DOES SALBUTAMOL HELP CERTAIN ATHLETES PERFORM BETTER?

by

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1. Summary

In this study, forty-nine competitive male cyclists aged between 19 and 40 years inhaled a commonly used asthma drug called salbutamol and then performed a 10 km time trial in a lab located at the University of British Columbia (UBC). We found that the inhalation of salbutamol leads to an increased forced expiratory volume in one second (FEV_1) but no significant change in performance as measured by mean power output relative to weight. We also found that the asthmatic cyclists have a greater improvement of lung function than non-asthmatic cyclists when treated with salbutamol, but no significant difference in mean power output. Finally, the A46G and C79G single nucleotide polymorphisms (SNPs) of the adrenergic beta-2-receptor gene (ADRB2) are selected because they are associated with the regulation of cardiorespiratory responses. An SNP of the epithelial sodium channel (ENaC) is also included. The improvement in mean power output for cyclists who inherit the CC genotype in C79G SNP after inhaling salbutamol is lower than those with the CG genotype for the same SNP. Likewise, cyclists with AA genotypes in the ENaC gene perform better than those with AT/TT.

2. Introduction

Beta2-agonists as the primary treatment of asthma can help patients breathe smoothly by decreasing airflow obstruction and relaxing the smooth muscle around the lung. In the history of the Olympic Games, asthmatic athletes tended to win more medals than non-asthmatic athletes (McKenzie and Fitch, 2011). The effect of beta2-agonists is believed to improve the performance of non-asthmatic athletes, and most beta2-agonists are banned from the Olympic Games. Only salbutamol and a few other kinds of beta2-agonists can be used in inhaled form under Therapeutic Use Exemption (TUE) (Kindermann, 2007). There have been many studies about how asthmatic medication affects the performance of athletes, but their relationship still remains mysterious. The first objective of this research is to determine the impact of salbutamol on performance of cyclists. The second objective would be to show if salbutamol has a better effect on asthmatic cyclists than the non-asthmatic. Although studies conducted in the past failed to provide a physiological explanation, one possible explanation could be that a genetically defined subgroup of athletes enjoys greater ergogenic benefit from such drugs. In the third objective, a new component, pharmacogenomics, is added. The concept is that when beta2-agonists act on beta2-receptors, the beta2-receptor genes with different variations may respond to the drugs uniquely. Therefore, the efficiency of salbutamol on the cyclists with different genotypes at the ADRB2 A46G, ADRB2 C79G and ENaC A663T SNPs is compared.

3. Data Description and Collection

This experiment focused on asthmatic versus non-asthmatic cyclists. Participants were forty-nine male, competitive cyclists ranging from 19 to 40 years old. Their maximal oxygen consumptions were at least 60 mL/kg/min (relative) or 5 L/min (absolute), and they were nonsmokers without a history of heart or lung diseases.

In the study visit, the participants did a graded exercise test on a stationary bicycle and gave a sample of their DNA to analyze for the genetic codes for beta2-receptors. There were three genotypes at each SNP. ADRB2 A46G SNP had AA, AG and GG genotypes. ADRB2 C79G had CC, CG and GG genotype. ENaC A663T had AA, AT and TT genotypes. They also did some baseline measurements for breathing function and lung function. In the first measurement, participants were asked to take a series of breaths out into a spirometer to measure the amount of air expelled. For the lung function measurement, participants were asked to breathe at a relatively fast rate after breathing a gas mixture for six minutes.

In days 2 and 3, the participants performed a simulated 10-kilometer time trial on cycling after taking a dose of 400-µg salbutamol or a placebo, which was assigned randomly. They were asked to finish in the shortest time possible in the trial. The collected data represented the variable of primary interest, which was called mean power output relative to weight (watts/kg). They also performed a lung function test right before and 30 minutes after the inhalation of asthma medication or the placebo. The collected data was the variable of secondary interest, which was forced expiratory volume in 1 second (liters per second). The experiment was double-blinded; neither the investigators nor the participants knew the order of placebo or salbutamol until the end of the study.

4. Methods

We used a paired t-test to compare the athletes who took salbutamol to the athletes who took the placebo drug, in order to address the first research question. For the second and third research questions, we first calculated the difference between treatments for each subject, and then performed a t-test using the differences between treatments to test on asthmatics versus non-asthmatic or coding levels for a specific SNP.

5. Results

5.1 Research Question 1:

Does inhalation of salbutamol increase % change in forced expiratory volume in one second or mean power output relative to weight?

We found that athletes had a 4.9% greater change in FEV_1 when taking salbutamol versus placebo ($P < 0.001$). We did not find any evidence that athletes who inhaled salbutamol had a greater mean power output relative to their weight ($P = 0.723$). The average % change in FEV_1 of athletes who took salbutamol was 6.1%, whereas athletes who took the placebo had 1.2%.

