

ORIGINAL ARTICLE

Disconnect between standardized field-based testing and mannitol challenge in Scottish elite swimmers

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Summary

Background Elite swimmers have high rates of rhinoconjunctivitis and exercise-induced bronchoconstriction. Moreover, exposure to chlorine and chlorine metabolites is known to induce bronchial hyper-reactivity.

Objective To assess the early and late effects of chlorine and exercise on the unified airway of elite swimmers, and to compare the response to mannitol and field-based exercise challenge.

Methods The Scottish national squad underwent exhaled tidal (FE_{NO}) and nasal (N_{NO}) nitric oxide measurement, peak nasal inspiratory flow (PNIF), and forced expiratory volume in 1 s before, immediately after, and 4–6 h post-swimming. A sport-specific exercise test was carried out during an intensive lactate set (8 min at $\geq 80\%$ maximum heart rate). All swimmers underwent mannitol challenge, and completed a health questionnaire.

Results $N = 61$ swimmers were assessed: 8/59 (14%) of swimmers had a positive mannitol challenge. Nine out of 57 (16%) of swimmers had a positive exercise test. Only one swimmer was positive to both. Swimmers with a positive mannitol had a significantly higher baseline FE_{NO} (37.3 vs. 18.0 p.p.b., $P = 0.03$) than those with a positive exercise challenge. A significant decrease in FE_{NO} was observed pre vs. immediate and delayed post-chlorine exposure: mean (95% CI) 18.7 (15.9–22.0) p.p.b. vs. 15.9 (13.3–19.1) p.p.b. ($P < 0.01$), and 13.9 (11.5–16.7) p.p.b. ($P < 0.01$), respectively. There were no significant differences in N_{NO} . Mean PNIF increased from 142.4 L/min (5.8) at baseline to 162.6 L/min (6.3) immediately post-exposure ($P < 0.01$). Delayed post-exposure PNIF was not significantly different from pre-exposure.

Conclusions No association was found between mannitol and standardized field-based testing in elite swimmers. Mannitol was associated with a high baseline FE_{NO} ; however, exercise/chlorine challenge was not. Thus, mannitol may identify swimmers with a 'traditional' inflammatory asthmatic phenotype, while field-based exercise/chlorine challenge may identify a swimmer-specific bronchoconstrictor response. A sustained fall in FE_{NO} following chlorine exposure suggests that a non-cellular, perhaps neurogenic, response may be involved in this group of athletes.

Keywords bronchial challenge, exercise-induced asthma, mannitol, nitric oxide

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Introduction

Exercise-induced bronchoconstriction (EIB) is defined as a transient increase in airway resistance that occurs after vigorous exercise [1]. Proposed aetiological mechanisms include airway drying and cooling as a consequence of increased ventilatory rates during strenuous exercise [2, 3]. Exercise is an indirect airway challenge, which has been found to have a high level of specificity, but a low

sensitivity for identifying EIB in cold weather and track athletes [4]. Sport-specific exercise in the field (FBT) is limited with respect to the standardization of both the workload and environmental conditions such as allergens, temperature, and humidity. Eucapnic voluntary hyperpnoea (EVH), a laboratory-based challenge involving hyperventilation with dry air, has therefore been recommended as the 'gold standard' test for the diagnosis of EIB by the International Olympic Committee [5]. Mannitol, an

osmotic challenge, has been found to correlate strongly with EVH [6].

Elite swimmers have higher rates of rhinoconjunctivitis and EIB compared with any other groups of athletes [7, 8]. This may seem counterintuitive as they exercise in a warm moist environment. In a recent study, Pedersen *et al.* [9] evaluated airway response in swimmers following four different challenge tests and found that EVH had a much lower sensitivity than had been reported previously in other athletes. Chlorine and chlorine metabolites are known to induce bronchial hyper-reactivity following accidental intense exposure [10]. Swimmers are repeatedly exposed to chlorine gases and their metabolites, which accumulate at the water/gas interface on the swimming pool surface. It has been reported that adult elite swimmers have significantly higher levels of airway inflammatory cells compared with healthy controls [11].

