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The potential role of direct and indirect bronchial challenge testing to identify overtreatment of community managed asthma

Dr. Arvind Manoharan MBChB, ¹ Prof. Brian Lipworth MD, ¹ Miss Elizabeth Craig BSc, ²

Prof. Cathy Jackson MD ²

¹ Scottish Centre for Respiratory Research, University of Dundee, Dundee, United Kingdom

² School of Medicine, University of St Andrews, St Andrews, United Kingdom.

Corresponding author: Brian J. Lipworth, Scottish Centre for Respiratory Research,
Division of Cardiovascular and Diabetes Medicine, Medical Research Institute, University of
Dundee

Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland, United Kingdom

Tel: +44 (0) 1382 383 902, Fax: +44 (0) 1382 644972

Email for correspondence: b.j.lipworth@dundee.ac.uk

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Accepted Article

The potential role of direct and indirect bronchial challenge testing to identify overtreatment of community managed asthma

Summary

Background Although airway hyperresponsiveness (AHR) is a defining feature of asthma pathophysiology, bronchial challenge testing is not routinely used in primary care asthma management.

Objective The aim of this study was to evaluate the potential role of direct (methacholine) and indirect (mannitol) challenge testing in community managed asthma.

Methods Patients currently treated for asthma from Tayside and Fife were identified by the Health Informatics Centre (HIC) and invited to take part in the study. At screening the following tests were carried out: spirometry, methacholine and mannitol challenge; exhaled nitric oxide (FeNO), Asthma Control Questionnaire (ACQ) and Mini Asthma Quality of Life Questionnaire (AQLQ).

Results A total of 3388 asthmatics were initially identified by HIC with 423 positive responses and 123 completing the study. 70% had either a positive methacholine ($PC_{20} < 8\text{mg/ml}$) or mannitol challenge ($PD_{15} < 635\text{mg}$) and 30% were non-responsive to both challenges. 14% of methacholine responders ($n=74$) were negative to mannitol and 16% of mannitol responders ($n=76$) were negative to methacholine. Spirometry, FeNO, ACQ and AQLQ were significantly better in the non-responder group who were exposed to high dose inhaled corticosteroids and frequent long-acting beta-agonists.

Conclusions and Clinical Relevance We found that 30% of unselected patients with community managed asthma were challenge negative and could be potentially misdiagnosed; or overtreated, in turn suggesting the need for supervised step-down.

Keywords asthma, airway hyperresponsiveness, mannitol, methacholine

Introduction

Asthma is characterised by chronic inflammation associated with airway hyperresponsiveness (AHR) which is measured using bronchial challenge testing[1]. Bronchial challenges are categorised according to their mechanism of action[2]. Thus histamine and methacholine act directly on smooth muscle receptors and are examples of direct challenges. Indirect challenges act via inflammatory mediators and include adenosine monophosphate, mannitol, exercise and allergen challenges. The more commonly used histamine and methacholine challenges require specific equipment and training and therefore are not used in primary care. Currently, bronchial challenge testing is usually only carried out in specialist respiratory clinics and for research purposes. More recently, mannitol challenge has become commercially available as a simple to use test kit which is well tolerated, safe and more practical to use in the community[3].

The diagnosis of asthma in the community is based on symptoms, peak flow diary and spirometry with or without bronchodilator reversibility testing. In the absence of a 'gold standard' test to confirm or refute the diagnosis, the criteria used to diagnose asthma can be relatively subjective. Therefore bronchial challenge testing could potentially be a more objective method to complement the clinical diagnosis of asthma in the community in selected cases perhaps where the diagnosis is more equivocal. In addition, bronchial challenge testing could be used to optimally titrate anti-inflammatory treatment such as inhaled corticosteroids (ICS)[3, 4]. In this regard, an added advantage of indirect

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bronchial challenge testing is that it is able to better detect active airway inflammation[5]. Thus, a positive indirect challenge might indicate a need to step-up anti-inflammatory therapy while a negative result might suggest the need for stepping-down. Therefore patients can be better managed with the lowest effective inhaled corticosteroid dose as per treatment guidelines[6].

