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EDITORIAL

# Exercise-induced asthma and late phase reactions

T.H. Lee*, S.P. O'Hickey

Exercise-induced asthma (EIA) occurs in 70–80% of asthmatic subjects. The early bronchoconstriction is typically maximal at 5–10 min after exertion and in most asthmatics recovery is spontaneous and usually complete within 30–90 min. Following exercise there is a refractory period of approximately one hour during which 40–50% of these patients will not bronchoconstrict after further exercise.

## Mechanisms of EIA

The hypothesis that respiratory heat loss was an initiating event in EIA was first proposed by CHEN and HORTON [1] and later supported by MCFADDEN *et al.* [2], who suggested that the severity of EIA is dependent upon the rapidity and magnitude of airway rewarming after exercise. It has been suggested that the airway cooling which results from hyperpnoea during exercise is followed by a rapid re-supply of heat to the airway mucosa when exercise ceases. This may cause an exaggerated rebound hyperaemia and airway oedema, thereby causing asthma.

However, HAHN *et al.* [3] exercised asthmatic subjects under varying conditions of temperature and humidity and demonstrated that the severity of EIA did not differ even when the inspired air temperature varied by 26°C as long as the humidity was kept constant. This suggests that the response to exercise depends on the degree of respiratory water loss rather than on cooling of the airways. ANDERSON [4] has suggested that the rate of respiratory water loss caused by the hyperpnoea of exertion induces a transient hyperosmolarity of the airway epithelium and that this is the stimulus for EIA. This hypothesis is supported by several lines of evidence. Inhalation of hypertonic aerosols will induce bronchoconstriction in asthmatic subjects which is attenuated by the prior administration of sodium cromoglycate [5] and specific histamine $H_1$ antagonists [6] in a similar manner to that seen for inhibition of EIA [7, 8]. In the previous issue of this Journal, BELCHER and co-workers [9] have demonstrated a correlation between airways responsiveness to inhaled hypertonic saline aerosol and to exercise in a group of ten asthmatic subjects. Asthmatic subjects demonstrate cross-refractoriness between hypertonic saline-induced bronchoconstriction and EIA [10], suggesting that refractoriness to these challenges is also induced by similar, if not identical, mechanisms.

Although further studies are required to confirm that there is a change in the osmolarity of the epithelial fluid lining the airways during EIA, an increase in the evaporative water loss during inhalation of cold, dry air in the nose increases the osmolarity of respiratory secretions [11]. *In vitro*, hyperosmolar buffers are potent secretagogues for the human airway mast cell [12, 13]. BELCHER and co-workers [14] have detected the release of neutrophil chemotactic factor into the circulation following both hypertonic saline-induced bronchoconstriction and EIA, suggesting that both stimuli result in the release of mast cell dependent mediators.

Previous work has indicated that the stimulus for bronchoconstriction after isocapnic hyperventilation (ISH) is identical to that following exercise [15]. This is disputed, however, by NOVISKI *et al.* [16] who have suggested that the exercise task itself may determine the magnitude of EIA. In the previous issue of the Journal, SMITH and ANDERSON [17] have studied the relationship between ISH and inhalation of hyperosmolar saline aerosol. Although the maximal falls in forced expiratory volume in one second ($FEV_1$) after both ISH and saline were similar, the rate of decline in $FEV_1$ was slower after ISH. They have suggested that changes in mucosal osmolarity induce bronchoconstriction and that airway cooling delays this response. The observations that indomethacin will abolish the refractory period of EIA and hyperosmolar stimuli [18], but will not alter the refractory period to ISH [19], support the view that ISH does not provide an identical stimulus to the airways as exercise and osmotic challenges do.

