

**Ignacio Garcia-Talavera, Marco Figueira, Armando Aguirre-Jaime**

Respiratory Department, Research Unit, Candelaria University Hospital, Tenerife, Spain

**Correspondence to** I Garcia-Talavera, Respiratory Dept. Candelaria University Hospital, C/ El Rosario, 145, 38010, Tenerife, Spain; igarmark@gmail.com

**Competing interests** None.

**Patient consent** Obtained.

**Ethics approval** This study was conducted with the approval of Candelaria Hospital.

**Provenance and peer review** Not commissioned; not externally peer reviewed.

Accepted 10 January 2011

Published Online First 11 March 2011

*Thorax* 2011;**66**:631–632.

doi:10.1136/thx.2010.158501

## REFERENCES

1. **Moore RP**, Berlowitz DJ, Denehy L, *et al.* A randomised trial of domiciliary, ambulatory oxygen in patients with COPD and dyspnoea but without resting hypoxaemia. *Thorax* 2011;**66**:32–7.
2. **Nonoyama ML**, Brooks D, Guyatt GH, *et al.* Effect of oxygen on health quality of life in patients with chronic obstructive pulmonary disease with transient exertional hypoxemia. *Am J Respir Crit Care Med* 2007;**176**:343–6.
3. **McDonald CF**, Blyth CM, Lazarus MD, *et al.* Exertional oxygen of limited benefit in patients with chronic obstructive pulmonary disease and mild hypoxemia. *Am J Respir Crit Care Med* 1995;**152**:1616–19.
4. **Garcia-Talavera I**, Hernández C, Macario C, *et al.* Time to desaturation in the 6-min walking distance test predicts 24-hour oximetry in COPD patients with a PO<sub>2</sub> between 60 and 70 mm Hg. *Respir Med* 2008;**102**:1026–32.

## Author's response

We thank Garcia-Talavera *et al* for their interest in our paper.<sup>1</sup> We acknowledge their finding, in a group of chronic obstructive pulmonary disease patients with only mild hypoxaemia, of a correlation between early oxyhaemoglobin desaturation during the 6-minute walk test (6MWT) and desaturation over 24 h.<sup>2</sup> The 6MWTs performed in our study were carried out according to American Thoracic Society guidelines.<sup>3</sup> Given their recommendations that oxygen saturation measured by pulse oximetry (SpO<sub>2</sub>) should not be used for constant monitoring during the test and that the technician must not walk with the patient to observe SpO<sub>2</sub>, saturation in our study was measured at rest and immediately at the end of the 6-minute period. We are thus unable to comment upon the presence or absence of early as opposed to late desaturation in our cohort of desaturators. Nonetheless, it is likely that our group of 50 'end test' desaturators would have included both early and late desaturators, according to the definition of Garcia-Talavera *et al.* We found no association between the degree of desaturation at the end of the 6MWT and our primary or secondary outcome criteria.

Others have similarly found an absence of association between the degree of desaturation and improvement in exercise capacity with supplemental oxygen.<sup>4</sup> Whether or not early desaturation during the 6MWT correlates with desaturation during activities of daily living or nocturnally, it remains unknown whether such early desaturation correlates with degree of dyspnoea or whether treating it with supplemental oxygen would improve this symptom.

**Christine F McDonald, Rosemary P Moore, David Berlowitz, Linda Denehy, Jeffrey J Pretto, Danny J Brazzale**

**Correspondence to** Christine F McDonald, Institute for Breathing and Sleep, Department of Respiratory and Sleep Medicine, Austin Hospital, Heidelberg, Victoria, Australia; christine.mcdonald@austin.org.au

**Competing interests** None.

**Ethics approval** This study was conducted with the approval of the Human Research Ethics Committee, Austin Health, Heidelberg, Victoria, Australia.

