Exercise-induced Bronchoconstriction Diagnostics:
Impact of a Repeated Exercise Challenge Test

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ABSTRACT

OBJECTIVE: The aim of the study was to evaluate whether a repeated exercise challenge test requires reconsideration of the final exercise-induced bronchoconstriction diagnosis due to a difference in test results, and if so, whether the difference is associated with exercise intensity.

METHOD: A total of 20 referred subjects with symptoms strongly suggesting exercise-induced bronchoconstriction performed two exercise challenge tests on a treadmill. The exercise protocol of the repeated test was adjusted. Forced expiratory volume in 1 second was measured before and at 1, 3, 6, 10, and 15 minutes after exercise. Ventilation and heart rate were measured during exercise.

RESULTS: The exercise intensity was not significantly different between the two tests, yet five subjects tested positive in both tests. Ten subjects tested negative in both tests. Three subjects tested positive in the first test only, while two subjects tested positive in the second test only.

CONCLUSION: Our study showed a 25% divergence in the diagnostic results of two consecutive exercise challenge tests on subjects with symptoms strongly suggesting exercise-induced bronchoconstriction. The difference in the test results was not explained by a difference in the exercise intensity.

Keywords: exercise challenge test, exercise-induced bronchoconstriction, forced expiratory volume in one second
SAMMENDRAG

MÅLSETTING: Hensikten med studien var å evaluere om en repetert anstrengelsestest krever en revurdering av den endelige diagnosen anstrengelsesutløst bronkokonstriksjon på grunn av en forskjell i testresultater, og i så fall, hvorvidt forskjellen er relatert til anstrengelsesintensitet.

METODE: Totalt tyve henviste subjekter med symptomer som tydet sterkt på anstrengelsesutløst bronkokonstriksjon gjennomførte to anstrengelsestester på tredemølle. Anstrengelsesprotokollen for den repeterte testen ble justert. Forsert ekspiratorisk volum på 1 sekund ble målt før og 1, 3, 6, 10 og 15 minutter etter anstrengelse. Ventilasjon og hjerterate ble målt under anstrengelse.

RESULTATER: Anstrengelsesintensiteten var ikke signifikant forskjellig mellom de to testene. Likevel var det fem subjekter som testet positivt på begge testene. Ti subjekter som testet negativt på begge testene. Tre subjekter som testet positivt kun første gang, mens det var to subjekter som testet positivt kun andre gang.

KONKLUSJON: Vår studie viste 25 % avvik i de diagnostiske resultatene av to etterfølgende anstrengelsestester på subjekter med symptomer som tydet sterkt på anstrengelsesutløst bronkokonstriksjon. Forskjellen i testresultatene kunne ikke forklares av en forskjell i anstrengelsesintensiteten.

Nøkkelord: anstrengelsestest, anstrengelsesutløst bronkokonstriksjon, forskert ekspiratorisk volum i ett sekund
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ABBREVIATIONS

ATS = American Thoracic Society
BF = breathing frequency
BR = breathing reserve
\( DL_{CO} \) = pulmonary diffusing capacity for carbon monoxide
ECT = exercise challenge test
EIB = exercise-induced bronchoconstriction
ERS = European Respiratory Society
\( F_{ENO} \) = fractional exhaled nitric oxide
\( FEV_1 \) = forced expiratory volume in one second
FVC = forced vital capacity
HR = heart rate
MVV = maximum voluntary ventilation
RER = respiratory exchange ratio
RV = residual volume (volume of gas remaining in the lungs after maximal exhalation)
TLC = total lung capacity (volume of gas in the lungs after maximal inspiration, or the sum of all lung volume compartments)
VE = ventilation
\( VO_2 \) = oxygen uptake
INTRODUCTION

Exercise-induced bronchoconstriction (EIB) is related to increased ventilation (VE) during exercise and describes the transient airway narrowing following exercise (Spooner, Saunders, & Rowe, 2002). Usually, maximum bronchoconstriction occurs 3–15 minutes after exercise (Brudno, Wagner, & Rupp, 1994) and subsides spontaneously within 20–60 minutes (Rupp, 1996). The symptoms of EIB may include coughing, wheezing, shortness of breath, premature fatigue, and chest tightness (Spooner et al., 2002; Spooner, Spooner, & Rowe, 2003). As EIB often is the first sign of asthma (Ernst, Ghezzo, & Becklake, 2002) a reliable diagnosis and optimal treatment are important for affected people’s physical performances and self-esteem.

PREVALENCE OF EXERCISE-INDUCED BRONCHOCONSTRICTION

EIB is reported in most asthmatic patients, and is also more frequent in atopic (allergic) individuals (Rupp, 1996). However, EIB can also occur in individuals without signs of clinical asthma or atopy, such as elite athletes (Rundell & Slee, 2008). The true prevalence of EIB in the general population is poorly defined (Rupp, 1996), and the reported prevalence in the literature varies due to discrepancy in methods used for diagnosis, e.g. self-reported symptoms versus objective lung-function measurements (Rundell et al., 2001). Nevertheless, Rupp (1996) reported the prevalence of EIB in the general population to be 12–15% and other studies suggest a prevalence rate between 26% and 50% among specific athletes (Mannix, Farber, Palange, Galassetti, & Manfredi, 1996; Rundell et al., 2001; Wilber et al., 2000). EIB may be most frequent in children and young adults (McFadden & Gilbert, 1994) and it is reported more prevalent in female Olympic winter sport athletes than their male counterparts (Wilber et al., 2000). However, in the absence of valid studies the true prevalence is uncertain.

EXERCISE CHALLENGE TEST

Symptoms alone are not sensitive nor specific predictors of EIB (Rundell et al., 2001). In order to diagnose the presence of EIB, reported symptoms can be evaluated using different provocation tests. A standardized exercise challenge test (ECT) on a treadmill is commonly performed, whereby a possible impairment of pulmonary function is measured by spirometry. The response to exercise is assessed as the post-exercise reduction in forced expiratory volume in one second (FEV₁) expressed as a percentage of the pre-exercise value. The European Respiratory Society (ERS) and American Thoracic Society (ATS)
recommendations both set a 10% reduction in FEV\textsubscript{1} as a criterion for EIB (Crapo et al., 2000; Sterk et al., 1993).

