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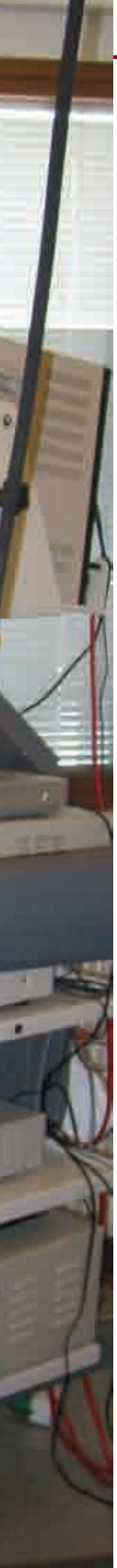

Not all who wheeze have asthma

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Educational aims

- Exercise-induced asthma is frequently found among children, adolescents and young adults.
- The diagnosis of asthma should be documented by variable lung function, airway hyperresponsiveness and inflammation.
- Not all people who report exercise-induced respiratory symptoms have asthma.

Summary

Asthma is characterised by respiratory symptoms such as shortness of breath and wheezing, and by exercise-induced symptoms. People with asthma frequently report symptoms during exercise; 90% of these people have exercise-induced asthma (EIA). Nevertheless, exercise-induced symptoms may mask other conditions or diseases, for instance poor physical fitness, exercise-induced laryngeal obstruction, hyperventilation and cardiomyopathy. Asthma symptoms should be documented and patients treated accordingly. With non-asthmatic exercise-induced symptoms, diseases in the laryngeal area are highly likely and patients should be examined while running. Although treatment options for laryngeal dysfunctions are limited, patients feel more in control when they know what is happening in their throat.

Asthma is one of the most prevalent chronic diseases in western societies, and its frequency has increased in recent decades [1, 2]. Respiratory symptoms, such as coughing, wheezing, chest tightness and shortness of breath, are the most frequent complaints among adolescents and young adults. Asthma that develops during exercise is commonly called EIA [3–7] and is classified as a reduction in lung function of >10% in FEV_1 [8]. It is likely that most patients with asthma have been diagnosed based on symptoms alone, even though the disease is characterised by variable airway limitation. International guidelines suggest that asthma control should be based on frequency of symptoms, in particular respiratory symptoms during physical activity [9, 10]. Perception of respiratory symptoms may, however, vary between individuals: some might feel minor changes more severely than others [11]. Many surveys have shown that physical activity is an important trigger of asthma symptoms. This is revealed by exercise-induced bronchoconstriction [12, 13], which is widely believed to be related to either airway inflammation [12] or smooth muscle dysfunction [14–17].

There is an epidemic of exercise-induced respiratory symptoms among children, adolescents and young adults [18, 19]. Although the presence of these symptoms could be EIA, because asthma is a frequent illness in those age groups, exercise-induced symptoms could mask a variety of other diseases or conditions, such as poor physical fitness, vocal cord dysfunction (VCD),

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exercise-induced paradoxical arytenoid motion (EPAM), exercise-induced laryngomalacia (EIL), exercise-induced hyperventilation and hypertrophic cardiomyopathy or arrhythmias with long QT [18, 20]. This review focuses on the pathology of the laryngeal area during exercise.

For the purposes of this review, primary literature and consensus publications relevant to the objective were selected from the English-language medical literature. The diagnosis and treatment of EIA are well characterised; the wording used in Medline is clear, and numerous surveys have been published. However, studies concerning nonasthmatic exercise-induced respiratory symptoms are few and inconclusive. Further, although VCD might be a less frequent disease in the laryngeal area, it is a frequently used term in Medline with a high hit rate (n=168). The papers published are mostly case reports, using different classifications and defining those with nonasthmatic exercise-induced respiratory symptoms as anything from neurotic to having a somatic illness. More recently, asthma and VCD studies have been published, but population studies remain neglected.

Respiratory symptoms

Asthma is characterised by several respiratory symptoms, such as shortness of breath, coughing, wheezing, chest tightness and exercise-induced symptoms. A study of elite athletes showed that as many as 69% of nonasthmatic elite athletes and 26% of subjects with an ordinary level of physical activity reported asthma-like symptoms during exercise [4], although none of them had a diagnosis of asthma. This indicates that symptoms alone cannot be used as diagnostic tools for asthma. There is a need for verification of variable airway disease, such as reversibility testing, airway provocation or exercise testing [10, 21].