In a recent preliminary study of young swimmers attending the district level squad, we evaluated the acute response to chlorine and exercise using exhaled nitric oxide (NO), a well-recognized surrogate of airway inflammation, and found no increase following a 2-h training session [12]. We hypothesized that we may have missed a late-phase response, and therefore performed a follow-up study in elite swimmers attending the national-level training squad. In the present study, we have evaluated the early- and late-phase exhaled NO response in both the upper and lower airways. We have also compared the response with mannitol and sports-specific physiological exercise challenges.

Methods

Participants and study design

The Scottish National swimming squad (61 swimmers) were assessed over a 3-day residential training weekend at the National Swimming Academy in Stirling. Swimmers are subdivided into two squads: the national squad (NS), and the national development squad. Swimmers underwent exhaled tidal (FE_{NO}) and nasal (N_{NO}) NO measurement, peak nasal inspiratory flow (PNIF) rate, and forced expiratory volume in 1 s (FEV_1) before, immediately after, and 4–6-h post-swimming. A sport-specific exercise test was carried out during an intensive lactate set. All swimmers underwent mannitol challenge, and completed a health questionnaire. Challenge tests were incorporated into the training programme. Swimmers were asked to withhold anti-histamines, leukotriene receptor antagonists (LRTAs), nasal steroid sprays, and long-acting β_2 -agonists (LABAs) for 1 week before the training session. Inhaled cortico-steroid inhalers could be taken as normal to avoid a significant negative impact on training. Participants were asked to refrain from taking short-acting β_2 -agonists (SABAs) 12 h before the training

Table 1. Subject characteristics

	National squad (<i>n</i> = 19)	National development squad (<i>n</i> = 42)	All swimmers (<i>n</i> = 61)
Age (years)*	17.74 (0.51)	14.95 (0.15)	15.2 (0.25)
Physician-diagnosed asthma	4 (21%)	6 (14%)	10 (17%)
Rhinitis	8 (42%)	16 (38%)	24 (40%)
Weekly training (h)*	19.39 (0.86)	15.45 (0.55)	16.69 (0.52)
Duration of competitive sport (years)*	8.47 (0.48)	5.95 (0.28)	6.74 (0.29)
Atopy	6 (40%)	7 (17%)	14 (24%)
Baseline FE_{NO} *	25.0 (1.1)	16.5 (1.1)	18.8 (0.2)
Positive FBT*	2 (13%)	7 (42%)	9 (16%)
Positive mannitol challenge*	5 (33%)	3 (8%)	8 (14%)

Data expressed as mean (SEM) unless otherwise stated.

*Significant difference between squads.

weekend. This study was approved by the local ethics committee (REC ref: 09/S1402/6) and all participants gave written informed consent. Combined (free) chlorine levels on each of the three training days were: 1.66 (1.42), 1.58 (1.44), and 1.68 (1.40) mg/L, which are within UK-recommended limits.

Demographics

Baseline characteristics are described in Table 1. The NS were significantly older, trained more hours per week, over more years than the national development squad (Table 2). Ten swimmers (17%) had physician-diagnosed asthma, three were taking inhaled corticosteroids, one was taking a LRTA. 24 (40%) had rhinitis according to ARIA guidelines (16 = intermittent rhinitis, 8 = persistent rhinitis).

Timing of tests

Complete baseline data were available on 60/61 swimmers. Exercise challenge was available in 57 (two were injured and thereby unable to take part, and two did not stay for the full training camp). Fifty-nine swimmers carried out a mannitol challenge; one was unable to tolerate the procedure due to excessive coughing. Challenge tests were incorporated to fit into the training programme; consequently, the NS underwent mannitol challenge 5.01 (0.01) h post-exercise, whereas the development squad had their mannitol 18.28 (0.33) post-exercise. Immediate post-swim measures were performed after a 2-h swimming session. Delayed post-swim measures were carried out 4.66 (0.18) h after swimming. These were performed before the mannitol challenge. During the

Table 2. %fall in FEV₁ in those with a fall $\geq 10\%$

Time post-exercise	Immediately post-exercise	At 5-min recovery	At 10-min recovery	Positive/negative test
% Fall in FEV ₁	8.92	12.45	20.12	P
	-11.55	-0.19	10.06	N
	13.59	13.36	3.23	P
	29.25	23.03	22.61	P
	21.23	10.31	10	P
	26.03	13.7	9.13	P
	11.53	-5.9	-6.7	N
	18.61	14.93	14.52	P
	11.03	4.93	-2.82	N
	12.41	15.95	15.19	P
	11	15.16	11.98	P*
	4.59	10.1	18.37	P
	10.67	-0.46	-2.09	N

*Subject was also positive to mannitol challenge (PC₁₅ = 335 mg).

