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Obtaining additional information by using exercise testing in the laboratory in the diagnosis of asthma

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Educational aims

❭ To explain how to get more information out of an exercise challenge.
❭ To obtain knowledge about different exercise test protocols and ergometers.
❭ To obtain knowledge about the importance of assessing different physiological variables during exercise.
❭ To obtain knowledge about how different climatic conditions influence exercise-induced bronchoconstriction (EIB) and exercise capacity.

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Summary

Different test protocols are commonly used in the diagnosis of EIB and in the assessment of exercise capacity ($V'_{O_2,peak}$). Recently one study has shown the possibility of combining assessment of EIB and $V'_{O_2,peak}$ into one EIB test protocol, even though the gold standard in assessment of $V'_{O_2,peak}$ is an incremental protocol. Additional and useful information about asthma can be obtained and differential diagnoses to EIB can be assessed by measuring different physiological variables during the EIB challenge. The following article will focus on the advantages of measuring exercise capacity during an EIB test, after a short discussion of different test protocols and ergometers.

❮ Exercise-induced bronchoconstriction (EIB) influences daily life activities and sports activities in children, adolescents and adults. To enable optimal choice of treatment, an accurate assessment of EIB is therefore important. EIB consists of bronchoconstriction occurring immediately or soon after physical exertion [1–3], and is best assessed by a standardised exercise test. Running on a treadmill for 6–8 min at a submaximal work load is a commonly used test [4, 5]. Lately it has been maintained that an exercise load corresponding to 95% of maximum heart rate (HRmax) is preferable to obtain a high sensitivity [3].

Elite athletes are more likely to report asthma and asthma symptoms than age-matched controls. The prevalence of asthma and bronchial hyperresponsiveness (BHR) is higher among elite athletes assessed both by questionnaire and objective measurements [6–9]. On the other hand, it is known that reduced physical fitness and physical activity are important for the development of chronic disorders, including asthma [10, 11]. Increasing prevalence of overweight, obesity [12] and asthma [13, 14] in children and adolescents is reported, and a number of longitudinal studies have reported increasing risk of developing new asthma or asthma symptoms in obese children and adolescents [15–18]. It was recently suggested that the lack of physical activity, more than the obesity itself, increases the risk of asthma [19].

An individual's pattern of physical activity and future activity level is often founded during childhood and adolescence. Assessment of physical fitness may give important information about physical functioning in patients with chronic lung disorders, including asthma.

Test protocols and ergometers

The choice of test protocol and ergometer should be based on the purpose of the exercise test and the patients performing the tests: children, adults, elite athletes, and untrained or obese patients. If the reason is to provoke EIB, an EIB test will be used. If the purpose is to measure physical fitness, an incremental test protocol is commonly used.

As asthma is a limiting factor for participation in physical activity and sport, assessment of physical fitness may give important information about physical functioning. Physical fitness is an umbrella concept covering a series of qualities related to the performance of physical activity

[20]. Maximum oxygen uptake ($V'O_{2,max}$) or peak oxygen uptake ($V'O_{2,peak}$) is widely recognised as one of the most important measures of aerobic capacity and physical fitness [20, 21]. $V'O_{2,max}$ provides an accurate measure of aerobic power, and it is highly related to cardiac output. ÅSTRAND et al. [20] define $V'O_{2,max}$ as the achievement of a plateau or "levelling off" in oxygen uptake ($V'O_2$) despite continued increase in workload (<2 mL per kg per min rise in $V'O_2$), to be the most important criterion to estimate $V'O_{2,max}$. Other factors indicating achievement of $V'O_{2,max}$ are respiratory exchange ratio (RER) ≥1.05 and heart rate (HR) ≥95% of HRmax (based on 220 beats per min – age in yrs). In young subjects, this levelling off does not occur, and $V'O_{2,max}$ may be determined as $V'O_{2,peak}$, the highest recorded $V'O_2$ during the exercise test [22–25].

