Cardiovascular Evaluation of Athletes

Recommendations concerning participation in athletics by persons with possible cardiovascular disorders arise in three contexts: first, the eligibility of potential athletes with a known cardiovascular disorder to participate in athletics; second, the athlete with symptoms that suggest a possible cardiovascular abnormality; finally, non-symptomatic, "healthy" young people may be found to have a possible cardiac abnormality during routine pre-participation examination.

Although the risk of sudden death is small, a few athletes die from cardiovascular disease each year, and the impact of these deaths is great. Persons with severe aortic stenosis, hypertrophic cardiomyopathy, and some congenital lesions are at increased risk of sudden death during and after exercise. Thus it is the physician's responsibility to make participation by these athletes as safe as possible. Also, the possible effects of exercise on the progression of existing heart disease must be recognised, assessed, and addressed.

A. Diagnostic Techniques

Most valvular and septal defects can be detected and diagnosed by physical examination. In order to make an informed opinion regarding sports participation, however, additional diagnostic tests are usually needed to determine the severity of the problem. The test to assess the severity of the defect is echocardiography, with electrocardiogram and chest X-ray providing additional measures of heart size. Other non-invasive tests must be used in specific situations. For example, two-dimensional and M-mode echocardiography can be used to assess chamber size, wall thickness, and valve motion. Doppler flow echocardiography is valuable in quantifying obstruction to flow or regurgitation. Radio-nuclide angiography can assist in determining coronary circulation and cardiac output.

Exercise electrocardiography may be necessary to determine an individual's response to exercise, especially if an arrhythmia or ischemia is suspected. Exercise testing should be modified to simulate the athlete's event or sport. If an intermittent rhythm or conduction disturbance is suspected, continuous ECG (Holter) monitoring will be needed.

Finally, cardiac catheterisation may be required to determine the degree of valvular stenosis, shunting, or pressure gradient.

B. The "Athlete's Heart Syndrome"

Athletes who participate regularly in athletics often develop changes in their heart, circulation, and electrocardiogram that may be difficult to distinguish from those associated with true cardiac pathology. This complex of changes is often referred to as the "athlete's heart syndrome." It is seen most often in endurance athletes. The athlete's heart syndrome is characterised by an increase in para-

sympathetic tone, especially vagotonia and consequent bradycardia, as well as a variety of conduction changes. Characteristics of the syndrome may include:

1. Increased left ventricular volume. This is seen as cardiomegaly during physical examination and X-ray. It is usually accompanied by a mild to moderate degree of ventricular wall thickness (hypertrophy).
2. Resting bradycardia
3. Electrocardiographic changes:
   a. Left ventricular hypertrophy
   b. Sinus bradycardia
   c. Anterior wall S-T and T wave changes
   d. Atrio-ventricular conduction abnormalities:
      i. First degree A-V block
      ii. Wandering pacemaker
      iii. Second degree A-V block, of Mobitz Type I (Wenckebach) variety
   e. Bundle branch block:
      Partial or complete *right* bundle branch block (the occurrence of left bundle branch block is usually indicative of cardiac pathology).

Athletes whose training includes primarily resistive exercises, such as strength training (weight lifting) or wrestling show evidence of left ventricular wall hypertrophy, but little or no increase in ventricular volume. However, the ventricular wall thickness does not exceed 13 mm, but a "gray zone" of 13–15 mm may exist in some large male athletes, and requires evaluation by additional criteria to exclude the possibility of hypertrophic cardiomyopathy (Figure 14-1). Female athletes have not been found to have a ventricular wall thickness of more than 13 mm, but those who train extensively with high intensity resistance exercise have not been studied.

C. Athletes with Known Cardiovascular Disorders

Athletes may exhibit a wide variety of disorders, but most fall into six general categories:

1. Congenital Disorders
2. Acquired Valvular Disease
3. Cardiomyopathies and Mitral Valve Prolapse
4. Hypertension
5. Rhythm and Conduction Disturbances
6. Ischemic Heart Disease

A careful, detailed medical history can help the physician determine the nature of a disorder and advise the athlete about participation in strenuous activities.

A thorough discussion of all possible defects in each category is beyond the scope of this brief review, but the high-risk conditions in each category are as follows:

