Tackling nasal symptoms in athletes: moving towards personalized medicine

Valerie Hox[1], Simon Beyaert[1], Dominique Bullens[2], Mariana Couto[3], Daniel Langer[2], Peter Helllings[4], Caroline Huart[1], Philippe Rombaux[1], Sven Seys[2], Pavol Surda[5], Abigail Walker[6], and Brecht Steelant[2]

[1]Cliniques universitaires Saint-Luc
[2]KU Leuven
[3]Hospital & Instituto CUF Porto
[4]University Hospitals Leuven
[5]Guy's and St Thomas' University Hospital
[6]St-George Hospital, London, UK

October 2, 2020

Abstract

Adequate nasal breathing is indispensable for athletes and nasal symptoms have been shown to inter-fere with their subjective feeling of comfortable breathing and quality of life. Nasal symptoms are caused by either structural abnormalities or mucosal pathology. Structural pathologies are managed differently from mucosal disease and therefore adequate diagnosis is of utmost importance in athletes in order to choose the correct treatment option for the individual. Literature suggests that nasal symptoms are more prevalent in athletes compared to the general population and certain sport environments might even trigger the development of symptoms. Given the high demands of respiratory function in athletes, insight into triggering factors is of high importance for disease prevention. Also, it has been suggested that athletes are more neglectful to their symptoms and hence remain undertreated, meaning that special attention should be paid to education of athletes and their caregivers. This review aims at giving an overview of nasal physiology in exercise as well as the possible types of nasal pathology. Additionally, diagnostic and treatment options are discussed and we focus on un-met needs for the management and prevention of these symptoms in athletes within the concept of precision medicine.

Main Text:

1. Introduction

For elite athletes an optimal health state is indispensable in order to deliver their best athletic performances. Athletes who undertake intense aerobic exercise meet metabolic demands by significantly increasing minute ventilation, making the airways one of their most important organ systems. The link between strenuous exercise and asthma has been a long-standing source of research and debate, but more recently, interest in the upper airways of athletes has gained more attention. Although it has been demonstrated that the nasal airway contributes only for 10 % of minute ventilation at maximal exercise intensity [1], the nose plays an important role in respiratory physiology due to its position at the entry of the airways. The most important functions of the nasal mucosa is to humidify and heat up the inhaled air, however, it is also the first barrier to encounter and respond to environmental particles such as allergens, pathogens or irritants [2].

Athletes seem to suffer more frequently from nasal symptoms compared to the non-sporting population [3] and some data in literature suggest that factors related to the excessive ventilation and/or environmental

exposures might be a causal factor for upper airway dysfunction [4, 5].

Up till now, very little data exists on the difficulties that may arise while choosing the adequate treatment strategy for this patient group that presents with specific demands related to their occupation.

The aim of this review is to give an overview on what is currently known on the relevance and causes of the different types of nasal dysfunction in athletes. Additionally, the different treatment options with their place within the anti-doping regulations as well as the open questions and unmet needs for the management of this patient group are discussed with an outlook towards further research necessities.

2. Role of sinonasal disease on wellbeing and performances in athletes

Thanks to filtration, humidification and heating of the inhaled air, nasal breathing is more comfortable than oral breathing and human beings are innate nose breathers at rest. The nasal septum and turbinates that are responsible for these functions, create a high-resistance airway passage inside the nose. During exercise, this resistance leads to an increased breathing effort sensation and when this sensation becomes too uncomfortable, the individual will switch from nasal to oral breathing[6]. Time points at which this occurs are very variable among subjects, but it is believed to occur when laminar nasal airflow becomes turbulent [7]. Oral breathing has been shown to be more efficient than nasal breathing [8] which means that blocking the nose does not form a limiting factor when looking at objective exercise parameters such as VO_2max[9]. Notwithstanding, multiple studies have shown a clear impact of nasal symptoms on patients' quality of life (QOL)[10-12] and consequently on athletic performances; Katelaris surveyed 214 Olympic athletes and found that 41 % suffered from a seasonal allergic rhinitis (AR) with significantly lower QOL scores than non-allergic athletes, which improved as the pollen count declined [13]. Walker recently published that QOL related to nasal symptoms (measured by the SNOT-22 questionnaire) was significantly reduced in athletes compared to sedentary controls[3] and lower in athletes suffering from nasal symptoms compared to healthy athletes [14]. Surda demonstrated that this effect was greatest in swimmers (measured by the rhinoconjunctivitis quality of life questionnaire [RQLQ])[15]. The reduced RQLQ results in swimmers were confirmed by Bougault who even showed a normalization of nasal symptoms and QOL after a 2-week resting period [4]. Nasal dysfunction has also been associated with a direct reduction in athletic performances; a recent German study questioning over 600 athletes demonstrated that more than 80 % of athletes suffering from AR reported a decrease in athletic performance during the pollen season[16]. Another study questioned recreational athletes suffering from exercise-induced rhinitis and found that around 45 % of these individuals stated their nasal symptoms adversely affected their athletic performances in a moderate or severe way [17]. Since rhinitis has a known detrimental effect on sleep quality[18], it can be extrapolated that it indirectly leads to competitive defeats [19].

Types and prevalence of nasal dysfunction in athletes

Nasal dysfunction can arise from either mucosal dysfunction or deformity of the anatomical structures (Figure 1). Mucosal dysfunction can be induced by multiple factors and can either present as rhinitis which causes symptoms of nasal obstruction, rhinorrhea, nasal itch and sneezing [20], while rhinosinusitis patients have additional symptoms of facial pain and smell loss. [21].

3.1 Infectious rhinitis

Viral rhinitis or 'common cold' is one of the most common diseases worldwide and it was the principal reason for athletes to consult a doctor during both the Summer and Winter Olympic Games of 2000-2002[22, 23]. Interestingly, elite athletes suffer more frequently from commons colds compared to recreational athletes[24] and they were more common in athletes with pre-existing nasal symptoms [3]. Data suggests that long-distance running increases the likelihood of having a common cold during heavy training or in the period following a marathon[24-28]. These findings imply a potential link between acute physical stress and susceptibility to upper respiratory tract infection. An exercise-induced decrease in immunoglobulin (Ig)A secretion is the most commonly reported explanation, although a study from Peters failed to show this link [28]. Other mechanisms that have been suggested are a decreased NK-cell activity and/or lymphocyte proliferative response after strenuous exercise[29], but clear evidence is lacking. Also, it should be noted

that in 30-40 % of studied cases no pathogen could be identified[2], so the infectious component might be overestimated and other causes might lay at the base of the nasal dysfunction.