### *The late response*

The possibility that exercise might precipitate a biphasic asthmatic response, similar to that seen after antigen challenge, was first suggested by BIERMAN *et al.* [20]. They reported the development of an immediate and late phase response in eight out of nine young adults with exercise-induced asthma after a standard 6 min treadmill exercise task. These preliminary observations were subsequently confirmed and extended by the study of LEE *et al.* [21], in which it was demonstrated that late phase asthmatic reactions following exercise occurred 3–6 h after exertion and were associated with an increase in serum neutrophil chemotactic activity. No significant differences were observed in the clinical severity of

* Dept of Allergy and Allied Respiratory Disorders, UMDS, Guy's Hospital, London.

asthma, in the diurnal variation in $FEV_1$, in airways reactivity to acetylcholine, and in the magnitude of the early reaction after exercise between subjects who developed an early and late phase response after exertion and those individuals who only had an isolated early response [22]. In subjects who have a dual phase response, there is a significant correlation between the magnitude of the early and late reactions [22], suggesting that the late reaction following exercise might be dependent upon the preceding early asthmatic response. The rate of spontaneous recovery from early reactions is slower in children who subsequently develop a late response than in those individuals who do not [22].

Although late reactions following exercise have now been reported by ten centres [20–30], their existence is still questioned [25, 27]. The major criticism has been the lack of an "appropriate" control day with which to compare the exercise day in many of the published studies. There are three possible designs for control days which would be considered "appropriate":

a. a day on which exercise was not undertaken;

b. a day on which the subject was given a nonspecific bronchial challenge, such as methacholine inhalation, (controlling for the sequelae of nonspecific bronchoconstriction);

c. a day on which exertion should be undertaken while breathing warm and humid air, which is known to inhibit the release of mediators and bronchoconstriction in many patients with exercise-induced asthma.

Studies have now been reported comparing an exercise day with each of these "appropriate" controls.

BIERMAN *et al.* [20], LEE *et al.* [21], IIKURA *et al.* [22] and BONER *et al.* [29], used a separate day when the subjects did not exercise as the control day and demonstrated the occurrence of late phase responses following exercise. The experimental design of some of these studies was criticized because of the time between drug withdrawal and experimental challenge [27]. Such criticisms cannot be levelled at the study by SPEELBERG *et al.* reported in the next issue of the Journal [30]. They report an incidence of 38% (33 out of 56 patients) for late phase responses to exercise, which corresponds closely with the reports of LEE *et al.* [21] and BIERMAN *et al.* [23]. In contrast, RUBINSTEIN *et al.* [27], in their study of 53 asthmatic patients, found little or no evidence for a biphasic asthmatic response to exercise and indicated that much of the controversy surrounding this issue may be related to methodological differences among studies. However, detailed analysis of the data in this study indicates that a biphasic asthmatic response occurred after exercise, and not on a control day, in one of the subjects that they studied. Furthermore, of the initial population studied, four subjects were excluded because they had prolonged asthmatic reactions after exercise. Thus, persons who were most likely to have late reactions may have been excluded. Finally, two subjects, who apparently had late responses, were excluded because baseline airways calibre on the exercise day was significantly different from that on the control day. Thus, additional subjects with a late reaction were selectively eliminated from the study.

The use of a non-exercise day as a control day makes it impossible to know whether the late asthmatic reaction would have occurred simply as a consequence of a previous nonspecific bronchoconstriction. Accordingly, three groups of investigators have subjected patients with documented exercise-induced late responses to acetylcholine or methacholine inhalation challenge as a control. In the studies of LEE *et al.* [21], BOULET *et al.* [28], and ZAWADSKI *et al.* [25], late phase responses were observed after exercise but not following acetylcholine or methacholine challenges, respectively. Finally, ZAWADSKI *et al.* [25] studied exercise-induced late phase asthmatic responses by comparing an exercise day, on which the subjects breathed cold and dry air during exercise, with an exercise day when they breathed warm and humid air during exertion. In two of the seven subjects studied, there was a clear exercise-induced late phase bronchial obstruction which occurred at a time when there was no similar change in $FEV_1$ on the control day.

The cumulative evidence indicates that late phase asthmatic reactions occur following exercise. In contrast to antigen-induced late responses, limited evidence suggests that there is no increase in bronchial hyperresponsiveness to methacholine in association with late reactions induced by exercise. The exact prevalence of late reactions induced by exercise is uncertain. In future studies of exercise-induced late reactions it is clearly critical to have a control day, preferably utilizing a nonspecific bronchial challenge, since decrements in airways calibre may occur simply as the result of withdrawal of medication. The issue is not whether exercise-induced late phase reactions exist, but rather the mechanisms for their development.

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