P, exercise test considered to be positive; N, test considered negative; FEV₁, forced expiratory volume in 1 s.

challenge, swimmers achieved a mean (SEM) heart rate of 85.0% (1.12) maximum predicted.

Measurements

Nitric oxide. All participants underwent the measurement of exhaled tidal NO (FE_{NO}) using a portable MINO (NIOX MINO[®] Airway Inflammation Monitor; Aerocrine AB, Solna, Sweden). A single reading was obtained in accordance with the manufacturer's guidelines. Nasal exhaled NO was measured using an adapted MINO device, as described previously [13].

Sport-specific field-based exercise challenge. The swimmers performed a high-intensity sport-specific field-based exercise challenge during an intensive lactate set. This was preceded by a standard low-intensity warm up of approximately 15–20 min, to avoid muscular injury. During the high-intensity lactate set, swimmers were required to maintain $> 80\%$ maximum heart rate ($220 - \text{age}$) for at least 8 min in order to optimally provoke EIB. Heart rate was measured objectively using pulse oximetry (M-pulseTM, Merlin Medical, Gwent, UK). FEV₁ was measured using a Piko-6[®] portable spirometer (Ferraris Respiratory, Hertford, UK). Results from PIKO devices have been found to be highly reproducible, and to correlate well with results from other portable and office-based spirometers [14]. Heart rate and FEV₁ were measured at baseline, immediately following challenge, and at 5 and 10 min during recovery. The best of two reproducible readings was utilized. A positive challenge was defined as a fall in FEV₁ of $\geq 10\%$ at ≥ 2 time-points during recovery [in accordance with recommendations by the drug-free sport United Kingdom for therapeutic use exemption (TUE) certification] [15].

Mannitol challenge. Mannitol challenge was performed by administering spray-dry mannitol powder in a gelatine capsule form (AridolTM Pharmaxis Ltd, Sydney, Australia), inhaled from a dry powder device (Osmohaler, Pharmaxis Ltd, French's Forest, NSW, Australia) as described previously by Anderson et al. [16]. FEV₁ was measured 60 s after the delivery of each dose (5, 10, 20, 40, 80, 160, 160, 160 mg) using a Piko-6[®] portable spirometer (Ferraris Respiratory). This device was used to ensure the standardization between both challenge tests. The test continued until the FEV₁ had fallen 15% or the maximal dose of 635 mg had been administered. The provoking dose of mannitol to cause a 15% fall in FEV₁ (PD₁₅) was calculated by a log linear interpolation. A positive challenge was taken as being either a 15% fall in FEV₁ at the threshold dose (PD₁₅) or a 10% fall at successive time-points.

Peak nasal inspiratory flow. PNIF was measured using the In-Check[®] PNIF meter (Clement Clarke International Ltd, Harlow, UK). After horizontal positioning and restoration to zero, participants forcefully inhaled through their nose and the best of three measurements was taken.

Health questionnaire (symptoms). A modified version of a questionnaire used previously in studies on elite athletes was used to assess the presence of exercise-induced symptoms [17]. Symptoms of chlorine-induced rhinitis (blockage/running) were assessed using a visual analogue scale. Atopy was defined as a history of rhinoconjunctivitis (in accordance with current ARIA definitions) and/or a positive skin prick test or IgE-specific RAST test within the last 2 years.

Statistical analysis

SPSS version 15 (SPSS Inc., ChicagoIL, USA) was used to perform the statistical analysis. Non-Gaussian data were log transformed before analysis. Normalized data were assessed using repeated measures ANOVA with Bonferroni correction. χ^2 test was used to check for associations in non-parametric data. Pearson's correlation was used for parametric data. A *P*-value of < 0.05 (two tailed) was considered significant. As this was an observational study, no formal power calculation was used.

Results

Challenge tests

Eight out of 59 (14%) of swimmers had a positive mannitol challenge. Nine out of 57 (16%) of swimmers had a positive exercise test. Only one swimmer was positive to both tests. There was no correlation between maximum FEV₁ drop in mannitol challenge and maximum FEV₁ drop in exercise challenge. Three out of 10

asthmatics were positive to mannitol, while only 2/10 were positive to exercise.