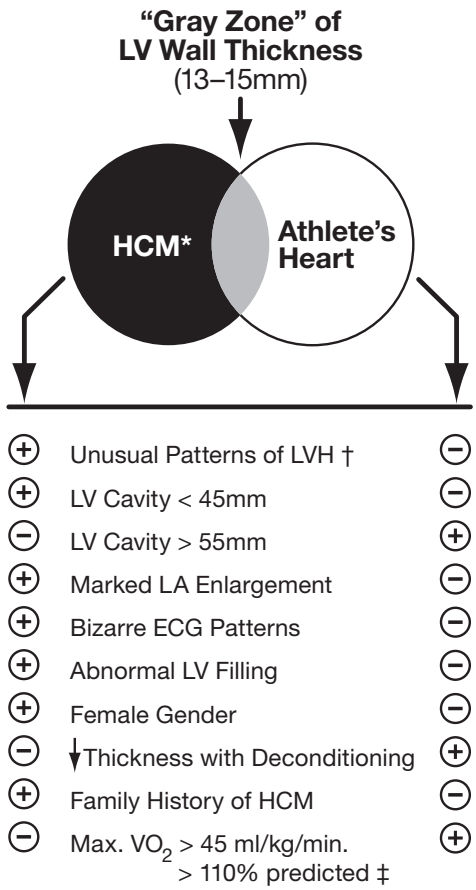

Figure 14-1. Chart showing criteria used to favour or distinguish hypertrophic cardiomyopathy (HCM) from athlete's heart when maximal left ventricular (LV) wall thickness is within shaded gray zone of overlap (i.e., 13 to 15 mm), consistent with both diagnoses. *Assumed to be the non-obstructive form of HCM (under resting conditions) in this discussion because the presence of substantial mitral valve systolic anterior motion would confirm the diagnosis of HCM in the athlete. † May involve a variety of abnormalities, including heterogeneous distribution of left ventricular hypertrophy (LVH) in which asymmetry is prominent and adjacent regions may show greatly different thicknesses with sharp transitions evident between segments, as well as unusual patterns in which the anterior ventricular septum is spared from the hypertrophic process and LV thickening may be in posterior portion of septum or anterolateral or posterior free wall or apex. ‡ Assessed with cardiopulmonary (metabolic) exercise testing. ↓ = decreased; ECG = electrocardiogram; LA = left atrial. Adapted from Maron, B. J., and D. P. Zipes (2005).

1. Congenital Heart Disease

Most congenital heart disorders are discovered in childhood, and repair will have been carried our before participation in sports. Mild defects that do not affect cardiac function or that have a good long-term prognosis should not affect the ability to participate in sports. In other cases, the ability to participate in sports will be determined by the extent of the defect, the success of the repair, and any residual

effects, such as pulmonary hypertension, chamber hypertrophy, or shunting and arterial desaturation.

2. Acquired Valvular Diseases
   a. Aortic Valve Disease
      i. Stenosis

         Sudden death can occur in individuals with severe stenosis but is rare in those with mild degrees of obstruction. Those with mild stenosis may participate in competitive athletics, but the disorder should be re-assessed periodically with Doppler echocardiography and possible catheterisation, as the lesion may progress in severity.

      ii. Regurgitation

         Individuals with any degree of aortic regurgitation should not participate in vigourous exercise.

   b. Mitral Valve Disorders

      Athletes with mild degrees of stenosis or insufficiency, and with normal left ventricular size and normal sinus rhythm, may participate in all sports.

3. Cardiomyopathies and Mitral Valve Prolapse
   a. Hypertrophic cardiomyopathy

      Hypertrophic cardiomyopathy (HCM) is the commonest cause of sudden death in young athletes, whereas coronary artery disease is the most frequent cause in older athletes. HCM is a relatively common genetic abnormality, occurring in approximately 0.2% (1:500) of the population. It is inherited as a mendelian autosomal dominant caused by a mutation in one of 12 genes (over 400 mutations have been found), each encoding proteins of the cardiac sarcomere that have contractile, structural, or regulatory functions. Due to the heterogeneity of the many identified mutations, there is considerable clinical variance in the presentation of this disorder. Genotyping of suspected individuals is available, but is time-consuming and expensive.

      The clinical presentation of HCM usually does not occur before the late teens. The diagnosis may be suspected if there is a systolic murmur associated with outflow tract obstruction, but this is not common. Other indications are a family history of premature sudden death, new symptoms of chest pain or dyspnea, an arrhythmia, or an abnormal ECG. A major clinical problem is one of distinguishing between the cardiac changes seen in highly trained athletes, and those due to cardiac diseases such as HCM, dilated cardio myopathy, and arrhythmogenic right ventricular cardiomyopathy (ARVC) .

      The ventricular wall thickness in trained athletes seldom exceeds 13 mm. However, some large male athletes who participate in resistance sports (weightliftng, wrestling) may have a ventricular wall thickness in the 13–15 mm “gray zone.” Similarly, some endurance athletes may have dilated left ventricular (LV) chambers that exceed the end-diastolic dimension of

60 mm or more, with low-normal LV function. Criteria for distinguishing between HCM and the "Athlete's Heart" are listed in Figure 14-1.

Cautions:

Athletes with probable or diagnosed HCM should not participate in most competitive sports. Prior treatment with drugs, surgical interventions, alcohol septal ablation, an implantable pacemaker or implantable defibrillator, should not be criteria for allowing sports participation. The stresses of the competitive milieu present unique challenges for which these interventions may not be able to adapt, or the devices may malfunction. Further, the presence of an automated external defibrillator (AED) at sports activities should not be considered as a protection against sudden death, or as a rationale for allowing participation of athletes with HCM or other high-risk cardiac disorders.

b. Marfan's Syndrome

Marfan's Syndrome is an autosomal dominant disorder of connective tissue. Over 400 mutations have been found in the gene that encodes fibrillin-1 (FBN-1). It has an estimated prevalence of 1:5000–1:10000 in the general population.