3.2 Allergic rhinitis

Allergic inflammation is the most common cause of chronic rhinitis and responsible for inducing nasal symptoms after allergen exposure in a sensitized individual through an IgE-induced pathway[30]. A recent systematic review mentions a prevalence of AR in athletes ranging from 21 to 56.5 % [31] which is comparable to the prevalence in the general population. When looking at specific sports populations however, aquatic athletes seem to suffer more frequently from AR compared to land-based athletes[32]. This might be explained by the fact that chlorination products might predispose to allergic sensitization[33], however, this could not be confirmed by *in vivo* [34] nor *in vitro* [5]studies. It has been suggested that strenuous exercise may contribute to the development of allergic sensitization after showing a potential shift of the T-lymphocyte population towards a T helper 2 subtype upon excessive exercise [35, 36]. To our knowledge, no study has demonstrated a causal relationship between exercise and allergic sensitization.

3.3 Non-allergic and mixed rhinitis

Non-allergic rhinitis (NAR) is defined as a chronic rhinitis in the absence of infection or systemic allergen-specific IgE and comprises a very heterogenous patient group [37]. In everyday life, an overlap between AR and NAR is very frequently seen and addressed as mixed rhinitis. So far, reliable data on the occurrence of NAR in the athlete population is scarce but studies reporting on mixed rhinitis show a prevalence as high as 74 % in athletes [31].

Within all sports disciplines NAR is again most frequently reported in aquatic athletes, possibly due to exposures to pool chlorination products. Several studies showed a significantly higher prevalence of NAR in swimmers compared to non-swimming athletes and controls[3]. Gelardi and colleagues showed that within a population of swimmers with rhinitis, 76 % had NAR of whom 35% presented with a neutrophilic nasal inflammation [38]. Another study confirmed this neutrophilic nasal influx in swimmers, in combination with an increased MCT compared to controls[38, 39]. A recent study showed an increase of neuropeptides and epithelial injury markers in nasal secretions of swimmers after training, suggesting a direct irritant effect on the airway mucosa of the chlorination products, which has also been shown in a mouse model of chlorine-induced airway hyperreactivity[34]. Also air pollution might induce non-allergic dysfunction: the nasal mucociliary clearance time (MCT) was prolonged in runners who ran in polluted streets when compared to running in the woods [40], although the inflammatory response to exposure to pollutants seems more mitigated in athletes compared to sedentary controls [41].

3.4 Exercise-induced rhinitis

It has been postulated that laborious exercise has a direct negative effect on nasal functioning and can lead to "exercise-induced rhinitis". In healthy individuals, exercise promotes a decrease in nasal airway resistance due to an increased sympathetic tone upon a rise in the arterial pCO2 [42], however, in patients suffering from pre-existing rhinitis, isometric exercise induces conversely an increase in nasal resistance, probably due to an abnormal neurogenic regulation of the nasal mucosa in these patients[43]. There is also data that strenuous exercise can lead to rhinitis symptoms and nasal inflammatory changes by itself. One study found a nasal neutrophil influx after a 20 km race in combination with an significantly prolonged MCT after the race [44].

3.5 Nasal hyperreactivity

Nasal hyperreactivity (NHR) which is a frequent hallmark of rhinitis, is characterized by the induction of nasal symptoms upon encounter of unspecific environmental stimuli and is believed to play an important role in athletes [45, 46]. Exposure to cold temperatures is one of the most important triggers for NHR [43, 47]and can be an issue for winter-sports athletes; This has been confirmed by Bonadonna who reported on a prevalence of almost 50 % of cold-induced rhinorrhea in over a hundred skiers, independent from their atopy state [48]. But also, exposures to pollution and chlorination products in outdoor and aquatic athletes, might induce rhinitis symptoms in those with pre-existing rhinitis with NHR, even in the absence of a direct irritant effect.

3.6 Rhinosinusitis

To our knowledge, hardly anything is known about rhinosinusitis in athletes. Gelardi mentions in his study that 3 % of swimmers had an acute rhinosinusitis [38] and one other study describes sinonasal mucosal hypertrophy in divers, possibly due to pressure differences [49]. However, to our knowledge, no study has investigated the presence of chronic rhinosinusitis (CRS) in the athletic population, although this lies within the line of expectation since infection and atopy are considered to be risk factors for the development of CRS [21].

3.7 Structural pathology

Not all nasal symptoms are due to mucosal pathology and structural abnormality of the nasal septum, pyramid or tip, is one of the most common reasons for nasal obstruction [50] and might be congenital or acquired. In these patients, nasal airway resistance is increased, which can lead to reduced or uncomfortable nasal breathing[51]. In certain contact sports, nasal trauma is a frequent complication that can potentially lead to structural pathology. This was confirmed by Passali who demonstrated in seventeen boxers a significantly higher nasal resistance, compared to the normal population reference values [52]. Other studies that support the importance of structural pathology in exercise are the studies that show a beneficial subjective effect of nasal dilators that decrease the nasal resistance and are discussed below.

4. Diagnosis

Diagnosis starts with taking a thorough history about symptoms, sport environment and a possible link between these two. Questions about triggering factors or symptom improvement after a resting break or treatment are useful. Clinical examination should include both evaluation of the external and internal nose. The general aspect of the nasal mucosa, the nasal septum and the nasal valve can be appreciated with anterior rhinoscopy. Nasal endoscopy offers the advantage of a global evaluation of the nasal cavity and sinus outflow tracts[53]. Examination of the external nasal pyramid and tip with valve tests will give information about important structural abnormalities, nasal valve dysfunction and alar collapse.[54].

