two types of mask ventilation. Although the questions of this study are relevant, I believe that the design of the study was not adequate to answer these questions.

First, all patients were on NM for >3 months and one patient even for 70 months, whereas they trained only for 1 day on FFM. In our centre (Dept of Pulmonary Diseases/Home mechanical ventilation, University Hospital Groningen, Groningen, The Netherlands), patients routinely need more time (~7 days) to adjust to their specific mask. As a result of this short time of training on FFM compared with a long-term adjustment on NM, it is not surprising that total sleep time and sleep efficiency were worse in the FFM group compared with the NM group. As a consequence of their longer experience with the NM mask, the patients also rated less leak and more comfort in the NM night compared with the FFM night. Secondly, no differences were found between pressure settings if NM was compared with FFM. However, this study will not detect any differences if pressure settings, optimised during their review night, remained unchanged during the subsequent mask trials.

Due to the previously mentioned issues, I believe that the study by WILLSON *et al.* [1], with its present design, makes it difficult to draw strong conclusions. It would have been preferable to compare both mask ventilations in a parallel study of naïve patients in whom noninvasive ventilation was started. In this way, it would have been possible to compare the time it takes to adjust to either nasal mask or full face mask. If the patients were adjusted to the mask, it would be possible to determine differences in terms of sleep quality, tolerability and pressure needed to maintain an effective noninvasive ventilation.

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References

1. Willson GN, Piper AJ, Norman M, *et al.* Nasal *versus* full face mask for noninvasive ventilation in chronic respiratory failure. *Eur Respir J* 2004; 23: 605–609.

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From the authors:

We welcome the interest of P. Wijkstra in our paper [1]. We agree that the choice of an effective interface for noninvasive ventilation (NIV) is integral to the success of this therapy and

would welcome future research in the area. We acknowledge that our study was not without methodological weaknesses, a number of which we mention in the discussion of our paper [1]. Whilst we would now consider a trial in naïve patients, this was not the situation at the commencement of data collection for our study. At that time the safety and efficacy of the full face mask (FFM) for NIV during sleep was largely unknown. Our adverse experience with this interface led us to be cautious with regard to its efficacy during sleep, especially in subjects with neuromuscular disease. Indeed, this concern was borne out in the study with the observation of upper airway obstruction in one subject on FFM *versus* an absence of respiratory events on the nasal mask. We would still recommend careful attention to the degree of upper airway closure during sleep in subjects using a FFM.

It was with these considerations in mind that rather than choosing naïve subjects we chose a group of subjects who were receiving effective NIV therapy *via* a nasal mask (NM). In this sense we were well aware that the NM *versus* FFM comparison may be weighted toward the NM. Alternatively, the acute application of a more effective interface may be argued to have biased our study toward the FFM. The proposals of P. Wijkstra in regard to the mask acclimatisation are well thought out and in line with many of our own clinical observations. We concur with P. Wijkstra that our study did not directly address the question of the difference in pressure requirements on the FFM. Our aim would have been more appropriately worded: To determine if the pressures titrated during NM ventilation were effective during FFM ventilation. We believe our study does show that the pressure settings titrated whilst wearing the NM will be adequate if the patient is changed to a FFM.

We would hope that the results of our study will be interpreted in light of the subjects studied and the methodology used. We would direct readers to the broader conclusions of our study that full face masks appeared to be as effective as nasal masks for the delivery of noninvasive ventilation.

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References

1. Willson GN, Piper AJ, Norman M, *et al.* Nasal *versus* full face mask for noninvasive ventilation in chronic respiratory failure. *Eur Respir J* 2004; 23: 605–609.

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Methacholine and macrolides

To the Editor:

The paper by KOSTADIMA *et al.* [1] provides a valuable insight into the effects of clarithromycin upon nonspecific airway hyperresponsiveness (AHR) to methacholine in asthmatics.

It is important to point out that AHR to methacholine is only very loosely related to the degree of underlying inflammation, whereas the use of an indirect bronchoconstrictor stimulus in the KOSTADIMA *et al.* [1] study would have provided more

convincing evidence of anti-inflammatory activity [2]. Bronchoprovocation with indirect stimuli, such as adenosine monophosphate (AMP), is considered to be particularly relevant to real life situations, since cold air, exercise and allergens also act in a similar fashion, in terms of the release of inflammatory mediators from primed mast cells. Indeed, shifts in the AMP threshold are more closely related to underlying airway eosinophilic inflammation and associated with symptoms of atopic asthma than direct stimuli, such as methacholine [3, 4].

Furthermore, it has been shown that in asthmatics treated with budesonide in a dose-escalation study, AMP was more sensitive than methacholine in detecting differences in AHR by approximately one doubling dilution [5].

