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Review Article

Exercise-Induced Bronchospasm Diagnosis in Sportsmen and Sedentary

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This paper aims to identify factors that may account for the high values and varied prevalence of exercise-induced bronchospasm (EIB), which occur in the population of athletes. Journal articles, indexed and peer reviewed, published in the MEDLINE and SPORTDiscus database were screened using a computer search. Keywords as "prevalence," "exercise," "bronchospasm," and "athletes" were crossed. The diagnosis of EIB based on the questionnaire or maximal decrease of ventilatory parameters was considered as inclusion criteria and selection of articles. Analysis of selected articles reveals higher values and varied prevalence of EIB (11–55%) compared to those in the general population (4–20%). Evaluation criteria of EIB are those based on the characteristics of sedentary subjects. Criteria sometimes do not seem adapted to specific sports. This paper suggests a differential diagnostic approach which takes account of both the EIB characteristics of sedentary and those of sportsmen.

1. Introduction

Asthma and exercise-induced bronchospasm (EIB) are terms used to describe the same phenomenon depending on the path of physiological nature of the subjects and the circumstances highlighted. However, these two terms are not always interchangeable. Indeed, asthma is a multifactorial disease resulting from the combination of factors predisposing congenital (hereditary factors) and environmental factors favoring (allergens, pollen, home and industrial dusts, and air pollution inhalation, etc.). It is defined as a disorder characterized by attacks of breathlessness or chest tightness paroxysmal wheezing, usually exhalation, indicating a sharp decrease of the caliber of the bronchi which combine progressive edema and hypersecretion of mucous tract air breathing (nasal cavity, pharynx, larynx, trachea, bronchi) can lead to inflammation. Clinically, asthma is characterized by attacks of breathing difficulty arising from crises, time varying and is reversible spontaneously or under the effect of treatment. These accesses coincide with episodes of varying degrees of airway obstruction and reversible [1]. As a result, the diagnosis of asthma is very delicate. The diagnosis of asthma is based on the examination, respiratory symptoms, family history, and pulmonary function at rest, during exercise and pharmacodynamic tests. To validate this diagnosis in the resting state, the criteria of the European Respiratory Society [2] and the American Thoracic Society [3] require a ratio of forced expiratory volume in 1 second (FEV) less than 80% of the theoretical value, a ratio of FEV on vital capacity (VC), that is to say, FEV/VC below 80% or 70% of predicted, a report of using peak expiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75}) of less than 65% of the theoretical aspect, and a concave upward curve flow/volume. In the sedentary, the diagnosis of exercise-induced asthma can be achieved either in the laboratory, using tests of incremental ergocycle, or field exercises being general or specific. According to the recommendations [2, 3], a stress test is considered positive when there is a fall in FEV from 10% to 15% from baseline after exercise performed at a level corresponding to the ventilatory at least 20 times the FEV

rest. The prevalence of asthma in the general population has doubled in Western Europe [4]. It reaches 6.8% in France, 6.9% in Germany, 5.7% in Spain, and 6.5% in Sweden. In England, the observed prevalence of around 16.1% is among the highest in the world [4]. A recent study [5] has revealed very few little data on asthma prevalence in Africa. However, studies in South Africa (Cape Town) in children aged 13 and 14 years, have high values of asthma prevalence (16–20%) [5]. The prevalence of asthma associated with the sport ranges from 4 to 20% in the general population [6–8]. Exercise, under certain conditions, may cause a crisis dyspnea, bronchospastic, or paroxysmal: this is known as exercise-induced bronchospasm or EIB. The role of exercise in this phenomenon is not easy to clarify. Indeed, it is difficult to say whether exercise acts as a developer or as an aggravating factor of asthmatic disease latent or patent. This difficulty arises probably from the double standards in the terminology currently used: exercise-induced asthma (EIA), when the exercise is indicative of patent asthma, exercise-induced bronchospasm (EIB), where the exercise is the source of a latent asthma. In addition, the terminology seems to be related to the status of the subjects, the EIA is used in sedentary subjects and the EIB in sportsmen. In sportsmen, the diagnosis of EIB is placed either in laboratory conditions, using incremental tests, or field, with specific exercises in relation to the requirements and environmental conditions of the sport concerned. The diagnosis is based on the examination, respiratory symptoms, tests, and pharmacodynamic classical criteria [2, 3]. The prevalence of the EIB varies from 11 to 55% in the athlete population [9–12]. In these studies, two observations emerge. Both in the general population than in sportsmen, assessment of asthma or EIB is achieved globally using the same methods and criteria. It was also found that the prevalence of asthma can vary from one to two, between the general population (4–20%) and sportsmen (11–55%), suggesting the strong involvement of sport and physical activity. A great disparity has also appeared in prevalence rates (11–55%) reported probably because the specific characteristics of sport and diagnostic methods used in different studies. This situation raises the issue of evaluation of exercise-induced bronchospasm in the athletic population as the cardiopulmonary adaptations and muscle induced by the sport are not taken into account. This paper aims to (1) remember the pathophysiology of the EIB; (2) present a critical analysis of the diagnostic methods of the EIB; (3) identify the extrinsic factors that may explain the high prevalence of EIB found in the athlete population.

