The Duration of Action of the Combination of Fenoterol Hydrobromide and Ipratropium Bromide in Protecting Against Asthma Provoked by Hyperpnea*

Christine M. Smith, B.Sc.;† Sandra D. Anderson, B.Sc., Ph.D.;‡ and J. Paul Seale, Ph.D.§

We compared the duration of the protective effect of two beta-adrenoceptor agonists, fenoterol (200 μg) and salbutamol (200 μg), the anticholinergic agent ipratropium (80 μg), and the combination of fenoterol (200 μg) and ipratropium (80 μg) against challenge by eucapnic voluntary hyperventilation (EVH). Twelve patients with asthma performed EVH for two or four min at 60 percent maximal voluntary ventilation, 30 min, 2 and 4 h after treatment. All treatments (Rx) produced significant bronchodilation after 30 min. The Rx containing a beta-adrenoceptor agonist maintained this bronchodilation for at least 2 h. While all the Rx with a beta-adrenoceptor agonist significantly reduced the fall in forced expiratory volume in one second after EVH at 30 min, only the combination of fenoterol and ipratropium provided significant protection after 2 h. We advise that the duration of protective effect of beta-adrenoceptor agonists is short and patients with moderate to severe exercise-induced asthma may be better controlled by combination therapy. (Chest 1988; 94:709-17)

Exercise is a common stimulus for provoking an attack of asthma in both children and adults. The mechanism whereby exercise induces attacks of asthma is related to the abnormally high rate of water loss from the airway mucosa, which is necessary to bring the inspired air to alveolar conditions.1 Evaporative water loss from the airway surface liquid leads to an increase in concentration of ions in the periciliary fluid, and cooling of the mucosa.1-4 The consequent increase in osmolarity and reduction in temperature of the periciliary fluid are thought to constitute a stimulus for the release of chemical mediators from mast cells situated in the airway lumen.2-10 These mediators probably cause airway narrowing in a number of ways. They could act directly, or indirectly via the vagal afferent pathway, to cause contraction of smooth muscle. They could increase microvascular permeability, leading to protein exudation and edema of the bronchial mucosa, or they could increase mucus production from glands. Any of these events may occur in response to the stimulus of evaporative water loss and cooling, and their relative contributions to airway narrowing is not known.7

Beta-adrenoceptor agonists, taken as an aerosol immediately before exercise, prevent post-exercise airway narrowing in 90 percent of patients with asthma, whereas anticholinergic agents are effective in only about 40 percent of patients.11-14 The superiority of the beta-adrenoceptor agonists in preventing exercise-induced asthma (EIA), compared with anticholinergic agents, may relate to their action at sites other than the smooth muscle. For example, it has been proposed that beta-adrenoceptor agonists may prevent EIA by inhibiting the release of mediators from airway mast cells.15-17

Both the beta-adrenoceptor agonists and anticholinergic drugs induce bronchodilation which is thought to result from their action on specific receptors on airway smooth muscle. However the onset of bronchodilation with these two drugs is different, occurring within 15 min after administration of beta-adrenoceptor agonists but taking 30 min or more after administration of anticholinergic drugs.

The duration of action of beta-adrenoceptor agonists in preventing EIA has been reported to be less than the duration of their bronchodilating action.16,18 When prescribed as bronchodilators, beta-adrenoceptor agonists are usually taken every 6 h. By contrast to control EIA it is recommended that these aerosols be inhaled immediately before exercise if more than 2 h has elapsed since the last dose.20-22 One aim in combining a beta-adrenoceptor agonist with an anticholinergic agent is to obtain a longer duration of protection against EIA than that afforded by either agent alone.

It is now appreciated that airway narrowing, analogous to that which occurs after exercise, can be

*From the Department of Thoracic Medicine, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia (Ms. Smith and Dr. Anderson) and the Department of Pharmacology, University of Sydney, Sydney (Dr. Seale).
†Research Fellow.
‡Principal Scientific Officer.
§Associate Professor.
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induced by hyperpnea. A challenge using eucapnic voluntary hyperventilation (EVH) has been developed recently and modified to simulate exercise as a provoking stimulus. The technique permits multiple tests to be carried out in the same subject on the same day. Because challenge by EVH is similar to challenge by exercise, the drugs which are effective in protecting against EVH should also protect against EIA.