Results of subjects who achieved a $\geq 10\%$ fall in FEV_1 are detailed in Table 2. Seven out of nine subjects deemed to have a positive exercise challenge had a fall immediately post-exercise, which was sustained at 5 min (7/7) and 10 min (5/7) recovery. The mean (SEM) %fall for these subjects immediately post-exercise was 18.9 (7.0), and 15.2 (6.0) at 5 min. Three subjects had a fall of $\geq 10\%$, which was not sustained; their mean (SEM) %fall was 11.1 (1.7) immediately and -0.47 (1.7) at 5-min recovery. Two subjects developed a sustained $\geq 10\%$ fall during recovery. The geometric mean (95% CI) mannitol PD_{15} was 209.9 (128.7–342.3). The degree of bronchial reactivity, measured in terms of response-dose ratio (final %fall in FEV_1 divided by the total administered dose of mannitol), was similar in swimmers with EIB and those who did not respond to either test, of 0.01 and 0.01, respectively. The response-dose ratio in those with a positive mannitol was higher at 0.06.

FE_{NO}

Baseline FE_{NO} was 26.7 (16.3–43.6) p.p.b. in asthmatic swimmers and 17.4 (14.9–20.4) p.p.b. in non-asthmatic swimmers ($P=0.03$). Swimmers with a positive mannitol had a significantly higher baseline FE_{NO} than those with a positive exercise challenge (Fig. 1). There was a significant association between positive mannitol challenge and baseline $FE_{NO} > 25$ p.p.b. ($X^2=7.76$, $P=0.01$). There was a weak correlation between maximal fall in FEV_1 during mannitol challenge and baseline FE_{NO} ($r=0.26$, $P=0.03$).

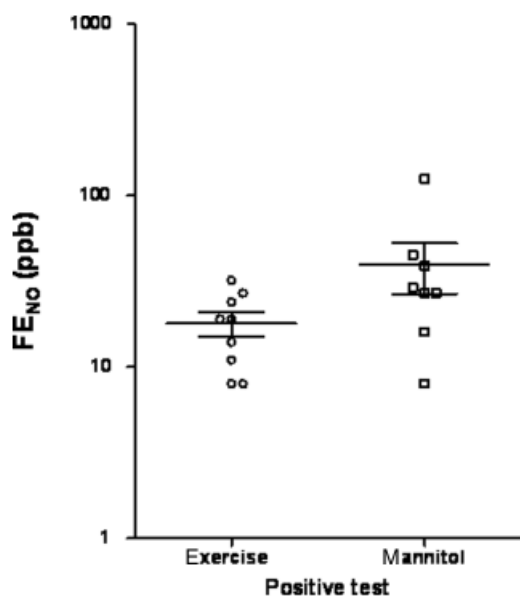


Fig. 1. Comparison of baseline FE_{NO} in patients with a positive exercise and positive mannitol challenge. Presented as geometric mean and 95% CI.

Table 3. Effects of swimming on FE_{NO} , N_{NO} , and PNIF

	Pre-swim	Immediate post-swim	4–6 h post-swim
FE_{NO} (p.p.b.)*	18.7 (15.9–22.0)	15.9 (13.3–19.1) [†]	13.9 (11.5–16.7) [†]
N_{NO} (p.p.b.) [‡]	98.68 (5.39)	100.93 (5.00)	98.22 (4.45)
PNIF (l/min) [‡]	142 (6)	162 (6) [†]	143 (6)

*Shown as geometric mean (95% CI).

[†]Statistically significant change from pre-swim measure.

[‡]Expressed as mean (SEM).

PNIF, peak nasal inspiratory flow.

There was no association between positive exercise and high baseline FE_{NO} ($\chi^2=0.127$, $P=0.54$). A significant decrease in FE_{NO} was observed pre vs. immediate and delayed post-chlorine exposure: mean (95% CI) 18.7 (15.9–22.0) p.p.b. vs. 15.9 (13.3–19.1) p.p.b. ($P<0.01$), and 13.9 (11.5–16.7) p.p.b. ($P<0.01$), respectively (Table 3). This was irrespective of squad, atopic, or asthmatic status.

N_{NO}

There was no significant difference in N_{NO} between pre-exposure, immediate, or delayed post-exposure: 98.7 (5.4) p.p.b., 100.9 (5.0) p.p.b. ($P=0.70$), and 98.2 (4.5) ($P=0.94$), respectively (Table 3).

