Correspondence

Erratum: Correction of Conflict of Interest Statement

From the Editor:

In an editorial by Claudia I. Henschke published in the November 15, 2003, issue of the *AJRCCM* (1), it was stated that Dr. Henschke had no declared conflict of interest. The Editor contacted Dr. Henschke in May 2008 concerning corrections issued in April 2008 by two other journals (2, 3) regarding the conflict of interest disclosures made by her in articles and letters to the editor concerning the International Early Lung Cancer Action Project (I-ELCAP). These corrections pertained to patents and royalties, as well as funding from the Foundation for Lung Cancer: Early Detection, Prevention and Treatment. I-ELCAP was also referenced in the *AJRCCM* editorial.

Dr. Henschke provided the Editor with the following corrected conflict of interest statement for her editorial, and also commented to the Editor that the funding of her and her colleagues' work referred to in the reference section of the editorial did not include any funding from the Foundation for Lung Cancer: Early Detection, Prevention and Treatment:

Conflict of Interest Statement: C.I.H. has reported being a coinventor of three (3) pending patent applications filed by the Cornell Research Foundation, Inc. (CRF), a subsidiary of Cornell University, from 2000 to 2003. These applications pertain to three-dimensional image rendering and analysis and/or small pulmonary nodule computer-aided diagnosis from computed tomography scans. The CRF licensed certain of these technologies to General Electric starting in 2001 and has received royalties, of which a portion has been distributed to C.I.H.

EDWARD ABRAHAM
Editor

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Whole-Body “Negative-Pressure” Ventilation: Is It Really Different?

To the Editor:

The article by Dr. Grasso and colleagues (1) in a rabbit model of acute lung injury claims to show superiority of whole-body “negative-pressure” ventilation (NPV) over conventional positive-pressure ventilation (PPV). They report that NPV resulted in better oxygenation, greater lung volume at FRC, less atelectasis on computed tomography (CT), and less ventilator-induced lung injury on histology. In respiratory mechanics, the term “negative pressure” denotes that the pressure at some location is slightly less positive than ambient atmospheric pressure, not that the pressure is less than zero (i.e., less than absolute vacuum). The idea that whole-body external “negative pressure” can have a different effect on the respiratory system than internal positive pressure has been a point of confusion for at least a century (2).

Conventional respiratory mechanics holds that volume change during passive mechanical ventilation depends on the transrespiratory pressure, P_{rs} (positive pressure at the airway opening minus slightly lower positive pressure at the body surface), and

the effects of the pressure difference are the same whether pressure is increased at the airway in PPV or reduced at the body surface in whole-body NPV (2). From this perspective, the dramatic results of Grasso and coworkers are surprising and require critical examination. The authors hypothesize that NPV “applies pressure over the whole lung surface,” and that “negative pressure must take effect through the chest wall before impacting on the pleural space.” These statements are equally true of ambient pressure.

Before discarding conventional respiratory mechanics, it is important to be sure that there are no differences between NPV and PPV with regard to ventilation parameters known to affect measured outcome variables: atelectasis, oxygenation, and lung injury. Several studies in acute lung injury have shown that these outcome variables improve with higher end-expiratory P_{rs} , usually brought about by higher positive end-expiratory pressure (PEEP) (3–6). A fair comparison of the different modes requires that P_{rs} and its waveform are matched throughout the duration of NPV and PPV. As the authors correctly point out, pleural and transpulmonary pressure measurements are subject to artifact, but if the respiratory muscles are relaxed, the essential information can be obtained from P_{rs} . Measurements of P_{rs} and its components (airway pressure and body surface pressure) were not reported in this study. Video-CT scans in the online supplement suggest that P_{rs} was substantially greater on NPV than PPV; this would explain the findings without requiring us to relinquish conventional respiratory mechanics.

Conflict of Interest Statement: Neither author has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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From the Authors:

We thank Drs. Loring and Banzett for their insightful comments. The crux of their commentary is the equivalence of transrespir-

atory pressure in positive- and negative-pressure ventilation. If the respiratory system is modeled as a balloon, with no heterogeneity in the distribution of inflation, then it is difficult (impossible, in our view) to imagine that Loring and Banzett (and ourselves, and generations of others) could be wrong: positive pressure is equal and opposite to negative pressure of the same magnitude. As we see it, the problem is that—in *in vivo*—these assumptions are not valid; inflation is heterogeneous, and this is in part because of the heterogeneous nature of the thoracic wall. We don't agree that relaxation of the respiratory muscles eliminates all impediments to the transmission of pressure across the chest wall. During dynamic conditions, it is difficult to match the pressure–time profile of positive- and negative-pressure systems; if it were accurately achieved, then concomitant documentation of the pattern of inflation would resolve the issue. In this we agree with Loring and Banzett. We suspect that, in the *in vivo* context (where it matters), inflation would be seen to differ, but that's conjecture.