Those with Marfan's Syndrome are typically tall and thin, with hyper-extensible joints, mitral valve prolapse, aortic valve regurgitation, aortic dilatation, and a potential for aortic dissection. Dissection can result in sudden death. The degree of aortic dilation must be assessed by echo-cardiography. Individuals without aortic root dilation or mitral valve prolapse may participate in low-intensity activities; a few may engage in activities with a high dynamic and low static demands (i.e., endurance activities).

c. Mitral Valve Prolapse (MVP)

This common, usually benign lesion affects 2–3% of the general population and rarely causes sudden death. Contra-indications to exercise include:

i. History of syncope
ii. Family history of sudden death due to MVP
iii. Chest pain, worse with exercise
iv. Repetitive ventricular ectopy or supra-ventricular tachycardia, worse with exercise
v. Moderate to marked mitral valve regurgitation
vi. Associated dilated aorta, with Marfan's Syndrome
vii. A prior embolic event

d. Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

This is a rare disorder, but it has been associated with sudden death in young athletes. It has a broad phenotypic spectrum, and is characterised by a loss of myocytes in the right ventricular myocardium, with replacement by fatty or fibro-fatty cells. There is thinning of the ventricular wall, and it is often associated with myocarditis. Diagnosis is difficult—a family history,

ventricular tachyarrhythmias, and T wave inversion in leads V1–V3 are diagnostic clues. These individuals should not participate in competitive sports.

e. Congenital Long Q-T Syndrome

The diagnosis of this syndrome is complex, as many individuals with this genotype may have a normal corrected Q-T interval (QTc), while normal persons (approximately 25%) may have a Q-T interval of 440 ms, which previously has been considered as the upper limit of normal. A Q-T interval of 470 ms in males, and 480 ms in females requires further study. A patient with the Long Q-T Syndrome (LQTS) and a resting QTc of 500 ms or longer is considered at risk for severe arrhythmias.

There are at least 150 mutations in 7 cardiac ion-channel genes that are responsible for 75% of these cases, and a diagnostic test is now available. Other diagnostic criteria include: family history, T wave abnormalities, and symptoms such as syncope, in addition to the finding of a long QTc.

All competitive sports should be prohibited in those who have had an out-of-hospital cardiac arrest, or a suspected LQTS-precipitated syncopal episode. Athletes who are genotype-positive/phenotype-negative (i.e., mutations but no symptoms and a non-diagnostic QTc) may be allowed to compete. Non-symptomatic patients with a baseline QT (QTc 470 ms in males, 480 ms in females) should be restricted to mild activities.

f. Other Inherited Arrhythmias

Other inherited arrhythmias include the Brugada Syndrome (J wave in V1-3, ST segment elevation, and negative T wave), Short Q-T Syndrome (QTc less than 300 ms), and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT), which are caused by mutations in various conduction and receptor systems. All of these may precipitate a sudden fatal arrhythmia during exercise or with a rise in body temperature, and must disqualify the subject from participation in vigorous exercise until further studies are carried out and the extent of the abnormality is determined.

g. Anomalous L. Coronary Artery from the R. Sinus of Valsalva

This rare condition is difficult to diagnose pre-mortem, but can cause sudden death. After surgical repair, participation is permissible if an exercise ECG is normal.

4. Hypertension

Secondary causes of hypertension, including coarctation of the aorta and polycystic renal disease, must be excluded.

Sports participation depends on the extent of organ involvement (left ventricular hypertrophy, renal, or eye disease) and the ability to control blood pressure with appropriate medications. Calcium channel blockers or angiotension-converting enzyme inhibitors are the most suitable for those who participate in athletics. Blood pressure control should be assessed during exercise or immediately post-exercise.

5. Arrhythmias/Conduction Disturbances

Arrhythmias are often transient and difficult to diagnose, and are not always reproduced by exercise. Autonomic "tone," which is higher in trained athletes, affects arrhythmia occurrence. Changes in sinus node function and low-grade A-V conduction delays may result from chronic endurance exercise itself.

a. Ventricular Pre-excitation

This disorder is characterised by a P-R interval of less than 120 ms and a QRS that exceeds 120 ms and has a slurred, slowly rising onset and secondary ST-T changes. It is often associated with tachy-arryhthmias, i.e., the Wolff-Parkinson-White Syndrome (WPW). The tachycardia is usually 150–250 beats per minute.