Peak nasal inspiratory flow

Mean PNIF increased from 142 L/min (6) at baseline to 162 L/min (6) immediately post-exposure ($P<0.01$). Delayed post-exposure PNIF was not significantly different from pre-exposure readings ($P=0.90$) (Table 3). There was no significant increase in the visual analogue scale at any point post-exposure.

Symptoms

Forty-three percent (26) of swimmers complained of exercise-related symptoms. 36% (8/22) of these had a positive exercise challenge (four symptomatic swimmers were unable to take part in the challenge). Thirty percent (7/26) of symptomatic swimmers had a positive mannitol challenge. Forty-four percent (4) of participants with a positive exercise challenge were symptomatic, 56% (5) were asymptomatic. Seventy-five percent (6) of participants with a positive exercise challenge were symptomatic, 25% (2) were asymptomatic.

Discussion

This study aimed to compare the response to standardized exercise testing and mannitol challenge in elite national level swimmers. We also aimed to investigate the combined effects of chlorine and exercise on the unified

airway. No association was found between mannitol and exercise challenge. Fourteen percent swimmers were positive to mannitol, 15% were positive to exercise challenge, while only one swimmer was positive to both. While these findings are not supported by studies performed in cold weather or track athletes [6, 18, 19], they are consistent with the findings of Pedersen et al. [9] who reported that EVH had a relatively low sensitivity in swimmers. This is not entirely unexpected as the humidified air inspired by swimmers during exercise should decrease the rate of expired water loss during hyperpnoea. Despite this, swimmers have one of the highest prevalences of EIB, which would suggest that the theories of heat and water loss as a cause of EIB may not be totally applicable and other factors (such as the presence of chlorine) may be pertinent.

In the current study, a disconnect was observed between BHR detected by standardized-FBT and mannitol challenge. Traditionally, FBT in athletes has been non-standardized and centred on a challenge using their primary exercise [19]. This will limit the ability to standardize both the cardiovascular workload and environmental conditions for repeated challenges or between athletes, making it inappropriate for a direct comparison with highly standardized tests such as EVH or methacholine challenge. For example, a sprinter whose main event is a 50 m freestyle will be unlikely to sustain the adverse effects on the airways for long enough to induce bronchoconstriction; however, EIB in longer aerobic training sets may still have a significant effect on training and may still therefore be of importance to the swimmer. We, therefore, decided to use a standardized, rather than event-specific protocol based on the ATS (1999) guidelines for exercise challenge and using an objective measure of heart rate monitoring [20]. In the current study, all athletes were required to achieve an average heart rate of 80% of maximum, and maintain this for at least of 8 min. Environmental conditions within the pool over the 3-day period were constant. A positive test required the presence of a sustained fall in FEV₁ post-exercise (i.e. a fall of $\geq 10\%$ at two time-points post-exercise) in order to exclude those who may have had a drop secondary to exhaustion.

In this study, mannitol challenge was positively associated with high baseline FE_{NO}, whereas exercise challenge was not, suggesting that mannitol challenge may be more sensitive at picking out swimmers with a traditional 'inflammatory' asthmatic phenotype, rather than EIB. Leukotrienes are known to play a significant part in sustaining the contraction of airway smooth muscle and airway narrowing in EIB. It is, therefore, also of interest that mannitol-positive swimmers, who have demonstrated that their airway is susceptible to endogenous release of leukotrienes, do not respond to exercise. This suggests that a different mechanism is responsible for the fall in FEV₁ to high-intensity swimming. Mannitol challenge has been

previously shown to correlate very closely with eosinophils in induced sputum [21]. Swimmers are thought to have higher levels of eosinophils and neutrophils in their sputum [11]. However, a closer inspection of the data by Helenius and colleagues reveals that most swimmers with sputum eosinophilia were in fact known asthmatics, while the greater majority of study population had eosinophil levels comparable with controls. Findings in participants without known asthma or BHR to methacholine (14/29) were not separately reported. A study by Boulet et al. [22] suggested that sputum neutrophils are up-regulated in swimmers following high-intensity training. This is of interest as asthmatic subjects with high sputum neutrophil counts have been found to have milder AHR to mannitol compared with those with a preponderance of other inflammatory cell types [23]. However, high sputum neutrophil counts would not serve to explain the disconnect observed between the two challenge tests.