The aims of the present study were (1) to assess the degree and duration of protection of a combination of the beta-adrenoceptor agonist, fenoterol, and the anticholinergic agent, ipratropium, against asthma induced by EVH and (2) to compare the responses with either drug given alone or with another beta-adrenoceptor agonist (salbutamol).

**Subjects and Methods**

We studied 12 patients with asthma who ranged in age from 13 to 30 years. Their anthropometric details and current medications are given in Table 1. Their medications during the trial, and for four weeks before the trial, remained constant. For entry into the trial the following criteria were fulfilled. The subjects had (1) a forced expiratory volume in one second (FEV₁) greater than 1.2 L, (2) well-controlled asthma and could manage without bronchodilators for at least 4 h; (3) no other chronic illness or evidence of a recent infection and; (4) on a control day, a reduction in FEV₁ greater than 20 percent of the pre-challenge level after challenge with EVH. The patients volunteered for the trial after an explanation of the protocol which was approved by the Hospital's Ethics Committee. Written consent was obtained from each participant. Each patient attended the laboratory on six occasions within a seven-week period, having refrained from taking any therapy by aerosol for a period of at least 6 h and orally administered theophylline for 12 to 24 h before each visit.

Response to the drugs and their placebos was assessed by measuring FEV₁ using a Minato Autospirometer No. 500 (Osaka, Japan). Measurements of FEV₁ were made in duplicate on arrival at the laboratory. On the tests days the FEV₁ was required to be 85 percent or more of the value measured on the control day.

The treatment was administered using three canisters of aerosol (Table 2) and a spacing device (Inhaler Aid, Boehringer Ingelheim, Artarmon, New South Wales, Australia). An observer was present to check that the correct number of inhalations of each test canister was administered by the investigator and inhaled by the patient. Thirty minutes later the FEV₁ was measured and then the challenge procedure was started.

The patients inhaled dry gas containing 4.9 percent CO₂, 21 percent O₂, balance N₂. The gas mixture passed from a cylinder via a demand valve (CIG-Medishield, Sydney, Australia) into a rotameter (GEC-Elliot, Series 2000, Croyden, United Kingdom)
and meteorological balloon (Kaysam Corporation, New Jersey). The patient was instructed to breathe from the balloon for either 2 or 4 min at a ventilation rate equivalent to 60 percent of his predicted maximal voluntary ventilation (MVV). The duration of each challenge remained the same for each patient. The predicted MVV was determined by multiplying the predicted FEV₁ by a factor of 37.5. The patient's expired air passed through a two-way valve (Hans-Rudolph No. 2700, Kansas City, MO) into a 350 L Tissot Gasometer (W. E. Collins, Braintree, MA) and ventilation was recorded (Devices M19, Electromed, S. Peter, Jersey, Channel Is, UK).

Measurements of FEV₁ were made 1, 3, 5, 7, 10, and 15 min after EVH. The challenges were repeated at 2 and 4 h after initial challenge if the values for FEV₁ had returned to within 70 percent of the values measured immediately before the initial challenge.

**Analysis of Results**

The percentage fall in FEV₁ was calculated by subtracting the lowest value for FEV₁, measured after the challenge, from the value measured immediately before each challenge (pre-challenge value), and expressing it as a percentage of the pre-challenge value. When the fall in FEV₁ was less than 10 percent the response was regarded as negative. A fall in FEV₁ between 10 and 25 percent was regarded as a mild response, and a reduction greater than 25 percent, a moderate to severe response. A value of 25 percent was chosen because patients usually complain of symptoms only after this degree of reduction in lung function.

The values for FEV₁ also were expressed as a percentage of predicted normal values for adults and for children. A two-way analysis of variance was used to determine whether there was a difference between the five treatments. Where a significant difference was found by ANOVA (p<0.05) the multiple range test of Duncan was used to determine those treatments that had a statistically significant difference. The level of statistical significance was determined at p<0.05.

**Results**

**Effect of Treatments on Lung Function at Rest**

The patients in this study generally had lung function that was within the normal range (Table 2). For the group, the mean values for FEV₁ on each test day were always greater than 83 percent of the predicted value and the mean maximum difference in FEV₁ between test days was 13.3 ± 6.9 percent. There was no significant difference between the pre-challenge values on each test day (Table 2). Thirty minutes after each active medication had been given, the FEV₁ was significantly higher compared with placebo and the value measured before treatment. Two hours after the combination of fenoterol and ipratropium, fenoterol, and salbutamol, the values for FEV₁ also were significantly higher than after placebo (Table 2). There were no significant differences between these treatments at this time. There was no significant bronchodilatation with ipratropium compared with placebo after 2 h. After 4 h none of the treatments was significantly different from placebo (Fig 1).

