

## ORIGINAL ARTICLE

## Asthma tests in the assessment of military conscripts

D. Miedinger<sup>1</sup>, N. Mosimann<sup>1</sup>, R. Meier<sup>1</sup>, C. Karli<sup>2</sup>, P. Florek<sup>2</sup>, F. Frey<sup>2</sup>, K. Scherer<sup>1</sup>, C. Surber<sup>1</sup>, B. Villiger<sup>3</sup>, F. Michel<sup>3</sup> and J. D. Leuppi<sup>1</sup><sup>1</sup>University Hospital, Basel, Switzerland, <sup>2</sup>Medical Service, Swiss Armed Forces, Ittigen, Switzerland and <sup>3</sup>Swiss Paraplegic Centre, Nottwil, SwitzerlandClinical &  
Experimental  
Allergy

## Summary

**Background** Respiratory diseases such as asthma may affect individuals' fitness for military service. In order to assess fitness for military service in subjects with asthma symptoms at conscription, objective and reliable tests are needed.

**Objective** To prospectively determine the diagnostic value of the mannitol and methacholine bronchial provocation test (BPT) as well as exhaled nitric oxide in assessing physician-diagnosed asthma in a group of Swiss Armed Forces conscripts.

**Methods** Questionnaire, spirometry, BPT with methacholine and mannitol, exhaled nitric oxide (FeNO) and skin prick testing were conducted in 18–20-year-old male conscripts.

Asthma was diagnosed by a military physician not involved in this study according to the medical record, results of BPT, current respiratory symptoms and use of asthma medication.

**Results** Two hundred and eighty four subjects participated in the study. Complete data for the BPT with methacholine, mannitol and measurement of FeNO were available on 235 subjects. Forty-two conscripts (17.9%) had physician-diagnosed asthma. The sensitivity/specificity of mannitol to identify physician-diagnosed asthma was 41%/93% and for methacholine it was 43%/92%. Using a cut-off point of 36.5 p.p.b., FeNO had a similar negative predictive value to rule out physician-diagnosed asthma as BPT with mannitol or methacholine.

**Conclusion** BPT with mannitol has a sensitivity and specificity similar to methacholine for the diagnosis of physician-diagnosed asthma in military conscripts but is less costly to perform without the need to use and maintain a nebulizer.

**Keywords** asthma, conscripts, exhaled nitric oxide, mannitol, methacholine, military

*Submitted 14 May 2009; revised 26 August 2009; accepted 28 August 2009*

## Correspondence:

Dr David Miedinger, University Hospital,  
Internal Medicine, 4031 Basel,  
Switzerland.

E-mail: dmiedinger@uhbs.ch

## Introduction

Asthma is a chronic inflammatory disorder of the airways that is associated with airway hyperresponsiveness and respiratory symptoms such as wheezing, cough, breathlessness and chest tightness [1].

Several asthma-triggering or aggravating factors are present in a military environment. Subjects are exposed to an increased level of psychological and physical stress that can exacerbate asthma. During service, military personnel have to fulfil their duty in different climates, where the air is cold and dry, or they might be exposed to different kinds of airway irritants such as smoke and fumes. When encountering these latter conditions, soldiers need to be able to tolerate wearing respiratory protection devices. In addition, troops are often deployed in remote areas without appropriate health care provision where acute asthmatic exacerbations can be treated appropriately.

This has led to many armies not allowing subjects to serve if they have current active asthma. In the Swiss Armed Forces (SAF), conscripts are evaluated for asthma by military physicians during the compulsory conscription process [2]. Conscripts are evaluated regarding the severity of the disease (course of past disease, current medical treatment and, if available, lung function testing) and their attitude towards their disease and serving for the SAF. Subjects with intermittent (symptoms less than once a week, nocturnal symptoms not more than twice a month) and well-controlled disease are allowed to enlist if they are motivated to serve [3]. To evaluate their fitness to serve, subjects with pre-existing disease are requested to present a medical letter from their treating physician regarding their disease before or at the time of conscription. Nevertheless, > 50% of SAF conscripts who are subsequently diagnosed with asthma present without letters from their treating physician or proof of medical investigation for asthma [4].

On the other hand, the diagnosis may be missed as conscripts may have a poor perception of their asthma symptoms or may choose to withhold information about current respiratory symptoms or childhood asthma during history taking. The missed diagnosis affects both the conscript and the SAF. Conscripts who need to end basic military training need to seek alternative employment and the SAF are left with significant costs in addition to having lost a member of their workforce. In the US Navy and Marine Corps, Connelly estimated that a premature discharge from base camps creates costs of about US\$4500 [5].

As there is no universally accepted gold standard for the diagnosis of asthma, it would be desirable to perform a standardized evaluation that includes objective measurement of lung function and bronchial hyperresponsiveness in conscripts.

We conducted this study to evaluate the feasibility of performing bronchial provocation testing (BPT) during the recruitment process and to compare the diagnostic validity of different BPT and the measurement of exhaled nitric oxide in the diagnosis of physician-diagnosed asthma in SAF recruits.