2. Selection Method of Articles

The articles were selected from databases PubMed and SPORTDiscus. Other articles were identified using the reference list of items previously consulted and Google Scholar. The key words as prevalence, exercise, bronchospasm, asthma, sedentary, and sportsmen were used to conduct the research articles. Articles published from 1971 to 2011 were reviewed, although the vast majority of these writings were published in the last ten years. Whereas the objective of this paper issue was to provide a general picture of the state of knowledge on the evaluation of exercise-induced bronchospasm (EIB) in sportsmen, articles were selected as they allowed adding elements essential to understanding the diagnosis of EIB. First, the articles cited in the sections on the mechanisms involved in the development of EIB should contain at least one explanatory theory of the path physiology of the EIB. Regarding the section of the criteria and diagnostic methods of the EIB, the studies address the conditions allowed assessment of lung volumes and maximum flow rates as required by the American Thoracic Society [3] and the European Respiratory Society [2] (ATS/ERS). The section of factors associated with differences in prevalence between sportsmen and sedentary items was retained if the relationship between air pollution, climatic conditions and the EIB is highlighted. Most of the studies reviewed involved the evaluation of the EIB in the athlete population and in healthy sedentary; the literature in a language other than English was not included. Finally, since this selection focused on the work done in sportsmen, studies strictly on children, adolescents, and subjects with chronic asthma were excluded.

3. State of Knowledge

3.1. Mechanisms Involved in the Occurrence of EIB. The pathophysiology of exercise-induced bronchospasm in athletes is not well known. However, two schools of thought propose each an explanatory theory, that is, the theory of dehydration/osmolarity and the theory of the cooling/heating [13, 14]. This theory is based on the bronchoconstriction provoked in the resting state, and the inhalation of hyperosmolar saline. By analogy, the authors of this theory hypothesize that the hyperosmolarity of the airway induced by hyperventilation is the cause of bronchospasm that occurs in sportsmen. Indeed, during sports activities, the gradual increase in the intensity of exercise induces an increase in ventilatory rate. Similarly, for the inspired air at high frequency to reach the distal airways, it must be heated and saturated with water vapor. For this to happen, cells of the upper airway (UA) intervene by selling water as heat to condition the inspired air. This dehydration would result in increased concentrations of ions $[Na^+]$, $[Cl^-]$, $[Ca^{2+}]$, and $[K^+]$ that caused a hyperosmolar state of the airways and bronchial spasm. Proponents of this theory have concluded that the hyperventilation induced by exercise is the cause of UA hyperosmolarity and, indirectly, of bronchospasm [15]. The sequences of events that occur between the state of osmolar UA and synthesis of mediators remain to be elucidated. During exercise, the conditioning (warming and saturation) of the inspired air begins with the complex oronasopharynx to reach the tracheobronchial tree. The air inspired, transiting from the mouth to the periphery of the lung, is exposed to the effects of global warming and saturation from the airway epithelium. The net effect of this heat exchange during inspiration would be a cooling of the airways [16, 17]. This theory suggests a transfer of heat from blood vessels in the small bronchi to the pulmonary blood vessels. Indeed, after exercise, heat transfer is followed by

dilation, a warming and increased blood flow in pulmonary vessels. This hypothesis is based on the vascularization of subepithelial capillaries which liaise between the trachea and small airways. As a result, the clogging of these vessels could put physical pressure on the airways, which would result in bronchospasm. The basic premise of the hypothesis of global warming is based on increasing the temperature inside the airways, such as a replica of the increased blood flow in the airways [16]. However, the authors noted that global warming could simply be due to the prolonged stay of the air in the alveoli. However, the amount of blood flowing through the airways cannot justify the increase of heat in the airways, since this amount of circulating blood represents only 1% of cardiac output [18]. Hyperventilation of air pollutants, cold air, dry air, hot air, and humid air, on the one hand, and the mechanisms of cooling warming the airways on the other hand can be various causes that might account for the higher prevalence of asthma in the athlete population.