Technical exams such as anterior rhinomanometry, acoustic rhinometry and peak nasal inspiratory flow (PNIF) measurements and can be used to objectify reported nasal blockage and measure nasal resistance[55]. However, these objective measurements do not always correspond well with symptoms of nasal obstruction and results should always be correlated with subjective parameters.

Every athlete with airway symptoms should be screened for allergies as a causal factor of rhinitis. The validated AQUA questionnaire is often used as a screening tool to identify athletes with allergic disease (specificity 97.1%, sensitivity 58.3% when score > 5)[56, 57]. However, the final diagnosis of AR is based upon a correlation between the typical history and the systemic detection of allergen-specific IgE, either by skin prick test (SPT) or in the serum [58]. When a mismatch exists between symptoms and systemic IgE detection, a specific nasal allergen challenge can be considered [59]. Nasal cold dry air challenge can objectify the presence of NHR [47]. Unlike exercise-induced bronchoconstriction (EIB), no specific test is currently available to diagnose exercise-induced rhinitis which is consequently solely based on self-reporting.

Treatment options

Different types of nasal pathology in athletes should be treated according to the respective guidelines [20, 21, 60]. However, due to the World Anti-Doping Agency (WADA) regulations[61], athletes ought to adhere to strict regulations in terms of pharmacological treatment. Treatment differs between mucosal and structural pathology and options are summarized in table 1.

5.1 Treatment of mucosal pathology

5.1.1 Trigger avoidance

A very safe, cheap and adequate treatment option is the avoidance of triggering agents [62]. For AR patients, this means allergen avoidance, but for all athletes suffering from NHR, exposure to unspecific triggers such

as airway irritants, pollution and cold temperatures should be circumvented whenever possible. For some athletes this may be hard to accomplish; winter sport athletes cannot avoid exposure to cold temperatures and outdoor athletes will always be exposed to pollens and/or pollution. Also, for swimmers, exposure to chlorination products is basically unavoidable. In indoor pools, trichloramine is the chlorination byproduct that is most closely related with respiratory symptoms [63, 64] and the WHO regulations demand a maximum level of 0.5 mg/m^{3}trichloramine in the air of indoor swimming pools [65]. Yet, in most countries regular monitoring of swimming pool water and air is rarely performed.

5.1.2. Saline douches:

Nasal douching is cheap and safe, and an important part of the management of both rhinitis and rhinosinusitis that do not interfere with the WADA regulations. Especially in symptomatic athletes exposed to irritants (swimmers, runners in polluted areas) this is a valuable option. Since the WHO recommends to shower and clean off the chlorine after exposure to a chlorinated swimming pool [65], it seems logical to clean the nasal mucosa after swimming, although no data are available on the action of nasal saline douchings in rhinitis prevention.

5.1.3. Decongestants

Short-course treatment with nasal or oral decongestant can be beneficial in treating a common cold but should be limited to a maximum of 7 days. WADA allows some decongestants (caffeine, phenylephrine, phenylpropanolamine, adrenaline, xylometazoline and synephrine) and restricts others to a certain dose ((methyl)ephedrine $<$ 10 µg /ml and Pseudoephedrine $<$ 150 µg /ml in urine). Most other decongestants, especially those containing sympathomimetic amines or stimulants are currently prohibited by the WADA [61]; The list of prohibited drugs changes annually, so physicians should verify when prescribing these products to athletes. Moreover, the use of oral decongestants can lead to a series of side effects such as tachycardia, tremor, insomnia, elevated heart rate and blood pressure, which can be problematic for athletes. Unfortunately, in many countries these drugs are available on an over-the-counter base and therefore athletes need to be counseled about the actual prohibited substances.

Decongestants do not have a part in the treatment of AR, NAR or CRS because of the risk of inducing rhinitis medicamentosa, a decongestant-induced paradoxical swelling of the nasal mucosa.

5.1.4. Glucocorticosteroids

Intranasal steroids (INS) as a maintenance treatment are the first therapy of choice in moderate/severe and persistent AR, CRS and most forms of NAR [20, 21, 60]. In athletes specifically, they have shown to reduce symptoms and improve QOL significantly for AR[66]. Furthermore, they are known to have a beneficial effect on asthma symptoms [20]. Interestingly, the use of INS has been reported to revert the paradoxical increase in nasal resistance upon isometric exercise which is seen in NAR[43] and might therefore be the ideal treatment for athletes with NAR and/or exercise-induced rhinitis.

The use of INS is presently permitted by WADA without a therapeutic use exemption (TUE) [61]. However, literature suggests that athletes may not be fully aware of those regulations since several studies show that athletes with rhinitis are much less adherent to their INS compared to non-athletes; Surda showed that chronic nasal medication was significantly less taken by elite swimmers with nasal symptoms (18 %) compared to symptomatic non-sporting controls (67 %)[3] and Walker showed that elite hockey players were much less adherent to their INS compared to non-elite players and sedentary controls [14]. Adverse effects of INS include minor epistaxis, crusting, nasal dryness and irritation of the throat and nose, however, most of these side-effects are transient and rarely require stopping INS treatment, even on a long-term base.

It is worthwhile mentioning that WADA allows physicians to treat severe AR with systemic glucocorticosteroids under the TUE rule. However, in view of the possible side effects, indications for treating AR with oral or depot steroids are extremely rare and preserved for uncontrolled AR with severe symptoms not responding to any other medical therapy including allergen immunotherapy [67].

5.1.5. Antihistamines

Antihistamines are a first-line treatment for athletes suffering from AR and are currently allowed by the WADA regulations [61]. They are very effective for treating histamine-induced symptoms such as rhinorrhea, sneezing and itch, but are somewhat less effective on nasal obstruction [68] and therefore often combined with INS. Surprisingly, two RCTs have also shown a beneficial effect of topical azelastine in NAR patients [69, 70], probably due to secondary effects on neuropeptide release. In most countries, a combination formulation of intranasal azelastine with the INS fluticasone proprionate (MP-029) is available and has been shown to be effective in reducing symptoms in a population of both AR and NAR patients [71] with a specific reduction of NHR in AR patients [72].

