Sorichter S

Exercise-Induced Bronchoconstriction – a Short Review with Practical Recommendations

Belastungsinduzierte Bronchokonstriktion – eine kurze Übersicht mit Praxisempfehlungen

Deputy Head, Division of Pneumology, University Hospital Freiburg, Freiburg

ZUSAMMENFASSUNG

Fragestellung: Übersichtsdarstellung der aktuellen Literatur zum Thema belastungsinduzierter Ventilationstörungen (exercise-induced asthma (EIA); exercise-induced bronchoconstriktion (EIB)) mit kurzer Zusammenfassung der Pathogenese, Diagnose und Behandlung. Methode: Literatursuche in Pubmed, Medline und Sichtung weiterer Literaturangaben. Zusammenfassung: Die Termini EIA und EIB beschreiben einerseits belastungsinduzierte Symptome im Sinne asthmatischer Beschwerden wie Atemnot, Husten, Giemen mit thorakale Enge andererseits eine exspiratorische obstruktive Ventilationsstörung nach einer definierten Belastung. Pathophysiologisch kommt es bei beiden Ereignissen durch Abkühlen und Feuchtigkeitsverlust der Atemwege zu einem relevanten Anstieg von Mediatoren sowie zur Aktivierung von Entzündungszellen bis hin zu Ausbildung einer chronischen Entzündungsreaktion. Die Diagnose ist über die Anamnese sowie o.g. lungenfunktionelle Änderungen in der Belastungsuntersuchung oder Metacholinprovokation stellbar, in manchen Fällen ist der eukapnische Hyperventilationstest, die inhalative Mannitol-Provokation oder ein Feldtest hilfreich. Bei Olympiateilnehmern im Zeitraum von 1996 bis 2006 konnte eine behandlungsbedürftige Problematik bei bis zu 20% der Spitzenathleten in einzelnen Sportarten festgestellt werden, wobei der Schwerpunkt eindeutig bei den Ausdauersportarten lag. Die wichtigsten und häufigsten Differentialdiagnosen sind die Vocal cord dysfunktion mit dem Leitsymptom des inspiratorischen Stridor, verminderte Fitness sowie das Übertraining. Die Therapie orientiert sich an der Asthmabehandlung mit frühzeitigem Einsatz von einer antientzündlichen Medikation (inhalative Steroide, Leukotrienrezeptoranatagonisten) sowie der bedarfsweisen Anwendung von inhalativen ß 2-Mimetika unter der Berücksichtigung der Antidopingregeln. Fehlendes Ansprechen dieser Therapie sollte frühzeitig an die Differentialdiagnosen denken lassen.

Schlüsselwörter: Belastungsinduziertes Asthma, Belastungsinduzierte Bronchokonstriction, Leistungssport, Vocal-cord dysfunction, inspiratorischer Stridor.

SUMMARY

Purpose: This article reviews the recent literature on exercise-induced bronchoconstriction (EIB) or exercise-induced asthma (EIA) and briefly summarizes the pathogenesis, diagnosis, and treatment of these conditions. Method: A literature research using PubMed, Medline and selective personal readings was performed to obtain articles on EIA and EIB. Summary: The term EIA covers exercise-induced symptoms and signs of asthma such as recurrent breathlessness, cough, wheezing, and chest tightness. EIB describes an expiratory obstructive reaction in lung function after a standarised exercise test. The pathophysiology of both diseases includes cooling of the airways, an increased loss of water from the respiratory tract and a relevant release of mediators from inflammatory cells of the airways, which could, on the long term, induce a chronically inflammatory response of the bronchi. The diagnosis of EIA or EIB includes the typical anamnesis and a positive exercise reaction or lung function testing with metacholine provocation. A eucapnic hyperventilation test, mannitol bronchial provocation or a field exercise test may be of help in some subjects. Data from the Olympic Games from 1996 until 2006 indicate a sport specific incidence of up to 20% amongst all athletes applying inhaled $ß_2$-agonists with a verified diagnosis, emphasising on endurance disciplines. While diagnosing EIA / EIB numerous differential diagnoses have to be considered. Vocal cord dysfunction, poor physical fitness or overtraining are the most common. Therapeutically, adequate warm-up helps to reduce symptoms and inhaled corticosteroids or leucotrienreceptorantagonist are considered useful drugs for long term control and prevention. Supplementary, inhaled β_2-agonists are effective drugs for immediate inhibition of bronchoconstriction. Nevertheless, for all athletes the anti-doping regulations have to be applied. Further diagnostic evaluation should be considered if adequate treatment does not control the problem.

