



Effects of Terbutaline Sulfate on Physiological and Biomechanical as Well as Perceived Exertion in Healthy Active Athletes: A Pilot Study

by

Hanen Hafedh¹, Maamer Slimani², Bianca Miarka³, Ramzi Bettayeb¹,
Nicola Luigi Bragazzi^{2,4}

This study aimed to investigate the effects of beta2-agonist terbutaline sulfate (TER) at a supra-therapeutic dose (8 mg) on aerobic exercise performance. Twelve (6 females and 6 males) amateur athletes familiarized with all experimental procedures had their anthropometric data obtained on day 1. On days 2 and 3 either 8 mg of TER or a placebo (PLA) was administered orally (double-blind manner) to participants who had rested for 3 h prior to aerobic exercise performance 20 m multistage fitness test (MSFT). This test was used to predict maximal oxygen uptake (VO_{2max}) and velocity at which VO_{2max} occurs (vVO_{2max}). The Borg rating of perceived exertion (RPE), cardiovascular variables [heart rate (HR) and blood pressure (BP)] and blood glucose concentration [BGC] were obtained 15 min pre- and immediately post-MSFT. Significant mean group differences were reported between PLA and TER groups ($p < 0.05$), respectively, in the RPE (15.6 ± 1.2 vs. 17.3 ± 1.5 a.u.), maximum heart rate (HR_{max} : 191.2 ± 7.1 vs. 197.2 ± 8.6 bpm) and BGC (118.4 ± 18.3 vs. 141.2 ± 15.8 mg/dL) post-MSFT. The main effect of gender (male vs. female) in TER and PLA groups ($p < 0.05$) was observed, with higher estimated VO_{2max} , vVO_{2max} , HR_{max} and a lower mean HR pre-test in male than female athletes. For these reasons, the inclusion of TER in the Prohibited List should be re-discussed because of the lack of ergogenic effects.

Key words: β_2 -agonist, doping, blood glucose concentration, blood arterial pressures, heart rate.

Introduction

Beta-2 adrenergic agonists (β_2 -agonists) are a family of drugs including compounds such as salbutamol, fenoterol and terbutaline (TER). These are commonly prescribed for bronchospasm and exercise-induced asthma (Le Fur et al., 2012), even though their potential ergogenic effect could lead to misuse by athletes (Collomp et al., 2010; Hostrup et al., 2014; Pluim et al., 2011).

Inhalation of 4–6 mg of salbutamol may

extend time to exhaustion (constant work test) or the final sprint during an endurance exercise bout in healthy male individuals active in a variety of sports such as track and field, hockey, soccer, or cycling (Collomp et al., 2000; Van Baak et al., 2000). On the other hand, high doses of oral TER did not improve any variable of aerobic performance in well-trained/competitive (Sanchez et al., 2013) or moderately trained male healthy athletes (Kalsen et al., 2014). However, it is unclear whether these results could also apply to

¹ - Research Unit "Sports Performance and Physical Rehabilitation", Higher Institute of Sport and Physical Education El Kef, University of Jendouba, Tunisia.

² - School of Public Health, Department of Health Sciences (DISSAL), Genoa University, Genoa, Italy.

³ - Federal University of Juiz de Fora, Brazil.

⁴ - Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), Section of Psychiatry, Genoa University, Genoa, Italy.

amateur or recreational male and female athletes: theoretically speaking, it seems plausible that the physiological response evoked by β_2 -agonists is dependent on training status in that β_2 -receptors are widely distributed in tissues affected by training. Thus, training-induced alterations in enzymes involved in those metabolic pathways which mediate the activity of β_2 -agonists are likely to impact physiological responses elicited by β_2 -agonists themselves (Kalsen et al., 2014). Moreover, β_2 receptor density is dependent on training status (Butler et al., 1982) and fiber type composition (Martin et al., 1989), which, further, seems to suggest a differentiated response to β_2 -agonists according to training status.

