A LETTER FROM

FREIBURG, GERMANY

Spring in the Black Forest, the desert dust and the respiratory system of the athlete

– Written by Yorck Olaf Schumacher, Qatar

Spring is just around the corner and arguably the nicest of the four seasons in Freiburg, a town with 220,000 inhabitants in the south western corner of Germany, very close to both France and Switzerland. The town hosts one of Germany's most traditional universities and is located in the heart of the Black Forest, a wooded area that extends over 200 km adjacent to the Rhine River over a major part of south western Germany to the Swiss border. It is the sunniest and warmest part of Germany, thanks to a microclimate that often delivers pleasant weather all year long. The name "Black Forest" stems from the colour the trees have in summer, referring to the enormous density of vegetation. In spring, the forest blossoms with new fresh leaves that are light green and looking at the hilly landscape covered with vegetation, it makes one realise how many shades of green nature can create. These greens turn darker as spring turns to summer, finally almost becoming black.

Although the most beautiful season for many, spring also brings back a load of allergens and pollen that impair the life of numerous athletes with allergic dispositions. During several weeks of the year, very often closely related to the blossoming of certain type of plants, these athletes suffer typical allergic symptoms such as itchy eyes or a watery and runny nose. 90% of the athletes with allergic disposition also show signs of asthma, an inflammation of the airways caused by an inadequate immune response. A similar, but not identical, inflammatory response in athletes can also be triggered solely by the inhalation of large volumes of air with or without pollutants during exercise, without any allergens. Thus, the resulting condition has been called exercise induced bronchoconstriction (EIB) or airway hyper responsiveness (AHR) and shows distinct similarities to but also clear differences from, normal asthma.

While very different to the Black Forest in types of vegetation and climate, the environment in Qatar is also challenging for the lung of the athlete. Although scientific evidence is still lacking on this topic, recent air quality measurements have revealed above-threshold concentrations for particulate matters, which are known to contribute to a large number of diseases encompassing impaired respiratory, vascular and cardiac function[1].

Particulate matters (PM) are a mixture of small solid particles and droplets containing dust, carbon, various acids, organic chemicals and metals. In general, the smaller the size of the particles, the more harmful they are to health as the penetration in the lung and the tissue is inversely correlated to the particle size. Therefore PM are usually classified according to their diameter (measured in micrometre), such as PM2.5 (particles with a diameter of less than 2.5 micrometre) or PM10 (PM between 2.5 and 10 micrometre).

Although no data on the prevalence of respiratory problems such as EIB in Qatar exists, it is highly likely that the dry desert environment and its dust loaded with PM might also be predisposing for this respiratory condition in elite athletes, similar to indoor ice rings and swimming pools with evaporating chemicals, cold air in winter or the pollen-loaded air of the Black Forest in spring.

EXERCISE INDUCED BRONCHO-CONSTRICTION

EIB is a common pathology in elite sports, where the prevalence ranges between 10 and 50%[2]. Several factors, in addition to the environmental influences outlined above, contribute to the exacerbation of EIB in athletes: sporting disciplines with

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high minute ventilation, such as most endurance sports ('high ventilation'), have a higher incidence of the condition than activities with lower air throughput (most team sports or 'low ventilation')[3]. It is also speculated that long-term activity in a 'high ventilation' sport will ultimately result in EIB in a large number of athletes due to the chronic irritation and remodelling ('wear and tear effect') of the airways caused by the high volume airflow in their respiratory system. In many elite endurance sports, prevalence of EIB is lower in younger athletes than in their older counterparts that have been in the sport for many years. This is a key difference to classical allergic asthma, which has a higher prevalence in younger athletes. EIB as an 'overuse' pathology is nevertheless reversible, when regular 'high ventilation' training activity is stopped or reduced (such as at the end of competitive careers in elite athletes).

It has to be highlighted that the true prevalence of EIB in athletes is also highly dependent on methodical issues such as the diagnostic criteria and the method of EIB assessment, the sporting disciplines (highest prevalence in Nordic sports, swimming and ice sports), the gender of the athlete (more common in girls), the season and the environments to which the athletes are exposed. Lastly, not all athletes with positive screening tests for EIB are symptomatic, as the respiratory system might not be performance limiting in each athlete.