In this regard, the current study used exhaled NO as a surrogate of airway inflammation [24]. There was a significant fall in FE_{NO} following a 2-hour swim, and a trend towards a continuing drop at 4–6 h post-exposure. This was seen in both squads, and was not affected by asthmatic or atopic status. Forced vital manoeuvres are known to 'wash-out' FE_{NO} from the airways; however, this effect has not been established in relation to exercise or hyper-ventilation [25]. Indeed, the continued decrease in FE_{NO} 4–6 h post-exposure would not support a 'wash-out' effect and suggests another action. Case series describing airway changes following accidental high-intensity chlorine exposure have described significant drops in FE_{NO} that persist for up to 2 months post-exposure [10]. It has been suggested that acute chlorine exposure causes widespread oedema of the respiratory mucosa, degeneration and desquamation of the bronchial epithelium, resulting in an exposure of vagal receptors, and consequently enhanced vagal activity with bronchial hyper-reactivity [26]. Therefore, it appears plausible that repeated low-intensity exposure to chlorine may cause bronchial hyper-reactivity by a non-cellular inflammatory response. This would explain the high prevalence of EIB diagnosed by standardized-FBT, even in swimmers with normal baseline FE_{NO}. There have been several case reports of acute pulmonary oedema in swimmers and divers. In 2004, Adir and colleagues published a case series of 70 swimmers with 'swimming-induced acute pulmonary oedema' [27]. However, they reported clinical haemoptysis and a decrease in mean oxygen saturations to 76%. Adir and colleagues hypothesized that the pulmonary oedema may have been due to exercising in the prone position, as this will have affected the distribution of blood throughout the lung. While no decrease in oxygen saturations was noted in our swimmers, it is possible that a combination of exercising in the prone position and exposure to toxic metabolites may have

caused a mild degree of airway oedema, which led to a decrease in bronchial flux. An alternative mechanism for the suppression of FE_{NO} is a direct blockage of production through the inhibition of NO synthase (the enzyme responsible for NO production).

Unlike FE_{NO} , there was no change in N_{NO} following a 2 h swim. The cause for this is unclear; however, a possible explanation is that at exercise capacity, athletes mouth breathe rather than breathing through their nose. Given this, the paranasal sinuses will have comparatively little gas exchange or chlorine exposure. There was also no change 4–6 h post-exposure, suggesting that there is no late-phase response in NO. This is substantiated by the PNIF results, which increase immediately post-exposure but returns to baseline after 4–6 h. The immediate improvement is most likely due to a 'nasal douche effect', given that saline irrigation is known to significantly improve nasal congestion [28]. There was additionally no significant change in the visual analogue scale either immediately or 4–6 h post-exposure. 27/60 swimmers had a PNIF ≤ 120 L/min at baseline. Given that national elite swimmers train on a daily basis during the season, it was not possible to establish a truly chlorine-free baseline.

The diagnosis of EIB based on symptoms alone, is known to be highly inaccurate [29]. In the current study, 43% of swimmers complained of exercise-related symptoms. However, only 38% of these had a positive challenge, which is in keeping with the results of our previous study [12].

There were significant differences in baseline values between the two squads. The NS were significantly older, trained more hours per week, over a greater number of years compared with the National Development squad (NDS). They also had a greater proportion of asthmatics, and a higher mean baseline FE_{NO} . It has been suggested that regular pool attendance is associated with an increased risk of asthma [30], which could explain why the older, more experienced team has a higher prevalence. However, this discrepancy may simply be due to the smaller number of swimmers in the NS.

We recognize some limitations in our study. Ideally, both challenges would have been performed on separate days; however, due to constraints of the training timetable, this was only possible for the national development squad. Edmunds *et al.* [31] found little evidence of a refractory period 4 h post-exercise; therefore, the mean of 5.05 h between challenges in the NS should have been sufficient to re-establish stored inflammatory mediators. In addition, Anderson *et al.* [32] noted that exercising while breathing in warmed humidified air, did not induce mast cell degranulation, bronchoconstriction or not prevent the development of severe exercise induced asthma in response to a standard exercise challenge 30 min later. These results are further substantiated by those of Hahn *et al.* [33] who found that exercise challenge with warm humidified air led to significantly lower fall in FEV_1 post-

challenge, and did not induce a refractory period. The national development squad performed mannitol challenge 18 h post-exercise; therefore, the refractory period is not relevant in this group. Although, the NS performed mannitol challenge 5 h after exercise, only one swimmer had a positive exercise challenge, subsequently followed by a negative mannitol challenge.

