Inhaled salbutamol does not affect athletic performance in asthmatic and non-asthmatic cyclists

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Accepted 13 September 2013
Published Online First 07 October 2013

ABSTRACT

Rationale Salbutamol may affect lung function and exercise performance differently in individuals with and without asthma.

Objectives To compare the effects of inhaled salbutamol on lung function, exercise performance and respiratory parameters during cycling exercise in athletes with a positive response to a eucapnic voluntary hyperpnoea (EVH+) and negative (EVH−) challenge, indicative of exercise-induced bronchoconstriction.

Methods In a randomised controlled trial with a crossover design, a total of 49 well-trained male athletes (14 EVH+ and 35 EVH−) performed two simulated 10 km time-trials on a cycle ergometer 60 min after the inhalation of either 400 µg of salbutamol or a placebo. Lung function, assessed by forced expiratory volume in 1 s, was measured immediately before and 30 min after inhalation. Performance was measured by mean power output.

Measurements & main results Despite a significant increase in lung function after the inhalation of salbutamol compared to the placebo ($p<0.001$), salbutamol did not affect athletes' perceptions of dyspnoea ($p>0.05$) or leg exertion ($p>0.05$) during exercise. Salbutamol did not affect mean power output: EVH+ and EVH− athletes averaged 4.0 (0.5) and 4.1 (0.5) W/kg after salbutamol and 4.0 (0.5) W/kg and 4.0 (0.4) W/kg after placebo, respectively ($p>0.05$ for each comparison).

Conclusions The inhalation of salbutamol induced a significant increase in resting lung function in EVH+ and EVH− athletes but this improvement in lung function did not translate to improved exercise performance. Salbutamol had no discernible effect on key ventilatory and exercise parameters regardless of EVH challenge outcome.

INTRODUCTION

The transient narrowing of the airways that follows vigorous exercise is defined as exercise-induced asthma (EIA).[1] Asthma is the most common chronic health condition in Olympic athletes,[2] and endurance athletes are the most likely group of athletes to be diagnosed with EIA.[1 2] While EIA is the general term for symptoms and signs of asthma provoked by exercise, exercise-induced bronchoconstriction (EIB) specifically describes the reduction in lung function that occurs during and after exercise. At the 2004 and 2008 Summer Olympics, an average of 25% of the triathletes and 17% of the cyclists were approved by the International Olympic Committee (IOC) to treat their asthma symptoms with inhaled adrenergic β_2-agonists (IBA).[2] Similarly to epinephrine, β_2-agonists act on adrenergic β_2-receptors that are distributed in the lungs (primarily), heart and skeletal muscles.[3] In the treatment of acute asthma attacks, IBAs, such as salbutamol, are the medication class of choice: IBAs relax the smooth muscle cells surrounding the airways, causing bronchodilation, which relieves asthma symptoms (eg, coughing, wheezing and chest tightness).[3] In the heart, β_2-agonists increase heart rate and contractility. Owing to their vasodilating effects, β_2-agonists can also increase blood flow in the coronary and skeletal arteries.[3]

Contrary to expectations, asthmatic athletes tend to be more successful at major sporting events compared to non-asthmatic athletes.[2 4] For example, only 17% of the cyclists competing in the 2008 Olympics were asthmatic, but this group won 29% of the individual medals.[2] Several studies have investigated the possible performance-enhancing effects of IBAs in non-asthmatic individuals, but a mechanism to explain the discrepancy in Olympic success between athletes with and without asthma remains elusive.[5 6] In non-asthmatic, well-trained individuals, IBAs did not affect maximal oxygen consumption (VO_{2max}), anaerobic threshold, alactic and lactic anaerobic power, strength performance, blood lactate, rate of perceived exertion or psychomotor performance.[7]

Previous investigations recruited non-asthmatic,[8–12] well-trained individuals[9 12] as participants, but it is likely that the effects of IBAs are more pronounced in participants with asthma compared to participants without asthma given the former's impaired lung function. To our knowledge, the respiratory and performance effects of inhaled salbutamol have not been directly compared between well-trained athletes with and without EIB; therefore, the purpose of this study was to compare the effects of inhaled salbutamol on lung function and time-trial performance in well-trained athletes with and without EIB. We hypothesised that athletes with EIB would show a greater bronchodilatory response to inhaled salbutamol compared to athletes without EIB, which would translate to improved ventilatory capacity and time-trial performance.