Exercise-induced asthma

There are several theories concerning the development of EIA. In one scenario, cooling of the airway gives rise to bronchoconstriction; in the other, dehydration of the airway surface results from hyperventilation during exercise [3, 12]. The truth may be a little of both; the most believeable picture seems to be that dryness of the airway surface leads to extensive osmotic activity from the inflammatory cells in the area, resulting in a substantial shrinkage of these cells, followed by a degranulation with release of mediators, resulting in bronchoconstriction: asthma. Nonasthmatic people without inflammatory cells on the airway surface can develop respiratory symptoms during exercise, but they do not develop bronchoconstriction. Their symptoms are related to the dryness of the airway surface, and although the condition is asthma-like, it is not asthma because bronchoconstriction does not occur. This is an important difference between the asthmatic and the nonasthmatic subjects. These differences in pathology should be taken into account in the diagnosis of asthma, especially in subjects with a high level of physical activity, as they are likely often to experience respiratory symptoms arising from their sport [4].

Exercise-induced laryngeal obstruction

When the diagnosis of asthma is based on respiratory symptoms alone, misclassification might occur. Not all who experience a wheezing-like sound during exercise have asthma; other causes and diseases could lead to a turbulent sound in the tracheal area. Patients may present with respiratory distress when experiencing a low level of physical fitness, a psychological condition, inhalation of airborne irritants, rhinosinusitis or gastro-oesophageal reflux disease [22]. Moreover, exercise-induced symptoms could mask a variety of other conditions and diseases, as mentioned earlier; other diseases include angioedema, vocal cord tumours and vocal cord paralysis [23].

The frequency of inspiratory trouble during exercise varies from low to high among the asthmatic subjects examined [24–26]. Laryngeal obstruction is frequently found among athletes. In one study, 5% of athletes had laryngeal obstruction during exercise [24]. Almost half of those athletes with exercise-induced laryngeal obstruction also had EIA, whereas the other half were nonasthmatic. The entire group, however, received anti-asthma medication. While there seems to be a substantial overlap between exercise-induced laryngeal obstruction (EILO) and EIA, at least in elite athletes, the frequency of laryngeal obstruction and the comorbidity with asthma in the general population remains unknown. It could be of minor importance, but it could also have a major influence on the diagnostic procedure in the daily care settings of those with asthma-like symptoms. If asthma-like symptoms among a substantial number of people in the general population and among athletes have been misclassified as asthma, many people are probably receiving asthma medication inappropriately. This medication is unlikely to alleviate the symptoms; consequently, patients discredit the treatment, probably resulting in an understandably low adherence. Moreover, although the side-effects of asthma medication are few, there are potential problems resulting from inhaled steroids. Additionally, asthma medication is on the doping list; accordingly, those athletes with only laryngeal obstruction could be taking a prohibited medication, highlighting the importance of making the correct diagnosis before treatment begins. Lastly, comorbidity with exercise-induced laryngeal obstruction and gastro-oesophageal reflux is also frequently seen [26], indicating that treatment of the reflux might reduce laryngeal symptoms.

The issue of VCD, exercise-induced laryngospasm, EIL, EPAM and the differential diagnoses of asthma are a hot topic. Different terms are used, "VCD" is often used wrongly to cover the entire area, and there is considerable confusion, primarily reflecting the difficulty in diagnosis. One of the most recent classifications of this group of illnesses in the laryngeal area during exercise is as EILO, used as an overall term. EILO then includes EIL, EPAM, exercise-induced VCD and other infraglottic tracheal disorders. EIL and EPAM are probably the same condition with two different names: it is a swelling and collapse of the supraglottic area (tuberculum cuneiforme and corniculatum), with a shortening of the plica aryepiglottica. This, in turn, creates a partial upper airway obstruction or closure driven by exercise. VCD involves in-appropriate vocal cord motion – periodic spasm – which creates partial airway obstruction during running [27].

Unawareness of EILO can lead to needless use of asthma medication or overtreatment in the event of persistent respiratory symptoms among well-treated asthmatic individuals. Recently, Parsons *et al*. [26] examined a group of asthmatic subjects with asthma in Global Initiative for Asthma treatment steps 1–4 who also had classic VCD symptoms. They demonstrated that there is no specific severity of asthma associated with laryngeal obstruction, but that persistent asthma symptoms resulted in unnecessary adjustment of asthma medication. This indicates that to prevent overtreatment, patients with both diseases (EIA and EILO) should have their asthma monitoring based on something other than the frequency of asthma-like symptoms.