**Intensity of the exercise challenge test**

Exercise intensity influences the sensitivity of an ECT because a major factor determining the severity of EIB is the pulmonary VE reached and sustained during exercise. An ECT can be sensitive and specific if exercise minute ventilation is standardized (Weiler et al., 2007). Therefore, ATS guidelines state that VE during an ECT should reach 40–60% of the predicted maximum voluntary ventilation (MVV), estimated as FEV\textsubscript{1}×35, for a period of 4 minutes with total test duration of 6–8 minutes. Correspondingly, the guidelines recommend an exercise intensity of 80–90% of heart rate maximum (HR\textsubscript{max}), estimated by the formula: HR\textsubscript{max} = 220 – age, for a period of 4 minutes (Crapo et al., 2000). However, as there is high individual variance in HR\textsubscript{max} (Tanaka, Monahan, & Seals, 2001) it has been reported that heart rate based ATS standard protocols may not ensure sufficient exercise intensity to induce bronchoconstriction (Trümper, Mäueler, Vobejda, & Zimmermann, 2009). Moreover, a study by Carlsen, et al. (2000) has demonstrated a significant increased reduction in lung function after an ECT performed at 95% of estimated HR\textsubscript{max} compared to an intensity of 85% of estimated HR\textsubscript{max}. Thus, adequate intensity of an ECT may be essential to achieve a reliable diagnosis of EIB.

**Repeated exercise challenge test**

The impact of a repeated ECT in a clinical setting is not well established. However, the reproducibility of an ECT has been investigated. Dahlén et al. (2001) demonstrated the reproducibility of maximum per cent reduction in FEV\textsubscript{1} as an outcome measurement after a standardized ECT to be 72%, hence the inter-subject variability accounted for 28% of the total variance. Furthermore, a recent study identified agreement of 76% in test results between two ECTs when examining subjects without a definite diagnosis of asthma. The results demonstrated variability in the presence and severity of EIB, despite standardization of intensity, duration, and condition of the inspired air, and also suggest that more than one ECT may be required to exclude or diagnose EIB (Anderson et al., 2010).

The HR formula recommended by the ATS is usually applied (Carlsen et al., 2008). Trümper et al. (2009) suggested in the previously mentioned study that individual HR\textsubscript{max} should be achieved before conducting an ECT in order to ensure adequate intensity of the test. In addition, a potential learning effect from foregoing practise tests has been reported in e.g.
COPD (chronic obstructive pulmonary disease) patients (ATS, 2003; Salzman, 2009; Swinburn, Wakefield, & Jones, 1985). Therefore, conducting a repeated ECT, based on the knowledge of the first test, introduces the possibility to adjust the exercise protocol on an individual basis and may also result in the subject tested becoming accustomed to the testing procedure. Thus, we hypothesized greater intensities of the repeated ECTs, and consequently a greater number of positive repeated ECT results. Also, because of the reported variability in repeated ECT results, an additional test may be useful. To our knowledge, no prior studies have examined the impact of a repeated ECT in which the exercise protocol can be adjusted. Thus, in our opinion the usefulness of performing a repeated ECT, as opposed to one test to achieve more reliable results in general, needs to be more extensively investigated.

The aim of the study was to evaluate whether a repeated ECT requires reconsideration of the final EIB diagnosis due to a difference in test results, and if so, whether the difference is associated with exercise intensity.
MATERIAL AND METHODS

STUDY DESIGN

We conducted a test-retest evaluation study in a clinical setting. The evaluation was designed to compare the number of positive ECTs versus negative ECTs performed on two different occasions, and to assess a possible association between the test results and exercise intensity. Recruitment and testing took place at the Clinic for Allergies and Airway Diseases (Klinikk for allergi og luftveissykdommer, KAL) in Oslo.

SUBJECTS

Two pulmonologists recruited males and females during consultations following routine testing at KAL. The subjects, all of whom were volunteers, were enrolled if they were aged between 16 years and 45 years and had been referred to KAL by their general practitioners. At least three out of five questions relating to symptoms strongly suggesting EIB (coughing, wheezing, shortness of breath, lack of physical performance, and chest tightness) had to be confirmed by the subject in order for them to be included in the study (Appendix 1: Inclusion form). This was to increase the positive predictive value of the ECTs. Subjects who had formerly been diagnosed with and treated for asthma and who still fulfilled the inclusion criteria were also included in the study. Written informed consent was obtained from each subject (Appendix 2: Informed consent).

Exclusion criteria were evaluated by the responsible pulmonologist and involved the lack of ability to perform an ECT with maximum effort, clearly abnormal electrocardiography (ECG), uncontrolled hypertension, or any known pulmonary diseases other than asthma.

A total of 20 subjects, 12 females and 8 males, between 18 and 39 years of age were included. All subjects were Norwegian with the exception of one who was African. Three subjects participated in competitive sports. Eleven subjects undertook regular physical activity in their leisure time, and six subjects rarely or never undertook physical activity. Three subjects had not used a treadmill before. One subject had performed an ECT at the age of 8 years, and two subjects had completed a laboratory assignment which involved performing an ECT. Ten subjects used asthma medication, ten subjects did not use any asthma medication and two subjects used antihistamines.
CONDITIONS BEFORE TESTS

All subjects reported feeling well on the days when the tests were performed and also in the three preceding days (no sick leave from school or work). Subjects with an ongoing respiratory tract infection or recent respiratory infection evaluated by the responsible pulmonologist had their designated day of testing postponed. No exercise was undertaken (prior to the ECT) on the days of testing. This was because of the possibility of developing refractoriness, whereby repeated exercise under identical conditions induces less than 50% of the initial asthmatic response (Lee & Anderson, 1985). Anti-asthmatic medication and antihistamines were withheld in accordance with ERS guidelines (Roca et al., 1997). Inhaled short-acting β2-agonists were withheld for 8 hours prior to testing, inhaled long-acting β2-agonists for the last 72 hours, inhaled steroids on the test days and antihistamines for the last 7 days.

PROCEDURES

Subjects were recruited between August 2010 and February 2011, and concurrent testing started in September 2010 and was completed in March 2011. The subjects visited KAL three times: on the inclusion day and on the two test days. There were between 1 and 90 (mean 24) days between the inclusion day and test day 1. After inclusion, the ECTs were performed on consecutive visits. The subjects completed the repeated ECT between 7 and 28 (mean 14) days after the first ECT. To minimize inter-observer variation, the same test technician (the researcher) performed the measurements on test day 1 and test day 2.

Inclusion day:
The routine testing consisted of anthropometric data registration, assessment of medication, allergy skin prick testing, lung function measurements including reversibility following inhalation of Salbutamol (asthma medicine), fractional exhaled nitric oxide (FeNO) measurements, static lung volume measurements (RV, residual volume and TLC, total lung capacity), and pulmonary diffusing capacity for carbon monoxide measurements (DL,CO). Elevated FeNO may indicate airway inflammation, and static lung volume measurements and diffusing capacity measurements may exclude other pulmonary diseases than asthma.
Test day 1:
The procedure on test day 1 included resting blood pressure measurement, resting ECG recording, MVV measurements, an ECT, and treatment (Salbutamol).