The above-mentioned study by Walker however, has shown that antihistamines were rarely used by elite hockey players when compared to recreational players or non-sporting controls [14]. It was believed to be due to the athletes' fear of side effects of these kind of drugs or misperception of WADA regulations. Nonetheless, it is well-known that second-generation antihistamines are much less sedative than older antihistamines and cardial arythmias are only seen with overdosing [73, 74]. Topical antihistamines have no side effects but the disadvantage of shorter duration of activity[20].

5.1.6. Cromoglycates

Cromolyns are mast cell stabilizers that can be used intranasally. They are moderately effective in treating mast-cell related nasal symptoms (itch, rhinorrhea, sneezing) [20] but inferior to antihistamines. Despite their short half-life and duration of activity, they show a very good safety profile and are at the moment authorized by the WADA's regulation [61].

5.1.7. Antileukotrienes

Leukotriene receptor antagonists block the functions of leukotrienes on the local environment and have been shown to have an efficacy in AR patients comparable to antihistamines [20] and might be an added value in athletes suffering from AR with concomitant asthma[75]. In contrast to antihistamines, they do not cause sedation and they are currently also permitted by the WADA regulation[61].

5.1.8. Allergen Immunotherapy

Allergen immunotherapy (AIT) is the only disease-modifying treatment option for athletes suffering from AR, because of its capability to induce immune tolerance leading to long term disease control[76]. Multiple studies have proven that AIT is effective in reducing symptoms and rescue medication, as well as in improving QOL in AR patients [76]. AIT is administered either subcutaneously (SCIT) or in a sublingual way (SLIT) with SCIT being slightly more effective but SLIT showing a better safety profile. Both types are permitted by the WADA regulations [61]. SCIT usually precludes performing exercise on the administration day, which should be a factor to be considered in athletes.

A recent questionnaire-based study in athletes with AR, has indicated that AIT had the most beneficial effect on AR symptoms with better outcomes than classical pharmacological treatments [16]. Despite these positive AIT results, a post-hoc analysis showed that the majority of athletes were not aware or had misbeliefs about this treatment option.

Practically, it is recommended to start AIT a few months before the competitive season because the initial phase can be accompanied with local or systemic side effects, more so for SCIT than fore SLIT.

5.2. Treatment of structural pathology

5.2.1. Nasal dilators

Nasal dilators can be either fixed on the nasal dorsum or introduced in the nostrils, in order to open up the nasal valve region and reduce airflow resistance at this highly resistant area. These dilators are an elegant, non-surgical solution for alar insufficiency, leading to an important increase of nasal flow and good patient satisfaction[77]. Dinardi recently reviewed the effects of external nasal dilators on physical exercise [78] and one

ohter study looked at an internal dilator [79]. Although most of the studies fail to demonstrate an effect on total VO_2max, heart rate or total exercise time[78], nasal dilators significantly improved subjective exertion rates [80] and nasal breathing[81] during exercise. It needs to be noted that most of these studies were performed in asymptomatic athletes. Only one study found similar results in adolescents with AR using an external nasal dilator [82], but none of these studies reported on nasal structural or rhinoscopic findings in the subjects.

5.2.2. Surgery

Nasal surgery can be a treatment option for medically resistant nasal obstruction due to structural pathology at the level of the nasal bones or cartilage.

Septoplasty is the most commonly performed surgical ENT intervention in adults; however, due to a lack of controlled trials, clear evidence on its effectiveness is currently lacking [83]. One of the possible reasons for septoplasty failure could be an unaddressed nasal valve insufficiency. In this case, septorhinoplasty could bring a solution, although also for this type of intervention, evidence on functional benefit is mostly lacking. Endoscopic sinus surgery is indicated in CRS patients who fail to respond to maximal medical therapy[21].

To our knowledge, a part from one study showing a benefit of early reduction of sports-induced nasal fracture [84], no studies are available on the benefit of nasal surgery in athletes. As is the case for the general population, the key factor is to make the correct surgical indication and mucosal pathology should be excluded and/or treated before deciding on surgical intervention.

6. Recommendations and unmet needs for the application of personalized medicine.

Due to a lack of knowledge and attention for the impact of nasal symptoms on athletic performances, several unmet needs persist for treating athletes [56, 85]. It is clear that more well-designed studies are needed that target this specific patient population in order to gain more insights in disease mechanistic as well as in specific diagnostic and treatment options for their nasal pathology.

To optimize their current management, we suggest to follow the concept of precision-based medicine, which is based on the 4 P's: prediction, prevention, personalization and participation [86].

Prediction: Sports-specific factors may predispose athletes to develop nasal disease and when dealing with (ultra-)endurance athletes and outdoor or aquatic athletes and awareness for nasal symptoms should be increased. Some athletes will be bothered more by nasal symptoms than others and questionnaires such as NOSE and RQLQ (rhinitis) or SNOT-22 (rhinosinusitis) can be helpful tools in assessing QOL impact. Predicting and identifying these athletes can lead to early intervention and possible improvement of their accomplishments.

For outdoor athletes diagnosed with a seasonal AR, symptomatology can be predicted according to the respective pollen seasons and should be anticipated with appropriated preventive measurements and if indicated, pharmacological therapy or ideally, AIT.

Because both rhinitis and rhinosinusitis are risks factors for developing asthma [87], symptomatic athletes should always be questioned for lower airway symptoms. In case of positive history, spirometry and/or bronchial provocation testing are indicated.

Prevention: Because of the potential negative impact of environmental irritants on nasal function, limiting these exposures to a minimum may prevent symptom development. For aquatic athletes this means monitoring and, if necessary, adapting the levels of chlorination products in the training pool. Ideally, training occurs in swimming pools that use alternative methods of disinfection such as ozone or cupper-silver ionization. The use of a nose clip in this matter can be debated and will depend largely on the preference of the swimmer. For non-aquatic sports, training in a polluted environment should be avoided at all cost.