PATHOGENESIS

The exact pathogenic mechanism of EIB is still controversial and not fully understood[4]. The central element seems to be the loss of fluids from the surface of the bronchi caused by the hyperpnoea during exercise. This will cause an osmotic and thermal imbalance by desiccating the respiratory epithelium of the distal airways, which will trigger an inflammatory response in susceptible persons. The mediators of this response (leukotriene, histamine) will activate mucus production and generate a cough, two of the main clinical symptoms of the condition.

Other authors speculate on a regulative consequence of training-induced vagal predominance, which elicits a dysfunction of the neuroendocrine–immune interface, causing a so-called neurogenic inflammation response.

Genetic factors related to osmotic electrolyte transport through Aquaporin[5], a cell channel protein, have also been linked to EIB susceptibility.

Interestingly, the inflammatory response observed in EIB shows similarities, but also differences to the inflammatory response observed in normal asthma[4]. Whereas the immune response in classical asthma is dominated by an eosinophilic airway inflammation, a mixed eosinophilic-neutrophilic pattern is observed in subjects with EIB, but without underlying atopy.

CLINICAL SYMPTOMS

EIB can present with a variety of symptoms[5]. The most common features are shortness of breath, chest tightness, expiratory wheezing, cough (often most prominent after the cessation of exercise) or increased mucus production. Typically, the symptoms only occur at higher exercise intensity of longer duration (>80% of maximal oxygen uptake [VO_2max] for 5 to 10 minutes) and peak in the minutes after cessation of the effort, as the level of catecholamines, which are increased during peak exercise and have a bronchodilative (and thus protective) effect, will drop off. The symptoms disappear within 30 minutes after exercise. After a period of EIB, a refractory phase lasting about 2 to 4 hours can be observed, where the likelihood of reoccurring EIB is reduced.

DIAGNOSIS

The initial diagnostic approach is made through the typical clinical symptoms of the condition. It is important to consider and exclude the potential differential diagnoses (Table 1). After thorough clinical assessment, further investigations with suitable tests of lung function can be initiated for confirmation. These tests will, in most cases, include a pharmacological or non-pharmacological challenge to elicit the typical obstructive picture in the flow volume curve (Figure 1), which might not be visible in the resting athlete.

The International Olympic Committee has defined the following criteria for the diagnosis of asthma or EIB[6]:

Resting pulmonary function:

- ≥12% increase in the athlete's resting FEV1 after application of a bronchodilator by inhalation. (Note: the athlete's FEV1 at rest can be in the normal range even if he is suffering from severe EIB/asthma).

Non-pharmacological challenge:

- ≥10% decrease in FEV1 within 30 minutes after exercise (exercise test protocol: >85% of maximum heart rate for at least 4 minutes.)
- ≥10% decrease in FEV1 after eucapnic voluntary hyperpnoea (EVH, 6 minutes breathing of dry air (5% CO_2, 21% O_2)).

Pharmacological challenge:

- ≥15% decrease in FEV1 after inhalation of a hypertonic aerosol (osmotic challenge, 22.5 ml of 4.5% saline).

Diagnosis	Main difference to exercise induced bronchoconstriction
Vocal Cord Dysfunction (VCD)	*Inspiratory wheeze, no response to ß$_2$ agonists*
Gastro-oesophageal reflux (GERD)	*No response to ß$_2$ agonists, proton-pump inhibitors help*
Laryngeal/tracheal processes	*Inspiratory wheeze, symptoms already at rest*
Respiratory tract infection	*Temporary symptoms, other signs of infection present*
Hyperventilation syndromes	*Difference in timing of symptoms compared to EIB*

Table 1: Differential diagnosis of exercise induced bronchoconstriction (EIB).