From a physiological standpoint, some studies suggest that endurance performance improvement after the inhalation of β_2 -agonists involves increased energy production from the carbohydrate metabolism (Collomp et al., 2000, 2010; Decorte et al., 2008). For instance, β_2 adrenergic stimulation with TER increases carbohydrate oxidation, muscle glycogen utilization, and lactate accumulation during 60 min of exercise at 65–70% of maximal oxygen uptake (VO_{2max}) with no difference in glycogen utilization, lactate accumulation, and performance during a 300-kcal time trial (that is to say, the ingestion of a 300-kcal load, performed 30 s after sub-maximal exercise at 65–70% of VO_{2max} , with serial measurements performed at the achievement of the 100-kcal, 200-kcal and 300-kcal mark) (Kalsen et al., 2014).

To the best of our knowledge, no study has comprehensively investigated the effects of acute supra-therapeutic TER sulfate administration on blood glucose concentration (BCG), cardiovascular variables and the Borg rating of perceived exertion (RPE). These variables are useful for quantifying effort intensity during training, whereas the RPE is defined as the whole of effort emotions, constraints, fatigue and discomfort that a person may experience during an exercise (Robertson and Noble, 1997). The RPE is often used as an intensity indicator in continuous aerobic activities (Coquart et al., 2016).

The aim of this study was to determine the ergogenic effects of an acute supra-therapeutic dose of TER sulfate on aerobic performance, metabolic adaptations,

cardiovascular variables and RPE in a sample of healthy active male and female athletes.

Methods

Participants

Twelve recreationally active athletes (6 female: age = 22 ± 0.89 years, body height = 1.63 ± 0.41 m, body mass = 59.78 ± 5.1 kg, body mass index (BMI) = 22.67 ± 2.64 kg·m⁻²; 6 male: age = 22.5 ± 0.84 years, body height = 1.75 ± 0.06 m, body mass = 74.97 ± 3.67 kg, BMI = 24.49 ± 1.81 kg·m⁻²), engaged in a variety of sports including tennis, athletics and taekwondo, volunteered to participate in this study, after being informed of the nature and of possible disadvantages associated with the present experiment.

To be eligible for this study, subjects were required to meet the following criteria: (a) no consumption of any supplements or drugs; (b) no history of use of medications that could alter the hypothalamic-pituitary-gonadal (HPG) axis, such as anabolic steroids; (c) no history of chronic disease, bronchospasm or atopy; (d) regular eating patterns; (e) no respiratory infections during the previous month; and (f) no recognized asthma or allergy during the 5 years preceding the study.

The study was conducted according to the 1964 Declaration of Helsinki and its subsequent amendments. The study protocol was fully approved by the Ethic Committee of the Unit of Research "Sports Performance and Physical Rehabilitation", Higher Institute of Sport and Physical Education El Kef, University of Jendouba, Tunisia. Both written and verbal informed consent was obtained from each participant following verbal description of all experimental details, prior to any experimental data collection.

Procedures

The study was carried out with a double-blind, randomized, crossover design. It consisted of one screening visit and two identical study visits with inhalation of either TER or a placebo (PLA). During the screening visit, anthropometric data were collected. Furthermore, participants were familiarized with the 20 m multistage fitness test (MSFT). During this step, no drug was administered. All participants gave maximum effort and were encouraged to do so. Two days following the screening visit, either the oral dose

of 8 mg of TER sulfate (Talin, 26.66 ml) or PLA (dissolved flour) was given to each participant 3 h before the test. PLA and TER sulfate were packed in identical bottles. An independent researcher was involved and he was the only one to know the order of the processing and the exact nature of the flasks. The experimenters asked the subjects which of the two treatments they had received first, and if they had noticed any difference. Additionally, a blood sample was obtained at the two time points (15 min before MSFT and immediately after the test) across the exercise test in order to assess BCG together with generic physiological assessments of the heart rate (HR pre-test, HR post-test, maximum heart rate [HR_{max}], mean HR), blood pressure (BP, diastolic arterial pressure or DAP, systolic arterial pressure or SAP, mean arterial pressure or MAP). After a 10 min warm-up, participants performed the MSFT and responded to the RPE scale immediately afterwards (Borg, 1998).