METHODS

Study participants

Seventy-five experienced male cyclists and triathletes between 19 and 40 years of age were screened for this experiment. Inclusion criteria were a maximal oxygen consumption (VO_{2max})≥60 mL/kg/min (or≥5l/min) and the absence of cardiac or pulmonary disease (excluding controlled asthma). The University of British Columbia Clinical Research Ethics Board provided ethical approval

To cite: Koch S, MacInnis MJ, Sporer BC, *et al*. *Br J Sports Med* 2015;**49**:51–55.

conforming to the Declaration from Helsinki and written informed consent was obtained from all participants prior to data collection.

Screening visit

A eucapnic voluntary hyperpnoea (EVH) test was performed to assess bronchial hyper-responsiveness to exercise.[13] Baseline lung function was determined using spirometry (TrueOne 2400 Metabolic Measurement System; ParvoMedics, Sandy, Utah, USA)[14]: the highest forced expiratory volume in 1 s (FEV_1) from three manoeuvers served as the baseline. Athletes then hyperventilated dry gas (5% CO_2) for 6 min. At 3, 5, 15 and 20 min posthyperventilation, participants repeated spirometry. Any athlete with a decrease in $FEV_1 \geq 10\%$ relative to the baseline for two consecutive measurements was classified as EVH+.

A cycle ergometer (Velotron Dynafit Pro, RacerMate Inc., Seattle, Washington, USA) and a metabolic cart (ParvoMedics) was used to measure VO_{2max}. The test began at 0 W and resistance was continuously increased by 1 W every 2 s until cycling cadence was<60 rpm.

Experimental design

Each athlete, who met the inclusion criteria, visited the laboratory for two time trial days. The athletes were asked to withhold from β_2-agonists for at least 12h prior to arriving at the laboratory but were allowed to continue their corticosteroid treatment. The washout periods ranged from 3 to 14 days between all visits.

Time-trial visits

Athletes performed two FEV_1 manoeuvers prior to and 30 min after inhalation to assess the effect of each treatment on lung function. The treatments were delivered in a randomly assigned, double-blind manner. In total, athletes completed two simulated 10 km time trials, one 60 min after inhalation of 400 µg salbutamol (GlaxoSmithKline; Mississauga, Ontario, Canada) and one after the inhalation of 400 µg placebo.

During each time trial, participants wore a facemask (Hans Rudolph, 7450V2 Mask; Shawnee, Kansas, USA) connected to a metabolic cart (ParvoMedics). A three-dimensional time-trial course (RacerMate) was displayed on a computer screen. Athletes were able to monitor their distances, cadences and gears. Every 2 km, athletes rated dyspnoea and perceived exertion (RPE) for legs on a 0–10 scale.[15] The main outcome variable was mean power output relative to body weight. Secondary outcome variables were heart rate, oxygen consumption, minute ventilation, tidal volume, respiratory rate, dyspnoea and RPE for legs.

Statistical analyses

All data are presented as mean (SDs). The effects of drug treatment and asthma status were tested with repeated-measures analysis of variance (ANOVA) tests. The role of lung size (ie, forced vital capacity (FVC)) in respiratory and performance outcomes was determined with analysis of covariance (ANCOVA) tests with FVC serving as the covariate. If a main effect was detected, posthoc analyses were performed using the Tukey's HSD test. Statistical analyses were completed using SPSS (IBM, V.21.0, Armonk, New York, USA).

RESULTS

Participant characteristics

Of the 75 athletes we screened, 18 were excluded because they did not meet the VO_{2max} requirements. Eight participants met all inclusion criteria but were unable to complete the study due to injuries and time constraints. Among the remaining 49 athletes, there were 14 EVH+ and 35 EVH− cyclists. Of the 14 EVH+ athletes, 13 had previously been diagnosed with asthma, while one EVH+ athlete was not aware of an airway hypersensitivity to exercise prior to participation in the study. Ten EVH+ athletes reported treating their asthma symptoms regularly with IBAs on an as-needed basis in addition to inhaled corticosteroids (ICS) as a baseline therapy for the underlying lung inflammation. The remaining three EVH+ athletes with a previous asthma diagnosis mentioned that they treated symptoms with IBAs and ICS upon their initial diagnosis but had not renewed their prescription or were not using any asthma medications in the weeks leading up to the study participation. No EVH− athletes reported a previous history or diagnosis of asthma.