In the current study, we measured FEV_1 for 10 min post-exercise. It has been reported that peak fall in FEV_1 may occasionally occur up to 30 min [34]. However, the ATS guidelines on exercise testing conclude that 'including a 30-min post-exercise observation is controversial, because such a delay is infrequently seen' [20]. As a compromise, to minimize the interference with the athlete's intensive training session, we decided that 10 min should be sufficient to pick up the majority of cases. It could additionally be argued that the non-intensive exercise preceding the challenge may have induced a refractory period in some swimmers, which may have led to an underestimate of the true prevalence of EIB. The low incidence of positive mannitol challenge in swimmers with a physician diagnosis of asthma was unexpected. Of those that were negative (7/10), two were taking regular ICS. Ideally, all preventer therapy would have been stopped before assessment; however, it was felt that this would have interfered excessively with training. Of the remaining five swimmers, two had a high FE_{NO} (> 30), and three had normal readings (< 20). A normal FE_{NO} in the presence of a negative mannitol and exercise challenge suggests that these patients were wrongly diagnosed with asthma.

Conclusion

We have found no association between mannitol and standardized-FBT in elite swimmers. Mannitol challenge was associated with a high baseline FE_{NO} ; however, exercise challenge was not. This suggests that while mannitol may select swimmers with a 'traditional' inflammatory asthmatic phenotype, there may still be a role for a standardized field-based challenge in high-performance swimming, where the bronchoconstrictor response may have a more complex aetiology. Swimmers show a sustained fall in FE_{NO} following chlorine exposure suggesting that a non-cellular, perhaps neurogenic, type-inflammation may be important in airway dysfunction in this group of athletes. Further large-scale studies are warranted to understand the pathophysiology of loose-dose chronic chlorine exposure in elite swimmers.