The purpose of this study was to evaluate the potential role of bronchial challenge testing, namely the directly acting methacholine challenge and the indirectly acting mannitol challenge in community managed asthma. We also evaluated the relationship between bronchial challenge testing with asthma control and quality of life.

Materials and methods

Subjects

Male and female patients aged 18 to 65 years with a physician diagnosis of asthma for at least 1 year and $FEV_1 > 50\%$ of predicted normal for age, height, sex and race. Exclusion criteria included exacerbation of asthma requiring oral steroids, hospitalisation or change in asthma therapy or respiratory tract infection in the previous 2 months. Patients with significant concomitant respiratory diseases such as chronic obstructive pulmonary disease, cystic fibrosis, allergic bronchopulmonary aspergillosis, active pulmonary tuberculosis or bronchiectasis were also excluded. The data for this study is from screening visits of a study to predict exacerbations which was approved by the East of Scotland Research Ethics Service (reference number: 10/S1402/6).

Study design

The Health informatics Centre (HIC), University of Dundee identified asthmatic patients in Tayside and Fife using prescribing databases. Eligible patients were sent information concerning the study and

an invitation to make contact for further information. The invitations and replies were handled by HIC. Only patients who consented to be contacted for the study were invited for a screening visit by the study team.

Study procedures

The following study procedures were carried out over two study visits: spirometry, exhaled nitric oxide (FeNO), skin prick test, mannitol and methacholine challenge; and questionnaires. The bronchial challenge testing was carried out on separate visits to avoid any carry-over effects. A SuperSpiro spirometer (Micro Medical Ltd., Chatham, Kent, United Kingdom) was used to perform spirometry in accordance with American Thoracic Society guidelines[7]. FeNO was performed using a handheld NIOX MINO (Aerocrine AB, Solna, Sweden) according to the manufacturer's instructions and American Thoracic Society guidelines[8] at a standard flow rate of 50ml/s. Skin prick testing was performed following a standard protocol (Allegra Pharma Testing Solution; Diagnostics Ltd, Nottinghamshire, United Kingdom) using extracts to grass, trees, weeds, house dust mite, aspergillus, feathers, cat and dog in addition to a positive (histamine) and negative control. A positive reaction was defined as a wheal diameter of 3mm or greater than the negative control for one or more allergens. Methacholine was dispensed via a nebulised solution (Methapharm Inc., Brantford, Ontario, Canada) and the challenge was performed in accordance with American Thoracic Society guidelines[9]. A dosimeter (Markos-Mefar, Bovezzo, Brescia, Italy) was used and the PC₂₀, the concentration of methacholine causing a 20% drop in FEV₁, was calculated. A positive response was defined as a PC₂₀ < 8mg/ml. Mannitol challenge was performed as previously described[10] with dry powder mannitol (Aridol Pharmaxis Ltd., Sydney Australia) to determine the PD₁₅, the cumulative dose causing a 15% drop in FEV₁. A positive response was defined as a PD₁₅ < 635mg. Asthma control was determined using the six point Juniper Asthma Control Questionnaire (ACQ)[11]. Disease specific quality of life was measured using the Juniper Mini Asthma Quality of Life Questionnaire (AQLQ)[12].

Statistical analysis

Unpaired Student's t tests were used to compare normally distributed continuous variables. Mannitol PD₁₅, methacholine PC₂₀ and FeNO were log transformed to achieve normality prior to analysis. Inhaled corticosteroid doses were compared using the non-parametric Mann-Whitney U test. Categorical data were compared using Chi square tests. Statistical significance for all analyses was set at $P < 0.05$ (two tailed). SPSS version 21 (SPSS Inc., Chicago, Illinois) was used for all analyses.

Results

A total of 3388 asthmatics were initially identified by HIC, with 423 positive responses and 123 completing the study. The mean age of study participants who completed was 47 years, 44 % were male and 71% were atopic. The mean FEV₁ was 91% predicted with 96 % of participants taking ICS. Participants' characteristics are presented in Table 1.