## Methods

### *Recruitment process and selection of participants*

In Switzerland, male citizens undergo compulsory conscription to the SAF in their assigned recruitment centre in general at 18–19 years of age. During the recruitment process, which takes between 2 and 3 days, conscripts undergo various assessments, medical and psychiatric evaluations and a fitness test to assess their aptitude to serve in the SAF [3]. We conducted our study in the recruitment centre of Nottwil during the period of January 2007 to October 2007.

On the first day of the recruitment process, conscripts were grouped into four to six conscription groups, each containing 20–30 subjects. Two conscripts out of every conscription group were randomly selected and asked to participate in this study. If conscripts were unwilling to participate, another subject in the same group was randomly selected and asked to participate. Selecting subjects from different groups allowed us to schedule the study examinations during the period when subjects were waiting for their regular medical assessment.

### *Questionnaire and measurements*

All subjects administered the validated German version of a specific respiratory disease questionnaire originally used in the SAPALDIA study [6].

Orally exhaled nitric oxide (FeNO) measurements were performed according to published guidelines [7] using a device with a built-in biofeedback mechanism (NIOX MINO, Aerocrine AB, Solna, Sweden) at a flow rate

of 50 mL/s before performing spirometry and BPT and measurement of carbon monoxide.

Spirometry was performed in the sitting position using a nose clip according to standardized guidelines. Spirometry was performed with devices using an ultrasound flow time measurement (Easyone, ndd Medizintechnik AG, Zurich, Switzerland). Predicted values were calculated using reference values derived from the Swiss population [8].

Carbon monoxide measurement was performed according to the method published by Jarvis et al. [9] using an electrochemical analyser (Bedfont EC50 MICRO III Smokerlyzer, Bedfont Scientific Ltd, Rochester, Kent, UK), which was calibrated just before the start of the study with a mixture of 50 p.p.m. CO in air.

Methacholine BPT was performed according to the protocol of the SAPALDIA study, which is identical to the protocol of European Community Respiratory Health Survey 'method 2 short-protocol' [6, 10]. Methacholine – prepared by the Institute of Hospital Pharmacy, University Hospital Basel according to cGMP guidelines – was delivered using a Mefar MB3 dosimeter (Mefar, Bovezzo, Italy) set to deliver the aerosol over a period of 1 s. All those whose pre-diluent forced expiratory volume in 1 s (FEV<sub>1</sub>) was at least 70% of predicted and > 1.5 L were invited to undergo methacholine BPT. The test commenced with inhalation of an isotonic saline diluent, and the maximum post-diluent FEV<sub>1</sub> recorded 2 min later was used as the baseline value. Subjects inhaled methacholine according to the protocol until there was a decline in FEV<sub>1</sub> > 20% from the baseline value or the maximum cumulative dose of 2.0 mg of methacholine was reached. A test was considered positive if the PD<sub>20</sub> was ≤ 2 mg.

BPT with mannitol was carried out using the standardized protocol originally described by Anderson et al. [11]. The mannitol was administered as a dry powder in capsule form (Aridol™, Pharmaxis Ltd, Frenchs Forest, NSW, Australia), inhaled from an osmohaler device (Pharmaxis Ltd). All those whose pre-0 mg capsule FEV<sub>1</sub> was at least 70% of predicted and > 1.5 L were invited to undergo mannitol BPT. The test commenced with inhalation of an empty capsule and the maximum post-0 mg capsule FEV<sub>1</sub> recorded 2 min later was used as the baseline value. Subjects inhaled mannitol according to the protocol until there was a decline in FEV<sub>1</sub> > 15% from the baseline value, a 10% incremental decline between consecutive doses or the maximum cumulative dose of 635 mg of mannitol was reached. Mannitol and methacholine BPT were performed within 48 h in random order; the rest period between the two tests was at least 24 h.

Skin prick tests (SPT) were performed according to the SAPALDIA protocol [6] with Stallerpoint needles. Different aeroallergens (grass mixture, trees mixture, *Alternaria*, *Cladosporium*, cat and dog epithelium and *Dermatophagoides pteronyssinus* and *D. farinae*) were used with histamine and saline/glycerol solution as the positive and negative control (Stallergènes S.A., Antony, France).

## Definitions

*Current smokers* were defined as subjects, who answered positively the question: 'Do you smoke now?' and *current smokers with significant exposure* were those who answered positively the question: 'Do you smoke now?' and 'Have you ever smoked for a year or more?' ('yes' means at least 20 packs of cigarettes or 360 g of tobacco in your whole life or at least one cigarette a day or a cigar a week for 1 year). *Allergic rhinitis* (AR) was defined if conscripts answered affirmatively the question: 'Do you have any nasal allergies including hayfever?' *Exercise symptoms* were defined as being present if conscripts answered one or both of the following questions positively: 'Have you had an attack of shortness of breath that came on following strenuous activity at any time in the last 12 months?' and 'Do you avoid strenuous exercise because of wheezing or asthma?' *Ever had asthma* was defined if conscripts answered positively to the question: 'Have you ever had asthma?'

