Correspondence

META-ANALYSIS OF TIDAL VOLUMES IN ARDS

To the Editor:

In their recent letter regarding trials of lower tidal volume ventilation in acute respiratory distress syndrome (ARDS) (1), Drs. Parshuram and Kavanagh asked, "... are the control groups representative of the standard of care?" None of the trials (2–6) included a standard or routine care study group because they were not designed to compare outcomes of patients who received lower tidal volumes with those who received routine care. Routine care encompassed broad ranges of tidal volumes and inspiratory airway pressures. These broad ranges reflected physicians' widely varying opinions regarding the value of different approaches to mechanical ventilation in acute lung injury (ALI) and ARDS (7, 8). Also, some physicians doubted the importance of adjusting tidal volumes and inspiratory pressures within these broad ranges. To determine if a lower tidal volume approach was superior to a traditional approach that used higher tidal volumes, the investigators for each of the trials designed study protocols to represent these two approaches. The tidal volumes and inspiratory pressure limits were consistent with contemporary opinion and within the scope of routine care (9, 10). How can the results of the trials be used to improve clinical practice? Our trial results strongly suggest that tidal volumes $\geqslant$ 12 ml/kg predicted body weight (PBW) and inspiratory plateau pressure limits $\geqslant$ 50 cm H_2O should not be used unless there are compelling reasons to do so. Moreover, analyses of the trial database strongly suggest that intermediate tidal volumes and inspiratory pressures are not as safe as the lower tidal volumes and pressures used in our lower tidal volume group (11).

Drs. Parshuram and Kavanagh also asked, "Does entry into the trial confer a disadvantage to patients randomized to the control group (versus not being in the trial)?" This question has been raised only with hindsight, after the results of the trial were known. To avoid risks to study participants, trial methodology included many safeguards and good practice procedures, including standardized weaning, which improve the process of care relative to routine care (12, 13). Our trial procedures were reviewed for safety and approved by Institutional Review Boards (IRBs) for 24 hospitals and two independent committees of experts in critical care, clinical trial design, and biomedical ethics. It is notable also that in many patients randomized to the traditional study group, tidal volumes were actually *decreased* from their routine care values to 12 ml/kg PBW or lower.

In their recent letter (14), Eichacker and colleagues correctly estimated that in nearly 80% of patients in our traditional study group, tidal volumes were increased from their routine care levels to the levels stipulated by protocol rules. Mean routine care tidal volume ($\pm$ SD) before patients were enrolled in the trial was 10.3 $\pm$ 2 ml/kg PBW (10). Mean tidal volume after randomization to our traditional study group was 11.8 $\pm$ 0.8 ml/kg PBW (6). Thus, there was substantial overlap in these ranges of tidal volumes. The value of 11.8 ml/kg PBW is equivalent to 9.9 ml/kg measured body weight, which is at the lower end of the range that had been recommended for the traditional approach that gave high priority to maintaining gas exchange, breathing comfort, and acid-base homeostasis (7). It is also lower than those used in ARDS patients in the early–mid 1990s (11). The modest increase in mean tidal volume after randomization to the traditional study group was associated with a modest increase in mean plateau pressure from 30 to 33 cm H_2O. For comparison, 33% of plateau pressures during routine care were $\geqslant$ 33 cm H_2O and 11% were $>$ 40 cm H_2O. Thus, the tidal volumes and inspiratory pressures in our traditional study group were consistent with the traditional recommendations and with a substantial portion of routine practices in the mid–late 1990s.

Eichacker and colleagues are correct that a small proportion of routine care tidal volumes was 6 ml/kg PBW or lower. We chose 6 ml/kg PBW as the tidal volume target in our lower tidal volume study group because it was consistent with the tidal volumes used in four encouraging reports of lower tidal volume ventilation in ALI/ARDS (8, 15–17) and with contemporary recommendations (18).

Eichacker and colleagues compared the 31% mortality of patients who were eligible but declined to participate in our trial (19) to the 40% and 31% mortalities in our traditional and lower tidal volume study groups. These comparisons are misleading because they fail to account for important differences between participants and the nonparticipants on whom the data are available. IRBs did not grant permission to use nonparticipant data at some Network centers. At the centers where permission was granted, mortalities for both participant study groups were lower than the mortalities cited by Eichacker and colleagues, which are for all Network centers combined. At the centers where permission was granted, mortality in nonparticipants was not significantly different from the mortality in either of the participant study groups.