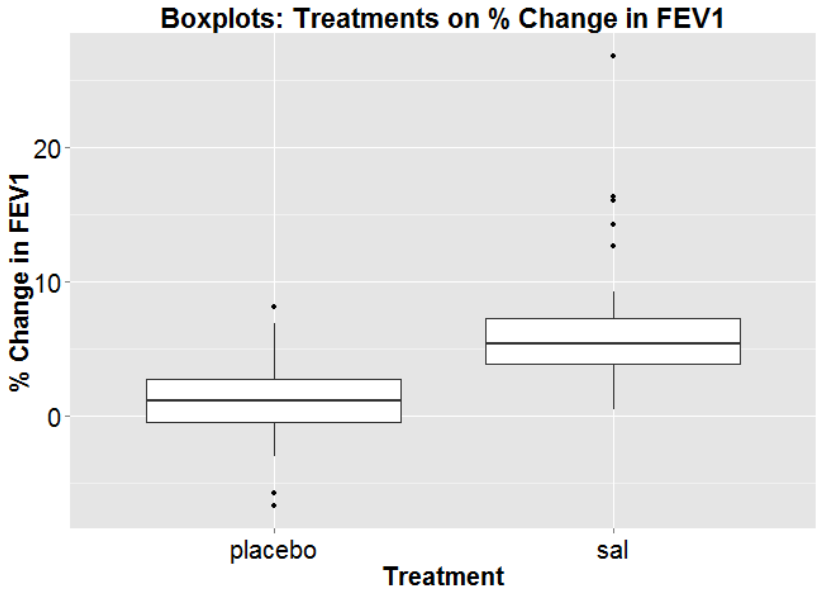

Figure 1 - Percent change in FEV1 (sal stands for salbutamol)

5.2 Research Question 2:

Does the inhalation of salbutamol increase % change in FEV_1 or mean power output relative to weight more for asthmatic athletes than non-asthmatic athletes?

We found that asthmatic athletes who inhaled salbutamol had a 4% greater change in FEV_1 versus non-asthmatics who inhaled salbutamol ($P = 0.01$). We did not find any evidence that asthmatic athletes who inhaled salbutamol had a greater increase of mean power output relative to their weight than non-asthmatic athletes who also inhaled salbutamol ($P = 0.693$). In Figure 2, asthmatic athletes had an average improvement in % change in FEV_1 of 7.46% after taking salbutamol. For non-asthmatic athletes, the average improvement in % change in FEV_1 is 3.45%.

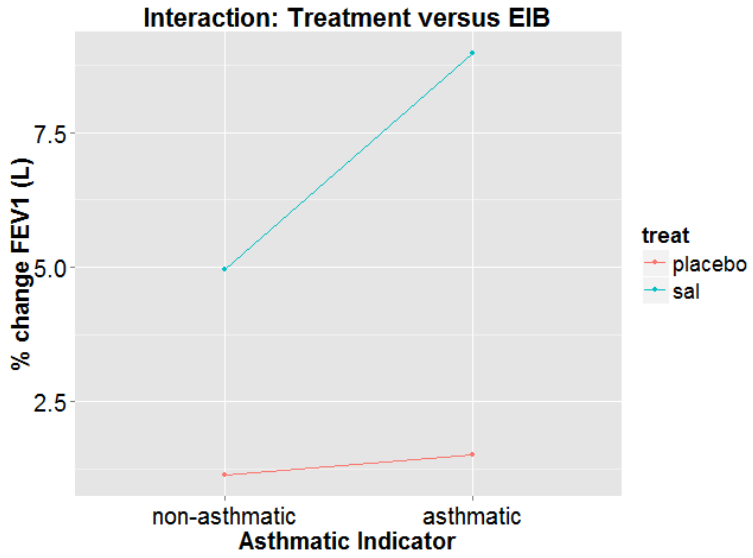

Figure 2 - Interaction Plot. Each point represents the mean for a cross-over of the groups asthma and treatment. The upper right teal coloured point represents the mean for asthmatic athletes who took salbutamol. The teal points are for salbutamol, and red points for placebo.

5.3 Research Question 3:

Do athletes with different coding levels in a particular A46G, C79G, or ENaC SNP respond differently from the inhalation of salbutamol in terms of their FEV_1 or mean power output relative to weight?

For each SNP, we were unsure which genotypes were high or low responders to salbutamol prior to our study. So, we performed tests that looked for differences rather than improvements in response to treatment between genotypes. We found that athletes with the CC genotype in C79G SNP after the inhalation of salbutamol resulted in a significantly lower improvement in mean power output relative to weight than athletes with the CG genotype in C79G SNP (P = 0.038). From Figure 3, we can see that athletes with the CG genotype had a positive effect of mean power output relative to weight (0.017 Watts/kg) from taking salbutamol over placebo as opposed to athletes with CC genotype who had an overall negative effect of mean power output relative to weight (-0.077 Watts/kg) from taking salbutamol.

We also found that athletes with the AA genotype in the ENaC SNP and the inhalation of salbutamol resulted in a near significant improvement in mean power output relative to weight than athletes with the AT/TT genotype in ENaC SNP (P = 0.059). From Figure 4, athletes with the AA genotype had an overall positive effect of mean power output relative to weight (0.0306 Watts/kg) from taking salbutamol over placebo as opposed to athletes with the AT/TT genotypes who had an overall negative effect of mean power output relative to weight (-0.044 Watts/kg).