![Graph](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21584/ on 06/26/2017)

**Figure 1.** Mean values and the standard error of the mean for forced expiratory volume in one second (FEV₁) (expressed as a percentage of the predicted normal value) measured before and after challenge with eucapnic voluntary hyperventilation (EVH) at 30 min, 2 and 4 h after the administration of treatments.
**Effect of Treatments on Lung Function after Challenge with EVH Thirty Minutes after Treatment**

The mean percentage of fall in FEV₁ after pretreatment with the combination of fenoterol and ipratropium, fenoterol and salbutamol was significantly less than that after pretreatment with placebo or ipratropium (Fig 2). There was no significant difference between protective effects of the three treatments containing a beta-adrenoceptor agonist. There was no significant protection afforded by ipratropium.

Only two patients had more than a 25 percent fall in FEV₁ 30 min after those treatments that contained a beta-adrenoceptor agonist (Table 3). In 20 of the 36 tests performed with these drugs the falls were less than 10 percent. By contrast, no patient was completely protected after ipratropium, seven of the 12 patients having falls in FEV₁ greater than 25 percent, thus retaining their marked responses to challenge by EVH.

The lowest values for FEV₁ (expressed as a percentage of the predicted normal value) after EVH with all treatments were significantly higher compared with placebo (Fig 1). The three treatments containing a beta-adrenoceptor agonist all gave significantly more protection than ipratropium.

**Two Hours after Treatment**

The combination of fenoterol and ipratropium was the only treatment for which the values for percentage of fall in FEV₁ were significantly different compared with placebo (Fig 2). However, there was no significant difference between any of the active treatments.

Six of the 12 patients had a fall in FEV₁ of 10 percent or greater in the presence of the combination of fenoterol and ipratropium compared with eight after fenoterol, nine after salbutamol, and ten after ipratropium.
pium. Of the 12 patients, six suffered moderate to severe falls in FEV$_1$, on at least one occasion, 2 h after taking a treatment containing a beta-adrenoceptor agonist. Eleven of the patients recovered to within 70 percent of baseline after the initial challenge on placebo and were able to perform EVH after 2 h.

The lowest FEV$_1$ after EVH (expressed as a percentage of predicted) was significantly higher after those treatments that contained a beta-adrenoceptor agonist, compared with the placebo (Fig 1). There was no significant difference between any of the active treatments. The lowest FEV$_1$, induced by EVH after ipratropium were no different from the values after placebo.

Four Hours after Treatment

There was no significant difference in the response to EVH after any treatment, compared with placebo (Fig 1 and 2). In only one subject was complete protection afforded by the treatments containing a beta-adrenoceptor agonist. Nine subjects had a fall in FEV$_1$, of 25 percent or more on at least one occasion with these treatments. Similarly nine subjects had 25 percent or more fall with ipratropium (Table 3).

All subjects returned to within 70 percent of baseline FEV$_1$ and were able to perform the challenge 4 h after the active drugs, but only ten were able to perform EVH 4 h after placebo.

Although the values in the presence of the combination of fenoterol and ipratropium were higher (Fig 1), there was no statistically significant difference between the lowest values for FEV$_1$, expressed as a percentage of predicted value on the active agents or the placebo. Clinically, all the drugs were ineffective at this time and most subjects required bronchodilator therapy to reverse their airway obstruction after this challenge.

Relationship between Resting Lung Function and Reduction in FEV$_1$, in Response to Challenge

In the presence of placebo the reduction in FEV$_1$, (percentage of fall) 30 min and 2 h after treatment could not be predicted from resting lung function, expressed as a percentage of predicted normal ($r = 0.1$; $p = NS$). However, after 4 h there was a significant relationship between percentage of fall and the lung function measured immediately before challenge ($r = 0.6$; $p < 0.05$). Those patients with the best pre-challenge level of lung function had the greatest falls in FEV$_1$.

In the presence of the active medications there was no significant relationship between the percentage of fall in FEV$_1$, and the resting lung function, either at 30 min ($r = 0.02$; $n = 48$; $p = NS$), 2 h ($r = 0.18$; $n = 48$; $p = NS$) or 4 h ($r = 0.10$; $n = 48$; $p = NS$).