Citing data from one of the ARDS Network centers, Eichacker and colleagues stated, "mortality associated with routine care reached less than 30% in 1996, the year that the ARDS Network started their trial of low tidal volume." This is misleading because it compares mortality for 1 year at a single center to the mortality in our lower tidal volume group at all Network centers without addressing differences in the populations. Subjects at the single center were younger than the patients at all centers who participated in the trial (48.6 $\pm$ 17.5 compared with 51.5 $\pm$ 17.2, p value = 0.0006). Regardless of primary risk for ARDS, 46% of the patients at this center were admitted after major trauma compared with 11% with trauma at all Network centers combined. Mortality from ARDS in younger patients and in those with trauma is lower than in other patient populations (20, 21). Finally, it is misleading to select the mortality in an outlier year at the single center for comparison with the overall mortality in our trial. From 1997 to 2001, mortality at the single center ranged from 36 to 41%.

Eichacker and colleagues claim that the unimodal distribution of tidal volumes in routine care (Figure 1 of their letter) does not represent the traditional and lower tidal volume approaches described in our previous letter (11). A reasonable explanation for this distribution of tidal volumes is that some physicians adhered to a traditional approach, some adhered to the lung-protective approach, and many used approaches that represented hybrids between the two approaches because they were unsure which approach was better.

Eichacker and colleagues suggested that one of the study groups in our trial should have used tidal volumes of 9 to 12 ml/kg PBW, a range that encompassed approximately 60% of the tidal volumes that were used before enrollment. This approach could potentially provide a method to test the same hypothesis addressed in our trial. Analyses of our trial database strongly suggest that, if properly designed and conducted in

other respects, such a trial would have demonstrated superiority of the lower tidal volume approach to the 9–12 ml/kg approach (11). However, substantial practice variations would have occurred in the 9–12 ml/kg study group, reducing the "signal to noise ratio." Therefore, it would have been necessary to enroll more patients in the trial to demonstrate the same result. More patients would have received an inferior approach in the course of such a trial.

At the time the trials were designed and conducted, nobody knew if the traditional or lower tidal volume approach was superior. Therefore, nobody knew if the trial design proposed by Eichacker and colleagues to avoid increases in tidal volumes from those used in routine care would be safer than a design that avoided *decreases* in tidal volumes from those used in routine care. We maintain that the approach we used was consistent with highest standards for clinical trial design because it addressed an important clinical problem using methodology that could answer the question while employing redundant mechanism of oversight and numerous safeguards and procedures to minimize risks to study participants.

For the NIH NHLBI ARDS Network investigators:

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STOPPING INHALING CORTICOSTEROIDS IN COPD

To the Editor:

We read with interest the COPE study, which determined that there is an increased COPD exacerbation rate when subjects are taken off of high-dose inhaled corticosteroids (1). The COPD subjects in the study all had an FEV_1 between 25–80% predicted with a prebronchodilator FEV_1/inspiratory vital capacity (IVC) ratio of 60% or less.

Reversibility of FEV_1 for inclusion in the COPE study needed to be less than 12% of predicted after 80 μg of ipratropium bromide via a metered dose inhaler with aerochamber. Traditionally, significant reversibility is defined using β2-agonist inhalation and at least a 12% improvement in FEV_1 from baseline and at least a 200 ml improvement in absolute FEV_1 (2, 3). Using less than 12% of predicted as a bronchodilator response could include some subjects who would be greater than 12% of baseline using the American Thoracic Society guidelines (4). In addition, it is possible that some subjects would respond differently with the use of a β2-agonist instead of an anticholinergic. This suggests that some of the COPE study patients probably have a significant degree of reversibility if classically defined. Therefore, it is possible that some of the patients had asthmatic characteristics that would predispose them toward an exacerbation of lung disease on withdrawal from inhaled corticosteroids as is seen in the asthmatic population.

Given the above, we were wondering why reversibility was not determined with β2-agonist therapy, since that is the traditional method. Are there studies validating that anticholinergic

reversibility gives the same or similar information as β2-agonist reversibility?

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From the Authors:

We appreciate the comments of Drs. Pesola and Dogra regarding our article in the November 2002 issue of *AJRCCM* (1) and would like to address their concerns.