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References

- Anderson SD. Exercise-induced asthma. In: Middleton E, Reed C, Ellis E, Adkinson NF, Yunginger JW, eds. *Allergy: principles & practice*, 4th Edn. St Louis, MO: CV Mosby Company, 1993; 343–1367.
- Anderson SD, Daviskas E. Pathophysiology of exercise-induced asthma: the role of respiratory water loss. In: Weiler JM, ed. *Allergic and respiratory disease in sports medicine*. New York: Marcel Dekker, 1997; 87–114.
- Anderson SD, Daviskas E. Airway drying and exercise induced asthma. In: McFadden ER, ed. *Exercise induced asthma – lung biology in health and disease*. New York: Marcel Dekker, 1999; 77–113.
- Rundell KW, Anderson SD, Spiering BA. Field exercise vs laboratory eucapnic ventilation to identify airway hyperresponsiveness in elite cold weather athletes. *Chest* 2004; 125:909–15.
- International Olympic Medical Commission. Beta2 adrenoreceptor agonists and the winter olympic games in Beijing. Available at http://www.turin2006.com/Documents/Reports/EN/en_report_1302.pdf (accessed 23 May 2009).
- Brannan JD, Koskela H, Anderson SA *et al.* Responsiveness to mannitol in asthmatic subjects with exercise and hyperventilation induced asthma. *Am J Respir Crit Care Med* 1998; 158: 1120–1126.
- Helenius IJ, Tikkanen HO, Sarna S *et al.* Asthma and increased bronchial hyperresponsiveness in elite athletes: atopy and sport event as risk factors. *J Allergy Clin Immunol* 1998; 101:646–52.
- Katellaris CH, Carrozzi FM, Burke TV *et al.* Patterns of allergic reactivity and disease in Olympic athletes. *Clin J Sports Med* 2006; 16:401–5.
- Pedersen L, Winther S, Backer V *et al.* Airway responses to eucapnic hyperpnea, exercise, and methacholine in elite swimmers. *Med Sci Sports Exerc* 2008; 40:1567–72.
- Bonetto G, Corradi M, Carraro S *et al.* Longitudinal monitoring of lung injury after acute chlorine exposure in a swimming pool. *Am J Respir Crit Care Med* 2006; 174:545–9.
- Helenius IJ, Ryttilä P, Metso T *et al.* Respiratory symptoms, bronchial responsiveness, and cellular characteristics of induced sputum in elite swimmers. *Allergy* 1998; 53:346–52.
- Clearie K, Vaidyanathan S, Williamson PA *et al.* Effects of chlorine and exercise on the unified airway in adolescent elite. *Scottish swimmers Allergy* 2010; 65:269–73.
- Maniscalco M, De Laurentiis G, Weitzberg E *et al.* Validation study of nasal nitric oxide measurement using a hand-held electrochemical analyser. *Eur Respir J* 2008; 38:197–200.
- Fonseca JA, Costa-Pereira A, Delgado L *et al.* Pulmonary function electronic monitoring devices. *Chest* 2005; 128:1258–65.
- Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE, Mellon JJ. Bronchial reactivity to inhaled histamine: a method and clinical survey. *Clinical Allergy* 1977; 7:235–43.
- Anderson SD, Brannan JD, Spring J *et al.* A new method for bronchial provocation testing in asthmatic subjects using a dry powder of mannitol. *Am J Respir Crit Care Med* 1997; 156:758–65.
- Holzer K, Anderson SD, Douglass J. Exercise in elite summer athletes: challenges for diagnosis. *J Allergy Clin Immunol* 2002; 110:374–80.
- Mannix ET, Manfredi F, Farber MO. A comparison of two challenge tests for identifying exercise-induced bronchospasm in figure skaters. *Chest* 1999; 115:649–53.
- Dickinson JW, Whyte GP, McConnell AK *et al.* Screening elite winter athletes for exercise induced asthma: a comparison of three challenge methods. *Br J Sports Med* 2006; 40:179–83.
- Crapo RO, Casaburi R, Coates AL *et al.* Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000; 161: 309–29.
- Gibson PG, Saltos N, Borgas T. Airway mast cells and eosinophils correlate with clinical severity and airway hyperresponsiveness in corticosteroid asthma. *J Allergy Clin Immunol* 2000; 105:752–9.
- Boulet LP, Turcotte H, Langdeau JB, Bernier MC. Lower airway inflammatory responses to high-intensity training in athletes. *Clinical and investigative medicine* 2005; 28:15–22.
- Porsbjerg C, Lund TK, Pedersen L, Backer V. Inflammatory subtypes in asthma are related to airway hyperresponsiveness to mannitol and exhaled NO. *Journal of asthma* 2009; 46:606–12.
- Porsbjerg C, Brannan JD, Anderson SD *et al.* Relationship between airway responsiveness to mannitol and to methacholine and markers of airway inflammation, peak flow variability and quality of life in asthma patients. *Clin Exper Allergy* 2008; 38:43–50.
- ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide. *Am J Respir Crit Care Med* 2005; 171:912–30.
- Benson MK. Bronchial hyperreactivity. *Br J Dis Chest* 1975; 69:227–39.
- Adir Y, Shupak A, Gil A. Swimming-induced pulmonary edema: clinical presentation. *Chest* 2004; 126:394–9.
- Harvey R, Hannan SA, Badia L *et al.* Nasal saline irrigations for the symptoms of chronic rhinosinusitis. *Cochrane Database Syst Rev* 2007; 3:CD006394.
- Rundell KW, Im J, Mayers LB. Self-reported symptoms and exercise-induced asthma in the elite athlete. *Med Sci Sports Exerc* 2001; 33:208–13.
- Bernard A, Nickmilder N, Voisin C. Outdoor swimming pools and the risks of asthma and allergies during adolescence. *Eur Respir J* 2008; 32:979–88.
- Edmunds AT, Tooley M, Godfrey S. The refractory period after exercise-induced asthma: its duration and relation to the severity of exercise. *Am Rev Respir Dis* 1978; 117:247–54.
- Anderson SD, Daviskas E, Schoeffel RE *et al.* Prevention of severe exercise-induced asthma with hot humid air. *Lancet* 1979; 629.
- Hahn AG, Nogrady SG, Burton GR *et al.* Absence of refractoriness in asthmatic subjects after exercise with warm, humid inspire. *Thorax* 1985; 40:418–21.
- Brudno DS, Wagner JM, Rupp NT. Length of postexercise assessment in the determination of exercise-induced bronchospasm. *Ann Allergy* 1994; 73:227–31.