Participants' characteristics according to AHR are shown in Table 2. 70% (n=86) were responsive to either methacholine or mannitol challenge, while 30% (n=37) were non-responsive to both challenges. The participants in the non-responder group were older, less atopic, had better spirometry and lower FeNO. The ACQ and AQLQ scores were also significantly better in the non-responder group. 14% (n=10) of methacholine responders (n=74) were negative to mannitol and 16% (n=12) of mannitol responders (n=76) were negative to methacholine.

When the whole cohort was divided in to those with ACQ < 1 or >1 (Table 3), the controlled group had a significantly lower mannitol PD₁₅ and methacholine PC₂₀, amounting to a doubling dilution difference of 1.92 (95% CI 1.69-2.16), $P < 0.001$ for mannitol PD₁₅ and 1.20 (95% CI 1.02-1.36), $P = 0.034$ for methacholine PC₂₀ when comparing the two groups. The uncontrolled group also had a

higher proportion of smokers (1% versus 13%, $P=0.012$) and were younger (42 years versus 50 years, $P=0.001$).

When we further compared a smaller subgroup participants with more extreme ACQ scores, i.e. an ACQ < 0.75 versus participants with ACQ > 1.5 (Table 4), there was a significant difference in terms of mannitol PD₁₅ but not methacholine PC₂₀.

Discussion

The key finding in the present study was that approximately 30% of community managed asthmatics were non-responsive to both methacholine and mannitol challenge testing, which would in turn imply that a significant proportion of community managed asthmatics could have been either misdiagnosed or overtreated.

A positive bronchial challenge test in our study was defined as a PC₂₀ < 8mg/ml for the methacholine challenge and PD₁₅ < 635 mg for the mannitol challenge. This approach assumes that AHR is either present or absent[9]. However, in reality AHR is a continuous spectrum and it is possible that some of the milder asthmatics could have received an accurate initial clinical diagnosis of asthma but classified as a non-responder in our study. We did not take into account possible seasonal variation of AHR in the present study and the diagnosis of asthma could have indeed been made during seasonal exposure to allergens or viral stimuli in the presence of AHR which may have subsequently resolved.

The diagnosis of asthma in the community is in reality mainly based on a patient's symptoms and therefore there is a potential for misdiagnosis. A Canadian study[13] found that one-third of participants who had received a diagnosis of asthma by a physician had no evidence of asthma when

their medications were tapered and when they were evaluated with serial assessments of symptoms, lung function and bronchial challenge testing. The proportion of misdiagnosed patients amounting to one-third is similar to the proportion of non-responders to both bronchial challenges in our study. There is no 'gold standard' test to diagnose asthma but bronchial challenge testing has a higher sensitivity in diagnosing asthma compared to spirometry with or without reversibility testing[9]. Pointedly, in our group of patients who were AHR responders, the mean FEV₁ was well preserved at 88% predicted, with FEV₁/FVC ratio of 0.75.

In our cohort of community diagnosed asthmatics, assuming that the initial clinical diagnosis was accurate, the sensitivity of the methacholine and mannitol challenge was 60% and 62 % respectively. In a non-selected population sample, Sverrild et al[14] report a sensitivity of 68.6 and 58.8% for methacholine and mannitol respectively using a clinical diagnosis of asthma as the 'gold standard' comparator. However, they used a PD₂₀ < 8µg/mmol (equivalent to a PC₂₀ of < 16mg/ml) as a cut-off for a positive methacholine challenge.

AHR measured by direct challenge has a persistent component which is thought to reflect airway remodelling and is often either non-responsive or incompletely responsive to anti-inflammatory treatment[15]. Therefore, treatment with ICS is unlikely to account for the high proportion of methacholine non-responders in our study. For example in one head to head study comparing methacholine and AMP challenge the dose response effect of ICS was greater on the latter, although in neither was AHR normalised per se[16]. In another dose response study there was a 0.5-1.0 doubling dilution shift in methacholine PC₂₀ in response to low or medium dose ICS in mild to moderate persistent asthmatics[17]. A positive response to mannitol requires an intermediate inflammatory pathway which could in theory be attenuated or fully abolished with anti-inflammatory treatment. In the present study, despite 95% of patients in the responder group taking ICS, only 14% of methacholine responders were negative to mannitol, while 16% mannitol responders were negative

to methacholine. The response to mannitol returns or increases following the withdrawal of ICS and hence non-compliance with ICS treatment could be a possible explanation for this observation[18].