Physician-diagnosed asthma was based on the judgement of a military physician who was not involved in the study: he reviewed all conscripts' files and evaluated whether the subjects had asthma or not. The military physician's asthma diagnoses were based on conscripts' self-report of respiratory symptoms (SAF medical file or study questionnaire), previous physician-diagnosed asthma, the use of asthma medication and the results of BPT.

## Statistical analysis

Proportions were compared using Pearson's  $\chi^2$ -test or Fisher's Exact Test if the expected cell count was <5. Distribution of data were tested using the Kolmogorov-Smirnov test. Continuous variables were compared using a student *t*-test if normally distributed or the Mann-Whitney *U*-test otherwise. A *P*-value of <0.05 was considered to be significant. All analysis was performed using SPSS Version 16 (SPSS Inc., Chicago, IL, USA).

## Results

Two hundred and eighty four conscripts agreed to participate in the study. Thirty-six subjects (13%) agreed to participate in the study but went home on the first evaluation day and so did not undergo the second BPT scheduled for the following day. In total, 248 subjects underwent both methacholine and mannitol testing. Thirteen subjects (5%) were excluded from the analysis because the BPT had to be terminated due to technical failure of either the methacholine nebulizer or the spirometer or because the reproducibility of the spirometry curves was insufficient. Data for both methacholine and mannitol BPT were therefore available for 235 subjects. All subjects were male. Seventy-seven subjects (32.8%)

**Table 1.** Basis on which a diagnosis of physician-diagnosed asthma was made (*n* = 42)

|                                                                              |                |
|------------------------------------------------------------------------------|----------------|
| Current respiratory symptoms suggestive for asthma                           | 42 (100)       |
| Diagnosis of physician-diagnosed asthma before<br>scription                  | 20<br>(48)     |
| Diagnosis of physician-diagnosed asthma and<br>treatment before prescription | 5 (12) 25 (60) |
| Positive bronchial challenge test result                                     | 25 (60)        |

Data presented as frequency and relative frequency.

admitted to current smoking and 60 (25.5%) were currently smoking and had significant exposure. Sixty-four conscripts (27.2%) had AR or hayfever, and 98 conscripts (41.7%) had at least one positive reaction on SPT. Fifty-four conscripts (23%) had AR or hayfever in addition to at least one positive reaction on SPT. Forty-two conscripts (17.9%) had physician-diagnosed asthma. Table 1 illustrates on what basis the diagnosis was assigned by the physician who reviewed the medical files. Five conscripts reported a diagnosis of asthma previously made by a physician and were taking asthma medications. Four conscripts were taking on-demand inhaled salbutamol and one subject could not recall the name of his asthma therapy. None of these conscripts were current smokers. A comparison of baseline data in those with and without physician-diagnosed asthma is shown in Table 2.

Thirty-three conscripts (14%) had a positive methacholine BPT, 31 conscripts (13.2%) a positive mannitol test, while 14 conscripts (6%) had positive results in both BPT. In those with a positive mannitol BPT result, one subject showed a decline of > 10% after inhaling the empty capsule, 20 showed a decline in FEV<sub>1</sub> of  $\geq 15\%$  from baseline and 10 a 10% incremental decline between consecutive doses. For the diagnosis of physician-diagnosed asthma, the BPT with mannitol and methacholine had the highest efficiency (83% efficiency = true positive + true negative results/total number of cases), followed by using FeNO cut-off values according to smoking status (74%) and SPT (67%) (Table 3). There was a lack of agreement between the clinical diagnosis of physician-diagnosed asthma and the results in the BPT in 36 (15.3%) of the subjects: 32 (13.6%) of the subjects with physician-diagnosed asthma were negative to mannitol and methacholine BPT and 4 (1.7%) without asthma showed a positive result in BPT to mannitol and to methacholine. The clinical findings in those subjects with a positive BPT to either mannitol, methacholine or both agents can be seen in Table 4.

Different threshold values for FeNO in the diagnosis of physician-diagnosed asthma were determined. The area under the curve for FeNO for the diagnosis of physician-diagnosed asthma in the whole population was 0.628, and the highest value of the Youden Index (sensitivity + specificity - 100) that could be achieved using a threshold value of 36.5 p.p.b. was 20 (Table 5).