An individual whose accessory pathway has a short refractory period (less than 200 ms) is at risk of very rapid heart rates and sudden death. Those with a history of palpitations or syncope should be examined to exclude structural heart diseases, and have 24-hour monitoring and an electro-physiologic study to determine the properties of the accessory pathway. Recently, surgery has been used to ablate the accessory pathway.

b. Ventricular Dysrhythmias (PVCs, Ventricular Tachycardia, Ventricular Flutter)

Individuals whose dysrhythmia is precipitated by exercise, who have underlying heart disease, or who have the "Prolonged QT Syndrome" should not participate in intense exercise.

c. Heart Block

First-degree heart block and Mobitz Type I block (Wenckebach) may occur as a result of endurance training itself. Athletes with these disorders who have no heart disease and whose block is not worsened by exercise may compete in sports. Persons with Mobitz Type II block or *acquired* complete (3rd degree) heart block should be treated with a pacemaker. Those with *congenital* complete block, a satisfactory response to exercise, and no dysrhythmias may participate in athletics.

d. Bundle Branch Block

Partial Right Bundle Branch Block (BBB) is common in endurance athletes. Left Bundle Branch Block is more often associated with structural heart disease, especially in older patients. Athletes with complete BBB, no structural defects, and no ventricular dysrhythmias may participate in all sports.

6. Atherosclerotic Coronary Artery Disease

Atherosclerotic coronary artery disease (CAD) is the commonest cause of cardiac events in older athletes, especially those over age 35–40. Although exercise has beneficial effects on the healthy as well as those with diagnosed CAD, vigorous exercise transiently increases the risk of a cardiac event (myocardial infarction or

sudden death). Plaque rupture or plaque erosion may be responsible for these events, even though the coronary arteries may not have been significantly narrowed.

Known risk factors such as hypertension, hyperlipidemia, obesity, and a positive family history, as well as other unknown factors, must be considered in evaluating the older adult athlete. As older athletes who have exercise-related CAD events may have less extensive vascular disease than the average, standard risk assessment is more difficult. Variations in the resting and exercise ECG may make interpretation difficult. Further, more precise imaging techniques such as computerised tomographic calcium scoring may identify early atherosclerotic lesions. Coronary calcium increases substantially with age, so that nearly 50% of males age 40 and older show measurable calcium in their coronary arteries. Presently, there are no clear guidelines as to how well coronary calcification per se can be used as an indicator to govern or restrict exercise in non-symptomatic individuals. However, progressively increasing calcification is associated with rising CAD risk.

The prognosis for patients with known CAD worsens depending on the extent of disease, left ventricular systolic dysfunction, inducible ischemia, and electrical instability. Therefore, older persons who contemplate or participate in a competitive athletics programme should have a maximal exercise test that simulates as closely as possible the metabolic demands of the training programme and competitive event, even though such testing cannot entirely replicate the actual stresses of training and competition. Any evidence of LV dysfunction, ischemia, or electrical instability should lead to a limitation of physical activity and further cardiovascular evaluation.

D. Athletes with Symptoms Suggestive of Cardiovascular Disorder

Athletes with known heart disease may exhibit symptoms of syncope, faintness, or palpitations, which suggest a cardiac origin. A careful history and physical examination are needed to clarify the condition; for example, to differentiate among vagal fainting, hyperventilation, and true syncope. Careful auscultation may detect valvular or other congenital defects. Selected non-invasive tests may also be necessary to clarify the problem. A baseline 12-lead ECG and an echocardiogram can reveal conduction or structural abnormalities. An exercise ECG may be needed to elicit the underlying problem, and 24-hour monitoring is often used if an arrhythmia is suspected.

Continued participation in sports should depend on the findings. Restrictions on participation may be necessary until the nature of the problem is identified.

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Asthma and Exercise-Induced Bronchospasm (EIB)

A. Definitions

According to the American Thoracic Society, asthma is a clinical lung disease characterised by reversible airway obstruction as a consequence of a wide variety of stimuli. The term "current asthma" is used when at least one asthmatic episode occurred during the last year.

Asthma is characterised by a variety of symptoms, including dyspnoea, shortness of breath, wheezing, cough, excess mucus, breathlessness, and chest tightness. The symptoms might be mild or severe; intermittent or continuous; and more frequent in the morning and at night. Upper or lower airway obstructions are reversible with or without therapy.

The generic definition can also include bronchial or airway hyperresponsiveness (BHR or AHR), that is, an above-normal airway constriction upon exposure to physical stimuli or sensitising agents.

A transient airway narrowing occurring in susceptible individuals during or after exercise is defined as EIB (exercise induced bronchospasm) when observed in a non-asthmatic and non-atopic population; or EIA (exercise induced asthma) when including asthmatic individuals. Here we will use EIB to also include those with EIA.

Exercise induced asthma or bronchospasm is a transient, reversible, and intermittent narrowing of small and large airways, occurring about 5–15 minutes after intense exercise (aerobic activity more than anaerobic), performed for 8–10 minutes. A post-exercise fall in forced expiratory volume in 1 second of >10% is required for diagnosis. After an attack lasting 20–60 minutes, a complete recovery usually occurs.