Key Words: Exercise-induced asthma, exercise-induced bronchoconstriction, athletes, vocal-cord dysfunction, inspiratory stridor.

INTRODUCTION

The symptoms of exercise-induced asthma (EIA) was first described by Aretaeus of Cappadocia in the 2nd century $_{AD}$ "... if from running, gymnastic exercises, or any other work, the breathing becomes difficult, it is called Asthma" (1). To date EIA is considered as an important clinical part of asthma bronchiale as exercise is a typical trigger of bronchoconstriction, especially in the younger population (29). However, physical exercise may also induce asthma like symptoms in susceptible individuals without an underlying asthma bronchiale, sometimes called exercise-induced bronchoconstriction (EIB). This is most commonly seen among elite endurance athletes, representing an increasing problem for active athletes (15). EIA or EIB are different terms describing both the transient narrowing of the airways after short and vigorous exercise. However, the pathophysiology is somewhat different. An ERS / EAACI-task force in 2008 defined that the term EIA should be used to describe symptoms and signs of asthma (such as recurrent breathlessness, cough, wheezing, and chest tightness) provoked by exercise and that EIB describes a reduction in lung function (obstructive expiratory flow limitation) after an standarised exercise test (6). These definitions were recently confirmed by the IOC and Wada committees favouring a broad comprehensive definition of these conditions in athletes (31,13).

accepted: September 2012
published online: November 2012
DOI: 10.5960/dzsm.2012.034
Sorichter S: Exercise-Induced Bronchoconstriction-a short Review with Practical Recommendations. Dtsch Z Sportmed 63 (2012) 294 - 297.

METHODS

A medical literature research using PubMed, Medline and selective personal readings was performed to obtain articles on EIB. Search terms included: exercise-induced asthma, exercise-induced bronchoconstriction, athletes, vocal-cord dysfunction, inspiratory stridor. Only English and German publications were considered. It has to be emphasized that recently several societies and journals have published reviews in this field. This short review focuses mainly on the reports of the American Academy of Allergy, Asthma & Immunology Work Group from 2007 (32), the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA^{2}LEN from 2008 (6,7,32) and the notable reviews on the breathless adolescent asthmatic by Carlsen and Olympic athlete by Haathela (5,14).

Pathogenesis

The mechanism for development of EIA and EIB in athletes includes two hypotheses. Both relate to the increased ventilation of up to >200 L/min in elite athletes during exercise, resulting in an increased loss of water from the respiratory tract and cooling of the airways. This results in vasoconstriction of bronchial vessels followed by secondary reactive hyperemia, edema and airway narrowing (21). Furthermore, a relevant release of mediators from mast cells and other inflammatory cells of the airways, by changing the osmolarity of the periciliary fluid lining the respiratory mucosal membranes, can be measured (3). These mechanisms affect the course of EIA/EIB significantly, especially by inducing a chronically inflammatory response of the bronchial airways.

The classic early onset pattern reflects the signs of allergic asthma characterized by atopy, eosinophilic airway inflammation and positive methacholine responsiveness with a rapid onset of symptoms at exercise initiation. The divergent pattern comprises a late onset phenotype during a sports career and therefore with more phases of high ventilation. Data on Finnish Olympic athletes support these findings and suggest these two different clinical phenotypes, which may reflect different underlying mechanisms due to the environmental conditions (14).