Participants were advised to avoid exercise, and to restrain from caffeine, and alcohol consumption 48 h before each laboratory visit. Any food/fluid intake was registered 48 h prior to the first visit to the laboratory, and subjects were asked to duplicate that intake before the second visit. Moreover, throughout the study, participants were instructed to maintain their regular dietary habits and exercise regimens. The experimental protocol was carried out in the ambient temperature of 25°C.

Evaluations

Blood glucose concentration (BGC)

Plasma concentration of glucose was determined by the enzymatic colorimetric method on an Architect C8000.

Arterial blood pressure (BP)

Arterial BP was measured by the same trained experimenter with an automatic tensiometer "Exacto KD 591" with an error margin of 5% (Rabi et al., 2011) under the direct supervision of a medical doctor (Slimani et al., 2017). SAP and DAP were measured in millimeters of mercury (mmHg) and registered as the mean of two consecutive BP measurements. MAP was defined as $DAP + 1/3 (SAP - DAP)$.

Heart rate (HR)

The HR (HR pre-test, HR post-test, mean HR and HR_{max}) was monitored at 5 s intervals throughout the experiment using a heart rate

monitor Polar TF4 (Polar Electro, Finland) and measured in beats per minute (bpm).

Aerobic performance

The MSFT was conducted as previously described (Léger et al., 1988). The participants ran back and forth between two lines, spaced 20 m apart, in accordance to the recorded "beep" sound. Each successful run of the 20 m distance was considered as a completed shuttle. The test started with an initial speed of 8 km/h that increased by 0.5 km/h every minute and was stopped if the subject failed to reach the line (within 2 m) for two consecutive ends after a warning. Maximal speed was calculated as the velocity of the last fully completed stage and considered as the speed associated with VO_{2max} for the shuttle run test (vVO_{2max}). VO_{2max} was estimated using the Léger et al. (1988) formula.

Rating of perceived exertion (RPE)

The RPE was recorded immediately after the MSFT using the adapted Borg's category scale (6-20) (Borg, 1998).

Statistical analysis

Data are presented as mean values \pm standard deviation (SD). The Shapiro-Wilk test (S-W) was used to determine whether data were normally distributed. Two-way repeated measures analysis of variance (ANOVA) [2 (group) \times 2 (time) \times 2 (gender)] was applied to test the main effects between pre- and post-test (time) and between the two groups (TER vs. PLA) with gender (male vs. female) as the independent factor. The Bonferroni test was used as a post-hoc test correcting for multiple comparisons. To allow a better interpretation of the results, the effect sizes were calculated (eta squared η^2). A significance level of $p \leq 0.05$ was used for all analyses. All statistical analyses were carried out using the commercial software "Statistical package for social sciences" (SPSS version. 16.0, IBM Inc., Chicago, IL, USA).

Results

All subjects were able to recognize the TER sulfate treatment and experienced adverse side effects such as tremors, tachycardia and pallor starting 1 h after TER sulfate intake. The manifestation of these ancillary effects was more pronounced in female subjects.

Aerobic performance and RPE

Descriptive analysis of aerobic

performance and the RPE are presented in Table 1. Statistical analysis indicated a significant main effect of gender for $v\text{VO}_{2\text{max}}$ ($F_{1,10} = 21.235$; $p < 0.001$; $\eta^2 = 0.68$), where the male TER group showed higher values than the female TER group ($p < 0.001$; 95% CI = 0.670 to 2.330) and the male PLA group demonstrated higher values than the female PLA group ($p < 0.001$; 95% CI = 0.924 to 2.409). No significant difference was observed when comparing $v\text{VO}_{2\text{max}}$ value between PLA and TER groups ($p = 0.34$; 95% CI = -0.269 to 0.102).