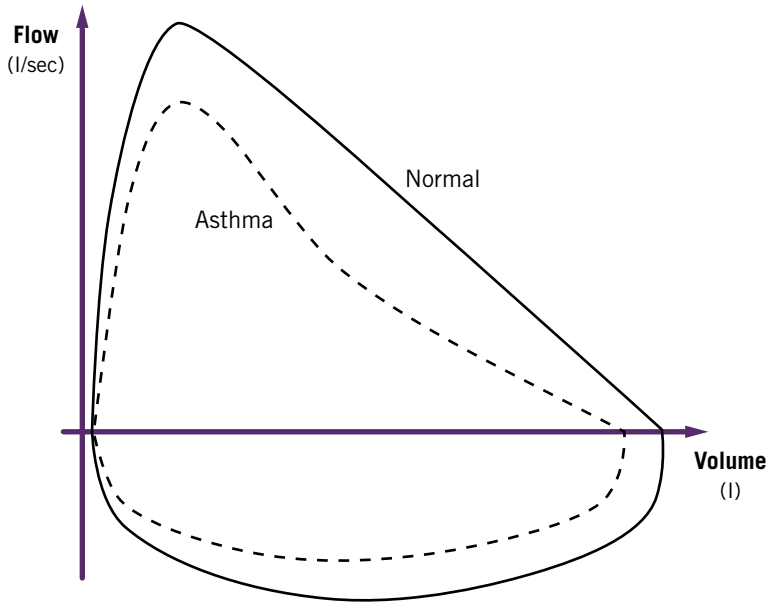

Figure 1: Flow Volume curve: Normal (full line) and obstructive pattern (dashed line) Republished with permission of *Journal of Allergy and Clinical Immunology*.

- ≥20% decrease in FEV1 after inhalation of metacholine (PC20<4 mg/ml, for athletes not under medication).
- ≥20% decrease in FEV1 after inhalation of histamine (PC20<8mg/ml) (exercise test protocol: graded test of 2 minutes).

Other pharmacological substances used to elicit EIB in pulmonary function tests include mannitol or carbachol. The tests using these substances are not recognised by the IOC for the diagnosis of EIB.

EIB associated with an underlying, classic asthmatic condition and atopic disposition will show good bronchial responsiveness to pharmacological challenges such as metacholin. In contrast, EIB without an underlying asthmatic condition is best diagnosed with eucapnic voluntary hyperventilation[4]. The decision flow chart proposed by the IOC in is illustrated in Figure 2.

TREATMENT

Treatment of athletes with asthma and/or EIB/AHR includes preventive, non-pharmacological management[3] and traditional pharmacological treatment[6].

First and foremost, preventive measures and non-pharmacological interventions should aim at reducing the airway injury which triggers the typical symptoms. Several environmental factors such as cold air, chlorine in swimming pools and pollutants should be avoided in training, where possible. Cold air exposure might be reduced by adapting the training to the weather and training indoors on very cold days or wearing face masks which moisturise the inspired air and thereby avoid dehydration of the airways. Rules regarding temperature limits for certain competitions have been introduced by skiing federations, where no competition is allowed when the air temperature drops below certain thresholds, depending on the skiing discipline. For swimmers, chlorine concentration in the ambient air can be markedly reduced by adequately ventilating the pool area. For outdoor athletes, air pollutants such as PM or NO are difficult to avoid.

Other preventive measures in athletes with known EIB/AHR include adequate warm-ups, as warm-up might induce a 'refractory period' of the lung parenchyma, where the susceptibility of the bronchial epithelium to dehydration and subsequent airway injury and bronchoconstriction is reduced due to increased blood flow.

There is only little scientific proof suggesting that pharmacological treatment might prevent EIB/AHR. For Montelukast, a leukotriene antagonist, there is accumulating evidence for a protective role of this substance in view of EIB/AHR in air-polluted environments. Interestingly, no data supports the preventive use of inhaled glucocorticoids (GCS) in the same context, although inhaled GCS are one of the pillars of traditional asthma therapy.

Although certain differences exist between the pathogenesis of asthma and EIB/AHR (see above), the pharmacological treatment of the acute symptoms is similar and should follow the current guidelines for the treatment of asthma in non-athletic subjects.

The first line treatments of EIB/AHR are inhaled GCS and ß2 mimetics. Most commonly, ß2 agonists are prescribed as on-demand medication when symptoms occur. The combination of inhaled GCS and long-acting ß2 mimetics might, however, improve therapeutic effect and prevent airway remodelling. Depending on the situation of the athlete, other substances such as cromolyn compounds (for athletes with allergic dispositions) and leukotriene antagonists (Montelukast, for athletes exposed to air-polluted environments) can also be beneficial.

ß2 mimetics have several side-effects that need to be kept in mind: repeated use of ß2 mimetics can trigger tachyphylaxis and desensitisation (due to down regulation of the receptors) requiring increasing dosage of the drug. Other side-effects of this substance class are tachycardia and an increased occurrence of upper respiratory tract infections, especially if the correct dosage is exceeded, which is commonly observed in athletes before competitions.