Test day 2:
The procedure on test day 2 was identical to that on test day 1, except for the exclusion of resting blood pressure measurement and resting ECG recording. In addition, the exercise protocol of ECT 2 was adjusted by the test technician in collaboration with the test subject, based on ECT 1. If the subject ran for less than 8 minutes in ECT 1, an increased running time was encouraged in ECT 2. If subject was not completely exhausted after 8 minutes in ECT 1, speed and/or elevation of ECT 2 was increased if feasible. If the subject reported that the mask was the reason for terminating ECT 1, he or she was informed of the possibility of taking it off and continuing to run rather than terminating ECT 2. If the subject reported stiff legs as the reason for terminating ECT 1, speed and/or elevation of ECT 2 was adjusted.

OUTCOMES
The primary outcomes were maximum reduction in FEV$_1$ from before to after ECT 1 and ECT 2 (% pre-exercise), and exercise intensity measurements (VE and HR) in ECT 1 and ECT 2. In addition, oxygen uptake (VO$_2$), breathing frequency (BF), respiratory exchange ratio (RER), and breathing reserve (BR) were measured.

MEASUREMENTS

Anthropometric data
Anthropometric data (age, sex, height, and weight) were recorded as a basis for determining individual predicted values and to express oxygen uptake related to bodyweight. Height (to the nearest centimetre) and weight (to the nearest kilogram) were measured while the test subjects were clothed, but without shoes.

Skin prick test
Skin prick tests were performed in accordance with published guidelines (Dreborg, 2005) with the following allergens: horse dander, dog dander, cat dander, rabbit dander, birch pollen, grass pollen (Timothy), mug worth pollen, Alternia tenuis, Cladosporium herbarum, house dust mites (Dermatophagoides pteronyssinus), and latex (Soluprick, ALK, Copenhagen, Denmark and Allergopharma, Hamburg, Germany).
The criterion for being considered allergic to an allergen was a wheal size > 3 mm (Sporik, Hendersom, & Hourihane, 2009).

**Fractional exhaled nitric oxide**

\( \text{FE}_{\text{NO}} \) was measured using an analyser (DENOX 88, ECO MEDICS AG, Dürnten, Switzerland) according to published guidelines (ATS & ERS, 2005). \( \text{FE}_{\text{NO}} \) is given in parts per billion (ppb). According to the manufacturer; \( \text{FE}_{\text{NO}} > 30 \text{ppb} \) may indicate airway inflammation.

**Lung function with reversibility**

Lung function with reversibility was measured by a spirometer (Flowhandy ZAN 100 USB, nSpire Health GmbH, Oberthulba, Germany) according to published guidelines (Miller et al., 2005). \( \text{FEV}_1 \) in litres and in % of predicted and the ratio \( \text{FEV}_1/\text{FVC} \) (forced vital capacity) are given. Reversibility was assessed following inhalation of Salbutamol (0.4 mg from a pressurized metered dose inhaler). An increase in \( \text{FEV}_1 \) of \( \geq 12\% \) and \( \geq 200 \text{ ml} \) above baseline was taken as a positive response to Salbutamol. We used accepted reference values and ethnicity was taken into account, i.e. a correction factor was applied to adjust European reference values for application to Africans (Quanjer et al., 1993).

**Static lung volumes**

Static lung volumes were measured using bodyplethysmography (ZAN 500 Body USB, nSpire Health GmbH, Oberthulba, Germany), according to published guidelines (Wanger et al., 2005). Among the subdivisions of static lung volumes, RV and TLC were recorded. We used accepted reference values as mentioned above (Quanjer et al., 1993).

**Pulmonary diffusing capacity for carbon monoxide**

\( DL_{\text{CO}} \) was measured using a CO/\( \text{CH}_4 \) (methane) analyser (ZAN 300 MGA USB, nSpire Health GmbH, Oberthulba, Germany), according to published guidelines (Cotes, Chinn, Quanjer, Roca, & Yernault, 1993). We used accepted reference values as mentioned above (Cotes et al., 1993).

**Blood pressure**

For safety reasons, resting blood pressure was measured prior to exercise by the use of an automated blood pressure device (M3 Intellisense HEM-7051-E, OMRON HEALTHCARE, Kyoto, Japan). We measured blood pressure once.
Electrocardiography
Resting 12-lead ECG was measured for safety reasons prior to exercise by the use of an ECG recorder (AR 1200 ADV, Cardiette, Cavareno, Italy). Prior to the ECT, interpretation of the electrocardiogram was performed by the pulmonologist responsible.

Lung function before and after exercise
Lung function was measured using a spirometer (Flowhandy ZAN 100 USB, nSpire Health GmbH, Oberthulba, Germany) according to published guidelines (Miller et al., 2005). FEV₁ and FVC were measured before and 1, 3, 6, 10, and 15 minutes after exercise and 10 minutes after inhalation of Salbutamol (0.4 mg). Full FVC manoeuvres were not requested after exercise because this might have tired the subjects (Weiler et al., 2007). Salbutamol was included to reverse possible bronchoconstriction. We used accepted reference values, as mentioned above (Quanjer et al., 1993).

Maximum voluntary ventilation
Before exercise, MVV was measured using an analyser (ZAN 600 USB, nSpire Health GmbH, Oberthulba, Germany) according to published guidelines (Miller et al., 2005). The value was multiplied by six which results in the MVV expressed in litres per minute (L min⁻¹). This was measured to calculate BR after measuring VEₚₑᵃᵏ during the ECT (MVV − VEₚₑᵃᵏ = BR) and to calculate ventilation in percentage of MVV (VE % MVV) for the last 4 minutes of the ECTs.

Exercise challenge test
The ECTs were performed under laboratory conditions according to ERS guidelines (Roca et al., 1997). ECT 1; the temperature was between 18°C and 21°C, the relative humidity was between 20% and 46%, and the barometric pressure was between 97.7 kPa and 101.4 kPa. ECT 2; the temperature was between 19°C and 22°C, the relative humidity was between 19% and 45%, and the barometric pressure was between 96.1 kPa and 102.0 kPa. The mean outdoor temperature in Oslo 30 minutes before scheduled testing at KAL was −2 (SD 6) °C and −4 (SD 4) °C on test day one and two respectively.

Exercise was performed by running on a motorized treadmill (h/p/cosmos quasar med 4.0, h/p/cosmos sports & medical gmbh, Nussdorf-Traunstein, Germany) for 6–8 minutes. The initial incline of the treadmill was 3%. The speed and incline were adjusted throughout the test with the aim of achieving a workload of ≥ 95% of estimated HRₘₐₓ (220 − age) in the last
4 minutes of each test. Each subject’s VE and HR were monitored according to ATS and ERS guidelines, for both ECTs. The ventilation was > 40% of measured MVV and estimated MVV (FEV₁×35) for each subject, during each of the last 4 minutes of the tests. Also, the HR was >80% of estimated HRmax for each subject during each of the last four minutes of the tests. In addition, the subjects assessed their own perception of effort and exhaustion immediately after completing the test by using the Borg CR 10 Scale for rating perceived exertion (Borg, 1998). The test could have been stopped at any time. Furthermore, the subjects were wearing a chest belt and a harness, attached by rope to the crossbar of the treadmill’s safety arch, and one pull on the rope would have activated the emergency stop.