In 50% of affected athletes, a refractory phase starts less than 1 hour after initial exercise; this may last up to 3 hours, with less than half the intensity of exercise bronchospasm. For this reason, the warm up period might be useful to ensure a refractory phase during competition. Sometimes, 6–8 up to 12 hours after the exercise, a late phase, less severe state with cough and wheezing is observed in 30% of subjects with EIB. The aetiology of the refractory period is probably due to the depletion of local mediators, or increased sympathetic activity.

EIB occurs in 12–15% up to 20–25% of the normal population, increasing to 35–40% in subjects with allergic rhinitis or hay fever and/or eczema, and up to 90% of those with asthma. The variability of the statistical data depends mainly on the method used (clinical or laboratory evaluation or epidemiologic questionnaires based on self reported symptoms or statistics performed in main competitions, based also on declared use of beta-2 agonists).

Sometimes, EIB is erroneously diagnosed in athletes who have respiratory stridor during inspiration, typical of vocal cord dysfunction (VCD, statistically up to 5%, by paradoxical narrowing of the vocal cords during inspiration or as described by patients, while "getting air in"), or with other upper respiratory disorders. Anxiety and hyperventilation syndrome may mimic asthma or EIB.

EIB is more prevalent in female athletes, and twice as prevalent in endurance athletes as in sprinters, jumpers and throwers in track and field. Furthermore, evidence exists that top athletes are at an increased risk of developing asthma or EIB during their career, particularly in endurance events.

High-level exercise performed on a regular basis by previously unaffected elite athletes, particularly in endurance activities, is liable to increase the incidence of asthma and airway hyperresponsiveness (AHR).

B. Aetiology

A basic genetic component associated with atopy is presupposed, but many other factors are involved and play a significant role both in asthma and AHR, particularly in athletes:

1. Recurrent airways infections or inflammations, in which many local cells and their related mediators are involved (mast cells, macrophages, eosinophils, neutrophils, etc.). Endurance athletes are particularly susceptible to upper respiratory tract infection and impaired function of the immune system after intense repeated training, with decreased activity of lymphocytes, neutrophils, macrophages, and natural killer (NK) cells and diminution of lymphokines and IgA levels.
2. Drug allergy (aspirin or NSAIDs are common), food allergy, or other allergic or anaphylactic medical conditions.
3. Environmental exposure to airborne allergens. Prolonged hyperventilation during intense training increases the possibility of exposure to different allergens, mainly in seasonal asthmatic patients. These include pollens or other allergens, or irritant pollutants such as cigarette smoke and sulphur dioxide (SO_2), carbon monoxide (CO), nitrous and nitric oxide (NO_2, NO_3) in smog, and—very important in track and field—also herbicides, pesticides, insecticides, and fertilisers. Training sessions in contaminated situations can cause chronic bronchial inflammation triggered by smoke, pollens, irritants, and allergens (IgE production).
4. Cold and dry air inhalation. Hyperventilation, mainly during endurance efforts, induces a loss of heat and water in the bronchial system: the bronchoconstriction response is due both to the direct effect of "cooling" in bronchial mucosa, and to the "hyperosmolarity" of mucosal fluid, inducing the release of pro-inflammatory mediators (histamine, leukotrienes, prostaglandins, neutrophil chemotactic factors). In addition, the "rewarming" after exercise generates a vasodilator effect on the pulmonary capillary system with vascular bronchial congestion, increased vascular permeability and oedema with bronchoconstriction.
5. Parasympathetic hyperactivity is a typical compensatory response to a prolonged sympathetic stimulation by intense and prolonged training sessions, which may increase the bronchomotor tone (normally and basically the parasympathetic system is dominant over the sympathetic system in the

bronchial apparatus), and may explain the higher incidence of AHR in endurance athletes.

C. Diagnosis

1. Self-Reported Symptoms

Self-reported symptom*s* are not valid to confirm the presence of asthma or EIB. The misinterpretation of post-exercise fatigue, prolonged recovery time, under-performances, or inadequate training might induce an erroneous diagnosis.

2. History

The history is very important, and permits, as a first step, the evaluation and discrimination of other possible diseases:

a. Chronic bronchitis, pulmonary fibrosis, lymphoadenopathy
b. Seasonal asthma
c. Infectious diseases
d. Laryngeal dysfunction; throat or nasal problems; upper airways obstruction; allergic rhinitis; hypertrophic turbinates; nasal polyps; sinusitis; hay fever
e. Cardiac problems with effort dyspnoea
f. Allergic conditions (medicines, food) or anaphylactic reactions
g. Blood disorders (anaemia)
h. Thyroid dysfunction
i. Gastro-oesophageal reflux
j. Anxiety

