## PROTOCOL TITLE

The effect of inspiratory muscle training on the build up of blood lactate in elite speed skaters

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<th>Protocol ID</th>
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<tr>
<td>Short title</td>
<td>PB on the metaboreflex</td>
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<tr>
<td>Version</td>
<td>1.00</td>
</tr>
<tr>
<td>Date</td>
<td>August 31(^{\text{th}}) 2011</td>
</tr>
</tbody>
</table>
| Coordinating investigator/project leader | J.M.M. Driessen MD, sportsphysician in training  
Thialfweg 41  
8441 PW Heerenveen |
| Principal investigator(s) (in Dutch: hoofdonderzoeker/uitvoerder) | J.M.M. Driessen MD, sportsphysician in training  
Thialfweg 41  
8441 PW Heerenveen  
jeandriessen@hotmail.com |
| Sponsor (in Dutch: verrichter/opdrachtgever) | A. van der Wulp Msc., InnoSportsLab Manager  
Pim Mulierlaan 1  
8443 DA Heerenveen  
aart.vanderwulp@innosport.nl |
| Independent physician(s) | M.H. Vegter MD, sportsphysician  
Groot Wezenland 20  
8011 JW Zwolle  
w.h.vegter@isala.nl |
| Laboratory sites | Functieafdeling ziekenhuis de Tjongerschans  
Thialfweg 41  
8441 PW Heerenveen  
www.tjongerschans.nl |
| Pharmacy          | Not applicable |
# PROTOCOL SIGNATURE SHEET

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
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| For non-commercial research, Head of Department:  
  *A. van der Wulp Msc.*  
  *InnoSportsLab Manager* | | |
| Coordinating Investigator/Project leader/Principal Investigator:  
  *J.M.M. Driessen MD*  
  *sportsphysician in training* | | |
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR  ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE   Adverse Event
AR   Adverse Reaction
CA   Competent Authority
CCMO Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV   Curriculum Vitae
DSMB Data Safety Monitoring Board
EU   European Union
EudraCT European drug regulatory affairs Clinical Trials
GCP  Good Clinical Practice
IB   Investigator’s Brochure
IC   Informed Consent
IMP  Investigational Medicinal Product
IMPD Investigational Medicinal Product Dossier
METC Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
(S)AE (Serious) Adverse Event
SPC  Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
Sponsor The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR Suspected Unexpected Serious Adverse Reaction
Wbp  Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen
SUMMARY

**Rationale:** Increased ventilatory demand during prolonged (sub)maximal exercise may lead to inspiratory muscle fatigue and consequentially a build up of blood lactate through anaerobic inspiratory muscle use. Inspiratory muscle training is a safe method to improve inspiratory muscle strength and may delay the build up of blood lactate. The aim of the study is to investigate the effect of IMT on lactate build up and inspiratory lung function.

**Objective:** To analyze the effect of inspiratory muscle training on the build up of lactate during physical activity and lung function.

**Study design:** Non placebo controlled, non randomized interventional pilot study

**Study population:** 20 Elite speed skaters aged 18-40

**Intervention:** Half the study population will be asked to use an inspiratory muscle trainer device for 30 inhalations against 50% of the maximum inspiratory pressure twice daily for 6 weeks.

**Main study parameters/endpoints:**

**Primary end point:**
- Change in lactate build up during sub-maximal exercise at 7’30” and 11’30 from start of exercise.

**Secondary end points:**
- Change in VO$_2$ at 12 minutes from start of exercise.
- Change in maximum inspiratory flow as measured with flow volume loops.
- Change in maximal inspiratory pressure.
- Change in inspiratory airway resistance as measured with the forced oscillation technique.

**Nature and extent of the burden and risks associated with participation, benefit and group relatedness:**
All subjects will perform full lung function and a VO$_2$ max test at the beginning of the trial after which the subjects will perform a full lung function every 2 weeks for 6 weeks in total. After 6 weeks they will perform a sub-maximal VO$_2$ test. The VO$_2$ testing is part of the regular training program.