VE, VO₂, BF, and RER were measured during exercise. Each subject wore a face mask attached to a flow sensor (ZAN VIP flow sensor, nSpire Health GmbH, Oberthulba, Germany) which was connected to an analyser (ZAN 600 USB, nSpire Health GmbH, Oberthulba, Germany). In order to determine the respiratory flow, gas concentrations were constantly sampled, and by using fast response selective analysers for O₂ and CO₂ the values were time aligned providing breath by breath measurements. Calibration was verified each test day. Heart rate was continuously recorded by use of a heart rate monitor (Polar WearLink W.I.N.D, Polar Electro Oy, Kempele, Finland).

Maximum percentage reduction in FEV₁ after exercise test was calculated by (pre-exercise FEV₁ – minimum post exercise FEV₁)/(pre-exercise FEV₁) x 100%. Minimum post-exercise FEV₁ was the lowest recorded value at 1, 3, 6, 10, or 15 minutes after test, taking the better of two acceptable attempts at each time point. Values were rounded. A subject was deemed positive if there was a reduction of ≥ 10% in FEV₁. A reduction of 10–20%, 20–40% and >40% was considered mild, moderate and severe respectively (Eggleston, 1984). The highest recorded VE, HR, VO₂, BF, and RER values during exercise were determined as VEpeak, HRpeak, VO₂peak, BFpeak and RERpeak. VO₂ and VE were both measured in L min⁻¹, BR in breath min⁻¹ and HR in beats min⁻¹. ZAN-Tech Software was used to interpret the results.
STATISTICAL ANALYSIS

Subject characteristics are given individually and as mean values and standard deviations. The results are given as means with 95% confidence intervals. Paired t-tests were applied to assess differences in lung function between baseline and ECT 1 and between baseline and ECT 2. They were also used to assess differences in intensity and maximum reduction in FEV$_1$ between ECT 1 and ECT 2. P-values of $< 0.05$ were considered statistically significant. All statistical analyses were performed using PASW V.18.0 for Windows software (SPSS Inc, Chicago, Illinois, USA). To create the graph, we used the SAS 9.2 statistical package (SAS Institute Inc., Cary, North Carolina, USA).

ETHICS

The study was performed in accordance with the principles stated in the Declaration of Helsinki, and was approved by the Regional Committee for Medical Research Ethics, Health Region North, Norway (Appendix 3: Regional Committee approval). The study was also registered with ClinicalTrials.gov, registration number NCT01214551 (Appendix 4: ClinicalTrials.gov-Protocol registration receipt). Patient data are kept confidential.

Study participation was evaluated to involve minimal health risk and the measurements were taken in concordance with regular clinical practice. To ensure subjects’ safety, a medically responsible pulmonologist was available at all times during the testing, and a defibrillator was accessible in the laboratory exercise room. ECG registration and blood pressure measurement were included prior to the first ECT to increase safety level of maximal effort exercise tests. Safety garments ensured that subjects could not fall off the treadmill, thus preventing any risk of injury.
RESULTS

BASELINE CHARACTERISTICS

Table 1 shows a summary of the subjects’ characteristics at baseline. Blood pressure, ECG, static lung volumes, and diffusing capacities were normal for all subjects. There were no significant differences in the group’s lung function (FEV$_1$ and FVC) between baseline and test day 1 or between baseline and test day 2 (data not shown).

Table 1: Baseline characteristics of the subjects

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<td>.0</td>
<td>1.6</td>
<td>46</td>
<td>67</td>
<td>55</td>
</tr>
</tbody>
</table>

Mean (SD)  18/15/16/5/18  11/9

Notes: Body mass index (BMI); symptoms (1: cough, 2: wheeze, 3: shortness of breath, 4: lack of physical performance, and 5: chest tightness); exercise (h/w, hours of endurance training per average week); forced expiratory volume in 1 s (FEV$_1$ in litres and in percentage of predicted); forced vital capacity (FVC); fractional exhaled nitric oxide (FE$_{NO}$ in ppb parts per billion); smoker, snuff user, African, positive reversibility test, medication (1: short-acting β$_2$-agonists, 2: long-acting β$_2$-agonists, 3: inhaled steroids); and m missing value.
COMPLIANCE AND ADVERSE EVENTS

The compliance with both ECTs was 100%. Dizziness and nausea were reported by several subjects, but with spontaneous recovery. On test day 1, irregular HR was recorded in three subjects and one subject did not measure VO₂ and RER due to equipment error. Also, one subject had a small face mask leakage, and one subject did not perform MVV due to having a headache. On test day 2, irregular HR was recorded in one subject. Also, two subjects were unable to complete the ECT wearing a face mask, due to the subjective feeling of not being able to breathe.

EXERCISE INTENSITY

On an individual base, exercise intensity measurements were similar for both tests. Also, the subjects’ perceptions of their own efforts and level of exertion were similar in ECT 1 and ECT 2, and they reported ≥ 9 on Borg CR 10 Scale on both tests. Moreover, when assessed at group level, there were no significant differences in exercise intensity measurements (Table 2). Mean VE % MVV during the last 4 minutes of ECT 1 was 82% while for ECT 2 it was 81%. Mean VE % estimated MVV was 79% on ECT 1 and 81% on ECT 2. Mean HR % predicted HRmax during the last four minutes was 94% on ECT 1 and 93% on ECT 2. Further, there were no significant differences in mean values of VEpeak, HRpeak, VO₂peak, BFpeak, RERpeak or BR between the two ECTs. The durations of the tests were also similar. The mean duration of ECT 1 was 6 minutes 52 seconds and the mean duration of ECT 2 was 6 minutes 49 seconds.
<table>
<thead>
<tr>
<th>Variable</th>
<th>ECT1</th>
<th>ECT2</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (95% CI)</td>
</tr>
<tr>
<td>VE % MVV</td>
<td>82 (16)</td>
<td>81 (18)</td>
<td>-2.7 (-7.4, 2.1)</td>
</tr>
<tr>
<td>VE % estimated MVV</td>
<td>79 (8)</td>
<td>81 (12)</td>
<td>-1.6 (-4.7, 1.5)</td>
</tr>
<tr>
<td>HR % estimated HR_{max}</td>
<td>94 (4)</td>
<td>93 (4)</td>
<td>-0.0 (-1.4, 1.3)</td>
</tr>
<tr>
<td>VE_{peak} (L min^{-1})</td>
<td>112 (27)</td>
<td>118 (32)</td>
<td>-0.5 (-3.8, 2.7)</td>
</tr>
<tr>
<td>HR_{peak} (beats min^{-1})</td>
<td>186 (8)</td>
<td>184 (9)</td>
<td>-0.2 (-1.8, 1.5)</td>
</tr>
<tr>
<td>VO_{2peak} (ml kg^{-1} min^{-1})</td>
<td>44 (6)</td>
<td>46 (8)</td>
<td>0.6 (-0.7, 1.9)</td>
</tr>
<tr>
<td>BF_{peak} (breath min^{-1})</td>
<td>56 (8)</td>
<td>56 (9)</td>
<td>-0.5 (-2.9, 1.9)</td>
</tr>
<tr>
<td>RER_{peak}</td>
<td>1.11 (0.05)</td>
<td>1.10 (0.05)</td>
<td>-0.013 (-0.033, 0.018)</td>
</tr>
<tr>
<td>BR (L min^{-1})</td>
<td>8 (22)</td>
<td>15 (19)</td>
<td>8.9 (-2.4, 20.3)</td>
</tr>
</tbody>
</table>