The median beclomethasone equivalent dose in the non-responder group was high at 1000 µg while 68% were also on a long-acting beta-agonist. Indeed the mean ACQ score in the non-responder group was 0.55 which is below the 0.75 cut-off point for 'well-controlled' asthma, along with normal values for AQLQ, spirometry and FeNO[19]. These findings would suggest that these individuals, assuming they had an appropriate initial diagnosis of asthma, were probably being overtreated. High doses of ICS can have adverse local systemic effects[20] and current asthma guidelines recommend that once asthma control has been achieved, the dose should be always stepped down to the minimal necessary maintenance dose[6]. Studies have shown that the ICS dose can be reduced significantly without detrimental effects on control in many cases[21, 22]. In this regard, there is perhaps a potential role for the mannitol challenge to guide supervised step-down of ICS treatment in the community[18]. The mannitol challenge reflects active airway inflammation more closely when compared with the methacholine challenge[23] and adjustments can be made to the patient's ICS dose accordingly as well as stopping LABAs.

We also analysed our cohort according to their ACQ score. The cohort was divided into those with an ACQ of < 1 (n=86) and > 1 (n=37)[19] on the basis that the cross-over point between 'well controlled' and 'not well controlled' asthma is close to 1 on the ACQ[19]. We found that there was a significant difference in terms of mannitol PD₁₅ [1.92 doubling dilution, (95% CI 1.69-2.16), P=<0.001] and methacholine PC₂₀ [1.20 doubling dilution, (95% CI 1.02-1.36), P=0.034] between the two groups. Pointedly, there was no significant difference in the various spirometry indices or FeNO between the 2 groups. FeNO although a surrogate marker of eosinophilic inflammation has been shown to plateau at around 200µg/day of beclomethasone equivalent dose[24], while the median beclomethasone equivalent dose in both of our groups was 800µg/day.

When we compared a smaller subgroup of patients with ACQ < 0.75 (n=62) and those with ACQ > 1.5 (n=29), interestingly only mannitol AHR was significantly different between the two groups, suggesting perhaps that this is the more sensitive challenge. An ACQ score of < 0.75 is used to identify patients with well controlled asthma more confidently with a higher negative predictive value than an ACQ score of 1[19]. Similarly, an ACQ score of >1.5 has a higher positive predictive value for not well controlled asthma compared to an ACQ score of 1[19].

The main strength of our study is that the data were prospectively collected from an unselected sample of asthmatic patients in the community. However, we excluded patients who had an exacerbation requiring oral steroids, respiratory tract infection, hospitalisation or change in asthma therapy in the 2 months prior to screening. Patients who had a FEV₁ < 50% predicted were also excluded from the study because they were unable to undergo challenge testing. Therefore, we might be underestimating the true proportion of patients treated for asthma with AHR in the community. However, as 42% and 23% respectively of our sample were British Thoracic Society Step 3 and 4, we do not believe that our sample may have been skewed towards less severe patients

In conclusion, our study showed that 30% of unselected community managed asthmatics could be potentially misdiagnosed or overtreated, in turn suggesting the need for supervised step-down. We also found that the presence of AHR was closely related to asthma control. Bronchial challenge testing may therefore have a role in complementing the clinical diagnosis and optimal management of asthmatics in the community, in particular with mannitol being simple to administer and safe to use in this setting. Indeed in the long term, routine mannitol testing in the community could be potentially cost-effective and randomised controlled trials in this area are required.

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Author contributions

EC performed the study procedures. AM analysed the data. AM, BJL, EC and CJ were involved in the interpretation of the data and in writing or revising the paper before submission.