Table 2. Descriptive data

| Variable                                      | Physician-diagnosed asthma (n = 42) | No physician-diagnosed asthma (n = 187) | P-value |
|-----------------------------------------------|-------------------------------------|-----------------------------------------|---------|
| Height (cm)                                   | 175±28                              | 179±7                                   | 0.853   |
| Weight (kg)                                   | 73 (64; 80)                         | 72 (65; 80)                             | 0.893   |
| FEV <sub>1</sub> % predicted                  | 95 (88; 102)                        | 98 (91; 105)                            | 0.060   |
| FVC% predicted                                | 95 (86; 101)                        | 96 (89; 103)                            | 0.340   |
| FEV <sub>1</sub> /FVC×100                     | 85 (79; 90)                         | 86 (79; 90)                             | 0.318   |
| Exhaled nitric oxide (FeNO) in p.p.b.         | 23.5 (15; 46)                       | 17.0 (10; 28)                           | 0.009   |
| FeNO ≥ 20 p.p.b.                              | 24 (57)                             | 73 (38)                                 | 0.021   |
| FeNO positive according to*                   | 16 (38)                             | 36 (19)                                 | 0.006   |
| Methacholine test positive                    | 18 (43)                             | 15 (8)                                  | <0.001  |
| Mannitol test positive                        | 17 (41)                             | 14 (7)                                  | <0.001  |
| Current smoker                                | 16 (38)                             | 61 (33)                                 | 0.527   |
| Exhaled carbon monoxide in p.p.m. (gmean/IQR) | 1 (0; 3)                            | 1 (0; 3)                                | 0.999   |
| Current smoker with significant exposure      | 14 (33)                             | 46 (24)                                 | 0.201   |
| Dyspnoea after exercise                       | 24 (59)                             | 38 (20)                                 | <0.001  |
| Not exercising because of wheezing            | 11 (26)                             | 7 (4)                                   | <0.001  |
| Allergic rhinitis or hayfever                 | 25 (59)                             | 39 (20)                                 | <0.001  |
| Ever had asthma                               | 24 (59)                             | 21 (11)                                 | <0.001  |
| Atopy                                         | 31 (74)                             | 67 (35)                                 | <0.001  |
| <i>Dermatophagoides pteronyssinus</i>         | 17 (41)                             | 28 (15)                                 | <0.001  |
| <i>D. farinae</i>                             | 12 (29)                             | 23 (12)                                 | 0.006   |
| <i>Cladosporium</i>                           | 1 (2)                               | 1 (1)                                   | 0.326   |
| <i>Alternaria</i>                             | 2 (5)                               | 2 (1)                                   | 0.149   |
| Cat dander                                    | 10 (24)                             | 9 (5)                                   | <0.001  |
| Dog dander                                    | 5 (12)                              | 12 (6)                                  | 0.197   |
| Grass mixture                                 | 19 (45)                             | 38 (20)                                 | <0.001  |
| Tree mixture                                  | 4 (10)                              | 5 (3)                                   | 0.057   |

Data are presented as mean±standard deviation, median (1. quartile; 3. quartile) or as frequency (percent).

\*FeNO ≥ 30 p.p.b. for non-smoker and FeNO ≥ 40 p.p.b. for smoker.

FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; FeNO, oral exhaled nitric oxide.

Table 3. Sensitivity and specificity for the diagnosis of physician-diagnosed asthma

| Test                                           | Sensitivity (%) | Specificity (%) | Positive predictive value (%) | Negative predictive value (%) |
|------------------------------------------------|-----------------|-----------------|-------------------------------|-------------------------------|
| Methacholine PD 20 (n = 33)                    | 43              | 92              | 55                            | 88                            |
| Mannitol PD 15 (n = 31)                        | 41              | 93              | 55                            | 88                            |
| FeNO > 36.5 p.p.b. (n = 45)                    | 36              | 84              | 33                            | 86                            |
| FeNO > 20 p.p.b. (n = 97)                      | 57              | 62              | 25                            | 87                            |
| FeNO > 30 p.p.b.* / FeNO > 40 p.p.b.† (n = 52) | 38              | 81              | 31                            | 86                            |
| Skin prick test positive (n = 98)74            |                 | 65              | 32                            | 92                            |

\*Non smoker.

†Smoker.

## Discussion

Our study is the first to assess the efficacy of BPT with mannitol in the diagnosis of asthma among SAF conscripts.

Subjects with current active and uncontrolled asthma are not allowed to enlist for military training in Switzerland [3]. Subjects with current respiratory symptoms and airway hyperresponsiveness are at an increased risk of exacerbations during their basic military training. During this period, they are exposed to several asthma-aggravating or -exacerbating factors that have the potential to cause serious morbidity and could lead to premature discharge from military training [5].

It is possible that conscripts withhold information about respiratory symptoms when answering the questionnaire or during history taking at the medical examination in order not to be discriminated against for military training, because serving in the army is their only job opportunity at the time of evaluation. Two studies are of interest regarding this matter: Nish and Schwietz [12] investigated 192 recruits who failed the fitness assessment test during basic military training and who declared themselves to be free of asthma symptoms since the age of 12 years. These recruits were further investigated and current active asthma was diagnosed in 113 (59%) after performing spirometry, histamine and exercise BPT. Sinclair and colleagues used exercise BPT to investigate conscripts, who had a history of childhood asthma, but who declared themselves to be free of respiratory symptoms in the last 4 years. They detected 29 subjects (29%) with a significant decline in FEV<sub>1</sub> post-exercise. The reporting of respiratory symptoms can be unreliable because the perception of respiratory symptoms and bronchial obstruction varies from individual to individual and that this perception is even more impaired in subjects with more severe disease [13, 14]. In the SAPALDIA cohort, asymptomatic individuals with airway hyperresponsiveness to methacholine at baseline had a higher risk of an accelerated decline in lung function and a higher risk of developing asthma than subjects without airway hyperresponsiveness [15]. It is therefore possible that subjects who have asymptomatic bronchial hyperresponsiveness at the time of conscription to the army are at a high risk of developing asthma in the future. Such individuals are likely to benefit from surveillance during their military service in order that treatment may be started early when the first respiratory symptoms occur, thereby avoiding a serious exacerbation of the disease.