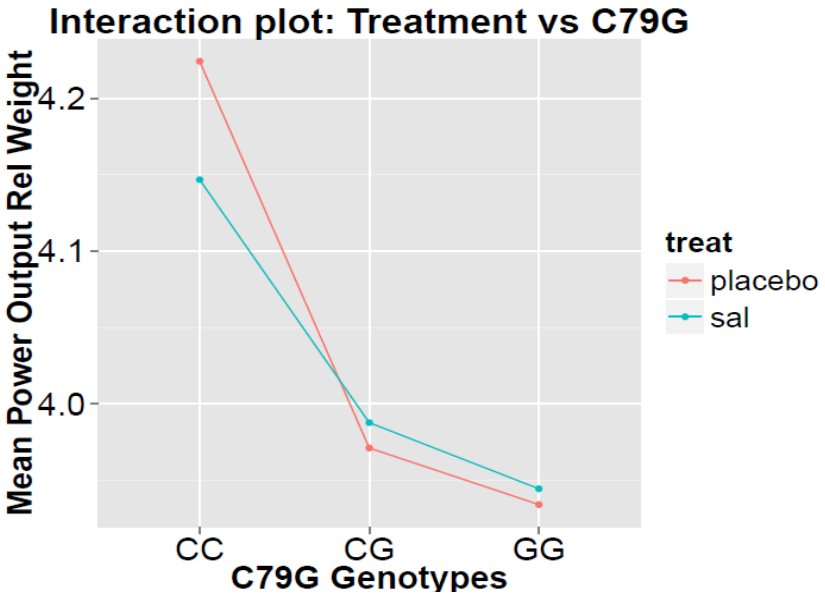

Figure 3 - Interaction Plot. Each point represents the mean for a cross-over of two groups. For example, bottom right red point represents the mean value of mean power output relative to weight for athletes of GG genotype who took placebo. The teal points represent salbutamol, and red points represent placebo.

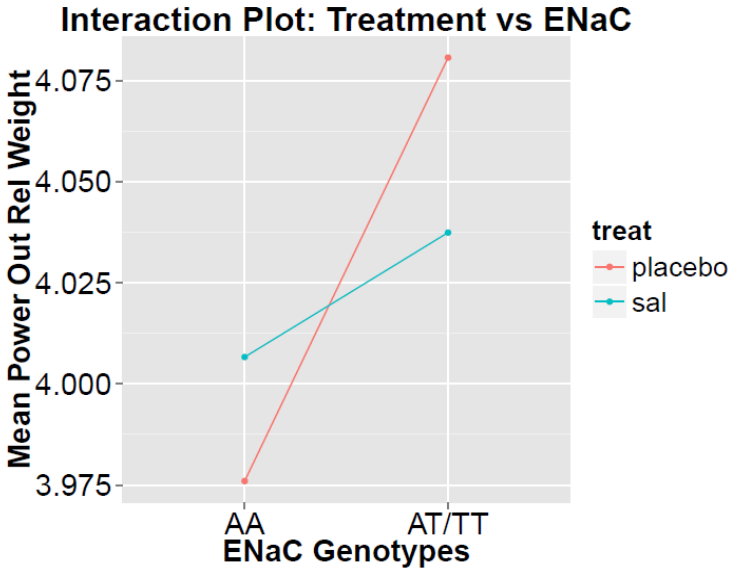

Figure 4 - Interaction Plot. Each point represents the mean for a cross-over of two groups. For example, bottom left red point represents the mean of mean power output relative to weight for athletes of AA genotype who took placebo. The teal points represent salbutamol, and the red points represent placebo.

6. Conclusions

As an asthma medication, salbutamol is one kind of beta$_2$-agonist that is permitted to be used in the Olympic Games in inhaled form under Therapeutic Use Exemption (TUE). We found that competitive cyclists who took salbutamol had a better forced expiratory volume in 1 second (FEV_1) than the ones who took placebo. In addition, there is not enough evidence that the competitive cyclists with salbutamol had a better mean power output than the ones without salbutamol. Asthmatic cyclists have a higher improvement of FEV_1 versus non-asthmatic cyclists when they both took salbutamol, but asthmatic cyclists did not show a higher improvement of mean power output versus non-asthmatic cyclists under the same circumstance. Lastly, A46G and C79G are single nucleotide polymorphism in beta$_2$-receptor genes, and ENaC gene is another gene that researchers are interested in. There are three genetic variations at each of these sites. There is evidence that cyclists who inherit the CC genotype in C79G SNP have a lower improvement in mean power output after taking the salbutamol drug versus cyclists with the CG genotype for the C79G SNP.

7. References

Kindermann W., Do inhaled β2-Agonists have an ergogenic potential in non-asthmatic competitive athletes? *Sports Med.* 2007; 37 (2): 95-102

McKenzie, D.C., and Fitch, K.D., 2011, Inhaled beta-2 agonists, sport performance, and doping. *Clin J Sport Med*. 2011 Jan;21(1):46-50