Problematic environmental conditions during the activity such as cold ambient temperatures for winter sports or organic chlorine products from indoor swimming pools clearly enhance the effect of intensive physical activity on both conditions. Especially swimmers, ice-hockey players, and cross-country skiers show a mixed type of eosinophilic and neutrophilic airway inflammation. Therefore, the inflammation may represent a multifactorial trauma, in which both irritant and allergic mechanisms play a role (14).

Prevalence

In general, exercise-induced asthma is a major problem for children and adolescents with known asthma bronchiale (20). Prevalence data of EIA/EIB among top athletes are conflicting due to methodological considerations. Most data for the prevalence of EIA or EIB in athletes were based on questionnaires without any attempts of clinical verification or other objective measures. Lung function based data with reversibility to inhaled ß$_2$-agonists or provocation test are rare. Recently published data on the usage of inhalative drugs after application for the Olympic Games from 1996 to 2004 show that only 6.7% of Winter Olympic and 4.6% of the Summer Olympic participants used inhaled ß$_2$-agonists (6). As expected, the usage of inhaled ß$_2$-agonists was the largest in endurance sports group: Cross-country skiing (17.6%), Speed skating (16.2%), Cycling (15.4%) followed by Nordic combined and Swimming (6). These findings are supported by results from Dickinson, appling the objective criteria for diagnosing asthma and/or BHR as given by the IOC Medical Commission (see Diagnosis), who showed an EIA/EIB prevalence among the British participants in the Olympic Games in 2000 and 2004 of 21.2% and 20.7%, respectively (11). In competitive athletes of various sports, a higher prevalence of bronchial hyperresponsiveness (BHR) to metacholine (49%) compared with sedentary subjects (28%) was reported by Langdeau (19), showing that the prevalence also varied in athletes performing their sports in cold air, dry air, humid air or in a combination of all. However, such high prevalence's up to 55% of exercise-induced respiratory symptoms, based on lung function data, were reported in elite athletes only in some studies, clearly represented in the excellent overview of prevalence studies in the Joint Task Force report by Carlsen et al (6). In conclusion there is evidence that top athletes, particularly in endurance sports, are at increased risk of EIA and EIB (6).

DIAGNOSIS

The diagnosis of EIA/EIB requests the synthesis of medical history including details on respiratory symptoms, physical examination and appropriate laboratory or field tests to verify or provoke respiratory symptoms (see figure 1). Typically, symptoms occur shortly after (sometimes during) intensive physical exercise with expiratory dyspnoea; regular rhonchi or wheezing may be observed by auscultation. A gradual improvement occurs either spontaneously or after usage of an inhaled bronchodilator (5,25). The symptoms of asthma should be verified by the evidence of the reversibility of airflow obstruction or bronchial hyperreactivity confirmed by tests (5,25) mentioned in Figure 1. It has to be considered, that there are athletes with mild BHR to medical stimuli who have negative exercise challenges, but there are also individuals who have positive exercise challenges and negative histamine or methacholine challenges (16,18). These possibly conflicting test results may be due to the difference in mechanisms involved. In example, the above mentioned late onset phenotype is more likely to respond to eucapnic hyperventilation tests (6). Additionally, a mannitol bronchial provocation or a field exercise test may be of help in some subjects (4).

If an exercise provocation is used, an ERS task force report on indirect airway challenges states the following recommendations: the subjects should exercise for six (children) to eight (adults) min at an intensity to raise the minute ventilation 14 times above the FEV_1 and preferably to 21 times the FEV1 (60% maximum voluntary ventilation) for the last four min of exercise. In the absence of a measure of ventilation the heart rate should achieve 90% predicted maximum in the last four min of exercise. Values for FEV_1 are measured before and after exercise and a reduction in FEV_1 of 10% of the pre-exercise value is widely accepted as outside the response observed in healthy individuals without asthma. Providing dry (and cold) air increase the severity of the airway response (18,28).

Additionally, reversibility of airflow obstruction or BHR can also be confirmed by the measurement of airway resistance using bodyplethysmograhy as sometimes obstructions occur only in the central airways. However, there are no international threshold value recommendations to confirm BHR in athletes, but an increase of more than 150% is generally accepted (9).