The prevalence of physician-diagnosed asthma in our study sample was 17.9%. This rate is significantly higher than in other studies that report prevalence rates between 3.5% and 10% for asthma in a population of male military conscripts in Europe or in the Mediterranean area [16–19]. In a cross-sectional survey among SAF conscripts, about 12% reported to have physician-diagnosed asthma [20].

**Table 4.** Clinical findings in subjects with positive bronchial provocation test results

| Variable                                        | BPT methacholine positive ( <i>n</i> = 19) | BPT mannitol positive ( <i>n</i> = 17) | BPT methacholine and mannitol positive ( <i>n</i> = 14) | No BPT positive ( <i>n</i> = 185) |
|-------------------------------------------------|--------------------------------------------|----------------------------------------|---------------------------------------------------------|-----------------------------------|
| FEV <sub>1</sub> % predicted                    | 93 (84; 98)                                | 96 (91; 100)                           | 94 (91; 100)                                            | 99 (91; 105)                      |
| FVC% predicted                                  | 96 (84; 98)                                | 95 (88; 101)                           | 94 (89; 102)                                            | 96 (89; 103)                      |
| FEV <sub>1</sub> /FVC × 100                     | 79 (75; 87)                                | 85 (80; 88)                            | 84 (78; 88)                                             | 86 (83; 90)                       |
| Exhaled nitric oxide (FeNO) in p.p.b.           | 25 (15; 42)                                | 19 (15; 33)                            | 46 (22; 61)                                             | 17 (10; 26)                       |
| Response to mannitol (%/mg)                     | 0.0150 (0.0083; 0.0200)                    | 0.0500 (0.0385; 0.2300)                | 0.0500 (0.0300; 0.4050)                                 | 0.0089 (0.0012; 0.0108)           |
| Response to methacholine (%/mg)                 | 24.0 (12.6; 101.6)                         | 5.5 (4.7; 7.6)                         | 18.7 (11.4; 31.5)                                       | 3.2 (1.6; 5.4)                    |
| Current smoker                                  | 6 (32)                                     | 8 (47)                                 | 4 (29)                                                  | 46 (25)                           |
| Respiratory symptoms                            | 9 (47)                                     | 9 (53)                                 | 10 (71)                                                 | 87 (47)                           |
| Allergic rhinitis or hayfever                   | 5 (26)                                     | 9 (53)                                 | 8 (57)                                                  | 42 (23)                           |
| Respiratory tract infection in the last 3 weeks | 5 (26)                                     | 3 (18)                                 | 5 (36)                                                  | 56 (31)                           |
| Atopy                                           | 12 (63)                                    | 13 (76)                                | 12 (86)                                                 | 61 (33)                           |

Data are presented as median (1. quartile; 3. quartile) or as frequency (percent).

Response was calculated: %fall in FEV<sub>1</sub> from FEV<sub>1</sub> after inhalation of an empty capsule or a normotonic saline/cumulative dose administered.

FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; FeNO, oral exhaled nitric oxide.

**Table 5.** FeNO in the diagnosis of physician-diagnosed asthma

| Selection of subjects                      | Area under the curve | Threshold with the highest Youden Index | Threshold for 100% sensitivity | Threshold for 100% specificity |
|--------------------------------------------|----------------------|-----------------------------------------|--------------------------------|--------------------------------|
| Non-smoker                                 | 0.736                | 22.5                                    | 3.5                            | 211                            |
| Atopy + non-smoker                         | 0.674                | 31.5                                    | 11                             | 211                            |
| Non-smoker + allergic rhinitis or hayfever | 0.642                | 22.5                                    | 14                             | 85.5                           |
| Non-smoker + exercise symptoms             | 0.709                | 31.5                                    | 4                              | 95.5                           |
| Atopy                                      | 0.570                | 51.5                                    | 7.5                            | 211                            |
| Atopy + allergic rhinitis or hayfever      | 0.499                | 53                                      | 6.5                            | 142                            |
| Atopy + exercise symptoms                  | 0.715                | 11                                      | 11                             | 82                             |
| Exercise symptoms                          | 0.693                | 11.5                                    | 4                              | 82                             |
| Allergic rhinitis or hayfever              | 0.693                | 11.5                                    | 4                              | 82                             |

One reason that would explain the higher prevalence in our sample is that subjects with respiratory symptoms were more likely to participate in our study in order to being assessed for asthma. It is possible that conscripts with persistent disease and treated with inhaled steroids chose not to participate in our study because they had already undergone diagnostic testing by a respiratory physician and therefore presented with a medical certificate. It is likely that such conscripts were discharged by the SAF physician during the initial evaluation on the first day and so were excluded from the study due to failure to attend the second test on the following day. However, these subjects do not pose a diagnostic problem during recruitment. The difficulty arises mainly in conscripts who declare having had asthma in the past, who present without medical certificates and intermittently treat their symptoms with bronchodilators. Furthermore, we do not have information regarding their asthma control status (e.g. how often they use their inhaler, nocturnal symptoms and activity limitation).