Reproducibility

In the presence of placebo there was a reduction in the airway response between the first and second tests but this did not reach statistical significance. The response observed at 30 min was restored 4 h after placebo.

The coefficient of variation was 27 percent for the responses on placebo. In only one patient (No. 8) was there marked variability in the response (range, 21 to 61 percent fall). For the other subjects, the mean difference between the highest and lowest percent fall observed on the three challenges was 10.6.

Discussion

The results of this study show that the anticholinergic agent ipratropium, the beta-adrenoceptor agonists fenoterol and salbutamol, and the combination of fenoterol and ipratropium all induce significant bronchodilatation within 30 min after administration. At this time all the treatments containing a beta-adrenoceptor agonist completely blocked or markedly inhibited the reduction in FEV$_1$, after challenge with EVH. Although there was a statistically significant inhibition of the response by ipratropium, this was not clinically relevant.

This study confirms previous findings that the duration of action of the bronchodilating effect of a drug is longer than its protective effect against asthma provoked by hyperpnea.$^{18,19}$ Thus, despite the persistence of good lung function 2 h after treatment with beta-adrenoceptor agonists alone, the majority of patients were not protected against challenge with EVH. However, half the patients were protected from asthma by the combination of ipratropium and fenoterol at this time. By 4 h after treatment, this combination no longer afforded any protection. These findings also demonstrate that, in the presence of bronchodilators, the severity of the airway response to hyperpnea cannot be predicted from pre-challenge levels of lung function.

We selected EVH rather than exercise to investigate the protective effect of a number of drugs against hyperpnea because we consider that hyperventilation-induced asthma (HIA) is a good model of EIA and has advantages when multiple tests are performed.

Although there are fundamental differences in the metabolic and physiologic events that accompany exercise and hyperventilation there is a remarkable similarity between the asthma provoked by these two challenges.$^7$ For example, the severity of the changes in lung function are the same when ventilation and the inspired air conditions are kept the same for the two challenges.$^7$ The time taken for the airway response to develop is the same in that the maximum response in lung function occurs 5 to 10 min after challenge. The drugs which inhibit EIA, for example
the beta-adrenoceptor agonists and sodium cromoglycate alone and in combination, have similar effects against exercise \(^{28}\) and EVH. \(^{30}\) A refractory period occurs in some but not all patients after exercise and EVH. \(^{14,30}\) Neither of these challenges renders the smooth muscle refractory to other stimuli nor do they change nonspecific bronchial hyperresponsiveness. \(^{31,32}\)

The major differences between exercise and EVH relate to changes in concentration of circulating substances and the development of a late response. Catecholamines, cyclic adenosine 5' monophosphate (AMP) and histamine levels increase in plasma with exercise but not EVH. \(^{33,34}\) Stimulation of beta-adrenoceptors by catecholamines may account for the bronchodilation recorded in the first few minutes of exercise, although this has not been proven. Substances known to be involved in the inflammatory reaction, such as histamine and the neutrophil chemotactic factor, have been found in the majority of patients with EIA\(^{19,35}\) but not with EVH. \(^{36,37}\) There is one report, however, of neutrophil chemotactic activity increasing after EVH. \(^{38}\) There is no record of a late response after EVH and this may reflect differences in the release of inflammatory mediators during exercise after which a late response has been recorded. \(^{39}\) There are also reports which suggest that a refractory period is not as common after EVH as after exercise, \(^{40}\) and inspired air conditions during these challenges may determine the state of refractoriness. \(^{41,42}\)

There are practical advantages for using EVH rather than exercise for provoking asthma in the laboratory. EVH can be performed in a steady-state for shorter periods than exercise because ventilation can be increased to the required rate immediately. This was of particular advantage in this study because the patients were required to perform numerous tests on the same day and EVH is less fatiguing than exercise. Furthermore for each subject identical rates of ventilation for a large number of tests is more easily achieved with EVH.