Table 1 Anthropometric, fitness and lung function parameters in athletes with a positive (EVH+) and a negative (EVH−) eucapnic voluntary hyperpnoea (EVH) challenge

	Total		EVH−		EVH+	
Parameter	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Age (years)	28 (5)	18–40	29 (5)	18–39	27 (6)	19–40
Height (cm)	183 (7)	165–198	183 (8)	165–198	182 (6)	172–196
Weight (kg)	75.4 (9)	61.0–105.0	76.3 (9.0)	61.0–105.0	73.2 (8.2)	63.4–85.0
Cycling experience (years)	6 (5)	2–25	6 (4)	2–17	7 (6)	2–25
FVC (L)	6.6 (0.9)	5.2–9.0	6.7 (0.9)	5.2–9.0	6.3 (0.8)	5.3–8.5
FVC predicted (%)	114 (12)	91–131	115 (11)	94–101	109 (12)	91–131
FEV_1 (L)	5.22 (0.77)	3.89–7.00	5.44 (0.72)*	4.08–7.00	4.67 (0.60)*	3.89–6.09
FEV_1 predicted (%)	111 (13)	81–141	115 (12)*	96–141	100 (11)*	81–117
FEV_1/FVC (%)	83 (7)	70–105	81 (6)*	70–100	75 (8)*	73–105
FEV_1/FVC predicted (%)	96 (8)	73–119	98 (7)*	85–119	91 (10)*	73–105
Δ Max FEV_1* (%)	11 (9)	3–50	8 (3)*	3–23	19 (14)*	5–50
VO_{2max} (ml/kg/mL)	65.5 (6.2)	53.2–85.3	65.7 (6.7)	53.2–85.3	65.0 (5.2)	59.1–76.5
Max Power (W)	433 (36)	360–526	438 (38)	360–526	430 (28)	386–480
Max Power (W/kg)	5.78 (0.46)	5.01–7.30	5.73 (0.43)	5.01–7.30	5.92 (0.50)	5.27–6.95

*Statistically significant difference between EVH+ and EVH− athletes ($p<0.05$).
FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; Δ Max FEV_1, decrease in FEV_1 to a eucapnic voluntary hyperpnoea test; VO_{2max} maximal oxygen consumption.

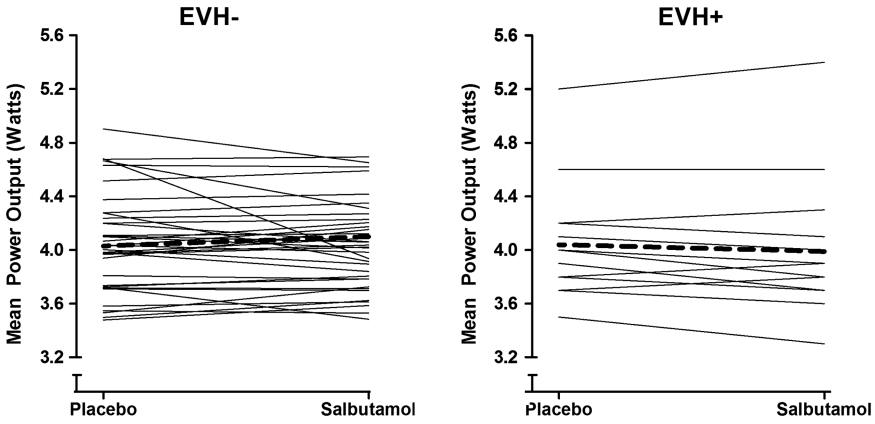

Figure 1 Athletic performance after salbutamol- and placebo-use in athletes without (EIB−) and with (EIB+) exercise-induced bronchoconstriction.

Eleven athletes had mild EIB (percent decrease in FEV_1 after EVH challenge≥10% but <25%) and three athletes had moderate EIB (per cent decrease≥25% but ≤50%). The EVH test induced a significantly greater decrease in FEV_1 in EVH+ athletes (−19.3 (14.2)%) compared to EVH− athletes (−8.1 (3.4)%, p=0.001). The percent predicted values for FEV_1 and FEV_1/FVC were significantly lower in EVH+ athletes than in EVH− athletes (p≤0.01; see table 1). There were no statistical differences in anthropometry between EVH+ and EVH− athletes. Maximal oxygen consumption relative to body weight and absolute maximal power output achieved on the maximal exercise test did not differ between EVH+ and EVH− athletes (see table 1).

