Correspondence: I. Bobolea, Dept of Allergy, Hospital Universitario La Paz, Paseo La Castellana 261, 28046 Madrid, Spain. E-mail: irinabobolea@yahoo.com

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The safety and feasibility of the inhaled mannitol challenge test in young children

To the Editor:

The mannitol challenge is an indirect challenge that increases airway surface liquid osmolality resulting in bronchoconstriction [1, 2]. Mannitol challenge tests are used clinically to diagnose asthma and, in particular, exercise-induced broncoconstriction (EIB) in adults and children above 6 years of age [3]. To date, mannitol has not been used as a challenge agent in children under 6 years of age and the feasibility and safety of its use in this age group is unknown.

The assessment of bronchial responsiveness in young children is difficult and limited by the cooperation of the child. The standardisation of lung function tests suitable for use in young children, such as the interrupter technique or the forced oscillation technique (FOT), provide an opportunity to assist in the assessment of bronchial responsiveness in young children and a variety of challenge tests using FOT have been reported in young children [4].

The aim of this preliminary study was to assess the feasibility and safety of the mannitol challenge test in young children using the FOT as the objective outcome measure.

20 children aged 3–7 years were recruited; 10 of these children were healthy and 10 children had a history of parentally reported exercise-induced symptoms (EIS) in the past year. The mannitol challenge test (Aridol; Pharmaxis, Frenchs Forest, Australia) was performed as previously published [2], with the exceptions that the respiratory resistance at 8 Hz (R_{rs8}) from the FOT was used as the primary outcome and the definition of a positive response was altered, as detailed below.

Prior to the mannitol challenge test the children were trained on the use of the mannitol dry powder inhaler using an inspiratory flow meter (In check; Clement Clarke International, Harlow, UK) configured to ensure that inhalation ranged between 30 and 50 $L \cdot min^{-1}$ to optimise deposition of mannitol. An examination including chest auscultation, baseline heart rate (HR), arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) and lung function using FOT (I2M; Chess Medical; Ghent, Belgium) was performed in all children. During the mannitol inhalation challenge FOT was performed 1 min after each stage and 15 min after salbutamol inhalation at the end of the challenge. For baseline, control and post-salbutamol

TABLE 1 Mannitol challenge results for the study subjects

Subject	Age years	Success[#]	Duration min[¶]	Response type[+]	Response dose mg	Inhalation per capsule[§]	Increase in R_{rs8}[f] %
EIS group							
1	6	Yes	48			2.3	17.6
2	6	Yes	37			1.3	5.4
4	6	Yes	40	Persistent cough	475	1.9	28.9
5	5	Yes	46			2.1	5.2
6	5	Yes	54	Wheeze	635	1.9	13.2
8	6	Yes	21	FOT	155	1.7	54.4
9	7	Yes	24	FOT	315	1.2	60.2
10	7	Yes	40			2.1	5.8
13	5	Yes	8	FOT	15	1.5	52.4
14	4	Yes	41	Wheeze S_{pO_2} 87%	635	1.3	38.2
Mean ± SD	6 ± 0.95		35.9 ± 14.06			1.73 ± 0.39	28.13 ± 21.82
Healthy group							
3	6	Yes	44			1.8	19.7
7	4	Yes	52			2.1	20.9
11	3	No	5			1.0	-8.8
12	5	Yes	48			1.9	15.3
15	3	No	27			2.2	46.5
16	5	Yes	51			2.3	40.3
17	4	Yes	53			1.9	5.4
18	5	Yes	38			1.4	37.1
19	3	No	0			0.0	17.6
20	6	Yes	41			1.7	9.2
Mean ± SD	4 ± 1.17		36 ± 19.30			1.63 ± 0.69	20.64 ± 17.97

[#]: categorised as yes/no and defined from the test being completed to the final dose or a positive response; [¶]: calculated from the first mannitol inhalation until forced oscillation technique (FOT) measurement following the last mannitol inhalation; [+]: response type is based on the criteria with which a positive mannitol response occurred; [§]: the mean number of inhalations needed to empty a mannitol capsule; [f]: from control at the final stage of the mannitol challenge. R_{rs8}: resistance of the respiratory system at 8 Hz; EIS: exercise-induced symptoms; S_{pO_2}: arterial oxygen saturation measured by pulse oximetry.

measurements, the R_{rs8} was an average of all acceptable FOT measurements at that stage; while the highest R_{rs8} following each mannitol inhalation was used as previously reported by our group [5]. The S_{pO_2} and HR were continually monitored throughout the test and the chest was auscultated within 1 min of each step of the mannitol inhalation.