In our study, we evaluated a direct (methacholine) and an indirect (mannitol) BPT. The BPT with mannitol has been

shown to correlate well with other indirect BPT; a PD10 to mannitol had a sensitivity of 96% to diagnose a 10% decline in FEV<sub>1</sub> during eucapnic voluntary hyperpnoea in elite athletes [21]. We wanted to evaluate this new test as it promises to offer advantages over the widely used methacholine BPT in this setting. The protocol for administering the test is standardized and validated and allows easy comparison. The duration for administering the test is <20 min in most of the subjects. Compared with the existing wet aerosol tests like methacholine, the equipment used for the test is simple and inexpensive and does not need any maintenance and cleaning [11]. As for all the BPT, only an office spirometer is needed. For the current widely used direct test with methacholine and histamine, solutions with appropriate concentrations need to be prepared by hospital pharmacies according to protocol. These solutions need to be transported to the point where the test is administered and the cold chain needs to be maintained; otherwise, the vials cannot be used. Mannitol test kits, on the other hand, come ready to use and can be stored at room temperature for a longer time period than methacholine solutions, even allowing testing at the subjects' workplace.

It is difficult to compare different BPT and to determine their clinical value as a universally accepted gold standard test for the diagnosis of asthma is not available. The comparison of our physician-diagnosed asthma definition with BPT has some limitations. About 14% of those with physician-diagnosed asthma were negative to both BPTs. In the SAF, the diagnosis of asthma is often assigned to conscripts, who report respiratory symptoms, suggesting asthma with or without a history of physician-diagnosed asthma. In every second conscript with a diagnosis of asthma recorded in the SAF database, information about how the diagnosis was made (medical letters, test results) is lacking [4]. It is possible that some of these conscripts were in fact suffering from another disease that is mimicking asthma such as chronic bronchitis, vocal cord dysfunction or upper airway cough syndrome and would not have been diagnosed with asthma when evaluated by a respiratory physician. In a recent study, Aaron et al. [22] objectively assessed subjects with physician-diagnosed asthma and found that one-third of patients did not have asthma on the basis of BPT results and problem-free withdrawal of medication. Four subjects were having a positive BPT to methacholine and to mannitol, but no diagnosis of asthma was assigned by the military physician who reviewed the medical records. All of these subjects declined having respiratory symptoms in the preceding 12 months and no information about symptoms was recorded in the SAF database. It is possible that these subjects consciously underreported symptoms in order to get enrolled. As neither of the two BPT has a 100% specificity for asthma, declaring these subjects as asthmatics would be inappropriate. Whether these subjects should be declared fit for military service is unclear. If they are enrolled, it would be advisable to re-evaluate these subjects at the beginning of the basic training and on a regular basis thereafter and start treatment if symptoms occur. However, recruits with mild asthma that was diagnosed during basic military training were more likely being discharged prematurely and tended to use more health care than those without asthma [23].

The sensitivity and specificity of mannitol and methacholine BPT for a clinical diagnosis of asthma were not different in our study. Anderson et al. [24] reported the sensitivity and specificity for a clinical diagnosis of exercise-induced asthma to be 56% and 75% for mannitol and 51% and 75% for methacholine. These two tests had a lower sensitivity but a higher specificity in our study, which could be explained by the fact that the reviewing military physician had access to the BPT results of our study. If we had omitted this information, the decision would have been made on information available from medical letters and investigations that were conducted before conscription. The mannitol BPT was not registered in Switzerland at the time of the study, and thus would not have been used by respiratory physicians and allergolo-

gists. Further, our study differs from that by Anderson, as we used a different method to administer methacholine, our study population consisted of subjects with a lower pre-test probability for asthma and we included smokers. We have previously shown that smoking is associated with increased airway hyperresponsiveness to mannitol and that this decreases significantly after smoking cessation [25]. Direct BPT such as histamine or methacholine are not necessarily specific for the diagnosis of asthma and poorly reflect the presence of inflammatory cells in the airways [26, 27]. The reason for this might be that the reaction to methacholine in asymptomatic individuals simply reflects airway remodelling as a result of childhood asthma [26]. Porsbjerg et al. [28] investigated 16 subjects with a positive test result to methacholine but without respiratory symptoms and performed BPT with mannitol. Only one of these subjects, a non-atopic smoker with normal levels of FeNO and blood eosinophil counts, showed a mild response to mannitol provocation.

