator release may act via cholinergic mechanisms in patients whose site of airways obstruction is in the large airways and via a direct action on smooth muscle in those in whom the site of obstruction is more peripheral. They base their hypothesis on the efficacy of SCG in preventing EIA in both groups of patients and the dual action of anticholinergic agents in inhibiting mediator release (49) and inducing bronchial smooth muscle relaxation.

In the laboratory we have found IPB in a dose of 80 μ g to be useful as additional therapy in patients with severe EIA and in whom a combination of beta-sympathomimetic aerosols and SCG has not prevented EIA.

Although aerosol steroids have previously been shown to be ineffective in the majority of patients (52) there is now some evidence that with chronic administration, aerosol steroids will inhibit EIA (42).

There are other pharmacological agents which have been shown to be beneficial in some patients with EIA. These include the alpha-adrenoceptor blocking agents and the calcium antagonists. The efficacy of thymoxamine was

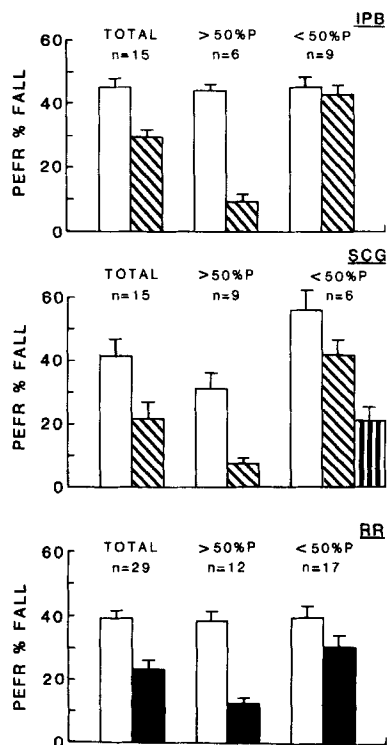


Fig. 4. The mean $\pm$ 1 SEM for the percent fall in PEFR after exercise in the same groups of patients illustrated in Figs. 1, 2. The patients have been divided into two groups according to whether they had 50% or more protection afforded by the active drug or on a repeat challenge. The runs following placebo or the first challenge are shown as the open columns. In six patients a third exercise test was performed after increasing the dose of SCG from 2 to 4 mg (vertical stripes).

reported in 1976 by Patel et al. (62). However, thymoxamine is non-specific for alpha-adrenoceptors and it was uncertain whether its efficacy could be attributed to its alpha-blocking properties alone. A recent study on the specific alpha-blocker prazosin demonstrated its efficacy as an aerosol in a dose of 2 mg in six of 10 patients with EIA (19). This observation supports the theory that alpha-receptor stimulation may occur as a result of the release of noradrenaline during exercise (see elsewhere in this review). These drugs appear only to be effective when given as aerosols.

There are a number of studies reporting the efficacy of the calcium "blockers" verapamil and nifedipine in some if not all patients with EIA (18, 28, 63, 64). These agents have no effect on lung function at rest and their mode of action in EIA is presumably by inhibition of the flux of calcium ions (across cell membranes), which are required for liberation of mediators from mast cells and the contraction of smooth muscle. They do not prevent histamine-induced bronchoconstriction (65) implying that their role in the prevention of EIA is more likely due to inhibition of mediator release from mast cells than an effect on smooth muscle contraction. Verapamil has now been shown to inhibit the release of slow-reacting substance of anaphylaxis (but with little effect on histamine release) from sensitized human lung fragments (55).

There are a variety of other pharmacological agents shown to inhibit antigen-induced release of histamine *in vitro* which have some effect in EIA. These include oxatomide (78), RS7640 a xanthone (82), doxantrazole (67) and FPL57787 an oral chromone (88). Oral ketotifen does not inhibit EIA (6, 66).

Antihistamines either delivered as aerosols (44), or by intramuscular injection (92), have been shown to be effective in the prevention of EIA, lending further support to the concept of mediator release in the pathogenesis of EIA.