A positive response to the challenge was recorded if there was one of the following: 1) an increase in R_{rs8} by 50% from the control inhalations; 2) persistent cough after mannitol inhalation; 3) wheeze on auscultation and 4) a drop in S_{pO_2} to <90%. At the end of the challenge all children received 600 μg of salbutamol using a metered-dose inhaler through a large volume spacer regardless of response and all children were discharged when R_{rs8} was within 20% of baseline.

The mannitol challenge was considered feasible if the child completed the test to the maximum dose of 635 mg, or until a positive response was noted. We considered the challenge safe if no serious adverse events were recorded, *i.e.* a fatal or life-threatening event, an event requiring inpatient hospitalisation, an event resulting in persistent or significant disability, or considered a medically important event or reaction.

All 10 children with EIS and seven healthy children completed the challenge (table 1). Three healthy children did not complete the challenge and refused to continue at different stages; all were 3 years old. None of the 17 children that completed the test developed any serious adverse events, according to the study criteria, and all participants were discharged in a stable condition. Based on the response criteria listed on the Aridol (Pharmaxis) product approved label, one child would be classified as having a serious adverse event during the mannitol challenge with both wheeze and a decrease in S_{pO_2} to 87% (subject 14). The family of this child also reported wheeze requiring reliever 2–4 h following discharge for which the parents administered salbutamol.

The mean (range) test duration in children that did not respond to the mannitol challenge was 45 (37–54) min and longer than the test duration in children with a positive response (31 (13–38) min). Transient cough during mannitol inhalation was present in 95% of the children, with intermittent cough post-inhalation noted in 70% and 20% of the EIS and healthy groups, respectively. Six of the 10 children with EIS responded to the mannitol challenge, while none of the healthy children had a positive response (table 1).

In this preliminary study we report that an inhaled mannitol challenge protocol, using FOT as an outcome, is feasible and safe in children aged 4–7 years, with 100% of children in this age group completing the test. The three children that failed to complete the test were 3 years-old and did not complete the test due to difficulty sustaining attention.

In this study there were no symptoms of serious respiratory distress noted during the challenge. One parent did report wheeze requiring reliever within 24 h following the challenge. Post-challenge asthma exacerbation within 24 h of a mannitol challenge has been reported in 0.2% of adults and older children [3]. Further, larger studies are required to accurately define the safety profile of mannitol testing in this younger age group.

Six of the 10 children in the EIS group responded to the mannitol challenge and none of the healthy children responded. While this study was not designed to assess the ability of the mannitol challenge test to identify EIB in young children, these results provide initial evidence that mannitol challenge tests may be useful in this young age group. Three of the six children that responded to the mannitol challenge did so by an increase in R_{rs8}, suggesting that FOT can be used with mannitol challenge to facilitate the diagnosis of EIS in young children.

We used a 50% increase in R_{rs8} as a positive response. Previous studies using FOT with an inhaled challenge test used cut-off levels ranging from a 25% to 50% increase in R_{rs} [5–7]. If a 25% increase in R_{rs8} is used to define a positive response the response rate in the EIS group would remain unchanged, with three of the healthy children being classified as having a positive response. Further studies to establish appropriate cut-off limits to be used for the mannitol challenge test with FOT as a primary outcome in young children are required.

In older subjects the mannitol challenge test is highly specific for a diagnosis of EIB when compared to exercise and hypertonic saline challenge tests [2, 3]. This preliminary study did not attempt to compare the mannitol challenge test with a free-running exercise challenge test [7], examine the reproducibility of the mannitol test in young children or explore methods for shortening the challenge test, and studies of this nature are required.

In summary, this preliminary study reports that mannitol challenge tests appear to be safe and feasible in children aged 4–7 years when combined with FOT to measure bronchial responsiveness. Further research exploring the role of mannitol testing in young children is required.