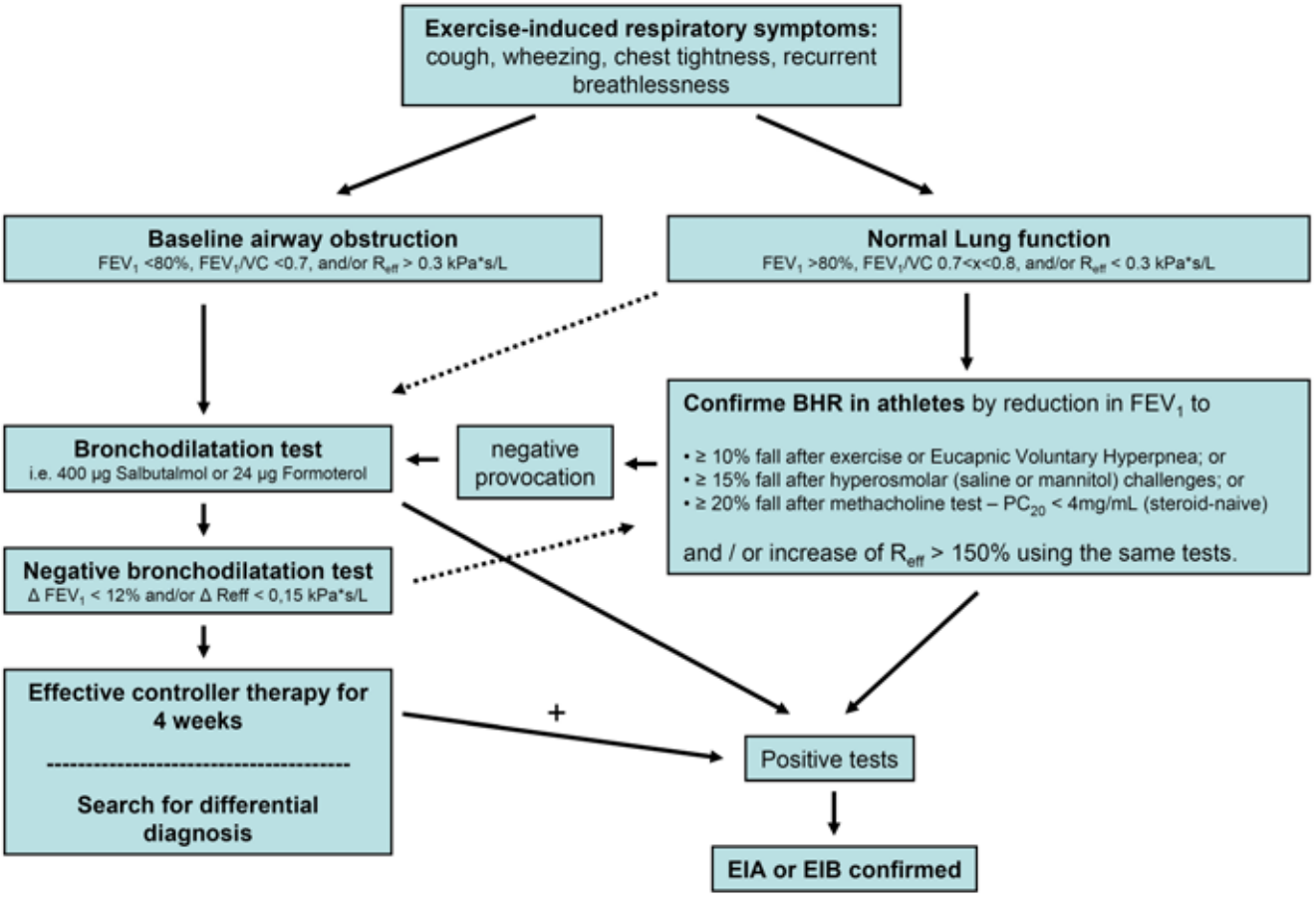

Figure 1: Chart flow for diagnosis of exercise-induced bronchoconstriction (adapted from Fitsch et al., 2008). FEV_1 = forced exspiratory volumen after one second, VC = Vital capacity, R_{eff} = effective Airway resistance, dotted arrow = considered test in individual decision + = $\Delta FEV_1 > 12\%$ and/or ΔReff > 0,15 kPa*s/L to baseline.