Ventilation (VE) % of maximal voluntary ventilation (MVV); VE % of estimated MVV and heart rate (HR) % of estimated HR maximum (HR_{max}) in the last 4 minutes (mean) of exercise challenge test (ECT) 1 and 2; Peak ventilation (VE_{peak}), peak heart rate (HR_{peak}), peak oxygen uptake (VO_{2peak}), peak breathing frequency (BF_{peak}), peak respiratory exchange ratio (RER_{peak}) and breathing reserve (BR) of the ECTs. Difference: negative values relate to greater intensity of ECT1. Mean ECT2 − mean ECT 1 ≠ mean difference due to missing values.
REPEATED EXERCISE CHALLENGE TEST

The agreement in ECT results was 75% with 50% (10) negative and 25% (5) positive on both tests (Table 3). Five subjects had a positive test result on only one of the two tests, three on the first test, and two on the second test. Disregarding test results, the maximum reduction in FEV\textsubscript{1} both increased and decreased from test 1 to test 2.

Table 3: Maximum reduction in forced expiratory volume in 1 s (% pre-exercise) from before to after exercise challenge test 1 and 2, and the test results (positive/negative)

<table>
<thead>
<tr>
<th>Subject No</th>
<th>ECT1 Reduction (Result)</th>
<th>ECT2 Reduction (Result)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>-65 (pos)</td>
<td>-58 (pos)</td>
</tr>
<tr>
<td>6</td>
<td>-13 (pos)</td>
<td>-33 (pos)</td>
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<tr>
<td>8</td>
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<td>-10 (pos)</td>
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<tr>
<td>11</td>
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<tr>
<td>20</td>
<td>-34 (pos)</td>
<td>-33 (pos)</td>
</tr>
<tr>
<td>2</td>
<td>-4 (neg)</td>
<td>-2 (neg)</td>
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<tr>
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<td>-10 (pos)</td>
</tr>
<tr>
<td>18</td>
<td>-9 (neg)</td>
<td>-13 (pos)</td>
</tr>
</tbody>
</table>

Note: Subjects sorted according to test results
When assessed at group level, there was no significant difference in mean maximum reduction in FEV₁ (% pre-exercise) between ECT 1 and ECT 2. The mean maximum reduction in FEV₁ was 12% and 11% after ECT 1 and ECT 2 respectively. The mean difference was 1 percentage point (−2.5, 4.0), (p = 0.63), (N = 20). Furthermore, the mean reduction in FEV₁ after 1, 3, 6, 10, and 15 minutes after exercise and 10 minutes after medication was not significantly different between ECT 1 and ECT 2 (Fig. 1).

Figure 1: Forced expiratory volume in 1 s (FEV₁) pre- (P) and 1, 3, 6, 10, and 15 minutes after exercise (exercise challenge test ECT 1 and ECT 2) and 10 minutes after medication (AM). Results are given as means with 95% confidence intervals. N = 20.
DISCUSSION

There were no significant differences in the exercise intensity between the two tests. However, five out of twenty subjects had different diagnostic test results. Hence, the differences in test results may not be related to the exercise intensity and it follows that accustomization to the testing procedure of the repeated ECT was not demonstrated.

In contrast to our hypothesis, the subjects seemed to achieve maximal performance already in the first ECT. Mean VE % measured and estimated MVV and mean HR % estimated HR$_\text{max}$ in the last 4 minutes of the tests were higher than minimum recommendation levels in both tests. Furthermore, mean heart rate in % of estimated HR$_\text{max}$ in the last 4 minutes of the tests was 94% and 93% in ECT 1 and ECT 2 respectively. This is close to 95%, which according to the study by Carlsen et al. (2000) may represent an adequate intensity level. The other intensity measurements (table 2) and the subjects’ perception of their own exertion may also indicate maximal exertion. Consequently we believe that adjustments to the repeated exercise protocols were not able to result in any significant intensity enhancements.

Because we did not demonstrate any significant intensity differences, we were not surprised that we did not find a greater number of positive repeated test results. In fact, no trend was demonstrated in the five subjects with different test results: three subjects tested positive in the first test only, and two subjects tested positive on the second test only. Also, disregarding test results, the maximum reduction in FEV$_1$ both increased and decreased from test 1 to test 2 and thus did not demonstrate a trend either. Furthermore, the five subjects with different test results had only mild (10–20%) reductions in FEV$_1$. This finding is in line with Anderson et al. (2010), who suggest that for some subjects with mild symptoms more than one test may be required. They could neither explain the variation in their test results by a difference in exercise intensity (standardized), and hypothesized that the variability could have been due to environmental or dietary factors or to the intrinsic reproducibility of the test itself.

Subjects 3, 6, 8, 11, and 20 tested positive in both tests. Subjects 3 and 20 demonstrated severe (> 40%) and moderate (20–40%) reductions in FEV$_1$ respectively leaving little doubt about diagnosis. Subject 6 demonstrated a great difference in maximum reduction in FEV$_1$ between test 1 and 2. We can only speculate why, but the subject experienced coughing fits on both days which may have influenced the lung function measurements. A total of 10 subjects tested negative in both tests. Only subjects 15 and 19 had borderline results.
However, subject 15 demonstrated technical improvements during lung function measurements on test day 2.