3. Basal Screening

Many clinical instruments are useful in basal screening, including:

a. Family history of asthma and allergic diseases
b. Personal history of atopy or asthma; use of bronchodilator substances; other, also occasional, allergic disorders
c. Physical and complete examination (lung auscultation is often quite normal)
d. Evaluation of presence or influence of environmental factors (cigarette smoke, smog, pollen, animal dander, dust mites, cold or dry air)
e. Blood cell count and erythrocyte sedimentation rate (infections)
f. Chest radiography (chronic pulmonary diseases, fibrosis, lymphoadeno-pathy, cardiomegaly)
g. Skin allergy tests, IgE and RAST (allergic problems)
h. Heart clinic and instrumental evaluation (ECG and/or echocardiogram)

4. Diagnostic Tests

Pulmonary function testing is the next diagnostic step. Note that the pulmonary function tests should be performed on days free from asthma symptoms and concurrent problems (rhinitis, allergies, sinusitis), without any prior short-acting

bronchodilator therapy in the last 8–12 hours, and any long-acting bronchodilator therapy in the last 12–24 hours. Antileukotrienes should be suspended in the last 48–96 hours prior to the test; cromolyn compounds in the last 12–24 hours; and anti-histamines in the last 48 hours. In addition, inhaled steroids should not be administered on the day of the test; no caffeine should be taken the morning of the test; and no vigorous exercise should be performed in the last 4–6 hours prior to the test, or preferably on the day of the test at all.

Laboratory basal spirometry is good for a simple and standard evaluation (Flow Volume Curve, FVC, FEV1, FEV1/FVC, PEFR, FEF 25–75).

In athletes with solitary EIB, the basal FEV1 will be normal, over 80% of predicted normal value, while in asthmatic athletes it will be lower than 80%.

For daily, practical, and on-field self-evaluation, athletes can use small and inexpensive peak flow meters.

Exercise challenge tests are commonly performed in the laboratory, using a treadmill, stationary cycle, or rowing equipment; sometimes an exercise test performed running free and outside, as in natural conditions, is practical but is less controlled in its intensity. However, for athletes, the chance to perform the specific field test of their sport is optimal for diagnosis. For exercise challenge tests:

a. No warm up is allowed to avoid a direct bronchospasm.
b. The intensity and duration of aerobic exercise should be 80–90% of the maximum heart rate for 6–10 minutes, preferably without crossing the anaerobic threshold, to avoid the exhaustion of the athlete and the release of catecholamines.
c. The inhaled air should have a relative humidity below 50% and an ambient temperature of 20º–25°C; the use of inhaled cold air during the exercise test increases the sensitivity in diagnosing EIB, without decreasing specificity.
d. After the exercise test, spirometric measurements are conducted every 3–5 minutes for 15–30 minutes, and possibly after 4–12 hours in late responders.
e. A decrease of FEV1 of 10% or more is considered positive for EIB. The severity of disease is classified as mild (10–20%), moderate (20–40%), and severe (more than 40%). Reversibility of bronchospasm after an inhaled bronchodilator will confirm the diagnosis.

Pharmacological challenge tests can be used to assess asthma, while being less specific and sensitive for EIB. The methacholine test, which is more sensitive and less specific, induces bronchoconstriction mainly in the distal bronchi, and increases airway inflation pressure and contraction of the trachealis muscle; histamine causes airway obstruction by activation of bronchial smooth muscle and mediator receptors.

Both for histamine and methacholine, cut-off levels are defined, in terms of concentration or cumulated dose, able to induce a 20% reduction of FEV1 (PC-20 or PD-20).

Osmotic tests include the dry powdered mannitol inhalation challenge and the nebulised hypertonic saline challenge. Increased doses of the stimulating substance are followed by pulmonary function tests until cut-off levels. Both tests act by altering the osmolarity of airway surface liquid (ASL) with release of mediators from sensitised mast cells. The osmotic tests are sensitive and specific, easy to perform, and economical.

The eucapnic voluntary hyperventilation (EVH) challenge can, in susceptible individuals, induce bronchoconstriction with increased ventilation rate by drying the airway surface liquid and changing the osmolarity of the mucosal surface membrane components. In athletes, the respiration rate achieved should be almost 85% of MVV (maximal ventilation rate), about 35 times FEV1. The test is performed with a dry air mixture containing 4.5% CO_2 to ensure eucapnia and protect from the hypocapnia induced by hyperventilation; this latter, in fact, may cause indistinct bronchoconstriction both in EIB positive and negative subjects. The inspired air can also be chilled, although chilling is not necessary.

The bronchodilator test is an indirect but limited method used to detect airway obstruction by airways reversibility to inhaled short-acting bronchodilators (terbutaline or salbutamol), when the resting FEV1 is below 70% of normal. The response is variable, and the cut-off criteria for a positive test is 15% FEV1 increase or, as recently stated by the European Respiratory Society, 12% increase of FEV1 expressed as % predicted.