Conflict of interests

The mannitol kits for the study were gifts from Pharmaxis Ltd. The authors have no other conflicts of interest to declare.

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Table 1: Participants' characteristics (n=123)

Age (years)	47 (45-50)
Sex (% male)	44
BMI (kg / m ²)	29 (27-30)
Skin prick test (% positive)	71
Current smokers (%)	6
Inhaled corticosteroids use (%)	96
Inhaled corticosteroids dose (BDP equivalent, µg)*	800
Long-acting beta agonist use (%)	65
Leukotriene receptor antagonist use (%)	14
ACQ score	0.91 (0.77-1.05)
AQLQ score	5.73 (5.55-5.91)
FEV ₁ (% predicted)	91 (89-94)
FVC (% predicted)	99 (97-102)
FEV ₁ / FVC (% predicted)	77 (74-79)
FEF ₂₅₋₇₅ (% predicted)	68 (63-72)
Mannitol PD ₁₅ [†]	240 (182-324)
Methacholine PC ₂₀ [†]	2.09 (3.02-4.37)
FeNO (ppb) [†]	22 (19-26)
BTS Step 1 (%)	4
BTS Step 2 (%)	29
BTS Step 3 (%)	45
BTS Step 4 (%)	23

Note: ACQ = Asthma Control Questionnaire, AQLQ = Asthma Quality of Life Questionnaire, BDP = Beclomethasone dipropionate, BMI = Body mass index, BTS = British Thoracic Society, FeNO = exhaled nitric oxide FEV₁ = Forced expiratory volume in 1 second, FEF₂₅₋₇₅ = Forced expiratory flow between 25% and 75% of forced vital capacity, FVC = Forced vital capacity, PC₂₀ = concentration of methacholine causing a 20% drop in FEV₁, PD₁₅ = cumulative dose of mannitol causing a 15% drop in FEV₁, ppb = parts per billion
Data presented as arithmetic mean (95% CI) unless otherwise indicated; * median †geometric mean (95% CI)

Table 2: Participants' characteristics according to airway hyperresponsiveness

	Responders n=86	Non-responders n=37	P-value
Age (years)	46 (43-49)	51(47-55)	0.047
Sex (% males)	42	49	0.48
BMI (kg / m ²)	28 (27-30)	29 (26-32)	0.71
Skin prick test (% positive)	79	50	0.003
Current smokers (%)	7	3	0.077
Inhaled corticosteroids use (%)	95	97	0.62
Inhaled corticosteroids dose (BDP equivalent, µg)*	500	1000	0.08
Long-acting beta agonist use (%)	64	68	0.70
Leukotriene receptor antagonist use (%)	12	19	0.28
ACQ score	1.07 (0.90-1.24)	0.55 (0.32-0.77)	<0.001
AQLQ score	5.59 (5.37-5.81)	6.05 (5.78-6.33)	0.015
FEV ₁ (% predicted)	88 (85-91)	100 (95-104)	<0.001
FVC (% predicted)	98 (95-100)	103 (98-108)	0.043
FEV ₁ / FVC (% predicted)	75 (72-78)	81 (78-83)	0.001
FEF ₂₅₋₇₅ (% predicted)	62 (57-68)	81 (73-89)	<0.001
FeNO (ppb)†	26 (21-32)	16 (13-20)	0.003

Note: ACQ = Asthma Control Questionnaire, AQLQ = Asthma Quality of Life Questionnaire BDP = Beclomethasone dipropionate, BMI = Body mass index, BTS = British Thoracic Society, FeNO = exhaled nitric oxide FEV₁ = Forced expiratory volume in 1 second, FEF₂₅₋₇₅ = Forced expiratory flow between 25% and 75% of forced vital capacity, FVC = Forced vital capacity, ppb=parts per billion
Data presented as arithmetic mean (95% CI) unless otherwise indicated; * median †geometric mean (95% CI)