The choice of exercise ergometer and test protocols may influence the $V'O_{2,peak}$ values both in children and in adults: treadmill running or cycling are the type of exercise most commonly used [20]. ÅSTRAND et al. [20] conclude that treadmill running is the best exercise ergometer for testing healthy people, especially children, because walking or running is the natural way to move and demands dynamic use of large groups of muscles. Exercise testing for athletes may be performed within the athletes' own discipline of the athletes, as exemplified for swimmers [26]. A rowing ergometer has been employed in fitness testing of children [27]. Special considerations need to be taken into account for children, related to age, sex, growth and physical performance. It has been maintained that in children it is preferable to employ running rather than cycling in testing [28].

Previous studies have compared different test protocols for assessing $V'O_{2,peak}$ both in children and in adults. In spite of a general consensus that an incremental test protocol lasting between 8–12 min will elicit the highest $V'O_{2,peak}$ with the lowest perception of difficulty and discomfort, studies have not found a difference in $V'O_{2,peak}$ between different test protocols [29, 30]. DAY et al. [31] concluded that $V'O_{2,peak}$ was not different with a constant workload protocol lasting between 4–10 minutes as compared to an incremental ramp protocol. ROSSITER et al. [32] suggested that $V'O_{2,peak}$ can be reached at a constant workload corresponding to 105% as well as 95% of maximum workload. This is in agreement with COOPER [33] who maintained that short bouts of high-intensity exercise are the physiological way of studying children, rather than repeated stepwise exercise testing. Different test protocols may

Figure 1

Bland–Altman plot (95% limits of agreement) for $V'O_{2,peak}$ (triangle) and peak minute ventilation ($V'E,peak$) (square) assessed with the EIB protocol and the stepwise protocol at 5.3% inclination of the treadmill (n=20). Reproduced from [34], with permission from the publisher.
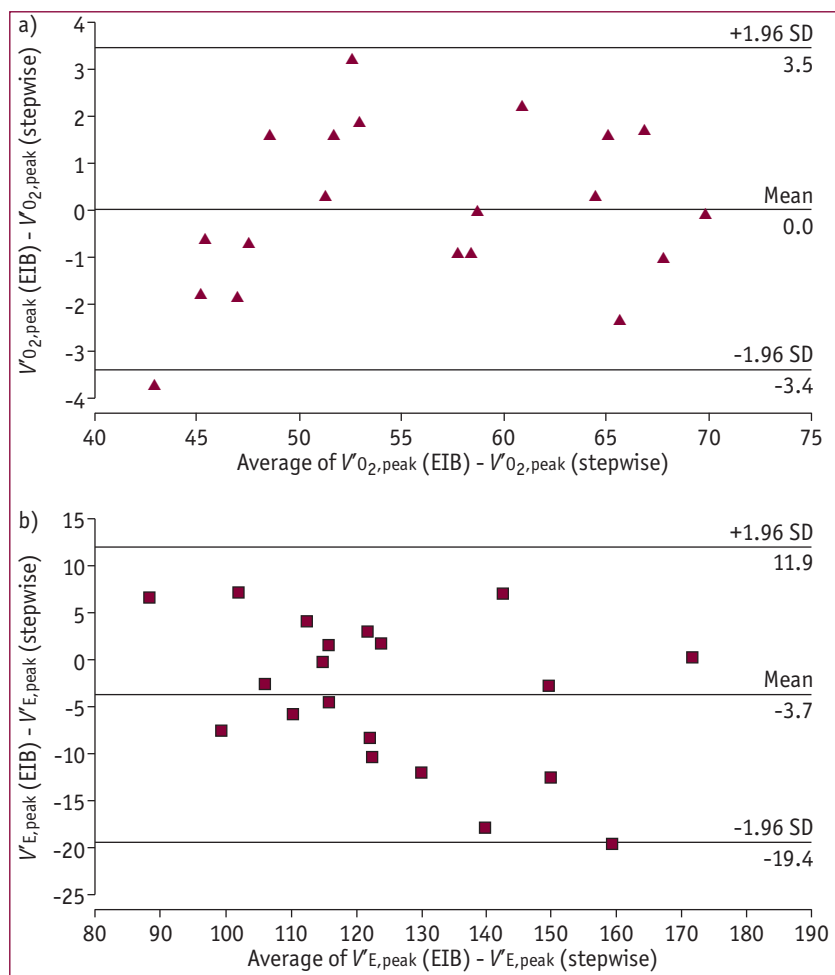
be needed to assess physical fitness in children and adolescents with different diseases. Whereas a gradual increase in speed and inclination of the treadmill may be beneficial for subjects with cardiac diseases, a more rapidly increasing protocol may be better suited for asthmatic children and adolescents [33].