3.2. EIB Diagnosis Methods. The criteria for evaluation of the EIB, as well as the nature of sports topics, differ significantly from one study to another. Indeed, some authors adopt the change in FEV, PEF, and $DEMM_{25-75}$; others speak only of the FEV as criteria for evaluating the EIB [12, 19]. Indeed, obstructive ventilatory deficit and restrictive ventilatory deficit experience very different definitions. The definition of obstructive syndrome proposed by the ATS in 1991 concerning the interpretation of pulmonary function does not conform to the definition suggested by the Global Initiative for Chronic Obstructive Lung Disease or to the joint recommendations of the ATS and the ERS about Chronic Obstructive Pulmonary Disease. In several countries, these shortcomings have even raised the development of official documents relating to quality standards, guidelines, and standardization of lung function tests. The diagnosis of exercise-induced bronchospasm in sportsmen is based primarily on the interrogation target, looking for respiratory symptoms and family history. The diagnosis also covers data from the pulmonary function at rest and on the detection of airway hyperresponsiveness, based on bronchoconstrictor and bronchodilator tests. St. George's Respiratory Questionnaire for asthma [20] aims to assess dyspnea, wheezing. It also aims to search through the history and clinical signs for the presence of asthma related or not to exercise. The questionnaire based on clinical symptoms, as the only means of investigation is not reliable for assessing EIB. Studies showed that in the athlete, the absence of clinical symptoms is not necessarily synonymous with the absence of bronchial hyperreactivity [19, 21, 22]. Indeed, various authors have shown that symptoms do not always coexist with EIB [7, 11].

3.2.1. Methacholine Challenge and Its Limits. Many pharmacological agents can cause bronchoconstriction. Methacholine (Provocholine) is the most used today. It is a synthetic choline ester that acts as a nonselective muscarinic receptor agonist in the parasympathetic nervous system. Either by continuous nebulization dosimeter or (probably the best method) a small break from 2 to 5 minutes is left between the inhalations and the measurement of FEV is between 30 and 90 seconds after inhalation. The expression of the result of provocation test is most often a doseresponse curve. The response to the test is expressed as PD20 (dosimeter method, that is to say, the dose that brings down the initial FEV 20%) or PC20 (continuous nebulization method, that is to say, the concentration that brings down the initial FEV 20%). Recently, a dose of 200 μg was set by the IOC Medical Commission as a reference value to confirm the positivity of methacholine. In patients under inhaled corticosteroids for at least 3 months, a PD20 less than or equal to 6.6 mmol or 1320 mg, a PC20 less than or equal to 13.2 $mg \cdot mL^{-1}$ can be accepted as evidence of bronchial hyperresponsiveness [23]. Where the criteria due to ERS/ATS are caught out in the pulmonary function tests in resting among subjects with bronchial hyperreactivity (BHR), the methacholine test is the key to the diagnosis of BHR, despite the criticisms against it in the literature. Indeed, Wagner and Jacoby [24] reported an animal model, which causes reflex contractions methacholine in contact with smooth muscle receptors. Under these conditions, the responses to methacholine observed in humans or animals not only would represent its direct effect on smooth muscle but also involve reflex contractions.

3.2.2. Eucapnic Voluntary Hyperventilation (EVH) Test and Its Limits. This test assumes that exercise is not, in itself, the trigger of bronchial obstruction. Hyperventilation is associated with exercise that is responsible for the appearance of disorders. Thus, the voluntary hyperventilation eucapnic test is suggested for sportsmen in the detection of the EIB. Generally, the protocol for this test is based on studies of Argyros and Anderson [25, 26] and, most recently, that of Sue-Chu [27]. After basic spirometry, subjects hyperventilate for 6 min at 85% of maximum voluntary ventilation calculated corresponding to 35 times the baseline FEV. The inhaled air must be dry and kept at room temperature and contain 4.9% CO_2, 21% O_2, and 74% N_2. A gas flow of 30 to 150 $L \cdot min^{-1}$ may be issued and the maximum speed can reach 200 released $L \cdot min^{-1}$. At the end of the period of 6 minutes of hyperventilation, the FEV is measured at 1, 3, 5, 7, and 10 minutes. At each time interval, the FEV is measured twice and the highest recorded value is used for calculations. After the test, a bronchodilator is administered if the fall in FEV exceeds 20%. The presence of BHR is confirmed when the fall in FEV, expressed as a percentage of the initial value, is greater than or equal to 10%. This test is more sensitive than the methacholine or conventional exercise test [28]. The Medical Commission of International Olympic Committee [29] recommends that athletes take the test of voluntary hyperventilation eucapnic which only allows the use of positive betamimetics. The implementation of the voluntary hyperventilation test eucapnic is internationally recommended as a baseline assessment of EIB [29]. The test subjects submitted to EVH, are they able to maintain more than 5 minutes of ventilation such levels close to their maximum ventilation real? The fall in FEV observed in the