D. Non-Pharmacologic Treatment

Non-pharmacologic treatment should be the primary focus of the problem, and is based on the following criteria:

1. Education of athletes, coaches, and families is a primary component: the disorder is frequent and common in the population, and does not limit performance when adequately treated.
2. Prevention is the main method: avoiding cold or dry air, training indoors, or covering the mouth and nose with a scarf during winter, or using a mask to warm and humidify the air may be helpful.
3. Predominant nasal, more than mouth breathing, may reduce EIB by inhaling more warmed and humidified air.
4. Exercise conditioning to lower ventilation rate decreases airway responsiveness.
5. Warming up well before exercise, with repeated short and high intensity exercises, may induce a refractory period and partially reduce the need for pre-medication.
6. Avoid training sessions that risk possible exposure to environmental situations of airborne allergens or irritants.
7. Avoid consumptions of foods with possible allergens, at least in the last 4 hours before an exercise or competition session.

8. Reduce training when exacerbation periods of rhinitis, sinusitis, or allergy are present.
9. Stop training during viral respiratory infections or acute bronchial exacerbations.

E. Pharmacologic Treatment

The treatment of seasonal allergic rhinitis by non-sedating anti-histamines or local intranasal glucocorticosteroids is an important step in preventing bronchial hyperreactivity. Generally, the correct use of medications, when needed, will help the patients to train well and live better, without pharmaceutical addiction and with limited adverse effects, both of which are possible risks of inhaled beta-2 agonists.

Proper inhalation of the medication will result in a better deposition of the substances into the bronchial system: after slow expiration, controlled breathe while inhaling to total lung volume and holding the breath for 10 seconds will enhance deposition. A pause of 30 second between the two inhalations will increase the quantity of drug delivered into the lungs.

While describing beta-2 agonists, we will mention only those permitted by inhalation with a previous exemption request:

Short acting beta-2 agonists (salbutamol/albuterol, terbutaline) administered by inhalation 20–30 minutes before exercise have a peak bronchodilator effect within 60 minutes, and maximal duration of 3–4 hours. They are effective in 90% of EIB, but sometimes they induce tachyphylaxis, worsening asthma, and, with continuous use, become ineffective in 2–3 years.

Long acting beta-2 agonists (formoterol and salmeterol) need to be administered well before exercise, because they have their maximal effect in 4 hours and may last up to 12 hours, permitting the prevention of EIB and asthma attacks in prolonged exercise sessions and in the night (particularly when used with glucocorticosteroids).

The beta-2 agonists, both short and long acting, work by increasing intracellular concentration of cyclic adenosine monophosphate (cAMP), which modulates the relaxation of bronchial smooth muscle and inhibits the release of mediators from mast cells. While beta-2 selective, they interact (short acting more than long acting) with alpha- and beta-1 receptors, causing tachycardia, tremors, and palpitations.

Inhaled glucocorticosteroids (beclomethasone dipropionate, budesonide, fluticasone propionate, flunisolide, momethasone, triamcinolone acetonide, etc.) are practically long-term drugs. They are not effective on an as-needed basis, but are useful for chronic asthma, or in EIB if used for at least one month, when the beta-2 agonists are not effective when used individually. They suppress the production of cytokines, reducing the eosinophils, and prevent inflammatory mediators release. Adverse effects are dysphonia, oral irritation, and candidiasis.

Cromolyn compounds (Cromolyn sodium and Nedocromil sodium) are mast-cell stabilisers without bronchodilator effects, which are useful—when inhaled 20 minutes before exercise—in preventing EIB and EIA symptoms in 80% of patients. They may also prevent the late-phase response of EIB. They can be used many times a day in the absence of adverse effects, and may be additive when beta-2 agonists

are not completely effective. Adverse effects include bad taste, throat irritation, cough, nausea, vomiting, and abdominal pain.

Antileukotrienes are used for long-term asthma therapy. Montelukast and Zafirlukast are leukotriene antagonists, while Zileuton is an inhibitor of biosynthesis by 5-lipoxygenase; they are effective in preventing EIA in chronic asthma. Leukotrienes are products of arachidonic acid metabolism, and increase eosinophil migration, mucus production, and bronchial oedema, with bronchoconstriction response 1000 times greater than histamine. The antileukotrienes, normally used orally for long-term therapy, offer 24-hour protection with very low adverse effects (dyspepsia, nausea).

Inhaled anticholinergics (ipratropium bromide, oxitropium bromide, tiotropium bromide) are not useful in preventing EIB, and are only used in chronic obstructive pulmonary diseases and chronic bronchial infections complicated by asthmatic attacks.

Antihistamines (astemizole, cetirizine, chlorpheniramine, desloratidine, phexophenadine, terphenadine, etc.) exhibit little effect; they might be useful in allergic asthma only when the disease is combined with allergic rhinitis due to air pollens. The oral dryness and some mild sedative effects are not helpful for athletes. Further, they are sometimes combined with stimulants not permitted by antidoping rules. Ketotiphen is a more widely used antihistamine substance; like cromolyn compounds, it acts on mast cells as a stabiliser, with fewer adverse effects.

Antibiotics are used in the presence of infections—sinusitis, rhinitis, bronchitis—that increase bronchial sensitivity.