From an anti-doping point of view, most ß2 agonists are still banned by the World Anti-Doping Agency, despite the fact that there is little evidence to suggest that these substances are performance enhancing in the non-asthmatic athlete when applied in therapeutic dosage[7,8]. To date, only Salbutamol, Salmeterol and Formoterol (the latter at a maximum dose of 36 micrograms over 24 hours), are allowed to be used without therapeutic use exemption. All other ß2 mimetics require such documentation. Aside from ß2 mimetics, the following other asthma drugs are not restricted by anti-doping regulations:

- Inhaled glucocorticoids.
- Cromolyn derivates.
- Leukotriene receptor antagonists.
- Theophyllines.
- Inhalative anticholinergic substances.

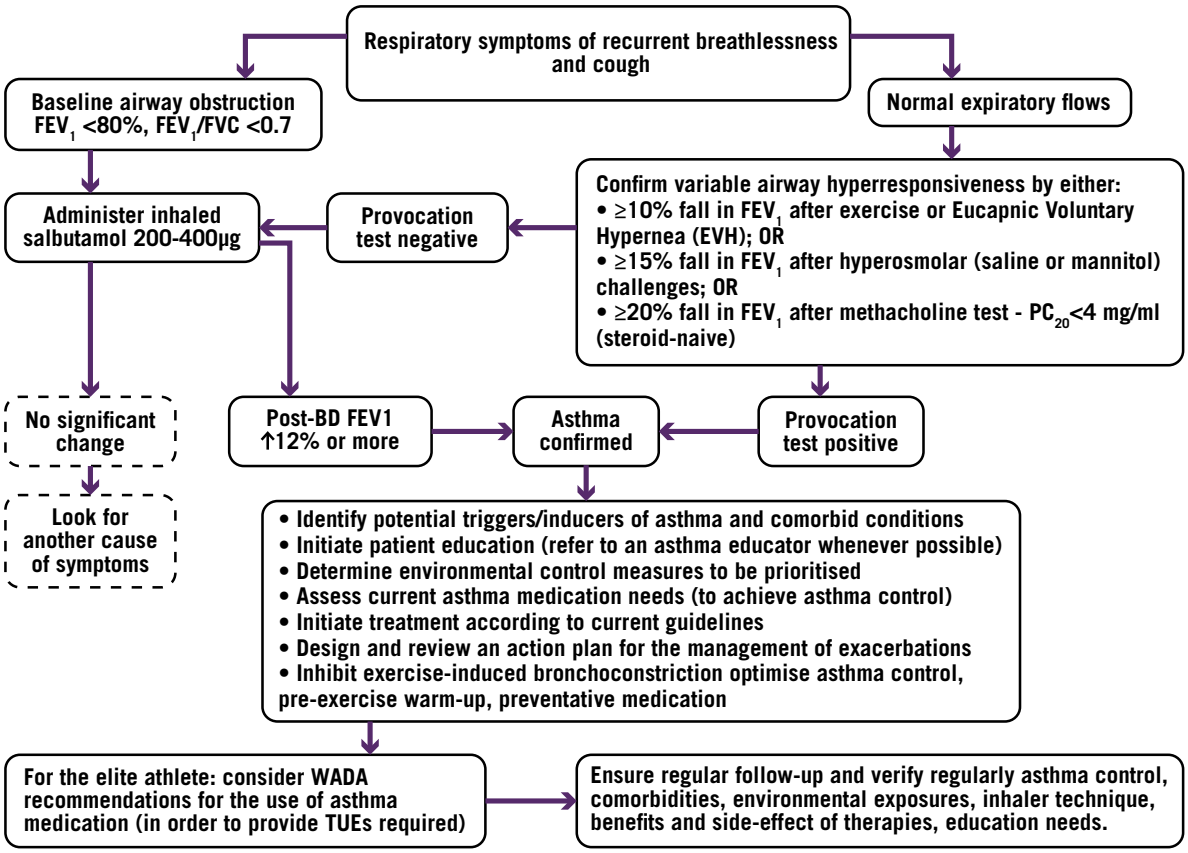

Figure 2: The diagnosis of Exercise induced Bronchoconstriction and asthma in the athlete as endorsed by the International Olympic committee[6].

SUMMARY & OUTLOOK

EIB is a common medical problem in 'high ventilation' sports and has been addressed as an occupational disease for professional athletes in some disciplines, such as cycling and cross-country skiing. Various other pathologies with similar symptoms exist, which should be considered in the differential diagnosis, the most common being vocal cord dysfunction. The treatment of asthma and AHR/EIB in elite athletes should include preventive measures and follow the currently accepted guidelines for these conditions in non-athletes, while respecting the constraints imposed by the anti-doping regulations.

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