Differential diagnosis

As described EIB symptoms typically occur shortly after (sometimes during) intensive physical exercise with expiratory dyspnoea (regular rhonchi, wheezing, cough) verified by the evidence of the reversibility of expiratory airflow obstruction or bronchial hyperreactivity confirmed by tests mentioned in Figure 1. Inhaled β_2-agonists are effective drugs for immediate inhibition of EIB (2). A failure to reduce the symptoms after ensuring a correct inhalation technique and adequate usage should direct to diagnostic considerations other than EIA or EIB. Although disorders affecting other organ systems enter into numerous differential diagnosis considerations, vocal cord dysfunction (VCD) is the most common and probably the most under diagnosed condition (8,24,25,26). Here an abnormal adduction of the vocal cords leads to inspiratory airflow obstructions at the level of the larynx. VCD should be considered in subjects with inspiratory problems and / or stridor, an acute beginning of the respiratory problems (during (heavy) exercise) and a poor response to inhalative drugs; however, the definitive diagnosis can be made by direct rhinolaryngoscopy.

From an athlete's point of view, lack of success in sports may also often be explained by minor respiratory complaints which are mistaken for asthma. Poor physical fitness or overtraining may represent possible differential diagnoses to EIA. This should especially be considered when the physical fitness and exercise performance are not up to the expectations of the athletes, trainers or parents (6,24). Among these two main differential diagnoses, several other differential diagnoses, such as exercise-induced arterial hypoxaemia and / or hyperventilation exist. It is therefore important for the diagnosis of EIA / EIB to perform a thorough examination, apparative examinations and to rule out other common differential diagnoses.

TREATMENT

EIA / EIB in athletes should be treated according to the same principles as in patients with asthma bronchiale. Adequate warm-up helps to reduce EIB (10,22,23) and inhaled corticosteroids (and / or leucotrienreceptorantagonist) are useful drugs for long term control and prevention (2,3,12,27). Supplementary, inhaled β_2-agonists are effective drugs for immediate inhibition of EIB (2). It should be emphasized that the overuse of short and long acting bronchodilators (ß$_2$-agonists) leads to tolerance and may have significant detrimental effects on health (17,24). Since 2012 all ß$_2$-agonists are prohibited for competitive athletes except salbutamol (maximum 1600 µg over 24 h), formoterol (maximum 36 µg over 24 h) and salmeterol when taken by inhalation (31). All ß$_2$-agonists (e.g. terbutaline, procaterol) not mentioned as exceptions above are prohibited and require a Therapeutic Use Exemption (TUE), with exception of clenbuterol, which is generally forbidden (31,30).

STATEMENT OF INTEREST

Dr. Sorichter receiving payment for service on an advisory board of MSD and lecture fees from AstraZeneca, Bayer, Boehringer Ingelheim, Chiesi Pharmaceuticals, GlaxoSmithKline, Lilly, Novartis, Nycomed, Talecris Biotherapeutics.