In interpreting the effects of pharmacological agents on EIA reported in the literature, and in undertaking future studies, there are some important factors to consider. Firstly, the effect of a drug on airways resistance at rest should be

taken into account when determining the percent fall index. For example the pre-challenge value of PEF_r or FEV₁ used to determine the percent fall should be the one recorded at a suitable time after the administration of the drug and immediately before exercise (6). Secondly, in determining the efficacy of a pharmacological agent, several questions should be asked. Is the severity of the EIA and its reproducibility in the patient adequate to justify his inclusion in the study? The patients who are least likely to require prophylactic therapy for EIA are frequently the ones most likely to respond to a drug, for this reason their inclusion may compromise the interpretation of the usefulness of the drug in patients with severe EIA. Does the drug inhibit the fall in flow rates and volumes by more than 50% of the response on placebo and is the value for percent fall on the active agent within the normal range (i.e. less than 10%)? If the severity of EIA is sufficient (i.e. greater than 25% fall in PEF_r or FEV₁) and the drug affords more than 50% protection then it is likely that the effect can be attributed to the drug and not to the inherent variation in the exercise response (6, 41, 76). It must be noted that moderately severe EIA can still occur even though a drug afforded significant protection (e.g. fall on placebo 70%, fall on active agent 35%). In this situation increasing the dose of the drug may improve the response. This is illustrated for SCG in Fig. 4. It is important to consider individual responses to a drug and if necessary separate the patients into groups (56, 77, 87). It is possible that the beneficial effect of an agent is concealed when mean data are given. This problem is illustrated in Fig. 4 for IPB and SCG. We have found the percent protection index (6, 41) useful for discriminating drug effects between patients though there are some reservations for its use (11).

When reporting the effects of drugs on EIA it may be necessary to document changes in lung function both as a percentage fall from the pre-challenge post-drug level (Fig. 1) and as a percentage of the predicted values (Fig. 2). It is not advisable to assess the effect of a drug using the ELI since the beneficial effect of

agents which do not effect resting airways resistance may be underestimated (Fig. 1).

Respiratory heat and water loss

Exercise-induced asthma may be inhibited or totally prevented when heat and water loss from the airways is minimised, and enhanced when subfreezing or dry air is inspired (7, 30, 83, 84). It is thought that the heat lost from the airways results in cooling of the bronchial mucosa and this in some way stimulates a chain of events leading to the contraction of bronchial smooth muscle.

Although there are no reports of direct measurements of airway temperature during exercise in asthmatics, inspiring air at subfreezing temperatures, the expired temperature has frequently been documented at 26–29°C suggesting that cooling of the airway does occur at high levels of ventilation (35, 69). A recent

study which recorded actual airway temperature in the 6th or 7th generation bronchii of normal subjects supports the airway cooling theory. When air at –17°C was inhaled at a ventilation of 60 l min⁻¹ the temperature of the airway on expiration was 32.3°C and on inspiration 27.3°C (57). It is highly likely that a similar level of temperature reduction would occur in asthmatics at similar levels of ventilation and inspired air conditions.

The concept of predicting airway response from the degree of heat loss was first introduced by Chen & Horton (30) and refined by Deal et al. (35). The concept appears to work very well for the individual asthmatic but within the asthmatic population the variation in response to the same level of heat loss is too great to make a predictive equation useful (9, 29, 60).

For the individual asthmatic, there is also a good correlation between water loss and the reduction in FEV₁ or PEF_R (9). This is not unexpected since, under ambient laboratory conditions, 80% of the heat lost from the airways is due to the evaporation of water. It does, however, raise the question as to whether water loss *per se* acts as an independent or as an additional stimulus to airway cooling in EIA.

There is some evidence to show that EIA may occur when air, conditioned to high temperatures, (greater than 34°C) but dry, is inspired during exercise (15, 35). Although airway temperatures have not been measured directly, the values for expired temperature at the mouth under these conditions (Table 1) suggest that significant reductions of airway temperature do not occur, particularly as airstream temperature falls on expiration. The question then arises as to whether the heat loss due to the evaporation of water alone is sufficient to induce significant cooling of the airways when air is inspired at these high temperatures. It is difficult to conceive that a similar degree of mucosal cooling will occur when subfreezing and high temperature air is inhaled, yet significant EIA may occur under both conditions (Table 1)! Thus it seems likely that water loss is the important factor and that airway cooling, from the inhalation of subfreezing air may potentiate the response to water loss.

Table 1

Inspired (Ti) and expired air temperature (Te) at the mouth in asthmatic and normal subjects, measured during exercise and hyperventilation challenge. The mean $\pm$ 1 SEM for the percent fall in forced expiratory volume (FEV₁) is given for the asthmatic subjects

	Ti °C	Te °C	VE l min ⁻¹	% Fall
<i>Exercise</i>				
Deal et al. (35)	–10.9	27.5	70.2	48.5 $\pm$ 1.3
n = 10	37.0	33.6	67.8	30.0 $\pm$ 3.6
	50.0	33.8	69.0	34.5 $\pm$ 2.7
	65.0	35.4	66.3	29.3 $\pm$ 3.6
	80.0	37.1	69.1	32.7 $\pm$ 3.6
Anderson et al. (15)	34.8	35.4	62.0	36.0 $\pm$ 5.1
n = 17				
<i>Hyperventilation</i>				
Resnick et al. (69)	–10.9	26.6	73.0	38.6 $\pm$ 4.5
n = 10				
McFadden et al. (57)	–17.0	32.3*	60.0	normals
n = 5	23.0	34.9*	60.0	normals

* Measured at the 6th or 7th generation bronchii.