Subjects 1, 7, and 10 tested positive in the first ECT only. In the case of subject 1, the reduction in FEV\textsubscript{1} from before to after exercise was only $\geq 10\%$ after 15 minutes. Reduction in FEV\textsubscript{1} is usually sustained over two time points. Because we did not measure FEV\textsubscript{1} beyond 15 minutes we do not know whether the reduction in FEV\textsubscript{1} was sustained or could have been due to respiratory muscle fatigue (Rundell & Sue-Chu, 2010). Also, occasional late phase responses may have been left out (Spooner et al., 2003). Nevertheless, we did not operate with the criteria of sustained reduction over two time points to identify a positive test because one time point has been common practice (Roca et al., 1997). Subject 7 on the other hand measured a reduction in FEV\textsubscript{1} from before exercise to 3, 6, and 10 minutes after exercise, but spontaneously recovered after 15 minutes. As maximum bronchoconstriction usually occurs 3–15 minutes after exercise, the spontaneous recovery after 15 minutes is ambiguous.

Subjects 12 and 18 tested positive in the second ECT only. In both tests both subjects felt discomfort while running with a face mask on. Subject 18 took the mask off during ECT 2, and ended up running for additional 2 minutes 45 seconds, which may have resulted in the sustained high ventilation required to elicit the EIB response.

Subjects 1, 10, 12, and 18 had borderline results in both tests. We used a cut-off value of 10% reduction in FEV\textsubscript{1} as criterion of a positive ECT. Interestingly, using a 15% cut-off value which also has been recommended (Eggleston, 1984; Haby, Peat, Mellis, Anderson, & Woolcock, 1995) left us with only one subject (7) with different test results.

Elevated $\text{FeNO}$ has been reported in subjects with asthma (Kharitonov et al., 1994). In our study, baseline $\text{FeNO} > 30$ ppb was measured in four out of the five subjects who had two positive tests and in three out of the five subjects who had different test results. In addition, none of the subjects with two negative tests had $\text{FeNO} > 30$ ppb (two missing values) at baseline. Thus, the $\text{FeNO}$ measurements might indicate a relation to the test results, which is interesting because baseline $\text{FeNO}$ has been suggested to predict airway obstruction following exercise (García-Río et al., 2006).
Ten subjects used asthma medication, but still complained of EIB symptoms. Four tested positive in both tests, three tested negative in both tests, and three had different test results. Further, five of the ten subjects used inhaled steroids. Two of these had two positive test results, while the other three had two negative test results. It cannot be ruled out that the use of inhaled steroids decreased the likelihood of a positive test result in these subjects. (Crapo et al., 2000).

The included subjects reported at least three EIB symptoms, yet 10 subjects tested negative in both ECTs. This finding is in line with those made by Rundell et al. (2001), who concluded that self-reported EIB symptoms may yield both false positive and false negative test results. Their study involved elite athletes, but their findings seem to agree with ours. Partly, the prevalence reported in the literature is based on self-reported symptoms (Voy, 1986; Weiler, Metzger, Donnelly, Crowley, & Sharath, 1986). Further, reported prevalence may also be based on ECTs. However, lack of standardization and especially inadequate intensity may reduce the sensitivity of exercise challenge tests (Carlsen et al., 2000). Consequently, objective testing and standardized ECTs with adequate intensity are of importance both for diagnostic purposes, but also with regards to epidemiological studies.

We included subjects covering a large age range, thus reflecting a physically active period of life. The subjects turned out to be somewhat physically active in their leisure time, but only three subjects participated in competitive sports. The subjects’ activity levels differed and this was reflected in their VO2 measurements (range 32–61, mean 45) ml kg⁻¹ min⁻¹. Moreover, three subjects had some previous ECT experience, in contrast to three subjects who had never run on a treadmill before. Regardless, this was not reflected in the subjects’ ECT performances. Further, we included one African subject. Africans may have smaller lungs with lower values for, for example, FEV₁ compared to Europeans (Quanjer et al., 1993). However, ethnicity differences do not interfere with our primary outcomes.

The testing lasted from September to March and the number of days between ECT 1 and ECT 2 differed between 7 days and 28 days. We avoided the pollen season, but we cannot exclude that variation in outdoor weather conditions may have influenced the test results. However, the mean difference in temperature between the two tests was only 2°C. Also, the ECTs were not performed on the same time of day which may have influenced the results as well (Vianna et al., 2002).
The same test technician gave thorough information about study participation, reminded the subjects on each test day, guided the subjects through all measurements on test day 1 and test day 2, and encouraged maximal effort on the treadmill. We believe this was strength of our study, as there was 100% compliance in the case of both ECTs, despite the fact that performing an ECT is mentally and physically demanding. Also, the study was conducted in a centre of expertise and involved specialists in pulmonary diseases. We wanted to conduct a study that reflected the challenges in an everyday clinical setting. Conversely, the study could not be repeated as a blind study and also psychological factors influencing the test technician (researcher) and the subjects tested cannot be excluded.

Limitation of time made it unfeasible to achieve a sample size that would generate sufficient statistical power. Therefore, the results should be interpreted with care and the findings should not be generalized. However, the small sample size made it possible for us to study the participants individually.

Knowledge about the usefulness of a repeated ECT may be of importance to patients, clinical practice, and research work. A reliable assessment of EIB is of great value as optimal choice of treatment can be enabled and adaptations relating to exercise and sports can be made. Also, for a drug to be regarded as beneficial, knowledge about variability in maximum reduction in FEV₁ is crucial. Nevertheless, a repeated ECT may identify extra subjects with EIB who tested false negative the first time, as well as over diagnosing subjects with EIB the second time. A repeated ECT may require reconsideration of the final EIB diagnosis. However, different test results make the diagnostic decision difficult. Which test should be emphasized? In any case, our results may suggest that a repeated ECT does not improve ECT performance with regard to exercise intensity.

In summary, our study showed a 25% divergence in the diagnostic results of two consecutive ECTs on subjects with symptoms strongly suggesting EIB. The difference in test results was not explained by a difference in exercise intensity. One objective of further research should be to develop a more precise exercise challenge test protocol with definite control parameters to provide a more reliable test.
REFERENCES


Rekruttering til forskningsprosjektet EIB

Pasienten er henvist til klinikken KAL. Pasienten har gjennomgått tester etter vanlig prosedyre, og rekrutteres ved konsultasjon dersom det kommer frem at pasienten har symptomer ved anstrengelse og legen mistenker EIB. Også pasienter som har fått astmadiagnose og behandling tidligere, men allikevel har symptomer på treningsindusert astma inkluderes i studien.
Rekrutteringen vil skje på grunnlag av inklusjonskriteriene nedenfor. 3 av 5 kriterier må oppfylles.

