Absence of refractoriness in asthmatic subjects after exercise with warm, humid inspirate

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ABSTRACT Twelve asthmatic adults each completed two six minute treadmill runs separated by an interval of 20 minutes. Running speed was constant for each subject, and inspired air temperature averaged 5.5°C (SD 1.5°) for both tests. Total minute ventilation and total respiratory heat loss showed no significant difference between the two runs. Forced expiratory volume in one second (FEV1) was measured before exercise and at five minute intervals throughout the recovery periods, during which subjects breathed room air at an average temperature of 17.8°C (1.8°). Reduction in FEV1 from pre-exercise readings averaged 39.3% (13.3%) for the first run and 11.5% (7.3%) for the second. On another day the subjects underwent an identical procedure except that the first exercise period was performed with the saturated inspirate at 37.3°C (1.7°). This run produced a mean FEV1 reduction of only 3.1% (7.3%). The ensuing run, during which the inspiratory temperature averaged 6.0°C (2.0°), led to a mean fall in FEV1 of 37.3% (17.3%). This was not significantly different from the value recorded for the first of the paired runs with cool air. We therefore have been unable to confirm that exercise with warm humid inspirate may induce refractoriness to exercise induced asthma. Our data are compatible with the theory that refractoriness may be due to depletion of mediators during an initial exercise induced asthma attack.

Exercise induced asthma is commonly followed by a refractory period during which the bronchoconstrictive response to further exercise challenge is much diminished.1-3 Depletion of mediators released by airway mast cells is widely accepted as the explanation.3-5 In support, Anderson et al6 noted that exercise with the subject breathing warm, humid inspired air, which provokes little bronchoconstriction and apparently does not induce mast cell degranulation,7 did not prevent development of severe exercise induced asthma in response to a standard exercise challenge begun 30 minutes later. Ben-Dov et al8 have suggested, however, that exercise with a warm, humid inspirate may produce substantial refractoriness. Resolution of this conflict is crucial to understanding the mechanisms of exercise induced asthma.

Method

Twelve adult asthmatic subjects (10 male) gave informed consent. None of the subjects were taking corticosteroids. Treatment with bronchodilators and sodium cromoglycate was discontinued at least six hours before each study. All subjects had a history of exercise induced asthma and, in response to preliminary exercise testing, showed a reduction in one second forced expiratory volume (FEV1) exceeding 15%.

The subjects completed two experimental protocols in random order and on different days. Each required two six minute treadmill runs separated by a recovery period of 20 minutes. On one occasion both runs were performed with a cool, dry inspirate. On the other occasion warm, humid air was breathed during the first run and cool, dry air during the second. For each subject the running speed was constant and was that found during preliminary testing to produce a heart rate of 80-85% of the age predicted maximum.9
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During exercise with a cool inspirate, subjects breathed dry medical air from a Koegel et valve connected to a balloon reservoir. Inspiratory temperature averaged 5.5°C (SD 1.5°C) for each of the paired cool air challenges and 6.0°C (2.0°C) for the run after exercise with a warm, humid inspirate. Minute ventilation rates were recorded by a Hewlett-Packard pneumotachygraph in the inspiratory line. Inspired and expired air temperatures were measured by thermistor probes positioned 3.5 cm upstream and downstream from the oral cavity. Respiratory heat exchange values were estimated for each minute of exercise from the formula of Deal et al.\(^2\)

The hot, humid inspirate was generated by two Hanksraft 207-V humidifiers and subsequently cooled to 37.3°C (1.7°C). There was substantial condensation along the inspiratory line, indicating saturation of the air at the point of inhalation.

Throughout the recovery periods after exercise with cool air the subjects breathed room air at 17.8°C (1.8°C). After completion of exercise with warm, humid air, exposure to the conditioned inspirate was continued for two minutes to reduce the possibility of mild bronchoconstriction due to inspiration of cooler room air while ventilation rates were still high. Room air was breathed throughout the remainder of the recovery period. FEV\(_1\) was recorded by a Vitalograph dry spirometer before and 5, 10, 15, and 20 minutes after each exercise challenge.

Maximum proportional reductions in FEV\(_1\) (from the pre-exercise baselines), total ventilation, and total respiratory heat loss were each compared across the various runs by one way analysis of variance. FEV\(_1\) values for the various challenges were compared by two way analysis of variance. The reductions in FEV\(_1\) were converted to logarithms before analysis.

Results

The mean maximum reduction in FEV\(_1\) (from the immediate pre-exercise reading) was 39.3% (SD 13.3%) for the first of the paired runs with cool inspirate and 11.5% (7.3%) for the second (p < 0.001; fig 1). This was despite a substantially lower pre-exercise FEV\(_1\) for the second trial (p < 0.01; fig 2). In nine of the 12 subjects the percentage fall caused by the second run was less than one third of that caused by the first, indicating considerable refractoriness.\(^3\) Neither total ventilation nor total respiratory heat loss differed significantly between the trials (p > 0.05).