**Provenance and peer review** Not commissioned; not externally peer reviewed.

Accepted 3 February 2011

*Thorax* 2011;**66**:632.

doi:10.1136/thx.2011.160648

## REFERENCES

1. **Moore RP**, Berlowitz DJ, Denehy L, *et al.* A randomised trial of domiciliary, ambulatory oxygen in patients with COPD and dyspnoea but without resting hypoxaemia. *Thorax* 2011;**66**:32–7.
2. **Garcia-Talavera I**, Garcia CH, Macario CC, *et al.* Time to desaturation in the 6-minute walking distance test predicts 24-hour oximetry in COPD patients with a PO<sub>2</sub> between 60 and 70 mmHg. *Respir Med* 2008;**102**:1026–32.
3. **ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories.** ATS Statement: Guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;**166**:111–17.
4. **Fujimoto K**, Matsuzawa Y, Yamaguchi S, *et al.* Benefits of oxygen on exercise performance and pulmonary hemodynamics in patients with COPD with mild hypoxemia. *Chest* 2002;**122**:457–63.

## CORRESPONDENCE

### Peripheral airway/alveolar nitric oxide concentration in asthma

We read with great interest the paper by Gelb and colleagues<sup>1</sup> who suggest that peripheral airway/alveolar nitric oxide (NO) concentration after correction for axial NO back-diffusion (CalvNO<sub>corrected</sub>) is normal during asthma exacerbation (with a hypothesis of an incidence of >30% of its increase). If one admits that an exacerbation constitutes the ultimate expression of loss of asthma control, their results are in line with ours demonstrating that CalvNO<sub>corrected</sub> is not a marker of asthma control.<sup>2</sup> Nevertheless, some of their patients with an exacerbation had an increase in CalvNO<sub>corrected</sub> since one can see in

their figure 5 that almost 20% of their patients are above the 95th percentile of healthy subjects (~7 ppb). The small size of their cohort (n=15) is an obvious limitation that is acknowledged by the authors.

We therefore reanalysed the results of our multicentre trial<sup>2</sup> to evaluate the prevalence of increased CalvNO<sub>corrected</sub>. When using an upper normal limit of 7 ppb for CalvNO<sub>corrected</sub> (that corresponds approximately to their upper normal value<sup>1</sup>), the prevalence of its increase is 23% (41/175) in our population of adults and children with asthma. In our study we further demonstrated a negative relationship between CalvNO<sub>corrected</sub> and mid forced expiratory flow (FEF<sub>25–75%</sub>), which may suggest that peripheral NO could be associated with airway remodelling.<sup>2</sup> This latter result was in line with the demonstration that peripheral airway/alveolar NO concentration (without correction for axial NO back-diffusion) correlated with FEF<sub>25–75%</sub> in children with refractory asthma.<sup>3</sup> Puckett and colleagues recently suggested that children with asthma with increased CalvNO<sub>corrected</sub> (46/179, 26%) had significantly worse asthma control and morbidity.<sup>4</sup> Overall, all these results emphasise that peripheral airway/alveolar NO concentration, after correction for axial NO back-diffusion, can be increased in some patients with asthma (~25%). Whether peripheral NO helps to identify a specific 'phenotype' of asthma which may be more closely linked to severity than to control warrants further studies.

Gelb and colleagues also show that 2/15 subjects with an exacerbation had normal exhaled NO values.<sup>1</sup> Similarly, we have previously shown in a multicentre trial that patients with acute asthma admitted to the emergency department can have normal exhaled NO levels (2/65 patients in our study).<sup>5</sup>

In conclusion, the clinical usefulness of techniques to discriminate NO gas exchange between large central airways and peripheral smaller airways/alveolar compartments in patients with asthma remains to be established, and the factors governing the increase in exhaled NO remain partly determined.

**Bruno Mahut,<sup>1</sup> Christophe Delclaux<sup>1,2,3</sup>**

<sup>1</sup>Service de Physiologie, Clinique de la Dyspnée, Hôpital Européen Georges Pompidou, Assistance Publique, Hôpitaux de Paris, France; <sup>2</sup>CIC 9201 Plurithématique, Hôpital Européen Georges Pompidou, Assistance Publique, Hôpitaux de Paris, France; <sup>3</sup>Université Paris Descartes, Paris, France

**Correspondence to** Professor Christophe Delclaux, Service de Physiologie, Clinique de la Dyspnée, Hôpital Européen Georges Pompidou, 20, rue Leblanc, Paris 75015, France; christophe.delclaux@egp.aphp.fr

**Competing interests** CD has received a free NO analyser (ENDONO 8000) from SERES (Aix en Provence, France) for the development of their software for NO analysis at multiple exhaled flow rates. BM has no competing interests.