Until now, assessments of EIB and $V'_{O_2,peak}$ have been performed with two different test protocols on separate days. One study has shown the possibility of combining assessment of EIB and $V'_{O_2,peak}$ into one exercise test [34]. STENSRUD and CARLSEN [34] compared $V'_{O_2,peak}$ by applying an EIB test protocol and a stepwise protocol and conclude that neither $V'_{O_2,peak}$ nor peak minute ventilation ($V'_{E,peak}$) differed between the two protocols (fig. 1) and thus gave useful information about both EIB and physical fitness.

The EIB test in the study of STENSRUD and CARLSEN [34], was performed at two different inclinations of the treadmill, 5.3% and 10.5%. Subjects ran for 8 min without warming up. The starting running speed was approximately 70–80% of estimated HRpeak. The speed was subsequently adjusted during the first 4 min to achieve a workload corresponding to the maximum speed the subjects were able to sustain during the last 4 min: about 95% of estimated HRpeak. V'_{O_2}, V'_E, RER, respiratory frequency (f_R) and HR were measured during the EIB test. Lung function was measured by maximal forced expiratory flow volume loops before and 1, 3, 6, 10 and 15 minutes after the test.

The stepwise protocol for measuring $V'_{O_2,peak}$ was according to the procedure described and validated by HERMANSEN [35] and ÅSTRAND et al. [20] and consisted of 20 min warm-up at a workload corresponding to approximately 50–60% of $V'_{O_2,peak}$. After warming up, the running speed was increased to a workload of ~80% of $V'_{O_2,peak}$ and further increased every minute until the subjects were close to exhaustion after about 4–6 min. V'_{O_2}, V'_E, RER, f_R and HR were measured during the test and the criteria to identify $V'_{O_2,peak}$ were used.

Even though no significant differences in $V'_{O_2,peak}$ or $V'_{E,peak}$ were found, it should be remembered that the results may not apply to all asthmatic subjects. Anti-asthmatic treatment has to be withheld before EIB testing according to European Respiratory Society and American Thoracic Society guidelines [2, 36], and this may influence $V'_{O_2,peak}$ if bronchoconstriction occurs during the test. However, several previous studies have shown that bronchoconstriction occurs soon after a 6–8 min exercise test and not during the

exercise [1–3, 36], and $V'_{O_2,peak}$ may thus not be affected. If bronchoconstriction occurs during the exercise test $V'_{O_2,peak}$ may be affected and a new test for measuring $V'_{O_2,peak}$ with pre-medication may be performed.

However, assessment of EIB and $V'_{O_2,peak}$ in a single test may reduce the burden for the patient by saving one test day; simplify diagnostic and monitoring procedures of the patients and the costs for the health system. The following text will therefore focus on the assessment of EIB and exercise capacity by using an EIB test protocol.

When performing an EIB test or a test for assessment of $V'_{O_2,peak}$ at a fixed inclination of the treadmill, it is common to use an inclination of 3° or 5.3% for children, untrained subjects and athletes [2, 25]. As regards athletes within endurance sports, with the exception of runners, both EIB tests and $V'_{O_2,max}$ tests are usually performed at 6° or 10.5% inclination to minimise the effects of seasonal changes in $V'_{O_2,max}$ caused by changes in running technique and running economy as a consequence of seasonal shifts in the type of training, *e.g.* running and skiing [37]. On the other hand, a steep inclination can cause local fatigue in the thigh and leg muscles, thus limiting the achievement of $V'_{O_2,peak}$, especially in children and untrained subjects [38].