EVH test, would not the fall be due to a chest muscle fatigue? Although the EVH test is indicated as a benchmark for evaluation of the EIB, its implementation raises difficulties, the most important are that (a) the eucapnic voluntary hyperpnea test imposes technical constraints related the need for a fixed gas mixture concentrations, which would limit its feasibility, for the moment, to a small number of laboratories for functional exploratory, and (b) the concentration of CO_2 in the inspired air increased to 4.9% seems high and may cause irritation of the airways and bronchoconstriction in isolation.

3.2.3. Laboratory and Field Tests and Their Limits. Generally, there are two optional feasible tests, that is, triangular (progressive incremental workload exercise) and rectangular (steady-state workload) tests with the aim, among other things, of detecting in sportsmen cardiopulmonary anomalies, assessing the physical capability to control the quality of drive and to detect signs of overtraining. These stress tests are performed on the ergometer adapted to sports activities practiced by the subjects and according to a protocol that leads to the resting state, to maximal aerobic power, requiring the stop of the race from exhaustion. Because of the risk of cardiac arrhythmias, syncope may occur during the event maximum, only a few laboratories are authorized to supervise and organize this type of evaluation. In laboratory conditions (22°C and 60% relative humidity), the rectangular stress tests are typically in 8 minutes and are performed at an intensity greater than or equal to 95% [30]. However, the diagnosis of bronchospasm produced in the laboratory is not sensitive enough to be reliable. Indeed, a study on the occasion of an evaluation of bronchospasm in winter sports games observed that the exercise tests performed in laboratory conditions to detect positive subjects but in reverse does not detect subjects actually carrying EIB [30]. It was, therefore, suggested to assess bronchospasm in sportsmen, according to the specificity and environmental conditions of their sports, according to the criterion of positivity requirement to 10% decrease in FEV. The field tests are more sensitive to detect the EIB than those carried out in laboratory conditions [30]. Similarly, environmental and climatic conditions (ambient temperature, relative humidity) in which sportsmen operate can help to influence airway responses. In the same way, the field evaluation carried out in the real conditions of pollution which are commonly experienced by athletes may be of interest. Ice hockey players, skaters, and cyclists who train several hours a day in a specific environment would have EIB evaluations in the field, close to reality. These assessment tests indeed take into account the requirements gesture, the specific nature of sport of these athletes [30]. However, field tests have some limitations and shortcomings that must be taken into account. Indeed, control of intensity and the collection of respiratory parameters pose some difficulties. Ultimately, the option of field tests or laboratory tests must be made according to the objectives. The challenge test of the EIB is the exercise itself. To induce the variability of lung function by exercise, the intensity is suggested by at least 85% of maximum heart rate [31]. Other studies suggest, however, intensities ranging from 95 to 100% of maximum effort in athletes [30]. If the level of exercise intensity is generally not a problem at the EIB evaluations among amateurs, it is not always easy to manage among elite athletes. Indeed, among these, physical ability may be underestimated in laboratory tests, because the maximum tolerated is often not in line with the actual physical ability of the athlete. The laboratory evaluation does not take into account the realities of the real athletes such as the atmosphere of competitive rivalry, the encouragement of the public, changes in routes, and environmental conditions. These observations suggest the inclusion of appropriate intensity level and the actual environmental conditions of athletes to make the assessment of bronchospasm more sensitive and specific. However, measurements in real athletes are not always reliable, because of disturbances related to the mobility of the subject. For cons, the laboratory measurements can be accurate, but are unreliable because the subjects cannot deliver their true physical potential.

3.3. Factors Associated with Prevalence Differences between Athletes and Sedentary. Values prevalence of exercise-induced bronchospasm observed in athletes are higher than those reported in the general population (4% to 20%) [6–8]. Extrinsic factors may explain this difference are, among others, air pollution and environmental and climatic conditions.