Inspiratory muscle training has not been associated with any side effects.
1. INTRODUCTION AND RATIONALE

Maximum human performance is determined through cardiac output, maximum ventilation, oxygen transport capacity, and muscle strength and endurance. Ventilation, under normal conditions, is not considered to be a limiting factor in maximal performance. In pulmonary disease and elite athletes however the ventilatory demand can exceed the need, limiting performance. Increased ventilatory demand during prolonged (sub)maximal exercise may lead to inspiratory muscle fatigue and consequentially a build up of blood lactate through anaerobic inspiratory muscle use\textsuperscript{1-3}. Anaerobic muscle use activates the metabo-reflex, causing an increase of cardiac output through vasopressin release\textsuperscript{4}.

Inspiratory muscle training (IMT) is a safe method to improve inspiratory muscle strength (IMS) in both health and disease\textsuperscript{5-8}, although the effects remain controversial\textsuperscript{5,8,10}. IMT increases the efficiency of breathing possibly delaying the metabo-reflex, increasing aerobic performance.

The aim of the study is to investigate the effect of IMT on lactate build up and lung function.
2. OBJECTIVES

The aim of the study is to investigate the effect of IMT on lactate build up and inspiratory lung function.

Primary objective:
- Change in lactate build up during sub-maximal exercise.

Secondary objectives:
- Change in VO$_2$ at 12 minutes from start of exercise
- Change in maximum inspiratory flow as measured with flow volume loops.
- Change in maximal inspiratory pressure.
- Change in inspiratory airway resistance as measured with the forced oscillation technique.
3. STUDY DESIGN

Non placebo controlled, non randomized interventional pilot study
Twenty elite skaters aged 18-40 years old will be recruited from professional skating teams and regional selection teams.

All skaters will perform a full lung-function and VO$_2$ max at the start of the study. After initial tests, 10 skaters will use the inspiratory muscle trainer (powerBREATHE®, Carefusion®, San Diego, USA) for 6 weeks, twice daily for 30 inhalations at 50% of their maximum inspiratory pressure. Ten skaters will not perform inspiratory muscle training and will form the control group. Full lung function will be measured at 2, 4 and 6 weeks from the start of the study to ensure an adequate training inspiratory resistance. Immediately following the last full lung function, a submaximal VO$_2$ test will be performed. A flow-chart can be seen in figure 1. The VO$_2$ measurements are part of the routine training regimen of the skaters.

Figure 1.

```
<table>
<thead>
<tr>
<th>Time</th>
<th>Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>T=0</td>
<td>sac function, VO$_2$ max</td>
</tr>
<tr>
<td>0 weeks</td>
<td></td>
</tr>
<tr>
<td>T=1</td>
<td>Full lung function</td>
</tr>
<tr>
<td>1 week</td>
<td></td>
</tr>
<tr>
<td>T=2</td>
<td>Full lung function</td>
</tr>
<tr>
<td>2 weeks</td>
<td></td>
</tr>
<tr>
<td>T=3</td>
<td>Full lung function</td>
</tr>
<tr>
<td>3 weeks</td>
<td></td>
</tr>
<tr>
<td>T=4</td>
<td>Full lung function</td>
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<tr>
<td>4 weeks</td>
<td></td>
</tr>
<tr>
<td>T=5</td>
<td>Full lung function</td>
</tr>
<tr>
<td>5 weeks</td>
<td></td>
</tr>
<tr>
<td>T=6</td>
<td>Full lung function</td>
</tr>
<tr>
<td>6 weeks</td>
<td></td>
</tr>
</tbody>
</table>
```
4. STUDY POPULATION

4.1 Population (base)
20 Elite speed skaters aged 18-35 from professional skating teams or regional selection teams. Of these there will be 10 sprint and 10 all round specialist skaters. We expect to have no trouble recruiting the subjects as they are highly likely to test non-invasive and safe methods which may enhance performance.

4.2 Inclusion criteria
- Elite speed skaters from professional skating teams or regional selection teams.
- Age between 18 and 40 years.
- Ability to perform reproducible lung function tests, i.e. coefficient of the predicted value variation in 3 of 5 consecutive measurements < 5%.
- Clinically stable period at least 3 weeks before the study period.

