To the Editor:

We appreciate the interest of Inoue et al in our recent article (January 2004). Although we acknowledge the role of cytokines in the pathogenesis of ARDS, we would question the relevance of some of the citations in their letter. Specifically, we fail to see how acute cross-clamping causing “ischemia/reperfusion of the lower body” and/or the inhalational exposure to diesel exhaust particles have relevance to the performance of open lung biopsy in ARDS patients, because our patients’ lung injuries did not have these etiologies. However, we do acknowledge that an inflammatory response to thoracic surgery could be one mechanism underlying the deterioration in gas exchange that we occasionally observed in our ARDS patients. Of note, some data suggest that limited surgery using a thoracoscopic approach can attenuate the cytokine response compared with that with open thoracotomy. However, thoracoscopy generally requires single-lung ventilation and therefore is not usually feasible in ARDS patients. We would also caution against the use of cytokines as an end point per se without corroborative physiologic and/or clinical outcome data.

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REFERENCES

Monitoring the Adjustment of Antiasthma Medications With Adenosine Monophosphate Bronchoprovocation

To the Editor:

Airway inflammation is the major feature of asthma, and represents the major target of the pharmacologic treatment. Currently, individual adjustment of antiasthma medications is mainly based on measurements of symptoms and airflow limitations, but this approach may not be adequate and more specific surrogate markers of airway inflammation should be considered in the routine management of asthma.

The available evidence indicates that adenosine monophosphate (AMP) bronchial provocation seems to offer substantial advantages over other noninvasive markers of airway inflammation because of its exquisite sensitivity in probing changes to airway responsiveness in response to topical glucocorticosteroids, or to the effects of specific immunotherapy.

In view of this, the article by Prieto et al (October 2003), assessing the utility of the determination of airway responsiveness to inhaled AMP as a predictor for safe dose reduction of inhaled glucocorticosteroids in patients with asthma, is of great value. However, although this work appears to provide enough information to support an important role for AMP provocation in the clinical setting, a number of assertions require judicious scrutiny.

Critical to the whole study is the choice of the cut-off points for AMP sensitivity used for the statistical analysis (400 mg/mL at baseline, and a single doubling concentration decrease in the provocative concentration of AMP causing a 20% fall in FEV1 from its baseline value 2 weeks after halving the dose of glucocorticosteroids). This is of particular value in view of the finding that a high level of sensitivity to inhaled AMP was measured in most of the patients who went on to have asthma exacerbations. By arbitrarily setting the cut-off values for PC20 too high, there is the chance of including patients with very mild asthma who are unlikely to have exacerbations. Unfortunately, an optimal cut-off value for PC20 to separate mild from severe asthma has not been established since there are no population-based data, but it would be of interest to repeat the statistical analyses utilizing a different cut-off point (eg, 100 mg/mL).

In addition, a single doubling concentration decrease in PC20 2 weeks after halving the dose of glucocorticosteroids was arbitrarily selected as an end point for establishing the predictive value of AMP responsiveness for failure in glucocorticosteroid reduction. Yet again, given that PC20 is known to return to near-baseline levels on glucocorticosteroid treatment discontinuation, it is important to consider that by arbitrarily setting a single doubling concentration decrease in PC20 2 weeks after halving the dose of glucocorticosteroids as a cut-off values, there would be less chance of identifying those patients who are likely to acquire asthma exacerbations. Perhaps repeating the statistics utilizing an alternative cut-off point (eg, three doubling concentrations decrease in PC20) would provide different results. This approach could also provide some explanation to the wide variation in individual clinical responses to glucocorticosteroid dose reduction (as suggested by the broad range in 95% confidence interval) observed in this study.

Finally, as the airway response to a direct bronchoconstrictor agonist is less sensitive to topical glucocorticosteroids, it could have been of critical importance to include methacholine provocation in the protocol so as to compare its responses to AMP in relation to the rate of asthma exacerbations provoked by glucocorticosteroid dose reduction.

Despite the emerging view that airway responsiveness to inhaled AMP may have useful clinical applications, specific recommendations for adenosine challenge testing will require further work. It is important that well-planned and well-conducted large clinical trials must be performed to demonstrate that information gained from this test will lead to improved patient management.