Peak oxygen uptake, presented as mL per kg per min, is the best measure of physical fitness or exercise capacity and a good predictor of the subject's potential to move and lift the body, but it does not reflect cardiac performance [20]. The total oxygen uptake (L per min) correlates with cardiac output, myocardial oxygen consumption and blood flow and both measures are thus useful [20].

Pulmonary hyperinflation

Assessment of physiological variables other than $V'_{O_2,peak}$ and HR during an EIB test may be useful. $V'_{E,peak}$, f_R, RER and arterial oxygen saturation (S_{a,O_2}) may give valuable information about dynamic hyperinflation and breathing pattern and be helpful in the diagnosis of differential diagnosis to EIB.

Pulmonary hyperinflation or dynamic hyperinflation is usually defined as an abnormal increase in functional residual capacity (FRC), for example volume at the end of a tidal expiration [39]. This is seen in patients with obstructive pulmonary diseases, including asthma. With increased airway obstruction causing increased resistance

to air flow, the lung may not have enough time to empty before the next inhaled breath and f_R will thus increase to maintain the ventilatory demand. Rapid breathing, for any reason, will trigger this vicious response, and even a mild episode of increased dyspnoea may result in anxiousness and fear leading to the rescue breathing pattern and rapidly making the dyspnoea worse. Learning to recognise and control the emotional aspects of the breathing pattern may help to control breathing.

f_R and RER may give helpful information about abnormal breathing pattern. Patients with EIB are reported to breathe faster during exercise in cold air than in normal indoor conditions and deeper and slower during exercise in humid air [40, 41]. It has been observed that patients with additional diagnoses to asthma, such as anxiety, eating disorders and obesity, show an abnormal breathing pattern during exercise. Obesity itself is a common cause of breathlessness on exertion and it probably acts synergistically with airway obstruction in the generation of breathlessness [42]. FRC is reduced in obese patients, due to abdominal fat tissue contents on the position of diaphragm, resulting in reduced expiratory reserve volume [20, 42].

Differential diagnosis to EIB

Exercise induced laryngeal stridor (EILS) is a frequent differential diagnosis to EIB and the condition is most often seen in young well-trained girls participating in endurance sports. The prevalence in athletes is reported to be 5.1% [39]. In 2004 STENSRUD and CARLSEN [43] reported a prevalence of 17.5% in athletes referred to a pulmonary clinic with exercise-induced respiratory symptoms. The symptoms of EILS are inspiratory stridor occurring during maximum exercise and stopping when exercise is terminated. During exercise, audible inspiratory sounds can be heard from the laryngeal area, with no effect of bronchodilators or other asthma medication. Hyperventilation is often seen in relation to EILS and measurement of $V'E$ (which often shows a sudden drop close to maximum), $V'O_2$, f_R and RER during exercise may serve as an additional tool to confirm the diagnosis of EILS. The correct diagnosis of EILS should be confirmed by direct fibreoptic laryngoscope during exercise.

Another differential diagnosis related to EIB is exercise-induced arterial hypoxaemia (EIAH). DEMPSEY et al. [44] reported a prevalence of 50% in elite male runners [45]. EIAH is defined by a reduction in Sa,O_2 of 8–10% from before to after strenuous exercise [46]. This occurs especially in highly endurance-trained athletes and is thought to be primarily due to diffusion limitations and/or ventilation/perfusion mismatch [47].

Elite athletes are also at risk of "overtraining" and this condition may sometimes represent a possible differential diagnosis to EIB.

If an athlete complains about respiratory symptoms during exercise and no bronchial hyperresponsiveness or EIB is found, one of the above conditions is a possible cause.

On the other hand, poor physical fitness in contrast to enthusiastic parental expectations is a frequent occurrence among children and adolescents participating in sports and can easily be assessed by measuring exercise capacity.

Assessment of breathing reserve and tidal breathing during exercise

In patients with obstructive chronic respiratory disorders, including asthma, assessment of physical fitness may give important information of the severity of illness and the ability to master physical exercise. Particularly important information can be obtained when this type of testing is combined with measurements of breathing reserve (BR), made by measuring maximal voluntary ventilation before exercise and comparing it to $V'E,peak$ achieved during exercise. The difference in is defined as BR: normal BR in healthy subjects is 20–40% [20].