The analysis showed a significant main effect of gender for the estimated $\text{VO}_{2\text{max}}$ value ($F_{1,10} = 24.948$; $p < 0.001$; $\eta^2 = 0.71$), where the male TER group showed higher values than the female TER group ($p < 0.001$; 95% CI = 35.749 to 40.951) and the male PLA group demonstrated higher values than the female PLA group ($p < 0.001$; 95% CI = 36.500 to 41.200). No other effect was observed in the estimated $\text{VO}_{2\text{max}}$ value between PLA and TER groups ($p = 0.14$; 95% CI = -0.205 to -1.205).

A significant main effect of the group for RPE value was reported ($F_{1,10} = 281.424$; $p < 0.001$; $\eta^2 = 0.96$), where the TER group showed lower values than the PLA group ($p < 0.001$; 95% CI = -25.130 to -19.237). No other difference was observed in the RPE when comparing genders for TER ($p = 0.48$; 95% CI = 14.8 to 16.3) and PLA groups ($p = 0.18$; 95% CI = 16.3 to 18.1).

Heart rates

Descriptive analysis of heart rates is presented in Table 2.

Statistical analysis showed a significant main effect of time for mean HR ($F_{3,10} = 83.151$; $p < 0.001$; $\eta^2 = 0.39$), with lower mean HR values for the PLA group in the pre-test than in the post-test ($p < 0.001$; 95% CI = -47.386 to -26.448). In addition, the TER group in the pre-test showed lower HR values than the post-test ($p < 0.001$; 95% CI = -40.537 to -21.130). No other effects were observed when comparing mean HRs between groups ($p = 0.22$; 95% CI = -1.279 to 4.779) and genders ($p = 0.95$; 95% CI = -13.813 to -2.178).

The analysis disclosed a significant main effect of the group for HR_{max} ($F_{1,10} = 30.000$; $p < 0.001$; $\eta^2 = 0.75$), where the TER group showed lower HR_{max} values than the PLA group ($p < 0.001$; 95% CI = 196.615 to 208.719). Furthermore, statistical analysis showed a significant main effect of gender in the TER group for the HR_{max}

($F_{1,10} = 7.772$; $p = 0.019$; $\eta^2 = 0.44$), where females showed lower HR_{max} values than males ($p = 0.019$; 95% CI = -16.193 to -1.807). Moreover, statistical analysis showed a significant main effect of gender for the PLA group in terms of the HR_{max} ($F_{1,10} = 8.200$; $p = 0.017$; $\eta^2 = 0.45$), where females showed lower HR_{max} values than males ($p = 0.017$; 95% CI = -19.559 to -2.441).

Arterial pressures

Descriptive analysis of arterial pressures is presented in Table 3.

Statistical analysis showed a significant main effect of time and group for SAP ($F_{3,8} = 11.735$; $p = 0.003$; $\eta^2 = 0.81$), where the PLA group during the pre-test showed lower values than the own SAP in the post-test ($p = 0.038$; 95% CI = -47.389 to -1.111). No other differences were observed in terms of SAP when comparing time for the TER group ($p = 1.0$; 95% CI = -9.027 to -11.860) and genders ($p = 0.25$; 95% CI = -30.715 to -9.049). No differences were observed for DAP when comparing gender ($p = 0.51$; 95% CI = -4.917 to 7.292), time and groups ($F_{3,8} = 3.595$; $p = 0.066$; $\eta^2 = 0.57$). Moreover, no differences were observed in MAP when comparing genders ($p = 0.37$; 95% CI = -6.889 to 7.378), time of testing and groups ($F_{3,8} = 3.379$; $p = 0.075$; $\eta^2 = 0.55$).

Blood glucose concentrations (BGC)

Descriptive analysis of BGC is presented in Table 4.

Analysis disclosed a significant main effect of time and group for BGC ($F_{3,8} = 21.024$; $p < 0.001$; $\eta^2 = 0.89$), where the PLA group during the pre-test showed lower values than during the post-test ($p = 0.014$; 95% CI = -45.927 to -4.739). No other differences were observed when comparing genders ($p = 0.49$; 95% CI = 3.417 to 4.723).