Inklusjonskriterier:

1. Hoste under anstrengelse eller innen 5 min etter anstrengelse.

2. Pipelyder under anstrengelse eller innen 5 min etter anstrengelse

3. Påfallende tungpustenhet, spesielt ekspirasjonsvansker e.l. under anstrengelse eller innen 5 min etter anstrengelse (varighet ca 5 min eller mer)

4. Manglende bedring av form/pust til tross for intensivering av trening

5. Tetthets-/tranghetsfølelse i brystet under eller etter anstrengelse

Pasientens navn: ___________________________ Føds dato: __________________________
Lege: _______________________________ Dato: _______________________________
Forespørsel om deltakelse i forskningsprosjektet:

“Sammenligning av to tredemølletester (provokasjonstester) for vurdering av anstrengelsesutløst astma”.

Bakgrunn og hensikt:
Vi henvender oss til deg for å be om ditt samtykke til deltakelse i dette forskningsprosjektet. Formålet med studien er å få økt kunnskap knyttet til diagnostisering av anstrengelsesutløst astma. Studien gjennomføres som et samarbeidsprosjekt mellom “Klinikk for allergi og luftveissykdommer” (KAL), Oslo, og ”Norges teknisk- naturvitenskapelige universitet”, (NTNU), Trondheim. Denne forespørselen går til personer av begge kjønn i alderen 16 til 45 år som er henvist til KAL og hvor det er misanke om anstrengelsesutløst astma.

Prosjektets innhold:

Den første testdagen vil du bli bedt om å svare på et spørreskjema angående astma og luftveisplager. Det vil også bli målt blodtrykk og hjertets elektriske aktivitet vil bli registrert (hvile EKG).

Ved begge testdagene vil det i tillegg til tredemøllestesten bli utført andre lungefunksjonsmålinger som foretas rutinemessig hos alle pasienter som er henvist for astma og/eller pustebesvær under anstrengelse: Maksimal frivillig ventilasjon måles for å beregne pustereserve etter at man har målt ventilasjon under tredemøllestesten. Nivå av nitrogenoksid i utåndingsluft kan si noe om betennelsestitstanden i luftveiene på måletidspunktet. Lungevolum, luftveismotstand og diffusjonskapasitet benyttes som hjelpemiddel i diagnostisering og behandling av lungesykdom.

Viktig: Dine forberedelser:
Ved de to testdagene må du **ikke** være under påvirkning av luftveisutvidende medikamenter (bronkodilatorer) og du må **ikke** trene samme dag som du skal testes.

Dette betyr at:
Ventoline®, Salbuvent®, Inspiryl®, Bricanyl®, Airomir® ikke skal taes de siste 8 timer før testene. Serevent®, Seretide®, Oxis® og Symbicort® må ikke brukes de siste 3 døgn før testene. Singulair® skal ikke brukes de siste 3 døgn før testene. Inhalasjonspreparater av cortison (Pulmicort®, Flutide®, Aerobec®, Becotide® m.m.) skal ikke brukes undersøkelsesdagene før testene. Teophylline preparater (TheoDur®, Nuelin deport®) skal ikke brukes de siste 3 døgn før testene. Atrovent® skal ikke brukes de siste 12 timer før testene. Lomudal til inahlasjon skal ikke brukes de siste 8 timer før testene.
**Hvorfor vi gjør denne studien:**
En tredemølleetest blir vanligvis utført med en intensitet som er beregnet ut i fra estimert maksimal hjertefrekvens. Det har blitt hevdet at intensiteten som oppnås ved en slik tilnærmning ikke nødvendigvis er tilstrekkelig for å utløse sammentrekning av luftrorene (bronkiene). En repetert test, basert på kunnskap fra den første testen, kan gjøre det mulig å justere intensiteten mer individuelt. I tillegg har vi en hypotese, basert på klinisk erfaring, om at pasienter som gjennomfører en tredemølleetest for andre gang utfører testen med en høyere intensitet da de er mer vant til testen og tredemølla. Hovedhensikten med prosjektet er å undersøke effekten av å gjennomføre en repetert tredemølleetest for å diagnostisere anstrengelsesutløst astma. Ny kunnskap kan bidra til å tilby pasienter mer presise prosedyrer for å diagnostisere anstrengelsesutløst astma.

**Mulige fordeler og ulemper:**

**Hva skjer med testene og informasjonen om deg:**

**Personvern og frivillig deltakelse:**

**Vennlig hilsen forskningsgruppen:**
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Samtykke til deltakelse i forskningsprosjektet

For deltakeren:

Jeg har lest informasjonsskrivet om å delta i forskningsprosjektet: "Sammenligning av to tredemølletester (provokasjonstester) for vurdering av anstrengelsesutløst astma” og gir mitt samtykke til deltagelse i prosjektet. Jeg er kjent med at jeg når som helst kan trekke meg fra prosjektet uten å måtte oppgi grunn for det. Jeg er klar over at de innsamlede data utelukkende brukes til forskning.

Jeg samtykker i å delta i prosjektet som innebærer følgende:

- Utfylling av spørreskjema
- Måling av blodtrykk og hvile EKG
- Målinger av utåndet nitrogenoksid
- Målinger av lungefunksjon før og etter tredemølletester
- Målinger av maximal frivillig ventilasjon
- Tredemølletester med registrering av oksygenopptak og puls
- Målinger av lungevolum og luftveismotstand
- Målinger av diffusjonskapasitet

-------------------------------------------------------------------------------
(Deltakers fulle navn, bruk BLOKKBOKSTAVER)

Dato:    Signatur:
-------------------------------------------------------------------------------

På dagtid kan jeg kontaktes på telefonnummer:

-------------------------------------------------------------------------------
Samtykket returneres til Klinikk for allergi og luftveissykdommer (KAL) i den ferdig adresserte konvolutten. Porto er betalt.

Utfylles av klinikken (KAL):
Herved bekreftes at informasjon om studien er gitt

-------------------------------------------------------------------------------
(Signatur, rolle i studien, dato)
APPENDIX 3: Regional Committee approval

Fra: Regional komite for medisinsk og helsefaglig forskningsetikk REK nord

Til: Liv.Berit.Augestad@SVT.NTU.NO

Dokumentreferanse: 2010/1551-17
Dokumentdato: 16.09.2010

TRENGSINDUSERT BRONKOKONSTRIKSJON - INFORMASJON OM VEDTAK

Vi viser til e-post av 16.09.2010 hvor det presiseres at personer under 16 år ikke vil bli inkludert i studien.

Etter fullmakt er det fattet slikt

Vedtak:
Med hjemmel i helseforskningsloven § 10 og forskningsetikklovens § 4 godkjennes prosjektet.

Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og protokollen, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Dersom det skal gjøres endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektlæder sende endringsmelding til REK. Vi gjør oppmerksom på at hvis endringene er vesentlige, må prosjektlæder sende ny søknad, eller REK kan pålegge at det sendes ny søknad.

Det forutsettes at forskningsdata oppbevares forskriftsmessig.