LITERATURE

1. **Adams F:** The extant works of Aretaeus the Cappadocian.The Sydenham Society, London, 1856.
2. **Anderson SD:** Single-dose agents in the prevention of exercise-induced asthma: a descriptive review. Treat Respir Med 3 (2004) 365-379. doi:10.2165/00151829-200403060-00004.
3. **Anderson SD:** How does exercise cause asthma attacks? Curr Opin Allergy Clin Immunol 6 (2006) 37-42. doi:10.1097/01.all.0000199797.02423.78.
4. **Anderson SD, Charlton B, Weiler JM, Nichols S, Spector SL, Pearlman DS:** Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. Respir Res 10 (2009) 4. doi:10.1186/1465-9921-10-4.
5. **Carlsen KH:** The breathless adolescent asthmatic athlete. Eur Respir J 38 (2011) 713-720. doi:10.1183/09031936.00068510.
6. **Carlsen KH, Anderson SD, Bjermer L, Bonini S, Brusasco V, Canonica W, Cummiskey J, Delgado L, Del Giacco SR, Drobnic F, Haahtela T, Larsson K, Palange P, Popov T, Van Cauwenberge P:** Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA2LEN. Allergy 63 (2008) 387-403. doi:10.1111/j.1398-9995.2008.01662.x.
7. **Carlsen KH, Anderson SD, Bjermer L, Bonini S, Brusasco V, Canonica W, Cummiskey J, Delgado L, Del Giacco SR, Drobnic F, Haahtela T, Larsson K, Palange P, Popov T, van Cauwenberge P:** Treatment of exercise-induced asthma, respiratory and allergic disorders in sports and the relationship to doping: Part II of the report from the Joint Task Force of European Respiratory Society (ERS) and European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA(2) LEN. Allergy 63 (2008) 492-505. doi:10.1111/j.1398-9995.2008.01663.x.
8. **Christensen PM, Thomsen SF, Rasmussen N, Backer V:** Exercise-induced laryngeal obstructions: prevalence and symptoms in the general public. Eur Arch Otorhinolaryngol 268 (2011) 1313-1319. doi:10.1007/s00405-011-1612-0.
9. **Criee CP, Sorichter S, Smith HJ, Kardos P, Merget R, Heise D, Berdel D, Köhler D, Magnussen H, Marek W, Mitfessel H, Rasche K, Rolke M, Worth H, Jörres RA:** Body plethysmography--its principles and clinical use. Respir Med 105 (2011) 959-971. doi:10.1016/j.rmed.2011.02.006.
10. **De BC, Guenard H, Desnot P, Vergeret J:** Reduction of exercise-induced asthma in children by short, repeated warm ups. Br J Sports Med 33 (1999) 100-104. doi:10.1136/bjsm.33.2.100.
11. **Dickinson JW, Whyte GP, McConnell AK, Harries MG:** Impact of changes in the IOC-MC asthma criteria: a British perspective. Thorax 60 (2005) 629-632. doi:10.1136/thx.2004.037499.
12. **Duong M, Subbarao P, Adelroth E, Obminski G, Strinich T, Inman M, Pedersen S, O'Byrne PM:** Sputum eosinophils and the response of exercise-induced bronchoconstriction to corticosteroid in asthma. Chest 133 (2008) 404-411. doi:10.1378/chest.07-2048.
13. **Fitch KD, Sue-Chu M, Anderson SD, Boulet LP, Hancox RJ, McKenzie DC, Backer V, Rundell KW, Alonso JM, Kippelen P, Cummiskey JM, Garnier A, Ljungqvist A:** Asthma and the elite athlete: summary of the International Olympic Committee's consensus conference, Lausanne, Switzerland, January 22-24, 2008. J Allergy Clin Immunol 122 (2008) 254-260.
14. **Haahtela T, Malmberg P, Moreira A:** Mechanisms of asthma in Olympic athletes--practical implications. Allergy 63 (2008) 685-694. doi:10.1111/j.1398-9995.2008.01686.x.
15. **Helenius I, Lumme A, Haahtela T:** Asthma, airway inflammation and treatment in elite athletes. Sports Med 35 (2005) 565-574. doi:10.2165/00007256-200535070-00002.