4.3 Exclusion criteria
- Pulmonary disorders other than brochial hyperreactivity/asthma
- Other pulmonary, neurological or cardiac disorder.

4.4 Sample size calculation
Numbers of study participants were calculated using the calculations of Dupont, and setting power of the study at 80 % and p=0.05\(^{11}\). Data used to produce the following numbers came from research performed by Voliantisis et al. as referenced above\(^{5}\), with an expected difference in maximum inspiratory pressure of 38 cmH\(_2\)O and a standard deviation of the mean of 10.3 cmH\(_2\)O. Analyzing the effect of IMT the number of participants was set at 8 per group. Therefore the total number of randomized subjects will be 16. In research performed by Driessen et al. approximately 80% of tested patients completed the protocol\(^{12}\). Therefore enrolled subject count will be 1.25 times the required number of subjects (16•1.25=20).
5. TREATMENT OF SUBJECTS

Half the subjects will perform 30 inhalations against 50% of the maximum inspiratory pressure twice daily for 6 weeks as prescribed by the manufacturer of the powerBREATHE®.
6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint
- Change in lactate build up during sub-maximal exercise at 7’30” and 11’30” from start of exercise.

6.1.2 Secondary study parameters/endpoints (if applicable)
- Change in VO\(_2\) at 12 minutes from start of exercise.
- Change in maximum inspiratory flow as measured with flow volume loops.
- Change in maximal inspiratory pressure.
- Change in inspiratory airway resistance as measured with the forced oscillation technique.

6.2 Study procedures

*Pulmonary function measurements*

A Masterscope\textsuperscript{®} Jaeger\textsuperscript{®}, (IBM PS 235X) will be used to measure lung volumes and flow-volume loop. Total lung capacity (TLC) will be taken from inspiratory vital capacity (IVC). The flow-volume loop will be recorded by instructing the subjects using to perform a maximal expiratory effort from inspiratory vital capacity to residual volume and, immediately after that, a maximal inspiratory effort. Lung function will be calculated from the best curve. ERS/ATS reference values will be used to calculate the % of the predicted value of the spirometric indices\textsuperscript{13}.

FOT measurements will be performed with R.O.S., Oscilink\textsuperscript{®}, Carefusion\textsuperscript{®}, San Diego, USA) to measure general respiratory resistance. Measurements will be repeated 3 times with nose clipped and with hands supporting cheeks and base of the mouth\textsuperscript{14}.

Maximum Inspiratory pressure will be measured from maximum expiratory effort to maximum inspiratory effort with the KH1 (powerBREATHE\textsuperscript{®}, Carefusion\textsuperscript{®}, San Diego, USA).

*Exercise testing*

VO\(_2\) max testing will be performed in the function laboratory of the local hospital, De Tjongerschans, in Heerenveen. Subjects will breath through a full face mask (Hans Rudolph\textsuperscript{®}, Kansas City, USA) and an Oxycon Pro (Jeager\textsuperscript{®}, Carefusion\textsuperscript{®}, San Diego, USA) will be used for breath by breath analysis of CO\(_2\) and O\(_2\). An incremental workload protocol, based on previous VO\(_2\) max measurements and bodyweight, will be used to
continually increase workload up to a maximum load. The exercise will be performed on a fully customizable stationary bike (Excalibur Sport®, Lode®, Groningen, the Netherlands). Blood lactate will be measured with a handheld blood lactate measuring device (LactatePro®, FaCT®, Quesnel, Canada) at regular intervals after the start of exercise (7’30'', 11’30'', 14’30'', 19’30'') and immediately after reaching maximum workload. A chart of the VO₂ max protocol can be seen in figure 2.

For the submaximal VO₂ test the VO₂ max protocol will be followed up to 12 minutes from start from exercise.

Figure 2.