Despite improvements in airway hyperresponsiveness, clarithromycin conferred no worthwhile improvement upon lung function. Therefore, the study by KOSTADIMA *et al.* [1] provides a timely reminder that monitoring the effects of asthma pharmacotherapy based solely on lung function can miss potentially beneficial effects upon airway hyperresponsiveness and underlying inflammation [6]. Further long-term studies are needed to assess whether effects upon airway hyperresponsiveness with clarithromycin translate into clinically meaningful reductions in exacerbations. Moreover, whether macrolides confer benefit upon inflammatory biomarkers, such as airway hyperresponsiveness to adenosine monophosphate and sputum eosinophilia, requires investigation.

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References

1. Kostadima E, Tsiodras S, Alexopoulos EI, *et al.* Clarithromycin reduces the severity of bronchial hyperresponsiveness in patients with asthma. *Eur Respir J* 2004; 23: 714–717.
2. Cockcroft DW. How best to measure airway responsiveness. *Am J Respir Crit Care Med* 2001; 163: 1514–1515.
3. Van Den Berge M, Meijer RJ, Kerstjens HA, *et al.* PC(20) adenosine 5'-monophosphate is more closely associated with airway inflammation in asthma than PC(20) methacholine. *Am J Respir Crit Care Med* 2001; 163: 1546–1550.
4. De Meer G, Heederik D, Postma DS. Bronchial responsiveness to adenosine 5'-monophosphate (AMP) and methacholine differ in their relationship with airway allergy and baseline FEV(1). *Am J Respir Crit Care Med* 2002; 165: 327–331.
5. Wilson AM, Lipworth BJ. Dose-response evaluation of the therapeutic index for inhaled budesonide in patients with mild-to-moderate asthma. *Am J Med* 2000; 108: 269–275.
6. Currie GP, Lee DKC, Haggart K, Bates CE, Lipworth BJ. Effects of montelukast on surrogate inflammatory markers in corticosteroid treated patients with asthma. *Am J Respir Crit Care Med* 2003; 167: 1232–1238.

DOI: 10.1183/09031936.04.10057104

From the authors:

In our study [1], an 8-week treatment with clarithromycin was associated with a significant improvement in airway hyperresponsiveness to methacholine in asthmatic patients. As G.P. Currie and D.K.C. Lee correctly point out, this significant change was not accompanied by a clinically important increase in indices of expiratory flow function. We agree that further long-term clinical trials are necessary to identify any beneficial effects of clarithromycin on symptoms of asthma and on markers of airway inflammation.

We chose inhalation of methacholine, a direct stimulus, to detect changes in airway hyperresponsiveness in asthmatics treated with clarithromycin. Provocation with AMP (indirect bronchial challenge) could have also been used. Provocative concentration causing a 20% fall in forced expiratory volume in one second AMP reflects the extent of airway inflammation due to asthma more closely than provocative concentration causing a 20% fall in forced expiratory volume in one second methacholine [2]. In addition, as G.P. Currie and D.K.C. Lee appropriately emphasise in their letter, provocation with AMP is more sensitive than provocation with methacholine in detecting changes in airway hyperresponsiveness following anti-inflammatory treatment [3]. The fact that we were able to detect improvement in airway hyperresponsiveness using the less sensitive direct bronchial challenge further supports a potentially important role of clarithromycin in the treatment of asthmatic airway disease.

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References

1. Kostadima E, Tsiodras S, Alexopoulos E, *et al.* Clarithromycin reduces the severity of bronchial hyperresponsiveness in patients with asthma. *Eur Respir J* 2004; 23: 714–717.
2. Van Den Berge M, Meijer RJ, *et al.* PC(20) adenosine 5-monophosphate is more closely associated with airway inflammation in asthma than PC(20) methacholine. *Am J Respir Crit Care Med* 2001; 163: 1546–1550.
3. Wilson AM, Lipworth BJ. Dose-response evaluation of the therapeutic index for inhaled budesonide in patients with mild-to-moderate asthma. *Am J Med* 2000; 108: 269–275.

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"Chronic obstructive pulmonary disease": the diagnostic last refuge of the intellectually challenged?

To the Editor:

SUISSA [1] makes an important contribution to the debate on inhaled steroids and chronic obstructive pulmonary disease (COPD) in identifying, in an observational study, an artificial increase in death rate of the reference group leading to a spurious appearance of effectiveness. SUISSA [1] refers, in

discussion, to what I believe to be an equally important and curiously neglected source of bias, the unintended inclusion of asthma patients when selecting patients for studies from administrative databases using only age and bronchodilator use to define the disease entity. The term COPD is a too-convenient shorthand label for a group of conditions that can be shown, even with standard investigative tools, to be of