The effect of IBA on lung function

Thirty minutes after salbutamol-use, the mean FEV_1 increased by 6.1 (4.7%) compared to 1.2 (2.9%) after the inhalation of the placebo (p<0.001). The improvement in lung function due to salbutamol-use was significantly greater in EVH+ athletes (9.0 (7.0%)) compared to EVH− athletes (5.0 (2.7%), p=0.018).

The effect of IBA on athletic performance

The mean power output during the time-trial after inhaled salbutamol-use (4.07 (0.47) W/kg) was not significantly different from the mean power output achieved in the time trial after the inhalation of placebo (4.04 (0.38) W; figure 1). The per cent change in mean power across conditions was similar in both groups (figure 1; p>0.05). The inhalation of salbutamol caused 18 athletes to increase mean power output by more than 1% relative to placebo (4 EVH+ and 14 EVH−; χ^2=0.56, p=0.45) and 17 athletes to decrease mean power output by more than 1% (7 EVH+ and 10 EVH−; χ^2=2.03, p=0.15).

The severity of EIB, assessed by the percent decrease of FEV_1 in the EVH test, was not related to the change in mean power output between the placebo and salbutamol time-trials

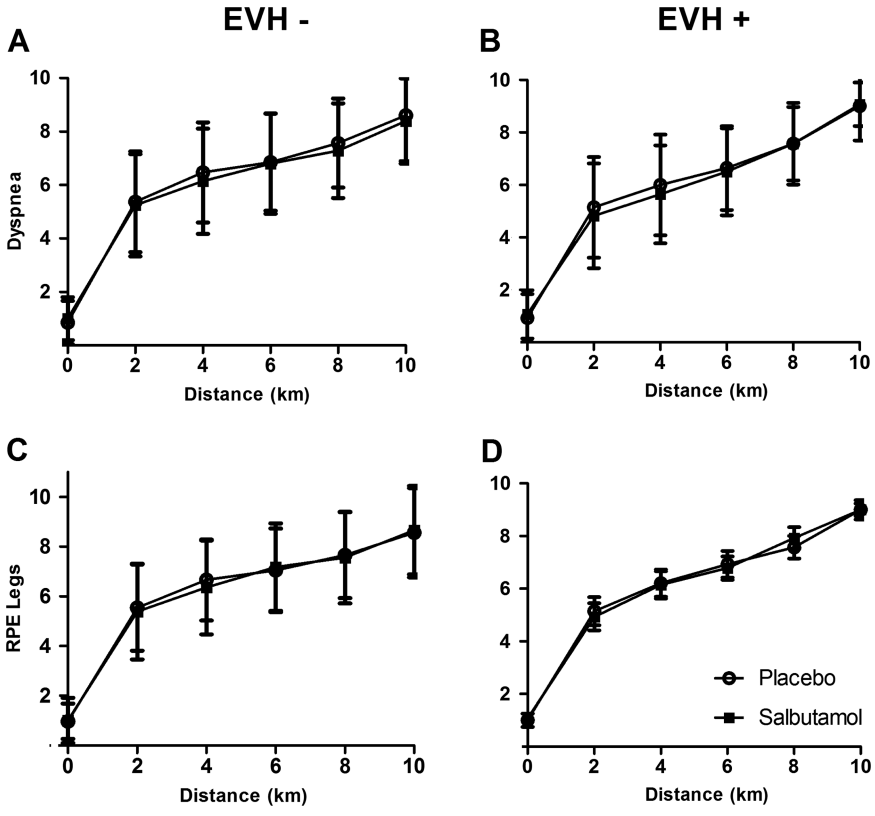

Figure 2 Rating of perceived dyspnea in athletes (A) without (EIB−) and (B) with (EIB+) exercise-induced bronchoconstriction; and rating of perceived exertion (RPE) for legs in EIB− (C) and EIB+ (D) athletes (means and standard deviation).