3.3.1. EIB and Atmospheric Pollution. Long-distance runners develop broadband lung compared to sedentary. They can vent up to 100 $L \cdot min^{-1}$ in stable condition with maximum oxygen consumption greater than 67 $mL \cdot kg^{-1} \cdot min^{-1}$. This large amount of air ventilated in environmental conditions and unfavorable climate can cause damage in the airways. It was indeed shown in animals that involvement of distal airways in the process of air conditioning favored the amplification of inflammatory lung disorders [32]. Since then, the significant mixing of air in the exercise, the airways of these athletes are so frequently exposed to many allergens. Also, microlesions produced by hyperventilation are the cause of cell permeability to Na^+, Cl^-, K^+, and Ca^{2+}. They induce the release of chemical mediators involved in the initial inflammatory process of asthma. Hyperventilation in a polluted atmosphere is so detrimental to the athlete's lung function when they practice in urban or suburban areas. Thus, environmental pollution promotes the onset of ventilatory disorders and contributes to the rise in the prevalence of asthma in athletes. Similarly, the effects of air pollution on health and sports performance are controversial. Work has, however, shown that the degradation of respiratory parameters in athletes was due to pollution [33]. Thus, the practice of sports during the summer where the rate of ozone (O_3) is the highest would also be conducive to the development of airway inflammatory process [34]. Moreover, according to the model of Hinds [35], for an amount of 100% of nanometric particles, 80% are retained in the nose and pharynx, while the remaining 20% enter the trachea and bronchi. Studies have shown that increased levels of air

pollution in fine particles, especially from vehicle emissions, leading to respiratory problems [36]. Similarly, treatment of the ice surfaces requires the use of engine oil or gas oil creates a high production of particulates, carbon monoxide (CO), and nitrogen dioxide (NO_2). These ultrafine particles in suspension, with diameters less than 2.5 micrometers are also involved in the dysfunction of the airways [37–39]. The concentrations of PM_1 (particulate matter with diameters less than 1 micrometer) evaluated in the rinks are 20 times higher than outdoor air [37]. Studies [40–43] on the toxicity of the airways have also revealed alterations of the airways. Consistent with these observations, Daigle and colleagues [44] showed in turn that exercise promotes an increase in deposit of ultrafine particles in the respiratory tract. The exposure of individuals to high concentrations of nitrogen dioxide in air, that is to say, about 3000 parts per billion (ppb) in a cold climate have been documented [45]. It was reported that brief exposure to concentrations of nitrogen dioxide (500 ppb) induces an increase in airway resistance in asthmatic subjects, whereas the same response observed in subjects without asthma required the exposure to a concentration of 1000 ppb [46]. The deposit of dust along the bronchial tree varies considerably depending on the size of ultrafine particles of dust and their behavior in the air. Particulate matters entering the cells are growing because of their small diameters. Given that the hyperventilation induced by exercise can be a source of increased inhaled particles, it is likely that air pollution is more harmful to athletes than to sedentary subjects.

3.3.2. EIB and Climatic Environment. The conditions of temperature and relative humidity also seem to influence the process of exercise-induced bronchospasm. Indeed, practitioners of the winter sports atmosphere of cooler air and/or drier are more susceptible to bronchospasm. The work of Wilber et al. [47] performed in the Winter Games athletes of both sexes in controlled environmental conditions has shown the importance of cold, dry air in determining the prevalence of EIB. These authors have observed that (1) in a group of 14 American skiers in the Olympics Games of 1998, a prevalence of 57% for women, 43% for men, and 50% for the whole team, at a temperature which varied from −18°C to 0°C and a relative humidity of 30–50%, (2) in a team of 26 ice hockey players, Olympic-level, a prevalence of 15% only in women (the evaluation was not performed in men) at room temperature which varied from 10 to 13°C and a relative humidity of 40–45%; (3) in a group of 60 sprinters on ice, a prevalence of 50% in women and 33% in men, at a temperature ranging from 8 to 10°C and relative humidity 30–35%. These authors recorded the highest prevalence (50%) in the coldest temperatures (−18 to 0°C) and the lowest prevalence (15%) under the highest temperatures (10 to 13°C). Among the athletes who practice their sport in cold and dry continental climate, the prevalence of asthma may be higher compared to those recorded among practitioners in hot and humid air. Thus, climatic conditions can be considered as factors explaining high rates of asthma prevalence observed in the athlete population.

4. Conclusion

This paper of the issue of evaluation of EIB in athletes allowed contributing to the clarification of the terminology of the EIB and the EIA. Particular emphasis was placed on the large extent of EIB prevalence observed in the athletic population, which can probably be justified by the nature of sports, the differing criteria for diagnosis of bronchospasm, the wide variety of EIB diagnostic methods, limitations and conditions of assessment that vary widely. The classical criteria for demonstration of EIB selected for sedentary subjects seem more suited to the new physical characteristics of athletes. This paper suggests a differential diagnostic approach which takes account of both the EIB characteristics of sedentary and those of sportsmen.

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