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Young children can complete a mannitol challenge: this may improve exercise-related asthma diagnosis in this age group http://ow.ly/nK9gX

Afaf S. Alblooshi[1,2], Shannon J. Simpson[2], Stephen M. Stick[1,2,3] and Graham L. Hall[2,3]
[1]School of Paediatrics and Child Health, University of Western Australia, Perth, [2]Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, Perth, and [3]Respiratory Medicine, Princess Margaret Hospital for Children, Perth, Australia.

Correspondence: G.L. Hall, Paediatric Respiratory Physiology, Telethon Institute for Child Health Research, P.O. Box 855, West Perth 6872, WA, Australia. E-mail: grahamh@ichr.uwa.edu.au

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Heart failure impairs cerebral oxygenation during exercise in patients with COPD

To the Editor:

Impaired systemic oxygen delivery, particularly during exertion, is the key pathophysiological feature shared by chronic obstructive pulmonary disease (COPD) and heart failure with reduced left ventricular ejection fraction (HFrEF). Unfortunately, COPD and HFrEF frequently coexist not only because of their high individual prevalence but also due to common risk factors, including cigarette smoking, advanced age, oxidative stress and systemic inflammation [1].

It is expected that any reduction in the rate of oxygen transfer due to COPD and/or HFrEF would be particularly deleterious to tissues heavily dependent upon constant oxygen flow, such as the central nervous system (as reviewed in [2]). Exercise cerebral oxygenation (Cox) (as noninvasively determined by near-infrared spectroscopy) depends upon the dynamic balance between the instantaneous rate of oxygen delivery and oxygen utilisation [3]. KOIKE *et al.* [4], for instance, reported that congestive heart failure (CHF) HFrEF was associated with appreciable decreases in COx during exertion. Our laboratory found that exercise COx might be impaired in some patients with more advanced COPD, even if not overtly hypoxaemic [5]. Moreover, improvement in cardiac output with noninvasive ventilation (under the same arterial oxygen content) had positive effects on COx in COPD [6]. These data suggest that reduced cerebral blood flow might be mechanistically linked to impaired exercise COx in some patients with moderate-to-severe COPD. It is conceivable that the presence of HFrEF would further deteriorate this scenario by adding components of dysfunctional cerebral autoregulation, lower cardiac output and hypocapnia-induced vasoconstriction [4]. The compound effects of HFrEF plus COPD on COx and its relationship with exercise tolerance, however, remain unknown. In order to address these issues, we simultaneously assessed COx, systemic haemodynamics and gas exchange during progressive exercise in COPD patients presenting or not with HFrEF as a comorbidity.

33 males with stable, nonhypercapnic (arterial carbon dioxide tension <45 mmHg at rest) COPD with a long history of smoking (>20 pack-years), breathlessness in daily life (modified Medical Research Council (MRC) scale scores >2) and moderate-to-severe airflow obstruction comprised the study group. Patients from the COPD+HFrEF group (n=18) presented with left ventricular ejection fraction by Doppler echocardiography <40% and well-established diagnosis of CHF (dyspnoea on exertion, elevated jugular venous pressure, cardiomegaly, peripheral oedema and pulmonary crepitations) due to underlying ischaemic heart disease. All patients were under standard contemporary therapy for HFrEF. 15 patients from the COPD clinic without clinical, echocardiographic and laboratorial evidence of CHF (n=15) were matched by age and MRC grade (table 1). The main exclusion criteria included long-term ambulatory oxygen therapy, severe pulmonary hypertension (mean pulmonary artery pressure ⩾40 mm Hg), anaemia (haemoglobin concentration <13 g%), and recent exacerbation (within 1 month). After providing informed consent (as approved by the local medical ethics committee), patients underwent a ramp-incremental cardiopulmonary exercise test with assessment of arterialised carbon dioxide tension (P_{CO_2}). Changes from rest (Δ) in pre-frontal COx (oxyhaemoglobin concentration ($[HbO_2]$)) were measured by near infrared spectroscopy (NIRO 200^{TM}; Hamamatsu Photonics KK, Hamamatsu, Japan) and cardiac output by transthoracic cardioimpedance (PhysioFlow PF-5^{TM}; Manatec Biomedical, Paris, France) [7]. Based on a pooled analysis of our previous data in normal older subjects and patients with COPD [5, 6],