**Provenance and peer review** Not commissioned; not externally peer reviewed.

Accepted 2 August 2010  
Published Online First 13 September 2010

*Thorax* 2011;**66**:632–633.  
doi:10.1136/thx.2010.147959

## REFERENCES

1. **Gelb AF**, George SC, Silkoff PE, *et al.* Central and peripheral airway/alveolar sites of exhaled nitric oxide in acute asthma. *Thorax* 2010;**65**:619–25.
2. **Mahut B**, Trinquart L, Le Bourgeois M, *et al.* Multicentre trial evaluating alveolar NO fraction as a marker of asthma control and severity. *Allergy* 2010;**65**:636–44.
3. **Mahut B**, Delclaux C, Tillie-Leblond I, *et al.* Both inflammation and remodeling influence nitric oxide output in children with refractory asthma. *J Allergy Clin Immunol* 2004;**113**:252–6.
4. **Puckett JL**, Taylor RW, Leu SY, *et al.* Clinical patterns in asthma based on proximal and distal airway nitric oxide categories. *Respir Res* 2010;**11**:47.
5. **Delclaux C**, Sembach N, Claessens YE, *et al.* Offline exhaled nitric oxide in emergency department and subsequent acute asthma control. *J Asthma* 2008;**45**:867–73.

## Author's response

I want to thank Drs Mahut and Delclaux for their interesting letter concerning our recent paper<sup>1</sup> and would offer the following response. During acute asthma exacerbation only two of 15 patients with asthma (13%) had a combined abnormally elevated central airways nitric oxide (NO) flux and elevated peripheral airway/alveolar NO concentration after correction for NO axial back-diffusion. Central airways NO flux remained the major site of 'NO-mediated inflammation' in 13 of 15 patients with asthma since two had normal NO gas exchange despite acute exacerbation.<sup>1</sup> This latter observation needs to be further investigated since the clinical response was similar to that in patients with asthma with abnormal NO gas exchange. Many years ago we investigated the simplified detection of peripheral airway disease and showed that analyses of the distal part of the maximum expiratory flow–volume curve were helpful.<sup>2</sup> However, in a subsequent study<sup>3</sup> we reported that, if the ratio of forced expiratory volume in 1 s to forced vital capacity (FEV<sub>1</sub>/FVC) was  $\geq 75\%$ , the occurrence of an isolated abnormal mid forced expiratory flow (FEF<sub>25–75</sub>) was rare. However, if the FEV<sub>1</sub>/FVC was  $< 75\%$ , it would not be unusual to find an abnormal FEF<sub>25–75</sub>, but it would not discriminate peripheral from large central airways obstruction.<sup>3</sup> I hope these comments are helpful and appreciate their interest.

**Arthur Franklin Gelb**

**Correspondence to** Arthur Franklin Gelb, Lakewood Regional Medical Center and Geffen School of Medicine at UCLA, 3650 E South St, Ste 308, Lakewood 90712, USA; afgelb@msn.com

**Competing interests** None.

**Provenance and peer review** Not commissioned; not externally peer reviewed.

Accepted 6 August 2010  
Published Online First 13 September 2010

*Thorax* 2011;**66**:633.  
doi:10.1136/thx.2010.148577

## REFERENCES

1. **Gelb AF**, George SC, Silkoff PE, *et al.* Central and peripheral airway/alveolar site of exhaled nitric oxide in acute asthma. *Thorax* 2010;**65**:619–25.
2. **Gelb AF**, Zamel N. Simplified diagnosis of small-airways obstruction. *N Engl J Med* 1973;**288**:395–8.
3. **Gelb AF**, Williams AJ, Zamel N. Spirometry. FEV<sub>1</sub> vs FEF<sub>25–75</sub> percent. *Chest* 1983;**84**:473–4.

## Definitions are important and not all wheeze is asthma

We read with great interest the paper by Moncayo *et al*<sup>1</sup> showing a predominance of non-atopic compared with atopic wheeze in children in rural Ecuador. Undoubtedly their study adds to the literature regarding the influence of environmental factors, particularly chronic helminth infections, on wheezing phenotypes. However, we feel that the interpretation and presentation of findings in this paper is open to question. This concern stems from the authors' lack of distinction between wheeze and asthma. While the analysis focused predominantly on current wheeze, subsequent discussion (and, indeed, the title) presents this as asthma.