Nitric oxide has been proposed as a quick and easy-to-perform test in the investigation of subjects with asthma. However, there are several factors such as smoking status, respiratory infection and nitrate-rich meal intake that can influence the levels of exhaled nitric oxide and need to be considered when interpreting the test [29–31]. Smith et al. [32] suggested a cut-off level of 20 p.p.b. that yielded the highest sensitivity and specificity for the diagnosis of asthma. In this small study, only steroid-naïve and non-smoking subjects were included, which limits the external validity of the study and the practical application as a screening tool in an unselected population. Rouhos et al. [33] investigated the value of FeNO in recruits referred for investigation for asthma and found a significant correlation of FeNO levels with exercise and histamine-induced bronchoconstriction in atopic but not in non-atopic recruits. Various cross-sectional studies have suggested different cut-off points for diverse clinical settings in firefighter and military personnel [34, 35]. These studies differ in the gold standard that was applied for the diagnosis of asthma. Oshikata et al. [36] suggested using a cut-off value of 30 p.p.b. for non-smokers and 40 p.p.b. for smokers. Applying these values in our study population increased the specificity of the test but the Youden index did not increase. The small sample size precluded determination of separate optimal cut-offs for smokers and non-smokers. In the whole population, the optimal cut-off with the highest Youden index was  $\geq 36.5$  p.p.b., regardless of the smoking status, having rhinitis symptoms or a positive SPT. We think that a single threshold value is more useful in this population, as smoking status might not be adequately reported and when SPTs are not routinely performed.

In today's clinical routine, BPT have become an indispensable diagnostic tool for the diagnosis of asthma. In our study, BPT with mannitol has a similar sensitivity and specificity to

methacholine for the diagnosis of physician-diagnosed asthma in military conscripts but is less costly to perform without the need to use and maintain a nebulizer. BPT results are independent from recall bias and could be performed in subjects who want to enrol for special units training where respiratory fitness is mandatory or in subjects with unclear respiratory symptoms who present at conscription without objective test results available. Symptomatic subjects with negative BPTs would need further investigation before a decision about fitness for military service can be made, whereas subjects with respiratory symptoms and positive BPTs should be started on asthma treatment and evaluated later regarding fitness for service. In those without symptoms but positive BPT the decision about fitness for military training needs to be carefully elucidated by considering the history, motivation for service and the intended military training. These subjects should be re-tested before starting basic military training and on a regular basis thereafter.

### Acknowledgements

We would like to thank all members of the team of the SAF medical service and Miss Claudia Muri for their invaluable help for conducting this study as well as Pharmaxis Ltd, Frenchs Forest, Australia, for providing the Aridol™ test kits, Aerocrine AB, Solna, Sweden, for providing a NIOX Mino Device including sensors and mouthpieces and ndd (Medizintechnik) AG, Zurich, Switzerland, for providing two easyone Spirometer with printer and mouthpieces at no charge for this study.