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asthma in good control with ICS, but not subjects with mild
to moderate asthma. Am J Respir Crit Care Med 1999; 160:
237–243
in sputum counts and airway hyperresponsiveness after
budesonide: monitoring anti-inflammatory response on the
basis of surrogate markers of airway inflammation. J Allergy
3 Phillips K, Osborne J, Lewis S, et al. Time course of action of
two inhaled corticosteroids, fluticasone propionate and
budesonide. Thorax 2004; 59:26–30
4 Polosa R, Li Gotti F, Mangano G, et al. Monitoring of seasonal variability in bronchial hyper-responsiveness and
sputum cell counts in non-asthmatic subjects with rhinitis and
effect of specific immunotherapy. Clin Exp Allergy 2003;
33:873–881
5 Prieto L, Bruno L, Gutierrez V, et al. Airway responsiveness
to AMP and exhaled nitric oxide measurements: predictive
value as markers for reducing the dose of inhaled cortico-
6 Spicuzza L, Bonfiglio C, Polosa R. Research applications and
implications of adenosine in diseased airways. Trends Phar-
macol Sci 2003; 24:409–413

Monitoring the Adjustment of Antiasthma Medications With Adenosine Monophosphate Bronchoprovocation

To the Editor:

We would like to thank Dr. Proietti and colleagues for their interest and stimulating comments on our article.1 We certainly agree with them that an alternative analysis utilizing a cut-off point of three doubling concentrations decrease in the provocative concentration causing a 20% fall in FEV1 (PC20) with adenosine 5’-monophosphate (AMP) 2 weeks after halving the dose of inhaled corticosteroids (ICS) would provide different results. However, only one of our patients showed a decrease in PC20 of three or more doubling concentrations 2 weeks after the dose of ICS was halved.

Dr. Proietti states that, “by arbitrarily setting the cut-off values for PC20 AMP at baseline too high (400 ng/mL), there is the chance of including very mild asthmatic patients who are unlikely to develop exacerbations.” We regret that our description of patient characteristics has led to misunderstanding. Our study examined the utility of the determination of airway responsiveness to AMP and exhaled nitric oxide levels as markers for safely reducing the dose of ICS. Thus, we selected patients with stable asthma in good control with ICS, but not subjects with mild asthma. Although asthma control is often used to define asthma severity, this assumption is incorrect.2 A significant proportion of patients included in our study had moderate-to-severe asthma, but were well controlled with ICS at medium-to-high doses (beclomethasone, 500 to 1,000 μg or equivalent daily).

Finally, Proietti et al state that it could have been of critical importance to include methacholine provocation in the protocol. In a previous study,3 we have shown that the detection of a plateau on the concentration-response curve to methacholine, but not the PC20 value, may be used as a marker for safely reducing the corticosteroid dose. However, it is clear that further studies are needed to clarify the potential value of the determina-
ation of the response to both methacholine and AMP as a means to identifying those asthmatic patients whose conditions will or will not deteriorate when the dose of ICS is reduced.

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Heartbeat Synchronizes With Respiratory Rhythm Only Under Specific Circumstances

To the Editor:

Yasuma and Hayano (February 2004)1 have theorized that respiratory sinus arrhythmia improves respiratory efficiency by the pairing of increases in heart rate with inhalation, when the concentration of oxygen in the alveoli is maximal. However, this phase relationship only occurs under specific circumstances. Saul et al2 applied vagal and sympathetic blocking agents, and found that the phase lag from breathing to heart rate is near 0°, but only under pure vagal conditions. Under pure sympathetic conditions, the phase relationship varies from 180° at low frequencies to approximately −180° at high frequencies.

We asked eight healthy subjects to breathe at seven frequencies between 0.04 and 0.5 Hz for 2 min each, matching their strain-gauge respiration record to a computer-generated sine curve3 to ensure a constant respiratory depth and a sinusoidal shape for respiratory curves. Using Fourier filtration,4 we determined that the phase relationship between heart rate and respiration was 0° only at a respiratory frequency of approximately 0.1 Hz, in which the target frequency heart rate variability also was highest (Fig 1).

When healthy people breathe regularly at this resonant frequency for the cardiovascular system, we also found that the baroreflexes are systematically stimulated and baroreflex gain increases.4 In addition, peak expiratory flow improves.4 There also is preliminary evidence for an improvement in clinical asthma,5 and for improvement in respiratory gas exchange efficiency and clinical function in COPD patients.6

Thus, the hypothesis of Yasuma and Hayano1 would be specifically relevant for sympathetically mediated heart rate variabili-

REFERENCES
237–243
9 Prieto L, Gutierrez V, Morales C. Maximal response plateau to methacholine as a reliable index for reducing inhaled budesonide in moderate asthma. Eur Respir J 1999; 13:1236–1244


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