<table>
<thead>
<tr>
<th>Total time</th>
<th>Steps</th>
<th>Load</th>
<th>Bloodlactate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2 minutes</td>
<td>1.0 Watt/kg</td>
<td>0.5 Watt/kg</td>
</tr>
<tr>
<td>4</td>
<td>2 minutes</td>
<td>1.5 Watt/kg</td>
<td>1.0 Watt/kg</td>
</tr>
<tr>
<td>8</td>
<td>4 minutes</td>
<td>2.0 Watt/kg</td>
<td>1.5 Watt/kg</td>
</tr>
<tr>
<td>12</td>
<td>4 minutes</td>
<td>+0.67 Watt/kg</td>
<td>+0.67 Watt/kg</td>
</tr>
<tr>
<td>16</td>
<td>4 minutes</td>
<td>+0.67 Watt/kg</td>
<td>+0.67 Watt/kg</td>
</tr>
<tr>
<td>20</td>
<td>4 minutes</td>
<td>+0.67 Watt/kg</td>
<td>+0.67 Watt/kg</td>
</tr>
<tr>
<td>21</td>
<td>1 minute</td>
<td>+0.17 Watt/kg</td>
<td>+0.17 Watt/kg</td>
</tr>
<tr>
<td>22</td>
<td>1 minute</td>
<td>+0.17 Watt/kg</td>
<td>+0.17 Watt/kg</td>
</tr>
<tr>
<td>23</td>
<td>1 minute</td>
<td>+0.17 Watt/kg</td>
<td>+0.17 Watt/kg</td>
</tr>
</tbody>
</table>

After last step

+0.17 Watt/kg every minute till exhaustion

6.3 Withdrawal of individual subjects
Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

6.4 Replacement of individual subjects after withdrawal
Subjects will not be replaced.

6.5 Follow-up of subjects withdrawn from treatment
Subjects will not be followed after termination of completion of the protocol.

6.6 Premature termination of the study
Disease requiring medical aid will receive adequate treatment and will promptly lead to termination of the study.
7. SAFETY REPORTING

7.1 Section 10 WMO event
In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects’ health. The investigator will take care that all subjects are kept informed.

7.2 Adverse and serious adverse events
Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / the experimental treatment]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that at any dose:
- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients’ hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.
7.3 Follow-up of adverse events
All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

7.4 Data Safety Monitoring Board (DSMB)
The advice(s) of the DSMB will be notified upon receipt by the sponsor to the METC that approved the protocol. With this notification a statement will be included indicating whether the advice will be followed.
8. STATISTICAL ANALYSIS

8.1 Descriptive statistics

Blood lactate at 7'30 and 11'30” and VO$_2$ at 12 minutes from exercise as well as best values of spirometric measurements and mean values of maximal inspiratory effort and FOT measurements will be used for statistical calculations. Data will be composed of a set comparing powerBREATHE® with the no treatment group. Once gathered, data will be analyzed with SPSS analytical software after testing for normality with a Shapiro-Wilk test.

8.2 Univariate analysis

Differences between the powerBREATHE® and no treatment groups with non-parametric variables will be performed by Chi-square tests, and an unpaired T-tests or Mann-Whitney U tests will be performed as appropriate for parametric data.

8.3 Multivariate analysis

A multivariate analysis of variances will be performed to exclude mitigating factors.

8.4 Interim analysis (if applicable)

Not applicable
9. ETHICAL CONSIDERATIONS

9.1 Regulation statement
The study will be conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO).

9.2 Recruitment and consent
Subjects will be recruited from skating teams and will be orally informed after which they will sign an informed written consent.

9.3 Benefits and risks assessment, group relatedness
The group receiving inspiratory muscle training may experience a positive effect on maximum skating performance. The control group are not expected to experience positive effects.

9.4 Compensation for injury
No risks will be involved in participating with this study.

9.5 Incentives (if applicable)
Subjects will not receive incentives.
10. ADMINISTRATIVE ASPECTS AND PUBLICATION

10.1 Handling and storage of data and documents
Data will be encoded in Access® for windows; statistical analysis will be performed using SPSS® for windows. Subjects will be coded in a separate file, number as used in analysis will not be traceable without the coding file.

10.2 Amendments
Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

10.3 Annual progress report
The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments.

10.4 End of study report
The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last subjects last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.5 Public disclosure and publication policy
No arrangements have been made about publication policy.
11. REFERENCES