We focused on static conditions where there is cessation of airflow: here there are no pressure gradients across open passages, but gradients can exist across closed surfaces (e.g., the semirigid chest wall or abdomen), as shown in our article (1). End-expiratory pressure was less efficiently transmitted to the pleural space with negative pressure because, we believe, of chest wall rigidity (1). For a given level of transpulmonary pressure, end-expiratory lung volume was greater when achieved with negative versus positive pressure; this could have been because of the differences in dynamic inflation before static conditions were achieved, or because the measurements of pleural pressure were inaccurate. For the latter to explain the results, the measurement of pleural pressure would have to have been differentially and systematically erroneous for positive versus negative pressure. Leaving aside pressure measurements, we documented that comparable levels of end-expiratory lung (i.e., static) volume achieved by negative pressure resulted in greater oxygenation that was independent of pressure measurements.

We certainly did not (and would not) suggest that conventional respiratory mechanics be “relinquished”; rather, we would hope that scientists with the insights of Drs. Loring and Banzett will continue to provide argument and data that will broaden our understanding of how lungs inflate.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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The INSPIRE Study: Influence of Prior Use and Discontinuation of Inhaled Corticosteroids

To the Editor:

In their article, Dr. Wedzicha and colleagues reported that the INSPIRE study found no difference in exacerbation rates of chronic obstructive pulmonary disease (COPD) between salmeterol/fluticasone (SFC) and tiotropium (1). They also reported more study withdrawals from the tiotropium group than from the SFC group. We wondered if withdrawing from the study may be related to changes in treatment. In patients with COPD, it has been shown that discontinuation of inhaled corticosteroids (ICS) “leads to a clinically significant deterioration” (2). This finding is pertinent because ICS are included in the SFC arm, but not in the tiotropium arm. Therefore, prior use of ICS would be discontinued only for patients randomized to tiotropium.

To evaluate the impact of prior use and discontinuation of ICS on withdrawal from the study, we used data from Wedzicha and coworkers’ Tables 1 and 2 to compute study withdrawal rates according to use of ICS at study entry (*see* Table 1 herein). The data in Table 1 show the following: (1) patients who were using ICS at study entry withdrew from the study at a higher rate than patients who were not using ICS at study entry and, among such patients, the greatest withdrawal rate was for those who had their ICS discontinued because they were randomized to tiotropium (49%); (2) among tiotropium patients who were not withdrawn from ICS at study entry, the withdrawal rate (35%) was similar to the withdrawal rate in the SFC group (35%), and slightly greater than the withdrawal rate for SFC patients who did not use ICS at study entry (31%).

In conclusion, outcomes during the study may be confounded by study design–induced changes in treatment at the outset of the study. Specifically, study withdrawals appear to be related to prior use and especially discontinuation of ICS. The data do not support the authors’ conclusion that “Withdrawing from the study after receiving tiotropium was unrelated to the subjects’ prior use of ICS” (1). Moreover, because ICS discontinuation would be expected to increase exacerbation rates as well as withdrawals, we encourage the authors to extend our table to include exacerbation rates and mortality rates according to use of ICS at study entry. Others have suggested that bias introduced by discontinuation of ICS for comparator patients may at least in part explain apparent benefits of ICS on mortality (3).

Conflict of Interest Statement: S.F.L. is an employee of Boehringer Ingelheim. M.J. is an employee of Boehringer Ingelheim.

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TABLE 1. STUDY WITHDRAWALS BY USE OF INHALED CORTICOSTEROIDS AT ENTRY

ICS at Entry	% SFC	% Tiotropium	% Total
Yes	40 (126/319)	49 (166/340)	44 (262/659)
No	31 (106/339)	35 (113/325)	33 (219/664)
Total	35 (232/658)	42 (279/665)	39 (511/1323)

Definition of abbreviations: ICS = inhaled corticosteroids; SFC = salmeterol/fluticasone.