Discussion

In this study examining the effects of oral systemic TER sulfate intake on aerobic performance, cardiovascular variables, metabolic adaptations and perceptual response in active male and female athletes, we could not report significant differences between TER and PLA groups in estimated $\text{VO}_{2\text{max}}$ and MAP values. The results also showed significant differences between experimental groups in the RPE, HR_{max} and BGC in active male and female athletes. As such, the current study showed higher estimated $\text{VO}_{2\text{max}}$, $v\text{VO}_{2\text{max}}$ and HR_{max} in male compared to female athletes.

Table 1

Descriptive analysis of aerobic performance variables and perceived exertion (values reported as mean \pm SD).

Gender	vVO _{2max} (km/h)	vVO _{2max} (km/h)	VO _{2max} (ml/min/kg)	VO _{2max} (ml/min/kg)	RPE (a.u.)	RPE (a.u.)
	PLA	TER	PLA	g) TER	PLA	TER
Female	10.3 \pm 0.8	10.3 \pm 0.8	33.1 \pm 4.8	33.1 \pm 4.8	17.8 \pm 1.8	15.8 \pm 1.0
Male	12.0 \pm 0.0*	11.8 \pm 0.4*	44.6 \pm 1.9*	43.6 \pm 3.1*	16.7 \pm 0.8	15.3 \pm 1.4
Total	11.2 \pm 1.0	11.1 \pm 1.0	38.8 \pm 6.9	38.3 \pm 6.7	17.3 \pm 1.5 [#]	15.6 \pm 1.2

*Different from female group; #Different from TER group, $p < 0.05$.

Table 2

Descriptive analysis of the heart rate (values reported as mean \pm SD).

HR variable/Gender	Female	Male	Total
HR pre-test PLA	86.5 \pm 14.2*	71.8 \pm 7.5	79.2 \pm 13.2 [#]
HR pre-test TER	99.8 \pm 6.0*	83.7 \pm 15.5	91.8 \pm 14.0
HR post-test PLA	115.5 \pm 9.4	116.7 \pm 15.5	116.1 \pm 12.2 ^{a,b}
HR post-test TER	119.3 \pm 4.9	125.8 \pm 11.6	122.6 \pm 9.2 ^{a,b}
HR mean PLA	169.7 \pm 4.9	175.6 \pm 8.3	172.7 \pm 7.2
HR mean TER	168.1 \pm 7.3	173.8 \pm 5.5	170.9 \pm 6.8
HR _{max} PLA	191.7 \pm 5.9*	202.7 \pm 7.3	197.2 \pm 8.6 [#]
HR _{max} TER	186.7 \pm 6.2*	195.7 \pm 4.8	191.2 \pm 7.1

Arterial HR analysis was performed using bpm; *Different from the male group at the same moment; #Different from the other group at the same moment; ^aDifferent from the pre-test moment; ^bDifferent from the other group during the pre-test moment, $p < 0.05$.

Table 3*Descriptive analysis of arterial blood pressure (values reported as mean \pm SD).*

Gender / Time		SAP PLA	SAP TER	DAP PLA	DAP TER	MABP PLA	MABP TER
Female	Pre-test	114.2 \pm 10.6	128.8 \pm 14.4	67.3 \pm 6.5	68.8 \pm 5.5	82.9 \pm 6.2	88.8 \pm 6.7
	Post-test	134.2 \pm 9.8	130.0 \pm 8.9	80.2 \pm 6.5	74.5 \pm 5.9	98.2 \pm 6.2	93.0 \pm 6.3
Male	Pre-test	126.3 \pm 20.9	136.7 \pm 17.6	71.0 \pm 7.4	67.3 \pm 18.0	89.4 \pm 11.4	90.4 \pm 16.7
	Post-test	154.8 \pm 33.1	132.7 \pm 24.2	96.0 \pm 56.3	76.2 \pm 28.3	115.6 \pm 47.4	95.0 \pm 25.0
Total	Pre-test	120.3 \pm 17.0 [#]	132.8 \pm 15.9	69.2 \pm 6.9	68.1 \pm 12.7	86.2 \pm 9.4	89.6 \pm 12.1
	Post-test	144.5 \pm 25.6 [#]	131.3 \pm 17.5	88.1 \pm 39.1	75.3 \pm 19.5	106.9 \pm 33.5	94.0 \pm 17.4

Arterial blood pressures analysis was performed using mmHg; # Different from the TER group at the same moment; ^aDifferent from the pre-test moment, $p < 0.05$.