Methylxanthines (theophylline and aminophylline or theophylline ethylendiamine) work by decreasing the metabolism of cAMP by inhibition of phosphodiesterase; they also have adrenergic effects. They are used systemically (oral or injections), mainly in chronic asthma and in acute exacerbations, under strict medical control for possible adverse effects (tachyarrhythmias, hypertension, peptic ulcers, hyperthyroidism, seizure disorders).

Systemic glucocorticosteroids and *beta-2 agonists* are restricted to more serious conditions and are administered in emergency situations by medical prescription.

Epinephrine (adrenaline) is administered subcutaneously, under strict medical control, only in life-threatening emergency situations.

F. Doping Related Issues

Since 1993, the beta-2 agonists have been submitted to restrictions by the IOC and IAAF, based on their possible effects as anabolic agents (see Chapter 15, *Drugs in Sports/Doping Control*). However, a large increase in the number of athletes with declared use of beta-2 agonists was reported in high-level competitions and Olympic Games, perhaps as a consequence of an incomplete or erroneous diagnosis and, sometimes, due to an over-use of and/or acquired tolerance to beta-2 agonists, with an under-use of inhaled glucocorticosteroids.

Further, the beta-2 agonists can potentially have positive ergogenic effects on skeletal muscle anabolism, and on aerobic and anaerobic performance. For this reason the control of their use in accordance with sport rules is becoming more strict. Also, glucocorticosteroids by inhalation have been subjected since January 1, 2004 to more limited use, and only after application for a therapeutic use exemption (TUE).

In accord with IAAF and World Anti Doping Agency (WADA) rules and IAAF Procedural Guidelines for doping control:

1. Glucocorticosteroid by inhalation are banned "in" competition, and submitted in competition to the "Abbreviated Therapeutic Use Exemption" application process.
2. Beta-2 agonists by inhalation, are prohibited both "in" and "out" of competition, and are submitted to the "Abbreviated Therapeutic Use Exemption" application process.
3. Systemic glucocorticosteroids in competition and systemic beta-2 agonists both in and out of competition are banned, and a "Standard Therapeutic Use Exemption" application must be applied for before use.

Note that particularly in the case of an abbreviated TUE application to the IAAF for the use of beta-2 agonists by International Level athletes, and in accord with the IAAF beta-2 agonists protocol, the medical notification justifying the therapeutic necessity must be accompanied by the athlete's detailed medical records and by a positive bronchial provocation test with graphic evidence, conforming to the IAAF specific protocol (see also Chapter 15, *Drugs in Sports/Doping Control*).

All of the doping rules are updated yearly by IAAF, in accordance with the yearly WADA prohibited list. The current list may be found on the websites of WADA (www.wada-ama.org), IAAF (www.iaaf.org), and IOC www.olympic.org. The list goes into effect three months after publication.

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Headaches and Exercise-Induced Anaphylaxis

A. Headaches

Headaches may occur with exercise, and are usually benign. However, exercise-related headache may occasionally signal the presence of an underlying organic disorder.

1. Benign Exertional Headache

These may occur with exercise, but also with coughing, sneezing, bending, and lifting. No distinct pattern is observed. Pain can occur at any site, and radiate in a variety of patterns.

2. Effort Migraine

Migraine can be precipitated by strenuous exercise, and has an atypical migraine pattern, with sudden onset, scotoma, photo-sensitivity, nausea, and vomiting, and unilateral headache that is often retro-orbital. It usually lasts 20–60 minutes. Treatment should initially consist of analgesics, but drugs such as ergotamine tartrate may be required.

3. Organic Disorders

a. Pheochromocytoma

Pheochromocytoma may appear as a pounding headache of sudden onset, accompanied by nausea and vomiting. The flushing, sweating, and tremor typical of this disease may be obscured by exercise. A rise in blood pressure is often associated with the symptoms, even at rest. Urinary VMA and catechols are elevated.

b. Vascular Malformations and Tumours

These rarely present with exertional headache. However, persistent headache, either diffuse or localised, warrants a thorough neurological examination, and possibly an EEG and or CT scan.

B. Exercise-Induced Anaphylaxis

This is an unusual type of physical allergy, but one that can become life-threatening.

1. Manifestations

a. Flushing, sensation of warmth
b. Giant urticaria (wheals 10–15 mm diametre)
c. Angioedema, respiratory distress, vascular collapse

2. History

There is a prior personal or family history in over half of the subjects. The condition occurs unpredictably, and under variable circumstances associated with exercise. Prior food allergy may be a factor.

3. Differential Diagnosis

EIA must be distinguished from Cholinergic Urticaria (CU). This latter is uniformly brought on by exposure to heat or exercise, and has punctate urticaria and wheezing, but is not life-threatening.

4. Treatment

Stop exercise at once, and administer epinephrine subcutaneously. Subjects should be taught to carry and administer their own medication. Exercise with a companion who is aware of the problem and who can administer the drug.

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