We chose EVH at 60 percent of MVV for two reasons. First, this level of ventilation would be realistically achieved during exercise. Second, it has been shown that the maximum response to EVH occurs after 5 to 7 min of EVH at this rate of ventilation, and is almost fully developed after 3 min. \(^{43}\) While most patients hyperventilated for 4 min, in two subjects only 2 min was required to induce a substantial reduction in FEV\(_1\). Traditionally a 6- to 8-min test is recommended for provoking EIA under standard laboratory conditions. The relatively shorter time required using EVH as the stimulus could relate to the extreme dryness of the air and the high rate of ventilation which is maintained over 4 min. With exercise, some minutes are required for ventilation to increase. In this study the average ventilation rate was 80 L min\(^{-1}\) which would result in a total respiratory water loss of 2.3 ml/min or about 9 ml over 4 min.

The fall in FEV\(_1\), in response to EVH, 30 min and 2 h after treatment, could not be predicted from the resting level of lung function, either in the presence of placebo or active drugs. Four hours after placebo, it was notable that those patients with the best lung function had the greatest falls in FEV\(_1\). This implies that airways already obstructed were less likely to obstruct further in response to drying and cooling, which is in contrast to the responses when stimuli such as histamine or methacholine are used to provoke asthma. \(^{44}\)

The reason for the shorter duration of protection afforded by these medications, relative to the duration of their bronchodilator effect, is not clear. One possibility is that the concentration of the drug within the airway lumen, rather than at the smooth muscle, is an important determinant of its ability to prevent asthma provoked by hyperpnea. \(^{15,18}\) After 2 h it is likely that much of the drug has either been absorbed across the bronchial mucosa or cleared from the airway by the action of the cilia. \(^{45}\) Bronchodilation was evident at 2 h because the concentration of the drug on the smooth muscle was still sufficient to cause relaxation.

The findings in this study with EVH are consistent with those reported in earlier studies with exercise which have demonstrated that the duration of the protection afforded by either beta-adrenoceptor agonists or sodium cromoglycate does not exceed 2 h. \(^{15,18,40,46}\)

It is possible that the relaxant effects of beta-adrenoceptor agonists on airway smooth muscle are insufficient to prevent asthma provoked by respiratory water loss. This has been considered in previous studies which compared oral with aerosol administration of salbutamol, \(^{15,47}\) and metaproterenol \(^{48}\) in protecting against EIA. It was shown that orally administered salbutamol and metaproterenol, while inducing equivalent bronchodilatation to the aerosol preparation, did not prevent the post-exercise fall in FEV\(_1\). \(^{15,40,47}\) Taken together with the findings in this study it suggests that the concentration of a beta-adrenoceptor agonist required in the airways to inhibit EIA or EVH is higher than the concentration required to relax bronchial smooth muscle.

These findings also suggest that actions at sites other than smooth muscle may be relevant to the protective effect of beta-adrenoceptor agonists against EIA. When delivered directly into the airways, beta-adrenoceptor agonists could act directly on mast cells or other target cells preventing the release of mediators, \(^{15-18}\) or they could reduce microvascular leakage in the bronchial mucosa. \(^{48}\) Since water loss from the airways is the stimulus to EIA, these drugs may play an important role in modulating water balance. For
example, beta-adrenoceptor agonists have been reported to increase the transport of chloride ions across the respiratory epithelium.40 By doing so, they enhance the active transport of water to the airway lumen. Beta-adrenoceptor agonists may also act to increase blood flow through the bronchial circulation which would not only improve delivery of water to the airway mucosa but also enhance clearance of mediators.47 Finally, by increasing the beat frequency of cilia, and thus the movement of water up the bronchial tree, they could modify the dehydrating effects of evaporative water loss, at least in the more peripheral airways. Indeed, any event which improves the transport of water to the airways will attenuate the increase in osmolarity which is thought to stimulate the release of mast cell mediators.

In a previous study which investigated the protective effect of ipratropium against exercise challenge in 15 patients, we reported that there were two subgroups. In six subjects, EIA was completely prevented and all had a significant improvement in lung function recorded in the 15 min after medication and before challenge.14 The remaining nine subjects were not protected against EIA and had no significant improvement in lung function in the 15 min after medication. We did not see this pattern in the present study. The reason for this is unknown but there are two differences between the studies. First, for the patients in the present study, the lung function at rest was superior to that for the group in the previous study. Second, in the previous study, the challenge used was exercise which causes catecholamine release and consequent stimulation of beta-adrenoceptors on airway smooth muscle. Moreover, giving ipratropium to the exercising patient might be analogous to giving the combination of fenoterol and ipratropium for EVH. Thus, although some patients are completely protected from EIA by pre-treatment with ipratropium, this is not so when EVH is used as the stimulus.