Table 4*Descriptive analysis of blood glucose (μ l) concentrations in mean \pm SD.*

Gender	Moment	BGC (mg/dL) PLA	BGC (mg/dL) TER
Female	Pre-test	90.0 \pm 6.3	114.2 \pm 17.1 [#]
	Post-test	116.8 \pm 18.1	142.8 \pm 15.3
Male	Pre-test	96.2 \pm 11.0	94.5 \pm 8.5
	Post-test	120.0 \pm 20.1	139.5 \pm 17.6
Total	Pre-test	93.1 \pm 9.1	104.3 \pm 16.5
	Post-test	118.4 \pm 18.3 [#]	141.2 \pm 15.8 [#]

**Different from the male group at the same moment; # Different from the TER group; ^aDifferent from the pre-test moment, $p < 0.05$.*

Aerobic performance and RPE

The lack of an ergogenic effect of TER sulfate on aerobic performance is in accordance with the findings of Kalsen et al. (2014) and Larsson et al. (1997), who proved that the inhalation of TER at a therapeutic dose had no effect on estimated $\text{VO}_{2\text{max}}$. Furthermore, Sanchez et al. (2013) found that an acute supra-therapeutic oral TER sulfate administration had no ergogenic

effect on aerobic and anaerobic performance in healthy competitive male athletes. Based on the present investigation and the available studies, we can assume that high doses (8 mg) of oral TER sulfate did not improve any variable of aerobic performance in athletes at any competitive level (i.e., active, moderately- and well-trained). In contrast, previous studies showed that the acute oral administration of 4–6 mg salbutamol

increased aerobic performance (Collomp et al., 2005; Le Panse et al., 2005, 2006; Sanchez et al., 2012). This contradiction may be due to the differences of the molecule used and the dose administered (high, 8 mg vs. low, 4-6 mg). In addition, it has been shown that β_2 receptor density is dependent on training status (Butler et al., 1982), which may not lead to a differentiated response to β_2 -agonists in subjects with different training status.

We found a significant difference between experimental groups in RPE value, with a lower RPE in the TER sulfate group than in the PLA group. This seems to suggest a positive effect of oral TER sulfate intake on perceptual effort. In contrast, previous reviews reported that inhaled β_2 -agonists were without effect on the RPE and psychomotor performance (Larsson et al., 1997; Kindermann, 2007). Thus, the present study also showed a significant main effect of gender in aerobic performance, with lower estimated VO_{2max} values in active female than male athletes after the MFST. In contrast, during supra-maximal exercise after salbutamol intake (3-4 weeks, 12 mg daily), some studies showed no potentiating effects of gender (Caruso et al., 2008; Le Panse et al., 2005). In addition, no significant differences were observed between males and females in both groups for RPE value in the current study.

Heart rates and arterial blood pressure

The present study showed a significant difference between groups in terms of HR_{max} , with lower HR_{max} value in the TER sulfate group than in the PLA group. Accordingly, Collomp et al. (2010) confirmed the ergogenic effects of inhaled β_2 -agonists on the HR. Our results are in accordance with those reported by Fleck et al. (1993), who described a very significant increase in the HR during exercise after salbutamol inhalation. These results seem to confirm the literature (Le Fur et al., 2012), concerning the role of β_2 cardiac receptors in terms of the HR increase (positive chronotropic, dromotropic and bathmotropic effects).