The tidal breathing loops obtained during exercise, most often during running on a treadmill, are related to the maximal expiratory flow–volume loops obtained before running [48, 49]. Limitations in physical fitness may be set by the baseline lung function, and assessment of flow limitation and end-expiratory lung volume during exercise may give important information about the possible training effect that may be obtained [50]. The simultaneous assessment of tidal breathing loops during exercise and assessment of BR is useful to show the patient whether there is a pulmonary limitation.

EIB and exercise capacity in different climatic conditions

More knowledge about different climatic conditions in relation to EIB and exercise capacity is needed in order to give optimal training advice and treatment to asthmatic patients in relation to physical activity. Elite athletes often practise altitude training in unfavourable environments. More knowledge is also needed in relationship to regular physical training of asthmatic subjects, especially in countries with sub-Arctic climates, where the winter season can be quite cold. Furthermore it is not unusual for children and adults to take part in activities such as mountain-climbing, skiing and tracking in medium or higher altitudes where atmospheric pressure is lower than at sea level.

It is known that cold, dry air increases EIB, and that humid air reduces EIB in subjects with asthma (fig. 2) [51–54]. However, few studies exist concerning the effect of different climatic conditions upon exercise capacity in subjects suffering from EIB, and these studies have given conflicting results [55–57]. Hypoxic gas inhalation has been reported to enhance bronchial hyperresponsiveness and result in bronchoconstriction in some animal models, and in humans with asthma [58, 59]. The data on humans have so far been conflicting [60, 61]. Several authors have, on the other hand, reported reduced exercise capacity in healthy, trained and untrained subjects in a hypobaric environment due to reduced S_{a,O_2} [62, 63].

The few studies that have been carried out to investigate the influence of cold and humid air upon exercise capacity in asthmatic subjects have shown conflicting results [40, 41, 55–57]. Only in three studies have the authors reported on $V'_{O_2,max}$ [40, 41, 57]. The inclusion criteria, test protocols and choice of ergometer vary between the studies, and the results are thus difficult to compare. Most studies also include few subjects. KALLINGS et al. [55] did not find any differences in V'_{O_2} or in other physiological variables in asthmatic subjects during exercise in room-temperature conditions when inhaling cold, dry air compared with warm, humid air. SANDSUND et al. [57] found no differences in V'_{O_2} at submaximal workloads, in $V'_{O_2,max}$ or in lung function in seven mildly asthmatic subjects between inhaling cold air and warm air during exercise in a cold environment. ESCHENBACHER et al. [56] found that the workload in watts per L per min of oxygen consumed was significantly greater with cold and dry
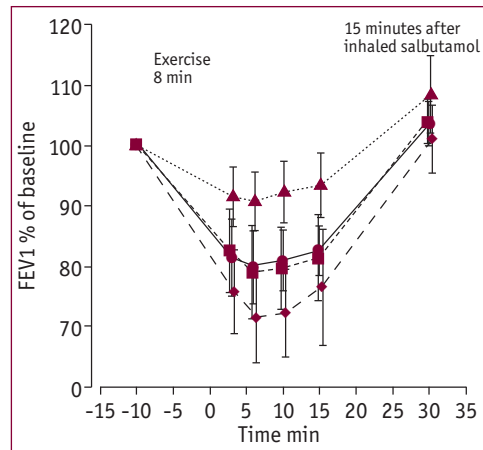
conditions compared with hot and humid conditions in eight male asthmatic subjects. STENSRUD and co-workers [40, 41] concluded that $V'_{O_2,peak}$ was reduced in cold air and increased in humid air compared to a normobaric environment in subjects with diagnosed EIB (fig. 3).