Warm-up exercises have shown to decrease symptoms in EIB patients[88] and might be useful for patients suffering from exercise-induced rhinitis. However, this has not been investigated and should be a topic of

future studies, as is the possible therapeutic option of pre-exercise nasal douching in order to prevent possible mucosal dehydration by hyperventilation.

Personalization: The most important topic within the concept of precision-based medicine is the attempt to deliver personalized care to the patient. Therefore, a correct diagnosis of the nasal dysfunction is essential and the patient should be treated according to the respective guidelines. For athletes suffering from mucosal disease, the sport-specific environment should be maximally optimized and if necessary, pharmacological therapy administered. If the athlete suffers from AR and fits the criteria for AIT, this is the preferred therapy[16]. For those presenting with a structural pathology, nasal surgery might be the treatment of choice and nasal valve surgery might be preserved for those with a subjective effect of an external or internal nasal dilator during a sport-specific test.

Participation: Athletes are a challenging patient population with regards to therapeutic adherence; in a recent German study, only less than half of athletes suffering from AR used a treatment for this condition. This percentage was even lower in the elite and semi-elite athletes (34.8% and 30.2% respectively) [16]. Also, the majority of subjects had concerns about pharmacological treatment options and feared side effects, negative impact on sports performance and lack of long-term effects [16]. These findings emphasize the need of patient education about their disease, the potential impact on his/her performance, possible preventive measurements and especially the available pharmacological therapies including side-effects and how they fit within the WADA regulations. Disease-specific smartphone applications delivering patient education and following symptoms might be useful within this regard[89]. Not only athletes, but also their health care providers should be informed about anti-doping regulations and the fact that prohibited drugs are published annually by WADA.

7. Conclusion

Regarding the obvious importance of adequate breathing for athletes, a lot of attention has been paid to lower airway symptoms in this population. Because of the minor effects of improving nasal patency on objective physiological exercise parameters, nasal symptoms are often overlooked in athletes However, in addition to the well-known impact of nasal symptoms on QOL in general, subjective exercise parameters such as exertion perception and breathing comfort are affected by nasal dysfunction. Therefore, we plead for an increased awareness for nasal symptoms in the athletic population in order to improve early diagnosis and provide precision-based treatment options to athletes suffering from nasal dysfunction.

References

1. Katz RM. Rhinitis in the athlete. J Allergy Clin Immunol. 1984;73(5 Pt 2):708-11.

2. Spence L, Brown WJ, Pyne DB, Nissen MD, Sloots TP, McCormack JG, et al. Incidence, etiology, and symptomatology of upper respiratory illness in elite athletes. Medicine and science in sports and exercise. 2007;39(4):577-86.

3. Walker AC, Surda P, Rossiter M, Little SA. Nasal disease and quality of life in athletes. J Laryngol Otol. 2018;132(9):812-5.

4. Bougault V, Turmel J, Boulet LP. Effect of intense swimming training on rhinitis in high-level competitive swimmers. ClinExpAllergy. 2010;40(8):1238-46.

5. Steelant B, Hox V, Van Gerven L, Dilissen E, Dekimpe E, Kasran A, et al. Nasal symptoms, epithelial injury and neurogenic inflammation in elite swimmers. Rhinology. 2018;56(3):279-87.

6. Classifying recommendations for clinical practice guidelines. Pediatrics. 2004;114(3):874-7.

7. Wang de Y, Lee HP, Gordon BR. Impacts of fluid dynamics simulation in study of nasal airflow physiology and pathophysiology in realistic human three-dimensional nose models. Clinical and experimental otorhinolaryngology. 2012;5(4):181-7.

8. Recinto C, Efthemeou T, Boffelli PT, Navalta JW. Effects of Nasal or Oral Breathing on Anaerobic Power Output and Metabolic Responses. International journal of exercise science. 2017;10(4):506-14.

9. Meir R, Zhao GG, Zhou S, Beavers R, Davie A. The acute effect of mouth only breathing on time to completion, heart rate, rate of perceived exertion, blood lactate, and ventilatory measures during a high-intensity shuttle run sequence. Journal of strength and conditioning research. 2014;28(4):950-7.

10. Campbell AP, Hoehle LP, Phillips KM, Caradonna DS, Gray ST, Sedaghat AR. Depressed mood is associated with loss of productivity in allergic rhinitis. Allergy. 2018;73(5):1141-4.

11. Canonica GW, Mullol J, Pradalier A, Didier A. Patient perceptions of allergic rhinitis and quality of life: findings from a survey conducted in europe and the United States. The World Allergy Organization journal. 2008;1(9):138-44.

12. Khan A, Huynh TMT, Vandeplas G, Joish VN, Mannent LP, Tomassen P, et al. The GALEN rhinosinusitis cohort: chronic rhinosinusitis with nasal polyps affects health-related quality of life. Rhinology. 2019;57(5):343-51.

13. Katelaris CH, Carrozzi FM, Burke TV, Byth K. A springtime olympics demands special consideration for allergic athletes. J Allergy Clin Immunol. 2000;106(2):260-6.

14. Walker A, Surda P, Rossiter M, Little S. Rhinitis in Elite and Non-Elite Field Hockey Players. International journal of sports medicine. 2017;38(1):65-70.

15. Surda P, Putala M, Siarnik P, Walker A, Bernic A, Fokkens W. Rhinitis and its impact on quality of life in swimmers. Allergy. 2018;73(5):1022-31.

16. Salem L, Dao VA, Shah-Hosseini K, de Marees M, Mester J, Mosges R, et al. Impaired sports performance of athletes suffering from pollen-induced allergic rhinitis: a cross-sectional, observational survey in German athletes. The Journal of sports medicine and physical fitness. 2019;59(4):686-92.

17. Silvers WS, Poole JA. Exercise-induced rhinitis: a common disorder that adversely affects allergic and nonallergic athletes. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2006;96(2):334-40.

18. Roxbury CR, Qiu M, Shargorodsky J, Lin SY. Association between allergic rhinitis and poor sleep parameters in U.S. adults. Int Forum Allergy Rhinol. 2018;8(10):1098-106.

19. Watson AM. Sleep and Athletic Performance. Curr Sports Med Rep. 2017;16(6):413-8.

20. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008;63 Suppl 86:8-160.

21. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. Rhinology. 2012;50(1):1-12.

22. Reeser JC, Willick S, Elstad M. Medical services provided at the Olympic Village polyclinic during the 2002 Salt Lake City Winter Games. WMJ : official publication of the State Medical Society of Wisconsin. 2003;102(4):20-5.

23. Robinson SR, Wormald PJ. Endoscopic vidian neurectomy. American journal of rhinology. 2006;20(2):197-202.

24. Nieman DC, Johanssen LM, Lee JW, Arabatzis K. Infectious episodes in runners before and after the Los Angeles Marathon. The Journal of sports medicine and physical fitness. 1990;30(3):316-28.

25. Gleeson M, Pyne DB, Austin JP, Lynn Francis J, Clancy RL, McDonald WA, et al. Epstein-Barr virus reactivation and upper-respiratory illness in elite swimmers. Medicine and science in sports and exercise. 2002;34(3):411-7.

26. Makela MJ, Puhakka T, Ruuskanen O, Leinonen M, Saikku P, Kimpimaki M, et al. Viruses and bacteria in the etiology of the common cold. J Clin Microbiol. 1998;36(2):539-42.

27. Peters EM, Bateman ED. Ultramarathon running and upper respiratory tract infections. An epidemiological survey. S Afr Med J. 1983;64(15):582-4.

28. Peters EM, Shaik J, Kleinveldt N. Upper respiratory tract infection symptoms in ultramarathon runners not related to immunoglobulin status. Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine. 2010;20(1):39-46.

29. Walsh NP, Gleeson M, Shephard RJ, Gleeson M, Woods JA, Bishop NC, et al. Position statement. Part one: Immune function and exercise. Exercise immunology review. 2011;17:6-63.

30. Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. Lancet. 2011;378(9809):2112-22.

31. Surda P, Walker A, Limpens J, Fokkens W, Putala M. Nasal changes associated with exercise in athletes: systematic review. J Laryngol Otol. 2018;132(3):191-7.

32. Surda P, Walker A, Putala M, Siarnik P. Prevalence of Rhinitis in Athletes: Systematic Review. Int J Otolaryngol. 2017;2017:8098426.

33. Bernard A, Nickmilder M, Voisin C, Sardella A. Impact of chlorinated swimming pool attendance on the respiratory health of adolescents. Pediatrics. 2009;124(4):1110-8.

34. Hox V, Vanoirbeek JA, Alpizar YA, Voedisch S, Callebaut I, Bobic S, et al. Crucial role of transient receptor potential ankyrin 1 and mast cells in induction of nonallergic airway hyperreactivity in mice. Am J Respir Crit Care Med. 2013;187(5):486-93.

35. Lakier Smith L. Overtraining, excessive exercise, and altered immunity: is this a T helper-1 versus T helper-2 lymphocyte response? Sports Med. 2003;33(5):347-64.

36. Steensberg A, Toft AD, Bruunsgaard H, Sandmand M, Halkjaer-Kristensen J, Pedersen BK. Strenuous exercise decreases the percentage of type 1 T cells in the circulation. J Appl Physiol (1985). 2001;91(4):1708-12.

37. Bachert C, Van Cauwenberghe P, Olbrecht J, Van Schoor J. Prevalence, Classification and Perception of Allergic and Non-allergic Rhinitis. Allergy. 2006;61(6):693-8.

38. Gelardi M, Ventura MT, Fiorella R, Fiorella ML, Russo C, Candreva T, et al. Allergic and non-allergic rhinitis in swimmers: clinical and cytological aspects. Br J Sports Med. 2012;46(1):54-8.

39. Ottaviano G, Staffieri A, Stritoni P, Ermolao A, Coles S, Zaccaria M, et al. Nasal dysfunction induced by chlorinate water in competitive swimmers. Rhinology. 2012;50(3):294-8.

40. Cavalcante de Sa M, Nakagawa NK, Saldiva de Andre CD, Carvalho-Oliveira R, de Santana Carvalho T, Nicola ML, et al. Aerobic exercise in polluted urban environments: effects on airway defense mechanisms in young healthy amateur runners. Journal of breath research. 2016;10(4):046018.

41. Santos J, Foster R, Jonckheere AC, Rossi M, Luna Junior LA, Katekaru CM, et al. Outdoor Endurance Training with Air Pollutant Exposure Versus Sedentary Lifestyle: A Comparison of Airway Immune Responses. International journal of environmental research and public health. 2019;16(22).

42. Baraniuk JN, Merck SJ. Nasal reflexes: implications for exercise, breathing, and sex. Current allergy and asthma reports. 2008;8(2):147-53.

43. Jones AS. Autonomic reflexes and non-allergic rhinitis. Allergy. 1997;52(36 Suppl):14-9.

44. Muns G, Rubinstein I, Singer P. Neutrophil chemotactic activity is increased in nasal secretions of long-distance runners. International journal of sports medicine. 1996;17(1):56-9.

45. Doulaptsi M, Steelant B, Prokopakis E, Ierodiakonou D, Tsinaslanidou Z, Cools L, et al. Prevalence and impact of nasal hyperreactivity in chronic rhinosinusitis. Allergy. 2020.

46. Van Gerven L, Steelant B, Hellings PW. Nasal hyperreactivity in rhinitis: A diagnostic and therapeutic challenge. Allergy. 2018.

47. Van Gerven L, Boeckxstaens G, Jorissen M, Fokkens W, Hellings PW. Short-time cold dry air exposure: a useful diagnostic tool for nasal hyperresponsiveness. Laryngoscope. 2012;122(12):2615-20.

48. Bonadonna P, Senna G, Zanon P, Cocco G, Dorizzi R, Gani F, et al. Cold-induced rhinitis in skiers–clinical aspects and treatment with ipratropium bromide nasal spray: a randomized controlled trial. American journal of rhinology. 2001;15(5):297-301.

49. Sonmez G, Uzun G, Mutluoglu M, Toklu AS, Mutlu H, Ay H, et al. Paranasal sinus mucosal hypertrophy in experienced divers. Aviation, space, and environmental medicine. 2011;82(10):992-4.

