METHODOLOGY

Provocation by eucapnic voluntary hyperpnoea to identify exercise induced bronchoconstriction

S D Anderson, G J Argyros, H Magnussen, K Holzer

Abstract
The International Olympic Committee Medical Commission (IOC-MC) requires notification for use of a $\beta_2$ agonist at the Winter Olympic Games in Salt Lake City. This notification will be required seven days before the event and must be accompanied by objective evidence that justifies the need to use one. The IOC-MC has expressed the viewpoint that, at present, eucapnic voluntary hyperpnoea (EVH) is the optimal laboratory challenge to confirm that an athlete has exercise induced bronchoconstriction (EIB). The EVH test recommended was specifically designed to identify EIB. EVH has been performed in thousands of subjects in both the laboratory and the field. The test requires the subject to hyperventilate dry air containing 5% carbon dioxide at room temperature for six minutes at a target ventilation of 30 times the subject’s forced expiratory volume in one second (FEV1). The test conditions can be modified to simulate the conditions that give the athlete their symptoms with exercise. A reduction in FEV1 of 10% or more of the value before the test is considered positive.

Keywords: hyperpnoea; bronchial provocation; exercise

At a recent meeting of the International Olympic Committee Medical Commission in Lausanne it was recommended that notification for the use of a $\beta_2$ agonist before an event would require clinical and laboratory (including respiratory function tests) evidence to justify the need for such medication. While acceptable evidence could be submitted in many forms, an abnormal airway response to a bronchial provocation test with eucapnic voluntary hyperpnoea (EVH) was identified as confirmation that an athlete has exercise induced bronchoconstriction (EIB). EIB is a well recognised medical indication for the prophylactic use of $\beta_2$ agonists, so that its documentation would appear to justify the need for prophylaxis with a $\beta_2$ agonist before exercise.

The need for objective testing to identify EIB is supported by the knowledge that, in athletes, respiratory symptoms do not predict EIB and cannot be used to justify the need for medication to prevent it. There are limitations in using laboratory based exercise tests to identify EIB in elite athletes, and there is a high prevalence of it in winter athletes. The EVH test is suggested as an alternative to exercise as a laboratory based test to identify EIB.

Reasons for recommendation
Bronchial provocation with EVH was recommended for the following reasons: (a) EVH is a potent challenge test for provoking bronchoconstriction in clinically recognised asthmatics responsive to exercise; (b) the symptoms provoked by EVH such as cough, dyspnoea, and wheeze are the same as those reported with exercise; (c) EVH testing requires less expensive equipment and fewer personnel than exercise testing; (d) EVH can induce ventilation rates equivalent to or higher than most forms of exercise, and the ventilation rate achieved can usually be sustained over six minutes; (e) the maximum airway response to EVH is similar to that achieved by exercise, and occurs within the first 10 minutes of cessation of the hyperpnoea; (f) as with exercise, $\beta_2$ agonists are effective in inhibiting the airway narrowing to EVH; (g) as with exercise, a variety of inflammatory mediators, including histamine, prostaglandins, and leukotrienes, are likely to be involved in the response to EVH; (h) EVH has a very high specificity for identifying persons with clinically recognised asthma; (i) publications are readily available on the standardisation, application, and interpretation of EVH testing; (j) EVH has been used safely in many thousands of subjects including adults and children; (k) EVH has been used with some success to identify EIB in cold weather athletes; (l) EVH testing has the potential to be tailored to simulate the respiratory demands of exercise and the inspired air conditions that provoke symptoms in the athlete.

Mechanism of airway narrowing to hyperpnoea
The mechanisms proposed to explain why the airways narrow in response to intense exercise or eucapnic hyperpnoea of dry air are also likely to account for other symptoms in athletes performing exercise, particularly in the cold. The response to breathing dry air is thought to cause the airways to narrow by osmotic and thermal consequences of evaporative water loss.
Testing for exercise induced bronchoconstriction

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necessarily predict EIB.1 Asthma, we recommend the progressive proto-

and we suggest that inhaled steroids are not

mechanism is present, a hyperosmolar environment

could explain why these symptoms do not necessarily predict EIB.1

and we recommend the progressive proto-

the narrowed airway caused by the normal contraction of the bronchial smooth muscle

cardiorespiratory values should agree to within 200 ml, and they

Airway cooling is also a consequence of respiratory water loss, partic-

PROHIBITED

conditioning or preventing the induced reduction in

were originally developed, standardised,

their protocol requires hyperventilation voluntarily for EVH.

inhibiting or preventing the induced reduction in

those known to have moderate to severe

their lung function. This protocol is relevant for

nitrogen. The simplest and safest way to
deliver the mixture is from a gas cylinder con-
taining the inspired concentrations of the gases. It is possible to add carbon dioxide to the
inspired air, but this requires careful monitoring
of the end tidal carbon dioxide to ensure eucapnoea. Unless the response under these
conditions is negative, it would not appear neces-
sary to have a longer duration of hyperpnoea
than six minutes or to condition the inspired air

cold air is equivalent to eight minutes of hyper-
pnoea with air at room temperature.27 If a cool
inspirate is required, commercially available
heat exchangers can be used, such as the Air-jet
PTS System (Stoneridge, New York, New
York, USA) or Jaeger RES (Erich Jaeger
GmbH, Wurzburg, Germany). Another simpler
device (Turboaire Challenge; Equilibrated Bio-
Systems Inc, Melville, New York, USA) is also
commercially available, but its use considerably
reduces the number of tests that can be performed per cylinder. It is also possible to
cool the inspired air by passing the air mixture
either through or over a cooling coil immersed
in substances such as ethylene glycol, a mixture
of ice and acetone, isopropyl alcohol, freon, or
methanol cooled to −35°C.