In contrast, previous investigations of the effect of formoterol or salbutamol on cardiovascular variables during exercise have shown no difference with respect to the placebo in non-asthmatic subjects (McKenzie et al., 1983; Meeuwisse et al., 1992). For that reason, it is difficult to explain the contradictory results

obtained in the aforementioned studies. Furthermore, the present study showed no significant differences between groups in MABP value. For instance, when comparing therapeutic doses to terbutaline sulfate (8 mg, our study), salbutamol (400 g), fenoterol (400 g) and formoterol (20-300 g), significantly increased HR and decreased BP (Bremner et al., 1993; Faulds et al., 1991) values could be found.

Therefore, the discrepancies between studies suggest the need for further research studying the difference between oral and inhaled different β_2 -agonists on cardiovascular variables during aerobic exercise. In addition, the current study found a significant main effect of gender in both groups for HR_{max} , with lower HR_{max} value in active female than male athletes.

Blood glucose concentrations

The present study showed significant differences between groups in BGC. Accordingly, during intense sub-maximal exercise at 80-85% of VO_{2max} , Le Panse et al. (2007) showed that short-term salbutamol intake significantly decreased blood glucose. Furthermore, the presence of hyperglycemia in male and female subjects seems to be similar to the study of Collomp et al. (2002) who showed a significant increase of plasmatic insulin concentration after 10 min of steady cycling at 90% of VO_{2max} after salbutamol intake in trained man. This hyperglycemia may be explained by the stimulation of adrenergic receptors, which has a positive effect on phosphorylase glycogen, the enzyme responsible for the glycogen degradation to glucose-1-phosphate during the first stage of the glycogen transformation to glucose in the glycolytic process (Le Fur et al., 2012). Based on the results of our study and the investigation of Sheidegger et al. (1984), we can associate hyperinsulinemia status to hyperglycemia to confirm the β_2 -agonist effect during endurance exercise.

Side effects

All participants complained of the same adverse side effects such as tremors, tachycardia and pallor one hour following TER sulfate administration. Based on the study by Sanchez et al. (2013), we can confirm that these marked adverse side effects may prevent possible ergogenic effects of TER sulfate. Accordingly, Sato et al. (2010) postulated that taking these substances repeatedly could engender a decline in

β_2 receptor contents and side effects exhibitions. In addition, Whitsett et al. (1981) reported that TER generated less side effects when compared with other β_2 -agonists. In contrast, Van Baak et al. (2000) indicated that oral salbutamol administration had ergogenic effects in non asthmatic subjects without severe adverse side effects.

Limitations of the study

Some limitations related to the present research have to be acknowledged. First, the major shortcoming is given by the small sample of athletes who participated in the present investigation. Second, the MSFT, which was used to estimate VO_{2max} , was applied as an indirect method, which may be considered not accurate and precise. Thus, further investigations to verify the effect of TER sulfate on aerobic performance, using a direct method to assess VO_{2max} , are highly recommended.

Acknowledgements

We would like to thank all athletes who participated in the study. The authors would also like to affirm that they have no conflict of interest that is directly or indirectly relevant to the content of the present manuscript.

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Conclusions

A number of non-asthmatic athletes consider inhaled β_2 -agonists ergogenic although scientific evidence clearly disregards a performance enhancing effect. In conclusion, despite the presence of ergogenic effect of TER sulfate on perceptual response, HR (HR_{max}) and BGC, the acute supra-therapeutic dose of TER sulfate seems to be without any relevant effect on aerobic performance in healthy active male and female athletes. The effect of gender in estimated VO_{2max} and HR after the MSFT was also reported. For that reason, the inclusion of β_2 -agonists in the Prohibited List should be re-discussed because their ergogenic effects have not been confirmed. Further studies are required to examine the effects of long-term β_2 -agonist use on aerobic performance.

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Corresponding author:**Maamer Slimani**

School of Public Health, Department of Health Sciences (DISSAL),
Genoa University, Genoa, Italy
Phone: +21697067695
E-mail: maamer2011@hotmail.fr