Their first concern pertains to our use of a cut-off point for reversibility of 12% *of predicted*, compared with 12% *of baseline*, which they state is used in the American Thoracic Society (ATS) guidelines (2). Use of the first would lead to a higher probability to include patients with asthmatic characteristics.

The European Respiratory Society lung function guidelines (3) follow the study of Brand and colleagues (4), which compared different expressions of bronchodilator response with respect to dependence on initial FEV_1. They conclude that the ΔFEV_1 predicted is the most useful method of expressing bronchodilator response, both for clinical and research purposes. Also, the ATS statement (2) mentions that expressing the change in FEV_1 as percentage of predicted deserves further study as it has been reported to have advantages over current methods. Moreover, the change in FEV_1 after bronchodilation compared with baseline level increases in patients with a low initial FEV_1. The use of the test with reversibility of 12% *of baseline* would have lead to overestimated bronchodilator response and so to inappropriate exclusion of real COPD patients. Additional analysis of two subgroups of reversibility in FEV_1 according the ATS guidelines, showed that the risk to develop a first exacerbation in COPD after discontinuation of fluticasone does not change substantially, and is even more prominent in the low reversibility group (*see* Table 1).

Their second concern is related to the use of ipratropium bromide for testing reversibility, instead of a β2-agonist. In a study by Hadcroft and Calverley (5), no significant differences were found in the magnitude of change in FEV_1 after either salbutamol or ipratropium given singly or in combination in COPD patients. One recent study in patients with asthma (6) concluded that both salbutamol and ipratropium are effective bronchodilators in patients with asthma, although the overall response to salbutamol appears to be superior in asthma. However, in older patients there was less difference in the reaction to one or other of the two drugs. Since the patients in our study are relatively old (mean age 64), the type of bronchodilator seems to be less important. Furthermore, all our patients had a clinical diagnosis of stable COPD, as defined by ATS criteria without a history of asthma as checked in their hospital records. We choose to test reversibility after inhalation of a high dose of ipratropium bromide via a metered dose inhaler with aerochamber since ipratropium is the first bronchodilator of choice in COPD in the Netherlands because it is virtually without systemic side effects. As mentioned by Pesola and Dogra, it is possible that some subjects would respond differently to the use of a β2-agonist compared with an anticholinergic, but this is also the case vice versa. Even when asthma is excluded, clinical COPD will always include some asthmatic features, which are hard to detect by simple reversibility testing.

TABLE 1. SUBGROUP ANALYSIS OF TIME TO FIRST EXACERBATION ACCORDING TO REVERSIBILITY GUIDELINES OF THE ERS AND ATS, RESPECTIVELY

Reversibility FEV_1	Hazard Ratio	95% Confidence Interval	No. of Patients
ERS guidelines#	1.5	1.1–2.1	244
ATS guidelines*			
Subgroup 1: only patients with reversibility ⩽ 12%	1.7	1.02–2.7	152
Subgroup 2: only patients with reversibility > 12%	1.3	0.7–2.4	92

* Reversibility of the FEV_1 is calculated as percentage of the predicted value: FEV_1 post-FEV_1 prebronchodilator/FEV_1 predicted.

Reversibility of the FEV_1 is calculated as percentage of the baseline value: FEV_1 post-FEV_1 prebronchodilator/FEV_1 prebronchodilator.

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ENVIRONMENTAL ENDOTOXIN AND ASTHMA

To the Editor:

Environmental endotoxin may have an atopy-protective effect according to several authors. Gehring and colleagues have shown that exposure to higher levels of house dust endotoxin is associ-

ated with lower prevalence of allergic sensitization in children. They could not correlate this observation with asthma due to lack of statistical significance (1). Recently, endotoxin levels in dust from children's mattresses were found to be inversely related to the occurrence of hay fever, atopic asthma and atopic sensitization (2). However, in both studies, the authors did not identify by culture or other methods the gram-negative bacteria producing the endotoxin. The endotoxin receptor CD14 and Toll-like receptor of immune cells play important roles in the induction of endotoxin tolerance and are affected differentially by diverse species of gram-negative bacteria (3). This fact underlines the need to identify the gram-negative bacteria involved. *Enterobacteriaceae* have often been isolated in dust. It would, therefore, be important to detect antibodies against *Enterobacteriaceae* in the children's sera to determine if their level or presence is also inversely related to allergic disease. Enterobacterial common antigen (ECA) would be an appropriate target for this investigation.