MEASUREMENT OF THE AIRWAY RESPONSE

The FEV1 is measured three times before the
challenge, and the highest measurement used
to calculate the airway response. The three
values should agree to within 200 ml, and they
should be performed in accordance with
American Thoracic Society criteria.28

The FEV1 is measured in duplicate immediately
after the challenge and at five, 10, 15, and 20
minutes after EVH. An additional measure-
ment can be made at three minutes.

THE TEST

The single stage protocol requires hyperventi-
latory for six minutes at a target ventilation rate
equivalent to 30 × FEV1 (litres corrected to
body temperature, pressure, and fully saturated
(BTPS)) measured immediately before the
test. This is only a target ventilation rate. Most
elite athletes should easily achieve 25 × FEV1,
and most asthmatics need only breathe at $21 \times FEV_1$ to have an abnormal response. Although the subject could inhale directly from a demand valve, these valves provide a significant inspiratory resistance at high flow rates. For this reason a meteorological balloon (120 litre capacity) is recommended to act as reservoir. The balloon is filled initially with 90 litres and then continuously filled at a rate close to the target ventilation rate during the challenge. The rate is checked by placing a rotameter between the cylinder and the balloon. The use of a rotameter is not essential if the expired ventilation is being measured continuously (figs 1 and 2). The subject breathes through a two way valve, and, when the hyperpnoea begins, is encouraged to keep the volume of the balloon constant while it is being filled at the target ventilation rate. The balloon should not be overfilled, as the distending pressure will cause the expiratory valve to open and hence the expired ventilation to be overestimated. A metronome can be used to guide the frequency of respiration in accordance with that attained during exercise. Expired ventilation can simply be measured either as the cumulative amount at the end of the test, corrected for time, or after each minute. A gas meter or other suitable device for measuring ventilation can be used. The volume is corrected to BTPS. Figure 2 gives an example of the equipment used for the EVH challenge. Most laboratories could readily adapt their exercise equipment to achieve a similar circuit. The minimal equipment needed for EVH is the gas mixture, a means of delivering it, and a spirometer to measure FEV$_1$. A measurement of ventilation, although highly recommended, is not needed to establish the existence of a response. However, a measure of the ventilation is needed to assess the stimulus to induce that response and the severity of the response.

### Expressing and interpreting the severity of the airway response

Airway narrowing in response to EVH is assessed by measuring changes in FEV$_1$. The percentage fall in FEV$_1$ is calculated as follows:

$$\frac{100 \times (FEV_1 \text{ (before the test)} - \text{lowest value for } FEV_1 \text{ measured in the 20 minutes after the test})}{FEV_1 \text{ before the test}}.$$

A reduction in FEV$_1$ of 11.3% or more is outside the 95% confidence limit for healthy subjects when the single six minute protocol is used with air at room temperature. Hurwitz et al concluded that in a “proper clinical setting subjects whose FEV$_1$ declines by 10% or more...”
at 5 or 10 min after EVH should be diagnosed as having asthma”. This value is in accord with the findings of others in thousands of healthy subjects subjected to cold air challenge.12 13 29 30 Further, a value of 10% would be in keeping with a diagnosis of EIB.

Expressing and interpreting the stimulus causing the response
The stimulus is reported as the average ventilation rate, in litres BTPS per minute over the period of the test, expressed as a percentage of the predicted MVV. MVV is defined as a multiple of 35 × measured FEV1. Expressing the provoking stimulus as a percentage of the predicted MVV gives a guide to the intensity of exercise that would be required to provoke the reduction in lung function. The maximum achievable ventilatory exercise in a healthy person rarely exceeds 60% of the MVV, and in an elite athlete it would rarely exceed 90% of their MVV.

Bronchial responsiveness to a provoking stimulus is often referred to and interpreted as mild, moderate, or severe. The response is mild if the fall in FEV1 is between 10 and 19.9% when the ventilation is 60% MVV or more and moderate when the fall is between 20% and 29.9%. The response is severe when the fall in FEV1 is 30% or more at any level of ventilation or if a fall greater than 10% occurs at a ventilation rate less than 30% MVV.

Safety
Thousands of EVH tests have been performed without serious unwanted side effects.1–13 However, EVH has the potential to provoke severe bronchoconstriction, and for this reason a bronchodilator and supplemental oxygen should be available at the site of testing. It is recommended that, as with the performance of any other bronchial provocation tests, medical personnel and resuscitative equipment be readily available.

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References

Take home message
Voluntary hyperpnoea with dry air is a standardised bronchial provocation test to identify athletes with exercise induced bronchoconstriction or exercise induced asthma in laboratory environment.
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