Table 3: Participants' characteristics according to ACQ < 1 and > 1

	ACQ < 1 n=75	ACQ >1 n=48	P-value
Age (years)	50 (47-53)	42 (38-46)	0.001
Sex (% males)	49	35	0.13
BMI (kg / m ²)	27 (26-29)	30 (28-33)	0.066
Skin prick test (% positive)	70	72	0.83
Current smokers (%)	1	13	0.012
Inhaled corticosteroids use (%)	99	92	0.055
Inhaled corticosteroids dose (BDP equivalent, µg)*	800	800	0.92
Long-acting beta agonist use (%)	65	65	0.93
Leukotriene receptor antagonist use (%)	12	17	0.46
FEV ₁ (% predicted)	92 (89-95)	91 (87-95)	0.63
FVC (% predicted)	100 (96-103)	99 (95-103)	0.80
FEV ₁ / FVC (% predicted)	77 (75-79)	76 (72-80)	0.72
FEF ₂₅₋₇₅ (% predicted)	68 (62-74)	68 (60-75)	0.94
Mannitol PD ₁₅ *	407 (295-562)	107 (66-174)	<0.001
Methacholine PC ₂₀ *	4.17 (2.57-6.76)	1.82 (1.00-3.34)	0.034
FeNO (ppb)*	22 (19-27)	22 (16-30)	0.86

Note: ACQ = Asthma Control Questionnaire, AQLQ = Asthma Quality of Life Questionnaire BDP = Beclomethasone dipropionate, BMI= Body mass index, FeNO= exhaled nitric oxide FEV₁ = Forced expiratory volume in 1 second, FEF₂₅₋₇₅= Forced expiratory flow between 25% and 75% of forced vital capacity, FVC = Forced vital capacity, PC₂₀= concentration of methacholine causing a 20% drop in FEV₁, PD₁₅= cumulative dose of mannitol causing a 15% drop in FEV₁, ppb = parts per billion
Data presented as arithmetic mean (95% CI) unless otherwise indicated; * median †geometric mean (95% CI)

Table 4: Participants' characteristics according to ACQ < 0.75 and > 1.5

	ACQ < 0.75 n=62	ACQ >1.5 n=29	P-value
Age (years)	50 (47-54)	45 (39-50)	0.064
Sex (% males)	48	41	0.53
BMI (kg / m ²)	28 (26-29)	29 (26-32)	0.27
Skin prick test (% positive)	70	65	0.70
Current smokers (%)	2	14	0.012
Inhaled corticosteroids use (%)	98	93	0.19
Inhaled corticosteroids dose (BDP equivalent, µg)*	500	800	0.62
Long-acting beta agonist use (%)	37	62	0.94
Leukotriene receptor antagonist use (%)	13	17	0.58
FEV ₁ (% predicted)	92 (89-96)	89 (84-95)	0.35
FVC (% predicted)	99 (96-103)	98 (93-103)	0.66
FEV ₁ / FVC (% predicted)	78 (75-80)	74 (68-80)	0.24
FEF ₂₅₋₇₅ (% predicted)	69 (63-76)	66 (56-76)	0.58
Mannitol PD ₁₅ †	417 (295-603)	112 (56-224)	<0.001
Methacholine PC ₂₀ †	4.57 (2.69-7.76)	1.82 (0.84-3.98)	0.053
FeNO (ppb)†	22 (18-28)	23 (14-35)	0.98

Note: ACQ = Asthma Control Questionnaire, AQLQ = Asthma Quality of Life Questionnaire BDP = beclomethasone dipropionate, BMI = Body mass index, FeNO = exhaled nitric oxide FEV₁ = Forced expiratory volume in 1 second, FEF₂₅₋₇₅ = Forced expiratory flow between 25% and 75% of forced vital capacity, FVC = Forced vital capacity, PC₂₀ = concentration of methacholine causing a 20% drop in FEV₁, PD₁₅ = cumulative dose of mannitol causing a 15% drop in FEV₁, ppb = parts per billion

Data presented as arithmetic mean (95% CI) unless otherwise indicated; * median †geometric mean (95% CI)