Table 2 Performance parameters measured during the 10 km time trials in athletes with a positive eucapnic voluntary hyperpnoea (EVH+) and a negative EVH− challenge

	Total (N=49)		EVH− (N=35)		EVH+ (N=14)	
Parameter	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**	**Mean (SD)**	**Range**
Power (W/kg)						
Salbutamol	4.1 (0.5)	3.3–5.5	4.1 (0.5)	3.5–4.7	4.0 (0.5)	3.3–5.5
Placebo	4.0 (0.4)	3.5–5.3	4.0 (0.4)	3.5–4.9	4.0 (0.5)	3.5–5.3
VO_2 (L/kg/min)						
Salbutamol	55.9 (6.4)	46.6–75.2	56.8 (6.5)	46.6–75.2	53.8 (5.5)	48.3–67.7
Placebo	54.8 (9.6)	43.5–73.6	56.7 (6.6)	44.9–73.6	54.4 (5.9)	43.5–67.7
Heart rate (b/min)						
Salbutamol	167 (10)	137–191	167 (10)	148–184	165 (16)	137–191
Placebo	168 (11)	135–190	169 (10)	144–187	166 (13)	135–190
Ventilation (L/min)						
Salbutamol	136 (25.0)	91–218	142* (25.0)	102–218	123* (19.9)	91–155
Placebo	136 (26.2)	90–217	143* (25.3)	97–217	120* (22.3)	90–169
Respiratory rate (b/min)						
Salbutamol	43 (8)	21–60	44 (8)	21–60	41 (6)	32–53
Placebo	43 (7)	31–61	44 (7)	31–61	40 (5)	34–52
Tidal volume (L/kg^1)						
Salbutamol	3.19 (0.49)	2.30–4.41	3.26 (0.53)	2.45–3.43	3.01 (0.32)	2.30–4.41
Placebo	3.18 (0.51)	2.23–4.33	3.26 (0.51)	2.23–4.33	2.98 (0.46)	2.23–4.03

*Statistically significant main effect between EVH+ and EVH− athletes, p<0.

(r=0.003, p=0.70). Furthermore, there was no correlation between fitness level, assessed by VO_{2max} on the screening day and the difference in mean power output between the two time-trials (r=0.007, p=0.22).

Neither EVH+ nor EVH− athletes perceived a difference in dyspnoea or RPE of legs during the two time-trials (see figure 2). Minute ventilation was significantly lower in EVH+ compared to EVH− athletes in both time-trials (p=0.007). None of the additional cardiovascular parameters describing performance were altered by the salbutamol treatment (table 2). Lung size (FVC) was not associated with respiratory or performance outcomes in EVH+ and EVH− athletes after salbutamol-use (data not shown).

DISCUSSION

This is the first study to compare the effects of inhaled salbutamol on lung function and cycling performance between trained EVH+ and EVH− athletes. Salbutamol did not affect time-trial performance in EVH+ or EVH− athletes despite significantly improving FEV_1. Athletes did not perceive a difference in dyspnoea or the RPE for legs during the time-trial after the inhalation of salbutamol. Our results support previous studies that demonstrated significant improvements in lung function after IBA use in EVH− athletes without any effects on athletic performance.[16–18] Our findings in EVH+ athletes are novel. As hypothesised for this study, athletes with a positive response to an EVH challenge, indicative for EIB, had a significantly greater bronchodilatory response to inhaled salbutamol; however, contrary to our hypotheses, inhaled salbutamol did not affect power output, exercise ventilation, dyspnoea and RPE of legs of EVH+ athletes.

Similar to our results, Meeuwisse *et al*[9] reported a statistically significant increase in FEV_1 (5.3%) after the inhalation of 200 µg salbutamol in non-asthmatic athletes. This response to salbutamol was described as clinically irrelevant. To be certain that the change in FEV_1 was not due to variability in the test itself, a difference in FEV_1 of 10–15% was reported to be necessary.[9] Owing to the number of spirometry tests performed on the screening day in our study, we are confident that our athletes were consistent in their spirometry techniques. Only five athletes (EVH−: 1; EVH+: 4) increased their FEV_1 by more than 10% after salbutamol use, ranging from 12.7% to 26.8%; however, even in this subset of athletes, there was no increase in performance. Mean ventilation was lower in EVH+ athletes compared to EVH− athletes after both treatments, even though EVH+ athletes experienced a significantly greater improvement in FEV_1; thus, our findings indicate that the key parameters (exercise performance, minute ventilation, dyspnoea and RPE of legs) are not influenced by a salbutamol-induced increase in FEV_1 in athletes, regardless of the EVH challenge outcome.