The effect of cold air upon physiological variables such as V'_{O_2}, V'_E and HR in healthy subjects is reported to vary depending on factors such as type, intensity and duration of exercise, amount of fatty tissue, wind, ambient temperature, clothing, fluctuations in body temperature and energy reserves [64]. In eight healthy males QUIRION et al. [64] found significantly reduced $V'_{O_2,max}$, maximum workload and time to exhaustion whereas V'_E did not change during a short exhaustive exercise at -20ºC and 0ºC compared with 20ºC. SANDSUND et al. [65] reported increased V'_E and V'_{O_2} at submaximal workloads in an environment of -15ºC *versus* 23ºC, whereas no difference was found for $V'_{O_2,max}$. They suggested that the exercise stress increased in a cold environment, probably as a response to increased metabolic demand. Their findings in healthy subjects are supported by CLAREMONT et al. [66].

Regarding exercise capacity in a hypobaric environment, only one study known to the present author has looked at $V'_{O_2,peak}$ in subjects with

Figure 2

Lung function (FEV1) before and 3,6,10 and 15 minutes after exercise and 15 minutes after inhaled salbutamol in normobaric (circles), hypobaric (squares), cold (diamonds) and humid (triangles) environments. Results are given as mean with 95% confidence intervals (n=20).
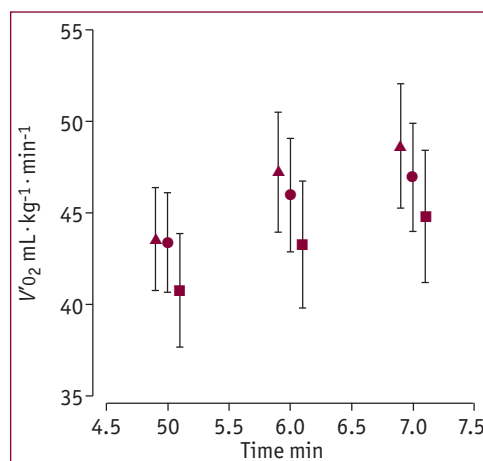

Figure 3

Oxygen uptake measured in the last 3 min of an EIB test in normobaric (circles), cold (squares) and humid (triangles) environment. Results are given as mean with 95% confidence intervals (n=20).

EIB. Berntsen *et al.* [67] reported no changes in EIB after exercising in a hypobaric environment (fig. 2) compared with a normobaric environment, but a reduction in $V'O_{2,peak}$ of 10.1% in hypoxia most probably due to the lower Sa,O_2 in the hypobaric environment. However, several authors have investigated how a reduced barometric pressure affects $V'O_{2,max}$ in healthy trained and untrained subjects [62, 63, 68]. "Untrained" healthy subjects ($V'O_{2,max}$ ≤60 mL per kg per min) are reported to have a 3.6% reduction in $V'O_{2,peak}$ per 1,000 m of increased altitude, while "trained" healthy subjects ($V'O_{2,max}$ ≥60 mL per kg per min) are reported to have a 6.5% reduction [62, 63]. The larger drop in $V'O_{2,max}$ in a hypobaric environment in athletes, who are more fit, could be explained by diffusion limitation at these high work rates [69].

Conclusion

In conclusion, an EIB test protocol can be used for both provoking EIB and for assessing exercise capacity. Physiological variables measured during the exercise challenge may give additional and valuable information about the asthma disease and how the patients master their disease. Additional diagnosis or differential diagnosis to EIB may also be assessed by measuring exercise capacity.

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Suggested answers

1. One paper has shown that an EIB test protocol can be used to provoke EIB and at the same time assess exercise capacity. This may: reduce the burden for the patient by saving one test day; simplify diagnostic and monitoring procedures for the patients; and reduce the cost to the healthcare system.

2a. Treadmill.

2b. Treadmill or exercise bicycle.

2c Sportspecific ergometers.

3. Valuable information about physical fitness, breathing pattern, how the patients master heavy endurance exercise and differential diagnosis to EIB can be obtained.

4. The most common differential diagnosis to EIB, exercise-induced laryngeal stridor, hyperventilation, EIAH and poor physical fitness can be assessed during an exercise test.

5. Measurement of tidal breathing loops and BR during exercise is used to assess pulmonary limitations during exercise and the assessment is useful to show the patients simultaneously whether there is a pulmonary limitation.

6. A hypobaric environment does not influence EIB but reduces exercise capacity. A humid environment improves both EIB and exercise capacity and a cold environment increases EIB and reduces exercise capacity in asthmatic patients.