In response to exercise with warm, humid inspirate the maximum reduction in FEV\(_1\) averaged 3.1% (7.3%) (fig 1). No subject showed a reduction exceeding 15%. The ensuing run with cool, dry inspirate was similar to the first of the paired runs with cool air in terms of immediate pre-exercise FEV\(_1\) (p > 0.05) and the rates of ventilation and respiratory heat loss evoked by exercise (p > 0.05 in both cases). It also produced a similar degree of bronchoconstriction (p > 0.05), with the maximum fall in FEV\(_1\) averaging 37.3% (17.7%) (fig 1). At no stage was there a difference in absolute magnitude of FEV\(_1\) between the first of the repeated cold air runs and the cold air run after the challenge with warm, humid air (p > 0.05).

Discussion

In our subjects preliminary exercise with warm, humid inspirate failed to attenuate significantly the

Fig 1  Maximum percentage reduction in FEV\(_1\) after exercise challenge during the breathing of cold and dry or hot and humid air. Bars indicate standard deviations.

![Graph](https://example.com/graph1.png)

Fig 2  Mean FEV\(_1\) before and at the lowest value after exercise challenge during the breathing of cold and dry or hot and humid air. Bars indicate standard deviations.

![Graph](https://example.com/graph2.png)
bronchoconstrictive response to a standard exercise challenge with cool air. This finding is consistent with the observation of Anderson et al.\textsuperscript{a} Ben-Dov et al.\textsuperscript{b} however, reported a different result: for most patients in their studies, exercise with warm, humid inspirate was highly effective in producing refractoriness to exercise induced asthma, despite having provoked little or no asthma.

There are several possible reasons for the divergent findings. The patients of Ben-Dov et al.\textsuperscript{b} were generally younger than those used in either the present investigation or the studies of Anderson et al.\textsuperscript{a} Possibly such age differences are associated with some difference in the aetiology of exercise induced asthma. Ben-Dov et al.\textsuperscript{b} considered all of their patients to be refractory to a second exercise challenge with cold air since, in each case, the percentage fall in FEV\textsubscript{1}, (calculated in terms of pre-exercise values) was substantially less for the second run than for the first. This criterion was met also by our subjects. For their patients the mean minimum FEV\textsubscript{1} after the second cold air run was significantly higher than after the first. Because of the lower FEV\textsubscript{1} before the second cold air run in our subjects the lowest postexercise values were almost identical. We could therefore argue that our subjects were refractory only in relation to the immediate pre-exercise readings. Given the bronchodilatation typically shown by asthmatics during the early stages of exercise,\textsuperscript{11} pre-exercise values may be an inappropriate baseline for assessing bronchoconstriction. Consequently, our failure to observe a refractory period after exercise with warm, humid inspirate might be a function of the higher baseline and might be attributed to inability of the subjects to show true refractoriness in any circumstances. The findings of Anderson et al.\textsuperscript{a} could be similarly explained, since they did not assess responses to repeated exercise with cool air.

The patients of Ben-Dov et al.\textsuperscript{b} continued breathing warm, humid air throughout the entire recovery period after exercise with this inspirate. By contrast, our subjects and those of Anderson et al.\textsuperscript{b} breathed the conditioned air for only the first few minutes of recovery. This may have influenced responses to the ensuing exercise challenge with cool air. The oropharynx and large airways probably contain thermosensitive nerve endings capable of reflexly affecting the vagal tone of the tracheobronchial tree,\textsuperscript{12,13} and sustained exposure to warm, humid inspirate may increase airway temperatures and reduce vagal tone. This may result in diminished airways reactivity to stimuli introduced immediately afterwards.\textsuperscript{14} McFadden\textsuperscript{15} has noted the close anatomical and functional similarities between the bronchial and cutaneous vascular beds. Heating of the large airways may promote local increases in blood flow, as happens in the skin.\textsuperscript{16} Such increases might buffer the effect of respiratory heat loss on airway temperatures during subsequent exercise challenge with cool air.

Recent evidence indicates that inspiration of saturated air at 37°C may result in a net water gain by the airways.\textsuperscript{17} Continued over a long period, this could reduce the osmolarity of the fluid lining the airway surface. In view of current speculation that exercise induced asthma may be initiated by increased osmolarity of this fluid\textsuperscript{14,18,20} the existence of a slightly hypo-osmolar state at the start of exercise could be protective. In the study of Ben-Dov et al.\textsuperscript{b} such a state might have been induced during the recovery period after exercise with warm, humid air.

The current publications on refractoriness to exercise induced asthma shows a startling lack of consensus. Experimental manipulation of the temperature and humidity of air inspired during recovery periods between successive exercise challenges may provide some insight. Our present findings are consistent with the theory that refractoriness after exercise induced asthma is due to depletion of mediators associated with airway mast cells, but alternative mechanisms are not excluded.

Further data

Further data have been lodged with the editor and copies are available on request from the authors.

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