50. Fischer H, Gubisch W. Nasal valves–importance and surgical procedures. Facial plastic surgery : FPS. 2006;22(4):266-80.

51. Chen XB, Lee HP, Chong VF, Wang de Y. Impact of inferior turbinate hypertrophy on the aerodynamic pattern and physiological functions of the turbulent airflow - a CFD simulation model. Rhinology. 2010;48(2):163-8.

52. Passàli D, Damiani V, Passàli GC, Passàli FM, Bellussi L. Alterations in rhinosinusal homeostasis in a sportive population: our experience with 106 athletes. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery. 2004;261(9):502-6.

53. Hellings PW, Scadding G, Alobid I, Bachert C, Fokkens WJ, Gerth van Wijk R, et al. Executive summary of European Task Force document on diagnostic tools in rhinology. Rhinology. 2012;50(4):339-52.

54. Hamilton GS, 3rd. The External Nasal Valve. Facial plastic surgery clinics of North America. 2017;25(2):179-94.

55. Ottaviano G, Fokkens WJ. Measurements of nasal airflow and patency: a critical review with emphasis on the use of peak nasal inspiratory flow in daily practice. Allergy. 2016;71(2):162-74.

56. Bonini S, Bonini M, Bousquet J, Brusasco V, Canonica GW, Carlsen KH, et al. Rhinitis and asthma in athletes: an ARIA document in collaboration with GA2LEN. Allergy. 2006;61(6):681-92.

57. Jonckheere AC, Seys SF, Dilissen E, Marijsse G, Schelpe AS, Van der Eycken S, et al. AQUA((c)) Questionnaire as prediction tool for atopy in young elite athletes. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2018;29(6):648-50.

58. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010;126(3):466-76.

59. Auge J, Vent J, Agache I, Airaksinen L, Campo Mozo P, Chaker A, et al. EAACI Position paper on the standardization of nasal allergen challenges. Allergy. 2018;73(8):1597-608.

60. Hellings PW, Klimek L, Cingi C, Agache I, Akdis C, Bachert C, et al. Non-allergic rhinitis: Position paper of the European Academy of Allergy and Clinical Immunology. Allergy. 2017;72(11):1657-65.

61. World anti-doping code, (2020).

62. Santos A CM, Delgado L. Best buys for allergic rhinitis and chronic rhinosinusitis prevention and control. In: Akdis CA HP, Agache I, editor. Global atlas of allergic rhinitis and chronic rhinosinusitis: European

Academy of Allergy and Clinical Immunology; 2015.

63. Fantuzzi G, Righi E, Predieri G, Giacobazzi P, Petra B, Aggazzotti G. Airborne trichloramine (NCl(3)) levels and self-reported health symptoms in indoor swimming pool workers: dose-response relationships. Journal of exposure science & environmental epidemiology. 2013;23(1):88-93.

64. Seys SF, Feyen L, Keirsbilck S, Adams E, Dupont LJ, Nemery B. An outbreak of swimming-pool related respiratory symptoms: An elusive source of trichloramine in a municipal indoor swimming pool. International journal of hygiene and environmental health. 2015;218(4):386-91.

65. WHO. Guidelines for safe recreational water environments. Volume 2, Swimming pools and similar environments. In: Organization WH, editor. 2006.

66. Katelaris CH, Carrozzi FM, Burke TV, Byth K. Effects of intranasal budesonide on symptoms, quality of life, and performance in elite athletes with allergic rhinoconjunctivitis. Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine. 2002;12(5):296-300.

67. Hox V, Lourijsen E, Jordens A, Aasbjerg K, Agache I, Alobid I, et al. Benefits and harm of systemic steroids for short- and long-term use in rhinitis and rhinosinusitis: an EAACI position paper. Clinical and translational allergy. 2020;10:1.

68. Simons FE. Advances in H1-antihistamines. The New England journal of medicine. 2004;351(21):2203-17.

69. Banov CH, Lieberman P, Vasomotor Rhinitis Study G. Efficacy of azelastine nasal spray in the treatment of vasomotor (perennial nonallergic) rhinitis. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2001;86(1):28-35.

70. Gehanno P, Deschamps E, Garay E, Baehre M, Garay RP. Vasomotor rhinitis: clinical efficacy of azelastine nasal spray in comparison with placebo. ORL J Otorhinolaryngol Relat Spec. 2001;63(2):76-81.

71. Price D, Shah S, Bhatia S, Bachert C, Berger W, Bousquet J, et al. A new therapy (MP29-02) is effective for the long-term treatment of chronic rhinitis. Journal of investigational allergology & clinical immunology. 2013;23(7):495-503.

72. Kortekaas Krohn I, Callebaut I, Alpizar YA, Steelant B, Van Gerven L, Skov PS, et al. MP29-02 reduces nasal hyperreactivity and nasal mediators in patients with house dust mite-allergic rhinitis. Allergy. 2018;73(5):1084-93.

73. Farre M, Perez-Mana C, Papaseit E, Menoyo E, Perez M, Martin S, et al. Bilastine vs. hydroxyzine: occupation of brain histamine H1 -receptors evaluated by positron emission tomography in healthy volunteers. British journal of clinical pharmacology. 2014;78(5):970-80.

74. Passalacqua G, Bousquet J, Bachert C, Church MK, Bindsley-Jensen C, Nagy L, et al. The clinical safety of H1-receptor antagonists. An EAACI position paper. Allergy. 1996;51(10):666-75.

75. Philip G, Nayak AS, Berger WE, Leynadier F, Vrijens F, Dass SB, et al. The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. Current medical research and opinion. 2004;20(10):1549-58.

76. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy. 2018;73(4):765-98.

77. Lekakis G, Dekimpe E, Steelant B, Hellings PW. Managing nasal valve compromise patients with nasal dilators: objective vs. subjective parameters. Rhinology. 2016;54(4):348-54.

78. Dinardi RR, de Andrade CR, Ibiapina Cda C. External nasal dilators: definition, background, and current uses. International journal of general medicine. 2014;7:491-504.