There is good evidence for the validity of a questionnaire-based definition of asthma.<sup>2</sup> Our understanding of the definition of asthma used in this paper was of a positive response to 'wheeze in the last 12 months'. Yet wheeze may not necessarily reflect asthma, particularly in childhood where both acute infection and chronic illness might be associated with wheeze. Using only one symptom therefore runs the risk of poor discriminatory value between asthma and other causes of wheeze, making this definition of asthma potentially problematic.<sup>3</sup>

Relying on 'current wheeze' to represent asthma may also exclude a substantial proportion of 'ever wheezed' subjects, given the heterogeneous nature of childhood wheeze<sup>4</sup> and the relapsing and remitting course it may run.<sup>5</sup> There is therefore an additional risk of misclassification where subjects with asthma who were currently asymptomatic are regarded as non-asthmatic. Given that the stated principal aim of this study was to investigate risk factors for asthma/wheeze, exclusion of those without current symptoms potentially provides an incomplete picture of risk, especially when one considers that 'ever wheezing' has been shown to be a superior predictor of lifetime asthma diagnosis.<sup>5</sup>

Ultimately, asthma is a clinical diagnosis and no questionnaire-based definition can be all-encompassing. Since none of the children in this study were on regular asthma medication, perhaps combining current wheeze with the number of wheezing episodes and including a variable of 'ever wheeze' in the

diagnostic criteria might have better selected participants with a greater likelihood of asthma.

In summary, we feel that the distinction between asthma and wheeze is important to recognise and this paper fails to clearly acknowledge this. Finally, we thank the authors for describing some of our previous findings from the Isle of Wight Birth Cohort,<sup>4</sup> but wish to clarify that those findings related to atopic/non-atopic wheeze and not asthma as they suggest in the introduction to their paper.

**Martha Scott,<sup>1,2</sup> Ramesh J Kurukulaaratchy,<sup>1,2</sup> S Hasan Arshad<sup>1,2</sup>**

<sup>1</sup>The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Newport, Isle of Wight, UK; <sup>2</sup>School of Medicine, University of Southampton, Southampton, UK

**Competing interests** None.

**Provenance and peer review** Not commissioned; not externally peer reviewed.

Accepted 6 August 2010  
Published Online First 10 September 2010

*Thorax* 2011;**66**:633.  
doi:10.1136/thx.2010.143941

## REFERENCES

1. **Moncayo AL**, Vaca M, Oviedo G, *et al.* Risk factors for atopic and non-atopic asthma in a rural area of Ecuador. *Thorax* 2010;**65**:409–16.
2. **Jenkins MA**, Clark J, Carlin J, *et al.* Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996;**25**:609–16.
3. **Lukrafka JL**, Fuchs SC, Moreira LB, *et al.* Performance of the ISAAC questionnaire to establish the prevalence of asthma in adolescents: a population-based study. *J Asthma* 2010;**47**:166–9.
4. **Kurukulaaratchy RJ**, Fenn MH, Waterhouse LM, *et al.* Characterization of wheezing phenotypes in the first 10 years of life. *Clin Exp Allergy* 2003;**33**:573–8.
5. **Pippo-Savolainen E**, Korppi M. Wheezy babies–wheezy adults? Review on long-term outcome until adulthood after early childhood wheezing. *Acta Paediatr* 2008;**97**:5–11.

## Author's response

Drs Marsh and colleagues are essentially correct in saying that the word 'wheeze' rather than 'asthma' may have been more appropriate in the title of our paper. Not all wheeze is asthma but, given the lack of a widely agreed definition for asthma, we chose to use a simple but widely used definition (wheeze in the past 12 months) in this Ecuadorian study to estimate prevalence. As the authors will have seen from the abstract, the aim of the study was to investigate risk factors for atopic and non-atopic wheeze illness to understand better those that may cause or protect against asthma in the study population.<sup>1</sup>

All subjects with wheeze in the past 12 months had a history of wheeze ever. A high proportion of children in the study population had a history of wheeze ever (32.5%), most of which could be attributed