As recommended by Sue-Chu *et al*,[11] we chose an exercise protocol with high-intensity and short duration workloads to maximally challenge the athletes' respiratory capabilities: if the respiratory system was the performance-limiting factor, the ergogenic effects of salbutamol-induced bronchodilation should have been maximised. The 10 km time trials in this study lasted between 14 min and 16 min and the ratings of perceived dyspnoea and RPE for legs indicated maximal efforts. Despite the improved lung function after the inhalation of salbutamol, EVH + and EVH− athletes had no change in perceived dyspnoea. Therefore, we conclude that the respiratory system was not the performance-limiting factor for our healthy, well-trained group of male athletes.

The effects of IBAs on athletic performance have been investigated in male athletes in multiple studies,[5] but highly-trained female participants have been overlooked. Owing to sex differences in pulmonary anatomy,[19] female athletes may benefit more from the use of IBAs compared to men; therefore, future studies should focus on the effects of IBAs on cardiorespiratory parameters and performance in women to determine whether our results can be applied to women.

In conclusion, the inhalation of 400 µg of salbutamol significantly improved resting lung function, but it did not affect exercise performance in well-trained EVH+ and EVH− athletes.

Even though EVH+ athletes showed a greater bronchodilatory response to inhaled salbutamol than did EVH− athletes, mean power output and minute ventilation were similar between groups. Furthermore, despite the significant improvement in lung function after salbutamol inhalation, dyspnoea and RPE for legs were not perceived as being easier compared to placebo in EVH+ and EVH− athletes. Based on our results, inhaled salbutamol had no discernible effect on key ventilatory and exercise parameters regardless of the EVH challenge outcome in 10 km time-trial performances.

What are the new findings?

- This is the first study to compare the acute effects of inhaled salbutamol during exercise between trained cyclists, who showed a positive and a negative response to a eucapnic voluntary hyperpnoea (EVH) challenge, which is indicative of exercise-induced bronchoconstriction (EIB).
- The inhalation of salbutamol caused a significant improvement in resting lung function in athletes with a positive EVH challenge (EVH+) and a negative EVH challenge (EVH−).
- Even though EVH+ athletes showed a greater bronchodilatory response to inhaled salbutamol than EVH− athletes, there was no difference in mean power output, minute ventilation, dyspnoea and perceived exertion for legs during a 10 km cycling time trial.
- Inhaled salbutamol had no discernible effect on key ventilatory and exercise parameters regardless of the outcome of the EVH challenge.

How might it impact on clinical practice in the near future

- Inhaled salbutamol does not affect ventilation, ratings of perceived exertion or dyspnoea or athletic performance in EVH+ and EVH− athletes; therefore, the use of inhaled salbutamol is not advantageous to cycling performance and is not performance-enhancing even in athletes with a positive EVH challenge.
- The EVH+ athletes in this study were warmed up prior to the exercise challenge and performed well even in the placebo trial; EVH+ athletes are thus advised to incorporate a sufficient warm-up prior to training and competition.
- Clinicians caring for athletes with EIB may want to review their current management; some athletes may no longer require prophylactic treatment with salbutamol prior to training and competition.

Contributors SK contributed significantly to the study design, collected and analysed data and acted as the main author of the manuscript. MJM contributed to the study design, assisted in the data analysis and the preparation of the manuscript substantially. BCS contributed to the study design, advised in questions around cycling performance, assisted in the preparation of the manuscript. JLR contributed to the study design and assisted in the preparation of the manuscript. MSK conceived and secured funding for the study, contributed significantly to the study design, assisted in questions regarding data collection and analysis, assisted in the preparation of the manuscript.

Funding This study was funded by the World Anti-Doping Agency (WADA).

Competing interests None.

Ethics approval Clinical Research Ethics Board of the University of British Columbia, Vancouver BC Canada.

Provenance and peer review Not commissioned; externally peer reviewed.

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Br J Sports Med 2015 49: 51-55 originally published online October 7, 2013
doi: 10.1136/bjsports-2013-092706