79. Gelardi M, Porro G, Accettura D, Quaranta VN, Quaranta N, Ciprandi G. The role of an internal nasal dilator in athletes. Acta bio-medica : Atenei Parmensis. 2019;90(2-s).

80. Tong TK, Fu FH, Chow BC. Nostril dilatation increases capacity to sustain moderate exercise under nasal breathing condition. The Journal of sports medicine and physical fitness. 2001;41(4):470-8.

81. Ottaviano G, Ermolao A, Nardello E, Muci F, Favero V, Zaccaria M, et al. Breathing parameters associated to two different external nasal dilator strips in endurance athletes. Auris, nasus, larynx. 2017;44(6):713-8.

82. Dinardi RR, de Andrade CR, Ibiapina Cda C. Evaluation of the effectiveness of the external nasal dilator strip in adolescent athletes: a randomized trial. International journal of pediatric otorhinolaryngology. 2013;77(9):1500-5.

83. van Egmond M, Rovers MM, Tillema AHJ, van Neerbeek N. Septoplasty for nasal obstruction due to a deviated nasal septum in adults: a systematic review. Rhinology. 2018;56(3):195-208.

84. Lennon P, Jaber S, Fenton JE. Functional and psychological impact of nasal bone fractures sustained during sports activities: A survey of 87 patients. Ear, nose, & throat journal. 2016;95(8):324-32.

85. Bonini M, Bachert C, Baena-Cagnani CE, Bedbrook A, Brozek JL, Canonica GW, et al. What we should learn from the London Olympics. Curr Opin Allergy Clin Immunol. 2013;13(1):1-3.

86. Hellings PW, Fokkens WJ, Bachert C, Akdis CA, Bieber T, Agache I, et al. Positioning the principles of precision medicine in care pathways for allergic rhinitis and chronic rhinosinusitis - A EUFOREA-ARIA-EPOS-AIRWAYS ICP statement. Allergy. 2017;72(9):1297-305.

87. Hens G, Hellings PW. The nose: gatekeeper and trigger of bronchial disease. Rhinology. 2006;44(3):179-87.

88. Stickland MK, Rowe BH, Spooner CH, Vandermeer B, Dryden DM. Effect of warm-up exercise on exercise-induced bronchoconstriction. Medicine and science in sports and exercise. 2012;44(3):383-91.

89. Seys SF, Bousquet J, Bachert C, Fokkens WJ, Agache I, Bernal-Sprekelsen M, et al. mySinusitisCoach: patient empowerment in chronic rhinosinusitis using mobile technology. Rhinology. 2018;56(3):209-15.

Tables

Table 1

Treatment/intervention	Disease	WADA rules	Notes
Trigger avoidance	AR, NAR, CRS	Allowed	Not always feasible to achieve.
Saline douchings	AR, NAR, ARS, CRS	Allowed	Very safe and cheap treatment option recommended as an adjunct for all mucosal pathology. Might be considered specifically for symptomatic swimmers after leaving a chlorinated pool.

Treatment/intervention	Disease	WADA rules	Notes
Decongestants	Infectious rhinitis, ARS	Allowed: phenylephrine, phenylpropanolamine, adrenaline, xylometazoline and synephrine Allowed in limited concentrations: cathine, ephedrine and methylephedrine, pseudoephedrine Not allowed: sympathomimetic amines	Overuse can lead to rhinitis medicamentosa with paradoxal chronic nasal obstruction.
Intranasal corticosteroids	AR, NAR, ARS, CRS	Allowed, TUE is not required	Transient side effects: minor epistaxis, nasal dryness and irritation of nose and throat. Golden standard for chronic mucosal sinonasal pathology.
Oral corticosteroids	Severe therapy-resistant AR	Allowed with TUE. Indications are rare for AR.	Gastro-intestinal, cardiovascular, ocular, psychiatric side-effects. Avascular necrosis, suppression of HPA-axis, osteopenia, diabetes mellitus, increased infection rate.
Antihistamines	AR	Allowed	Side effect: first-generation antihistamines can have a sedative effect. Second-generation and later antihistamines are less sedative.
Cromoglycates	AR	Allowed	Less effective in suppressing nasal symptoms than antihistamines.
Antileukotrienes	AR	Allowed	Comparable efficacy to antihistamines, but no sedation.
Allergen Immunotherapy	AR	SLIT: Allowed SCIT: Allowed	Immunotherapy should be started before competition. Local and systemic side effects are reported, more in SCIT than in SLIT. Exercise is prohibited on day of injection for SCIT.

Treatment/intervention	Disease	WADA rules	Notes
Nasal dilators	Structural pathology	Allowed	No clear effect on physiological parameters, however, beneficial effect on subjective breathing.
Surgery	Structural pathology, AR, NAR, CRS	Permitted	(Rhino)septoplasty is an option for medically resistant nasal obstruction in the presence of structural abnormalities. Turbinoplasty can be considered in medically resistant, reversible nasal obstruction due to turbinate hypertrophy. Endoscopic sinus surgery is an option in CRS patients in whom maximal medical therapy has failed.

Table 1: Treatment options for nasal symptoms in athletes according to the causal pathology and the current WADA regulations [72]. AR: allergic rhinitis; NAR: non-allergic rhinitis; ARS: acute rhinosinusitis; CRS: chronic rhinosinusitis; SCIT: subcutaneous immunotherapy; SLIT: sublingual immunotherapy; TUE: therapeutic use exemption; HPA: hypothalamic-pituitary-adrenal

Figure Legends

Figure 1. Presentation forms, causal factors and treatment options for persistent nasal symptoms in athletes.

Persistent nasal symptoms (column 1) in athletes can be due to either mucosal pathology (rhinitis or rhinosinusitis) or structural pathology (column 2). Within these groups, it is important to distinguish between the different causal factors (column 3) in order to choose an individually adapted treatment modality (column 4).

Hosted file

`Fig1.pdf` available at https://authorea.com/users/363820/articles/484510-tackling-nasal-symptoms-in-athletes-moving-towards-personalized-medicine