If water loss is important, what is the stimulus and what is the evidence to suggest that it is relevant to the mechanism of EIA? Firstly, it is likely that water loss may act as a hypertonic stimulus thus causing transient changes to the osmolarity of the respiratory tract fluid. It is now known that the airways of asthmatics are exquisitely sensitive to the inhalation of hypertonic aerosols (37, 73). The amount of inhaled aerosol required to induce a fall in FEV₁ of 20% or more is relatively small (14). It is conceivable that similar changes in the osmotic environment may occur with the extent of water loss from the airways during exercise. Over a period of 8 min of exercise when dry air is inspired, a water loss as high as 20 ml may occur (9). Although it is not known whether the rate or the total amount of water loss is the determining factor, previous studies on the intensity and duration of exercise (76) suggest that both are important.

There are some similarities between EIA and asthma induced by the inhalation of hypertonic aerosols. For example the bronchoconstriction induced by the inhalation of hypertonic saline is inhibited by SCG and only a minority of patients are protected by prior inhalation with atropine (14). Further the airway response is reduced when challenges with aerosols are repeated within an hour (14).

It is possible that the physical stimulus provided by a change in the osmotic environment (either by water loss or inhalation of hypertonic aerosols) may be sufficient to induce mediator release from mast cells and irritant receptor activation. This concept is supported by the knowledge that both basophils and irritant receptors are sensitive to changes in osmolarity (38, 85). A change in the osmotic environment of the respiratory tract is an attractive hypothesis for the mechanism of EIA. However, studies relating actual water loss to a change in osmolarity are required to confirm this suggestion.

The refractory period

The refractory period has been defined as the time after EIA during which a further exercise

challenge will induce less than 50% of the initial response (72). It was originally thought that the majority of patients would have protection from EIA when challenged within 1 h (36). However, the incidence of refractoriness has been reported to be as low as 40% (10, 72), although it is higher in patients with mild EIA (11, 40, 70). Again the importance of separating patients into groups according to their response is illustrated in Fig. 4.

The cause of refractoriness is unknown. Gillam et al. (40) have reported that the degree of protection afforded by an initial challenge is variable and appears to be related to the site of airways obstruction. They observed greater protection in patients who had obstruction predominantly in large airways.

It would appear that a refractory period can occur after exercise which has not induced asthma (21, 46, 70). Schnall et al. (71) found that 7 × 30 sec sprints separated by 2.5 min and performed 20–30 min prior to a 6 min run gave significant protection from EIA. By contrast, no protection occurred after 7 × 30 sec bouts of isocapnic hyperventilation. These authors suggested that an increase in circulating catecholamines during short-term exercise could increase the number of available beta-adrenergic receptors. Thus mast cell release of mediators and smooth muscle contraction may be inhibited on further challenge. This would appear to be a more likely suggestion than the one proposed by Stearns et al. (81) which considered that circulating catecholamine released on initial exercise challenge could serve to protect the airways from subsequent challenge. Ben-Dov et al. (21) have made the interesting suggestion that there is a decrease in bronchial reactivity in response to mediator release when warm wet air is inhaled during the exercise. Thus mediators may become depleted without EIA occurring! It is perhaps important to note that the patients of Ben-Dov et al. (21) continued to inspire warm humid air for 30 min after the initial challenge and this may have had a prolonged effect on airway reactivity.

The observation that a refractory period occurs after exercise which has not induced asthma is not universal. We have reported severe

EIA (mean $\pm$ 1 SD % fall FEV₁ 54% $\pm$ 12) 40 min after an initial exercise test which induced only a 6.5% $\pm$ 5 reduction in FEV₁ due to the inhalation of hot humid air during exercise (7).

These observations suggest that multiple mechanisms are involved in EIA and in the refractory period. Although mediator depletion is thought to be important as a mechanism for the refractory period, there is only one study in one patient which has demonstrated a decrease in histamine release and less EIA with repeated challenge (8). Furthermore, in a study of EIA in which subjects were rendered refractory, antigen induced an attack of asthma in half the subjects suggesting that mediators were still available (89)! Studies on the release of a neutrophil chemotactic factor with repeat challenge may be useful in determining the role of mediator depletion as a cause of the refractory period.