16. **Holzer K, Anderson SD, Douglass J:** Exercise in elite summer athletes: Challenges for diagnosis. J Allergy Clin Immunol 110 (2002) 374-380. doi:10.1067/mai.2002.127784.
17. **Elers J, Strandbygaard U, Pedersen L. Backer, V:** Daily Use of Salmeterol Causes Tolerance to Bronchodilation with Terbutaline in Asthmatic Subjects. The Open Respiratory Medicine Journal 4 (2010) 48-50. doi:10.2174/1874306401004010048.
18. **Joos GF, O'Connor B, Anderson SD, Chung F, Cockcroft DW, Dahlén B, DiMaria G, Foresi A, Hargreave FE, Holgate ST, Inman M, Lötvall J, Magnussen H, Polosa R, Postma DS, Riedler J:** Indirect airway challenges. Eur Respir J 21 (2003) 1050-1068. doi:10.1183/09031936.03.00008403.
19. **Langdeau JB, Turcotte H, Bowie DM, Jobin J, Desgagne P, Boulet LP:** Airway hyperresponsiveness in elite athletes. Am J Respir Crit Care Med 161 (2000) 1479-1484.
20. **Lodrup Carlsen KC, Haland G, Devulapalli CS, Munthe-Kaas M, Pettersen M, Granum B, Løvik M, Carlsen KH:** Asthma in every fifth child in Oslo, Norway: a 10-year follow up of a birth cohort study. Allergy 61 (2006) 454-460. doi:10.1111/j.1398-9995.2005.00938.x.
21. **McFadden ER Jr, Nelson JA, Skowronski ME, Lenner KA:** Thermally induced asthma and airway drying. Am J Respir Crit Care Med 160 (1999) 221-226.
22. **McKenzie DC, McLuckie SL, Stirling DR:** The protective effects of continuous and interval exercise in athletes with exercise-induced asthma. Med Sci Sports Exerc 26 (1994) 951-956. doi:10.1249/00005768-199408000-00004.
23. **Mickleborough TD, Lindley MR, Turner LA:** Comparative effects of a high-intensity interval warm-up and salbutamol on the bronchoconstrictor response to exercise in asthmatic athletes. Int J Sports Med 28 (2007) 456-462. doi:10.1055/s-2006-924583.
24. **Milgrom H:** Exercise-induced asthma: ways to wise exercise. Curr Opin Allergy Clin Immunol 4 (2004) 147-153. doi:10.1097/00130832-200406000-00002.
25. **Pedersen L, Elers J, Backer V:** Asthma in elite athletes: pathogenesis, diagnosis, differential diagnoses, and treatment. Phys Sportsmed 39 (2011) 163-171. doi:10.3810/psm.2011.09.1932.
26. **Rundell KW, Spiering BA:** Inspiratory stridor in elite athletes. Chest 123 (2003) 468-474. doi:10.1378/chest.123.2.468.
27. **Rundell KW, Spiering BA, Baumann JM, Evans TM:** Effects of montelukast on airway narrowing from eucapnic voluntary hyperventilation and cold air exercise. Br J Sports Med 39 (2005) 232-236. doi:10.1136/bjsm.2004.014282.
28. **Walterspacher S, Friedmann-Bette B, Sorichter S:** Belastungsuntersuchungen in der Pneumologie. Pneumologe 8 (2011) 98-104. doi:10.1007/s10405-010-0452-8.
29. **Storms WW:** Asthma associated with exercise. Immunol Allergy Clin North Am 25 (2005) 31-43. doi:10.1016/j.iac.2004.09.007.
30. **unkown:** The World Anti-Doping Code THE 2012 PROHIBITED LIST INTERNATIONAL STANDARD, www.wada-ama.org, 2012.
31. **unkown:** Medical Information to Support the Decisions of TUEC Asthma, www.wada-ama.org,Version 4 Dec 2011.
32. **Weiler JM, Bonini S, Coifman R, Craig T, Delgado L, Capão-Filipe M, Passali D, Randolph C, Storms W:** American Academy of Allergy, Asthma & Immunology Work Group report: exercise-induced asthma. J Allergy Clin Immunol 119 (2007) 1349-1358. doi:10.1016/j.jaci.2007.02.041.

Correspondence:
Prof. Dr. med. Stephan Sorichter
University Hospital Freiburg
Division of Pneumology
Killianstr. 5
79102 Freiburg
E-Mail: stephan.sorichter@uniklinik-freiburg.de