### References

- Global Initiative for Asthma. GINA Report, Global Strategy For Asthma Management and Prevention. Available at <http://www.ginasthma.com> (accessed 6 December 2008).
- Frey F, Huber R, Lupi GA. Rekrutierung XXI. *Schweiz Ärztz* 2003; **84**:341–5.
- Frey F. Diensttauglichkeit 2008. *Schweiz Ärztz* 2008; **89**:1578–83.
- Miedinger D, Buchli D, Frey F, Karli C, Leuppi JD. Asthma in Swiss Armed Forces conscripts. *Swiss Med Wkly* 2009; **139**:13–14 5S (abstract).
- Connolly JP, Baez SA. Asthma in the navy and marine corps. *Mil Med* 1991; **156**:461–5.
- Martin BW, Ackermann-Liebrich U, Leuenberger P *et al.* SAPAL-DIA: methods and participation in the cross-sectional part of the Swiss study on air pollution and lung diseases in adults. *Soz Präventivmed* 1997; **42**:67–84.
- Recommendations for standardized procedures for the on-line and off-line measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide in adults and children – 1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 1999; **160**:2104–17.
- Brandli O, Schindler C, Kunzli N, Keller R, Perruchoud AP. Lung function in healthy never smoking adults: reference values and lower limits of normal of a Swiss population. *Thorax* 1996; **51**:277–83.
- Jarvis MJ, Russell MA, Saloojee Y. Expired air carbon monoxide: a simple breath test of tobacco smoke intake. *Br Med J* 1980; **281**:484–5.
- Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994; **7**:954–60.
- Anderson SD, Brannan J, Spring J *et al.* A new method for bronchial-provocation testing in asthmatic subjects using a dry powder of mannitol. *Am J Respir Crit Care Med* 1997; **156**:758–65.
- Nish WA, Schwietz LA. Underdiagnosis of asthma in young adults presenting for USAF basic training. *Ann Allergy* 1992; **69**:239–42.
- Roisman GL, Peiffer C, Lacronique JG, Le CA, Dusser DJ. Perception of bronchial obstruction in asthmatic patients. Relationship with bronchial eosinophilic inflammation and epithelial damage and effect of corticosteroid treatment. *J Clin Invest* 1995; **96**:12–21.
- Boulet LP, Leblanc P, Turcotte H. Perception scoring of induced bronchoconstriction as an index of awareness of asthma symptoms. *Chest* 1994; **105**:1430–3.
- Brutsche MH, Downs SH, Schindler C *et al.* Bronchial hyperresponsiveness and the development of asthma and COPD in asymptomatic individuals: SAPALDIA cohort study. *Thorax* 2006; **61**:671–7.
- Braback L, Hjern A, Rasmussen F. Social class in asthma and allergic rhinitis: a national cohort study over three decades. *Eur Respir J* 2005; **26**:1064–8.
- Dubois P, Degraeve E, Vandenplas O. Asthma and airway hyperresponsiveness among Belgian conscripts, 1978–91. *Thorax* 1998; **53**:101–5.
- Latvala J, von HL, Lindholm H, Haahtela T. Trends in prevalence of asthma and allergy in Finnish young men: nationwide study, 1966–2003. *BMJ* 2005; **330**:1186–7.
- Lev-Tzion R, Friedman T, Shochat T, Gazala E, Wohl Y. Asthma and psychiatric disorders in male army recruits and soldiers. *Isr Med Assoc J* 2007; **9**:361–4.
- Miedinger D, Chhajed PN, Karli C, Lupi GA, Leuppi JD. Respiratory symptoms and smoking behaviour in Swiss conscripts. *Swiss Med Wkly* 2006; **136**:659–63.
- Holzer K, Anderson SD, Chan HK, Douglass J. Mannitol as a challenge test to identify exercise-induced bronchoconstriction in elite athletes. *Am J Respir Crit Care Med* 2003; **167**:534–7.
- Aaron SD, Vandemheen KL, Boulet LP *et al.* Overdiagnosis of asthma in obese and nonobese adults. *CMAJ* 2008; **179**:1121–31.
- Millikan AM, Niebuhr DW, Brundage M, Powers TE, Krauss MR. Retention of mild asthmatics in the navy (REMAIN): a low-risk approach to giving mild asthmatics an opportunity for military service. *Mil Med* 2008; **173**:381–7.
- Anderson SD, Charlton B, Weiler JM, Nichols S, Spector SL, Pearlman DS. Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. *Respir Res* 2009; **10**:4.
- Stolz D, Anderson SD, Gysin C *et al.* Airway reactivity to inhaled mannitol in cigarette smokers: a longitudinal study. *Respir Med* 2007; **101**:1470–6.
- Crimi E, Spanevello A, Neri M, Ind PW, Rossi GA, Brusasco V. Dissociation between airway inflammation and airway hyperresponsiveness in allergic asthma. *Am J Respir Crit Care Med* 1998; **157**:4–9.

- 27 Porsbjerg C, Brannan JD, Anderson SD, Backer V. Relationship between airway responsiveness to mannitol and to methacholine and markers of airway inflammation, peak flow variability and quality of life in asthma patients. *Clin Exp Allergy* 2008; **38**:43–50.
- 28 Porsbjerg C, Rasmussen L, Thomsen SF, Brannan JD, Anderson SD, Backer V. Response to mannitol in asymptomatic subjects with airway hyper-responsiveness to methacholine. *Clin Exp Allergy* 2007; **37**:22–8.
- 29 Kharitonov SA, Robbins RA, Yates D, Keatings V, Barnes PJ. Acute and chronic effects of cigarette smoking on exhaled nitric oxide. *Am J Respir Crit Care Med* 1995; **152**:609–12.
- 30 de Gouw HW, Grunberg K, Schot R, Kroes AC, Dick EC, Sterk PJ. Relationship between exhaled nitric oxide and airway hyper-responsiveness following experimental rhinovirus infection in asthmatic subjects. *Eur Respir J* 1998; **11**:126–32.
- 31 Olin AC, Aldenbratt A, Ekman A *et al*. Increased nitric oxide in exhaled air after intake of a nitrate-rich meal. *Respir Med* 2001; **95**:153–8.
- 32 Smith AD, Cowan JO, Filsell S *et al*. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. *Am J Respir Crit Care Med* 2004; **169**: 473–8.
- 33 Rouhos A, Ekroos H, Karjalainen J, Sarna S, Sovijarvi AR. Exhaled nitric oxide and exercise-induced bronchoconstriction in young male conscripts: association only in atopics. *Allergy* 2005; **60**:1493–8.
- 34 Miedinger D, Chhajed PN, Tamm M, Stolz D, Surber C, Leuppi JD. Diagnostic tests for asthma in firefighters. *Chest* 2007; **131**: 1760–7.
- 35 Arora R, Thornblade CE, Dauby PA, Flanagan JW, Bush AC, Hagan LL. Exhaled nitric oxide levels in military recruits with new onset asthma. *Allergy Asthma Proc* 2006; **27**:493–8.
- 36 Oshikata C, Tsuburai T, Tsurikisawa N *et al*. Cutoff point of the fraction of exhaled nitric oxide (FeNO) with the off-line method for diagnosing asthma and the effect of smoking on FeNO. *Nihon Kokyuki Gakkai Zasshi* 2008; **46**:356–62.