Diagnosis of exercise-induced laryngeal obstruction

The easiest way to diagnose upper airway obstruction should be to investigate changes in the flow–volume curve after exercise, which should show an inspiratory limitation when EILO is present [28]. This is a well known examination used, for instance, in intrathoracic enlargement of the thyroid gland, which enhances the

inspiratory flow due to pressure on the trachea. However, recent studies of patients with VCD have shown that it remains difficult to evaluate and diagnose EILO using spirometry or flow–volume loops. If VCD is suspected, due to a history of inspiratory problems or no effect of asthma medication, normal flow–volume loop patterns should not influence the decision to perform further diagnostic tests [29]. The definitive diagnosis of laryngeal obstruction might require laryngoscopy during exercise [22, 30]; Heimdal *et al*. [31] recently published a paper describing a model for use when performing the continuous laryngoscopy exercise test (CLE). Some physicians use a treadmill with increasing increment, while others use a bicycle. It has been shown, however, that running on a treadmill gives more intense respiratory provocation, both in the asthma test and the test for laryngeal obstruction. Consequently, the treadmill is preferable. The running protocol for the CLE test differs from the standard test used for asthma provocation [7]: the aim is running to exhaustion when examining for laryngeal obstruction, whereas EIA is standardised as a 6–8-min run with a constant increment of 10°. When there is comorbidity with asthma, two puffs of β_2-agonist are given before CLE testing. The test starts with a 3–4-min warm-up period, after which the laryngoscope is advanced through the nostril and nasal cavity into the oropharynx [31]. The laryngoscope is then fixed to a headset and the patient is secured with a safety belt before running begins. When using CLE, the entire running period is recorded, and the maximum obstruction can be evaluated after the test. The image of the maximum occlusion of the laryngeal area should be taken as the test result. The laryngeal obstruction can be evaluated using various methods, for example a grading from one to three (mild, moderate and severe); however, new methods using electronic calculation of the area not obstructed have been published [32]. These are suitable for both research and clinical purposes as they are more accurate than older methods and allow evaluation of the effect of treatment; however, they are currently more time-consuming than most other post-test evaluations. Pulmonary function testing with a flow–volume loop can be done either alone or with the flexible laryngoscopy; both are potentially valuable diagnostic tools to confirm EILO [23, 33, 34]. Conversely, CLE is probably too complex for use in all asthma clinics. New methods to evaluate upper airway obstruction are urgently needed. One such method could be sound transmission technology that would give specific evidence of upper airway obstruction with stridor during exercise; another method could be change in tissue appearance on ultrasound in the upper airway area during exercise. If these methods were used, the evaluation of EILO would be more widespread, and the CLE could be located at specific centres offering more sensitive evaluation. Patients with asthma should start asthma medication, and for those with satisfactory adherence who do not achieve well-controlled disease, other reasons for persistent respiratory symptoms should be explored. In such cases, CLE should be performed. To the author's knowledge no research has been published concerning side-effects of the CLE test. The author's experience in a clinical setting is that side-effects are restricted to vasovagal dizziness on introduction of the scope.

Treatment of exercise-induced laryngeal obstruction

It is one thing making the diagnosis of EILO; deciding what to do is another entirely. For laryngomalacia, surgery on the supraglottic area has been described and has been found safe and without significant side-effects in 12 patients [35]. Furthermore, for VCD, speech–language pathology management may give the patient control over his or her vocal cords [22, 30]. However, neither of these treatment strategies for EILO has been performed in large groups or has been tested in

Clinical experience with EILO and CLE

In the author's outpatient clinic at Copenhagen University Hospital, Denmark, many patients are referred with exercise-induced respiratory symptoms. Some of these patients have asthma, while others do not. All those with only partly controlled asthma and satisfactory treatment adherence are admitted for CLE.

We have trained personnel and have developed a CLE test without flow–volume curve in a routine set-up. More than 100 patients have been tested during the past 6–8 months, and although no treatments are currently available, patients are very satisfied with the information they receive about their laryngeal dysfunction during exercise. Before undergoing the CLE diagnostic test, some patients feared total collapse, fainting or even dying during exercise. After the test, patients and staff view the video film together and see the pathology; a senior physician then determines the disease and its severity. When laryngeal obstruction is present, patients are advised to increase their physical fitness by training: short interval running to decrease the need to hyperventilate during exercise. Clinical settings have shown this to give significant relief and to improve quality of life.

Our experience is that the increasing frequency of shortness of breath during exercise among nonasthmatic subjects needs further investigation. The CLE test is the standard test when laryngeal obstruction is suspected. However, CLE should be centralised as it is more complicated than most other asthma tests.

a placebo-controlled trial. There is a need for scientific studies in this area to reduce both stridor and respiratory symptoms in general. Treatment strategies in the management of EILO should aim to reduce the stridorous sound and the exercise limitation.

Conclusion

Asthma is characterised by recurrent respiratory symptoms, but the diagnosis cannot be based on symptoms alone. The diagnosis of asthma requires documentation of airway variability, airway hyperresponsiveness and airway inflammation. Asthma-like symptoms are frequently found in conditions and diseases other than asthma. In recent research, EILO has frequently been found in combination with asthma, but it can also be found alone. In patients with uncontrolled asthma, although treated sufficiently with asthma medication, further evaluation is needed. The CLE test is potentially suitable. Currently, no specific treatment for these laryngeal abnormities is available, but short-interval running training has shown to be of significant importance in a clinical setting.

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