Repercussions on the Refractory Period Following Repeated Exercise in Exercise-induced Asthma

(In Comparison with the Effects of Repeated Antigen Challenge in Antigen-induced Asthma)*

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Exercise-induced asthma refers to an acute airway obstruction following physical exertion. It interferes with most life activities of asthmatics. After successive periods of exercise, however, refractory period with less bronchospasm has been observed; the phenomenon has been ascribed to a decrease in chemical mediators released into the respiratory tract.[1-3] The present experiment was designed to investigate the reaction after repeated challenges with either exericse or antigen in exercise-induce asthma (EIA) and antigen-induced asthma (AIA) in order to increase the level of understanding about the physiopathology of the refractory period.

OBSERVATIONS

Six proven cases of EIA (three males and three females, aged 23 to 35 years) and six cases of antigen-induced asthma (two males and four females, aged 21 to 35 years) were selected as the subjects of this study. The duration of asthma in the EIA group was 13.2 ± 9.6 years (range 1-20 years) and in the AIA group, 8.7 ± 5.0 years (range 1-16 years).

None of the subjects had a recent asthmatic attack nor had they received any medication within the previous 24 hours. None of them were suffering from any associated disease. On the day of the experiment, the subjects were advised not to exert themselves.

The method carried out in the evaluation of EIA patients described by Anderson *et al*[4] was adopted. A constant, dynamic, regulating cyclo-ergometer and an electronic spirometer were used by each subject for six minutes with a workload sufficient to induce a pulse rate of 160 beats per minute. One hour after exercise each patient again exercised for same period of time with the same workload.

For the AIA patients, each of them inhaled 0.4 ml of 0.9% saline solution (80x0.005 ml) for five minutes; they showed no reaction 30 minutes later. Then they inhaled 160 to 640 PNU units of artemisia. One hour later, they inhaled the same number of PNU units of the same antigen for the second time.

Pulmonary function and chest auscultation were monitored at the following intervals: prior to challenge, then at 2, 5, 10, 15, 20, 30, 45 and 60 minutes after challenge respectively.

To quantify the severity of bronchoconstriction, the following equation was used:

$$\text{Fall in \%FEV}_1 = \frac{\text{FEV}_1 \text{ just before challenge} - \text{lowest FEV}_1 \text{ after challenge}}{\text{FEV}_1 \text{ just before challenge}}$$

The first challenge induced an asthmatic attack (tightness of the chest and wheezing) and a fall of at least 20 per cent in FEV_1 in every subject. The fall in FEV_1 following antigen challenge is shown in Figure 1; the second challenge gave a very significant difference in the fall compared with the first ($p < 0.001$). Figure 2 displays the level of FEV_1 after antigen inhalation; the second challenge also gave a very significant increase ($p < 0.001$) in the FEV_1 fall.

The percentage fall in FEV_1 on exercise challenge is shown in Figure 3. The change in bronchospasm of

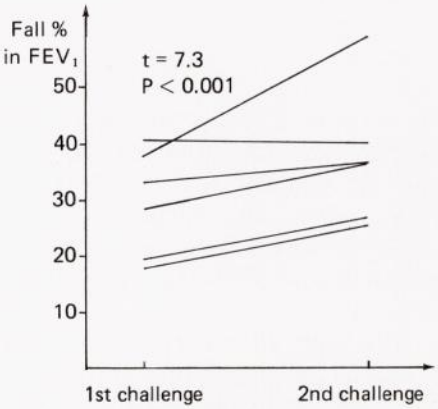

Fig. 1 Fall (%) in FEV_1 after two antigen challenges after a one-hour interval (six cases).

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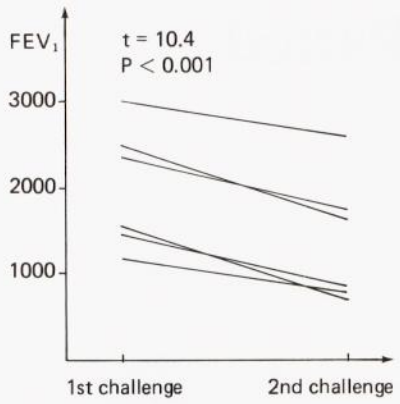

Fig. 2 The lowest FEV_1 after two antigen challenges after a one-hour interval.