Histamine is considered an important contributor to the airway narrowing which follows challenge by exercise or EVH.50,51 Since the bronchoconstricting effects of inhaled histamine are not completely blocked by anticholinergic agents,52,53 it is not surprising that ipratropium did not completely protect against challenge with EVH in this study. The small though significant reduction in the response to EVH by ipratropium suggests that the airway narrowing due to contraction of smooth muscle via acetylcholine receptors is a minor component of the overall response. It is possible that the action of histamine (released from mast cells in response to EVH) on the vagal reflex pathways is prevented by ipratropium while its major effect to cause airway narrowing via other pathways is not.

It is notable that eight of the 12 patients were taking the aerosol steroid beclomethasone dipropionate daily for treatment of their asthma. While steroids do not prevent the immediate type 1 response to histamine and other mediators, there is a study reporting the beneficial effect of aerosol steroids in reducing both the severity and the amount of medication required to prevent EIA.44 Most of our patients were taking doses similar to those of the subjects studied by Henriksen and Dahl,44 and their resting lung function values also were similar. We do not know if the reduction in FEV1 would have been more severe had our patients not been taking aerosol steroids; however, they still experienced enough asthma after EVH to suggest that they would require prophylactic treatment before undertaking exercise.

In this group of well-controlled patients with asthma who had levels of pre-challenge lung function within the normal range, the FEV1 at rest was improved by all treatments. The treatments containing beta-adrenoceptor agonists were very effective in preventing asthma induced by hyperventilation and we conclude that they would also protect against EIA given the similar or identical nature of the underlying mechanisms for these stimuli.7 However, the duration of protection for any of these drugs is no greater than 2 h. Even after 2 h only a minority of patients will be protected by a beta-adrenoceptor agonist alone, whereas half the patients were afforded protection by the combination of fenoterol and ipratropium. Therefore, it is likely that some patients will find the combination of these drugs, in the standard dose, superior in terms of duration of action against asthma than single-drug therapy. Some patients, particularly those who exercise frequently throughout the day, may benefit from combination therapy which could provide longer protection and cause fewer side effects than frequent inhalation of beta-adrenoceptor agonists.

The mechanism for the longer protective effect of the combination of these drugs is not understood. It is possible, however, that the clearance of the beta-adrenoceptor agonist from the airway lumen is retarded in the presence of ipratropium although there is no evidence for this. If the clearance from the airways is reduced, this might allow a critical concentration of the beta-adrenoceptor agonist to be maintained in the airways to prevent the release, or the action, of mediators from mast cells.

It is often suggested that patients should make measurements of flow rates before exercise. However, it is important to realize that recording a normal value cannot predict occurrence or severity of EIA. It is therefore best to advise patients that they should remember at what time they took medication and to repeat it if 2 h or more has passed. While it is likely that patients will find the combination of ipratropium and fenoterol superior in terms of duration of action
against EIA it is unlikely to find this combination, or any other medication, still active 4 h after administration.46

We believe that clearance of the drug from the airway lumen may account for the short protective effect of drugs against challenge by hyperventilation or exercise. It is also likely that a similar duration of protection would be afforded against asthma provoked by other inhaled stimuli such as allergens. To overcome some of these problems, future studies should consider investigating the possibility that, in patients with good lung function, attacks of asthma may be better controlled by reducing the dose of drug delivered by aerosol and by increasing its frequency of use.

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REFERENCES

10 Smith CM, Anderson SD. Hypermosmolarity as the stimulus to asthma induced by hyperventilation? J Allergy Clin Immunol 1986; 77:729-36.
37 Deal EC, Wasserman SI, Soter NA, Ingram RH, McFadden...
39 Bierman CW, Spiro SG. Characterization of the late response in exercise-induced asthma. J Allergy Clin Immunol 1984; 74:701-06
40 Stearns DR, McFadden ER, Breslin FJ, Ingram BH. Reanalysis of the refractory period in exertional asthma. J Appl Physiol Respirat Environ Exercise Physiol 1981; 50:503-08
48 Persson CGA. Role of plasma exudation in asthmatic airways. Lancet 1986 (Nov 15); 1126-28
50 O'Byrne PM, Thomson NC, Morris M, Roberts RS, Daniel EE, Hargreave FE. The protective effect of inhaled chlorpheniramine and atropine on bronchoconstriction stimulated by airway cooling. Am Rev Respir Dis 1983; 128:611-17

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