Finally, there may be different mechanisms causing EIA in those patients who are not refractory. This concept is supported by the finding of Wilson et al. (91) which demonstrated an inhibitory effect of ipratropium bromide in patients not refractory to repeated hyperventilation challenge, but failed to find a significant effect in those who were refractory.

Noradrenaline and the role of alpha-receptors

Strenuous exercise induces an endogenous release of noradrenaline. The levels measured during and after exercise in adult asthmatics with EIA are said to be similar to those in normal subjects (5, 13, 31, 93) though there is some evidence that the levels are decreased in asthmatic children (17). Since asthmatics with EIA have been shown to have significantly higher levels of noradrenaline released during exercise, compared with asthmatics without EIA (68) it has been considered that noradrenaline may stimulate alpha-receptors in the lung leading to bronchial smooth muscle contraction. The renewed interest in this mechanism has arisen because there is now substantial evidence that alpha-receptors are present in human lung (23, 79) and that EIA is blocked in some patients by alpha-blocking agents delivered as aerosols

(see section on drugs). Since airway cooling is thought to be the initiating stimulus in EIA and alpha-receptors are known to be activated at lower than body temperature (32) it is now thought that noradrenaline may serve to stimulate the alpha-receptors causing contraction of airway smooth muscle.

However, this concept is not supported by finding that EIA may occur without significant changes in airway temperature (15, 35) and that noradrenaline levels remain unchanged when similar levels of airways obstruction are induced by hyperventilation (17). There is one study describing the blocking effects of the alpha-antagonist phentolamine on asthma induced by hyperventilation with cold air (24) suggesting that the efficacy of alpha-blockers may be independent of the presence of significant levels of circulating noradrenaline. Although the local release of noradrenaline from nerve endings may be sufficient to induce alpha-receptor stimulation on bronchial smooth muscle there is no known sympathetic innervation of the lung. More studies are required to confirm or refute the role of alpha-receptors in the aetiology of EIA.

Mediator release

Mast cell degranulation and the release of mediators which are potentially capable of inducing bronchial smooth muscle contraction, either directly, or via the vagus nerve, has long been considered an important mechanism of EIA. The evidence for this is based on a number of observations over the last 18 years.

Firstly, pharmacological agents which have been shown to inhibit mast cell release *in vitro* generally inhibit EIA, particularly when given as aerosols (see drug section). The studies on SCG and the beta-sympathomimetics have been particularly convincing in this regard. Secondly, the recognition of a refractory period in some, though not all asthmatics, has led many workers to suggest that a depletion of mediators occurs in response to initial challenge and time is required to replenish these (36, 72). Thirdly, there are several studies which report an increase in plasma histamine levels (in some

though not all patients) at a time when exercise has induced an attack of asthma (8, 20).

The source of histamine is unknown. Since exercise is associated with an increase in the number of circulating basophils some authors (47) have suggested that the histamine may arise from "leaky" basophils and be a coincidence of exercise rather than a reflection of mast cell derived histamine. This concept is supported by the observation that histamine levels do not increase with hyperventilation asthma which is not associated with a basophilia (20). Furthermore, it could account for some of the increase in plasma histamine levels we noted after the administration of terbutaline sulphate (8) which also induces a leucocytosis (27). If the source of histamine is the basophil and not the lung mast cell, then asthmatics must vary in their ability to release histamine spontaneously from basophils because an increase in the level of histamine after exercise is not observed in all asthmatics (8). Indeed Neijens et al. (59) have reported a higher spontaneous release of histamine from leucocytes of patients with EIA compared with those who do not have EIA ($2.4 \mu\text{g l}^{-1}$ vs. $1.0 \mu\text{g l}^{-1}$). It is interesting to note that the severity of EIA also correlated with histamine reactivity. It is obvious that more studies are required to elucidate the source and role of histamine in EIA. Furthermore, the significance of relatively small increases in plasma histamine, perhaps reflecting larger changes in the lung, is not well understood (11).

Perhaps the most compelling evidence for mast cell activation, in the events which trigger EIA, has been the identification of a neutrophil-chemotactic-factor-like substance following exercise in patients with asthma but not in normal subjects. It is of interest that the increase in neutrophil activity after exercise is similar to that observed after allergen challenge and is inhibited by prior administration of SCG (54).

Although there is undoubtedly sufficient evidence to support a role for mediator release in the mechanism of EIA, further studies of the effects of pharmacological agents on mediator release are still required.

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