Godkjenningen gjelder til 30.07.2011 (i søknad er sluttdato oppgitt å være 30.07.2010 - dette antar vi må være feil)

Prosjektlæder skal sende sluttmelding i henhold til helseforskningsloven § 12.


Vennlig hilsen

May Britt Rossvoll Monika Rydland Gaare
seksretariatsleder førstekonsulent

REGIONAL KOMITÉ FOR MEDISINSK OG HELESEFAGLIG FORSKNINGSETIKK, NORDNORG
REK NORD
Besøksadresse: TANN-bygget, Universitetet i Tromsø, N-9037 Tromsø
telefon sentralbord 77 64 40 00 telefon ekspedisjon 77620758 e-post: post@helseforskning.etikkom.no
APPENDIX 4: ClinicalTrials.gov- Protocol registration receipt

Protocol Registration Receipt
10/05/2010

Sensitivity of Exercise Induced Bronchoconstriction Diagnostics: the Effect of a Repeated Exercise Challenge Test

This study is currently recruiting participants.
Verified by Norwegian University of Science and Technology, October 2010

<table>
<thead>
<tr>
<th>Sponsor:</th>
<th>Norwegian University of Science and Technology</th>
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</thead>
<tbody>
<tr>
<td>Collaborators:</td>
<td>Klinikk for allergi og luftveissykdommer</td>
</tr>
<tr>
<td>Information provided by:</td>
<td>Norwegian University of Science and Technology</td>
</tr>
<tr>
<td>ClinicalTrials.gov Identifier:</td>
<td>NCT01214551</td>
</tr>
</tbody>
</table>

Purpose

The purpose of this study is to increase the knowledge of the possible diagnostic effect of exercise induced bronchoconstriction performing a repeated exercise challenge test.

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<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Exercise Induced Bronchoconstriction</td>
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</table>

Study Type: Observational
Study Design: Prospective
Official Title: Sensitivity of Exercise Induced Bronchoconstriction Diagnostics: the Effect of a Repeated Exercise Challenge Test

Further study details as provided by Norwegian University of Science and Technology:
Biospecimen Retention: None Retained
Primary Outcome Measure:
  • Forced expiratory volume in one second (FEV1)  [Time Frame: Two days separated by maximum 4 weeks]
[Designated as safety issue: No]

Secondary Outcome Measures:

- Forced vital capacity (FVC)  [Time Frame: Two days separated by maximum four weeks] [Designated as safety issue: No]
- Forced expiratory flow at 50% FVC (FEF50%)  [Time Frame: Two days separated by maximum four weeks] [Designated as safety issue: No]
- Fractional exhaled nitric oxide (FENO)  [Time Frame: Two days separated by maximum four weeks] [Designated as safety issue: No]
- Total lung capacity (TLC)  [Time Frame: Two days separated by maximum four weeks] [Designated as safety issue: No]
- Specific airway resistance (sRAW)  [Time Frame: Two days separated by maximum four weeks] [Designated as safety issue: No]
- Specific airway conductance (sGAW)  [Time Frame: Two days separated by maximum four weeks] [Designated as safety issue: No]
- Residual volume (RV)  [Time Frame: Two days separated by maximum four weeks] [Designated as safety issue: No]
- Diffusing capacity (TLCO)  [Time Frame: Two days separated by maximum four weeks] [Designated as safety issue: No]
- Maximum voluntary ventilation (MVV)  [Time Frame: Two days separated by maximum four weeks] [Designated as safety issue: No]
- Breathing reserve (BR)  [Time Frame: Two days separated by maximum four weeks] [Designated as safety issue: No]
- Respiratory exchange ration (RER)  [Time Frame: Two days separated by maximum four weeks] [Designated as safety issue: No]
- Oxygen uptake peak (VO2 peak)  [Time Frame: Two days separated by maximum four weeks] [Designated as safety issue: No]
- Heart rate peak (HR peak)  [Time Frame: Two days separated by maximum four weeks] [Designated as safety issue: No]
- Questionnaire  [Time Frame: The first test day] [Designated as safety issue: No]
- Ventilation peak (VE peak)  [Time Frame: Two days separated by maximum four weeks] [Designated as safety issue: No]

Estimated Enrollment: 40  
Study Start Date: August 2010  
Estimated Study Completion Date: July 2012  
Estimated Primary Completion Date: July 2011

Number of arms: 1

Prior studies have shown that the intensity influences the sensitivity of exercise challenge tests (ECT) and that a heart rate-based protocol does not ensure sufficient exercise intensity to induce bronchoconstriction. It is not common clinical practice to perform a pre ECT to establish maximal heart rate or maximal oxygen uptake. The heart rate formula recommended by ATS (HRmax= 220–age) is usually applied to determine recommended intensity of the ECT. Conducting a second ECT, based on the knowledge of the first test, introduce the possibility to adjust the intensity on an individual basis. In addition, based on clinical experience, patients may seem
reluctant to perform maximal the first time they undergo an ECT on a treadmill. The hypothesis is that patients are less reluctant to perform maximal the second time they undergo the test when they are more accustomed to the procedure and the treadmill by itself.

Eligibility

Subjects referred to Klinikk for allergi og luftveissykdommer

Sampling Method: Non-Probability Sample
Ages Eligible for Study: 16 Years to 45 Years
Genders Eligible for Study: Both

Inclusion Criteria:

- Referred to Klinikk for allergi og luftveissykdommer
- Meet at least 3 out of 5 criteria (symptoms related to exercise):
  1. Cough during exercise or within 5 minutes after exercise
  2. Wheeze during exercise or within 5 minutes after exercise
  3. Heavy breathing, expiratory in particular, during exercise or within 5 minutes after exercise (duration 5 minutes or more)
  4. Improvement of physical fitness/breath is lacking despite of exercise intensification
  5. Chest tightness during or after exercise

- Patients former diagnosed with-and treated for asthma who have symptoms of EIB are included in the study.

Exclusion Criteria:

- Ongoing respiratory infection or recent respiratory infection, judged by the responsible doctor to be of importance of the result
- The inability to perform an Exercise challenge test with maximum effort

Contacts and Locations

Contacts

Thor A Gronnerod, MD 91854024 Ext. 0047 tagroenn@online.no
Trine Stensrud, Associate 23262346 Ext. 0047 Trine.Stensrud@nih.no

Locations

Norway, Ullevål
Klinikk for allergi og luftveissykdommer Recruiting
Oslo, Ullevål, Norway, 0855
Contact: Thor A Gronnerod, MD 91854024 Ext. 0047 tagroenn@online.no

Investigators

Principal Investigator: Liv B Augestad, Professor Norwegian University of Science and Technology
More Information

Responsible Party: NTNU (Program of Human movement science, NTNU (Maj Angell))
Study ID Numbers: 2010/1551-4
Health Authority: Norway: The National Committees for Research Ethics in Norway