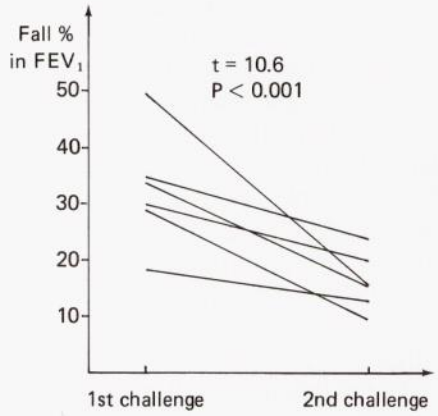

Fig. 3 Fall (%) in FEV_1 after two exercise challenges after a one-hour interval (six cases).

the second challenge was very significantly less than that of the first one ($p < 0.001$). The level of FEV_1 after the second exercise challenge was also very significantly less than that of the first ($p < 0.01$) (Fig. 4).

Although all patients who were exercise-challenged felt more difficulty physically during the second exercise challenge compared with the first, they suffered milder asthmatic symptoms than had occurred following the first exercise challenge. In contrast, the clinical features of the patients following the second antigen challenge were more severe than those following the first challenge.

With regard to the refractory period following repeated exercise, many investigators have suggested that a depletion of chemical mediators capable of inducing airways' smooth-muscle contraction occurs in response to exercise and renders the patient with EIA resistant to the new challenge for up to two hours.[1,3] The only direct evidence of depletion in mediators on repeated exercise came from a study on one subject in Anderson's laboratory who demonstrated a reduction in the release of histamine into the plasma and a simultaneous reduction in the severity of EIA episodes with repeated challenge.[1] Other evidence to support the suggestion that mediator release occurs in some patients came from a study of Weiler-Ravall *et al.*[5] Those authors demonstrated that six out of 12 subjects who were refractory to exercise challenge were also refractory to antigen challenge, which was also believed to involve release mediators. However, the phenomenon could also be explained by the changes in catecholamines during exercise.

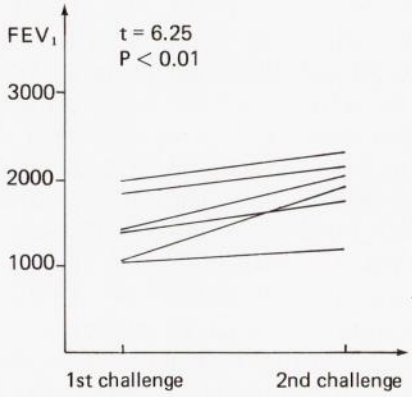

Fig. 4 The lowest FEV_1 after two exercise challenges after a one-hour interval.

McFadden *et al*[2] speculated on the refractory period of EIA as being the result of sympatho-adrenal activity during exercise; their findings showed that hyperventilation or cold air could induce the same bronchospasm as exercise, except for the refractory period, thus attributing the difference between these two stimulating causes to the increase in sympatho-adrenal activity in EIA, but not in the other. Some authors reported that the plasma levels of adrenaline increased after exercise.[7,8]

One of our AIA patients (Fig. 5), who had a more severe bronchospasm following the second antigen challenge compared with the first one, recovered very soon following an exercise challenge; thereafter he fared even better than he had prior to the antigen challenges. (These observations were monitored by clinical manifestations and pulmonary function study). Therefore, it is believed that sympatho-adrenal activity not only decreases bronchospasm, but also produces some bronchial dilatation effect, especially if the exercise is sufficiently strong.

In conclusion, the results of our study seem to support the notion that the refractory period following repeated exercise is produced by

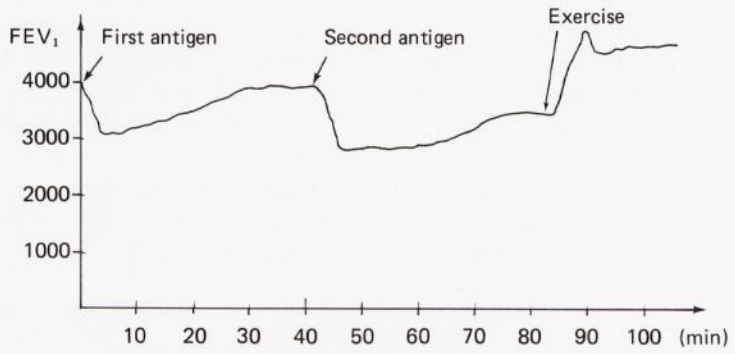

Fig. 5 Z.S., a 21-year-old male (case No. C296901), showed changes in FEV_1 with two antigen challenges followed by exercise challenge.

the direct effect of a sympathoadrenal activity arising during exercise. The depletion of mediators after a moderate challenge would not possibly influence the bronchial reactivity of the second challenge in such a one-hour interval. Regarding this phenomenon of a refractory period, the EIA patients would be rendered free of EIA attacks and be able to lead enjoyable lives performing normal activities, such as work, study and even sports.

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