ECA is a cell surface antigen shared by all members of *Enterobacteriaceae*, and the *wec* gene cluster is implicated in its synthesis. Antibodies against ECA are found in all adults, including pregnant women. They belong to the IgM class, and newborns do not have anti-ECA antibodies (4). It is a strong argument against the potential benefit of an *in utero* exposure to endotoxin, a hypothesis that has been raised in the literature (5).

The study of environmental endotoxin, using a kinetic limulus assay, has been widely used. We also need more specific methods to identify the gram-negative bacteria producing the endotoxin with protective effects, found in house dust of children who have lived in the same home since birth (1) or in a farm environment in their first year. We have devised consensus primers, using *wec* gene templates for the specific PCR-based detection of *Enterobacteriaceae* DNA (6). The nature of bacterial DNA in dust could be ascertained with this molecular method or another one able to detect viable and nonviable microorganisms. Such a combined approach, in a large prospective control study with statistical power, would help to define the role of *Enterobacteriaceae* in asthma and to develop a specific strategy for primary prevention of the disease.

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From the Authors:

We thank Dr. Bayardelle for his comments on our paper, which showed a protective effect of exposure to higher levels of house dust endotoxin on allergic sensitization in schoolchildren (1). Dr. Bayardelle correctly states that we did not distinguish different species of gram-negative bacteria as major sources of bacterial endotoxin. We agree with him that there is a need to identify the species of gram-negative bacteria that are responsible for the protective effect. The approach suggested by Dr. Bayardelle may give us further insight as to the species of bacteria involved if application to large epidemiological studies is feasible.

However, besides endotoxin there are other components of house dust with immunostimulatory properties, such as other bacterial components and β(1→3)-glucans. Cell–wall components from atypical mycobacteria or gram-positive bacteria such as lipoteichoic acid, are known to affect immune responses similar to endotoxin (2, 3). The levels of β(1→3)-glucans have been shown to be significantly correlated with levels of endotoxin in house dust (4). All these factors were not measured and may also be (at least partly) responsible for the observed protective effect. Therefore, more research is needed to elucidate the immune mechanisms involved.

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STANDARD DEVIATION SCORES OF MAXIMAL EXPIRATORY FLOW IN INFANTS

To the Editor:

Lung function testing in infants and toddlers with respiratory disease has developed into a very valuable tool for clinical and research purposes for the very young. Obviously, with the growing awareness that early interventions may contribute to improved long-term outcome in various respiratory disorders, there is a need for objective endpoints to evaluate treatment strategies (1, 2). One of the key issues in evaluating outcome is the availability of valid reference data, especially for maximal flow at functional residual capacity ($\dot{V}$maxFRC). However, much of the original published normative data for $\dot{V}$maxFRC had limited external validity, because equipment, techniques, and procedures were not standardized and comparable at that time. With the publication of sex-specific prediction equations for $\dot{V}$maxFRC in infants by Hoo and colleagues in *AJRCCM* (3), a major step forward has been made in tackling this issue. The data from this multicenter collaborative study are unique because they are based on a representative population of healthy control subjects, and are the first to detect and describe sex-specific lung function data. Because of its sample size, reliable standard deviation scores can be calculated, which improves expression of lung function parameters considerably. Using these data, differences

between study results and between research groups can be quantified, and multicenter studies have become a more attractive option.

However, the accessibility, and hence the widespread use of these reference equations, is currently limited because of their mathematical complexity (due to log-transformation and standard deviation score calculation). We therefore suggest that when publishing such data, authors should provide the necessary software for automatic calculation of Z-scores, and that manufacturers should incorporate such algorithms into the current generation of infant lung function equipment. Indeed, efforts should be made by the ATS/ERS to facilitate provision and/or distribution of such software required to stimulate international standardized procedures in the diagnosis and treatment of respiratory disorders, possibly by encouraging authors to deposit appropriate material in the electronic repository or on a website.

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From the Authors:

We thank Drs. Merkus and Gappa for highlighting the fact that when publishing prediction equations for lung function, they should be available in a suitable format for subsequent routine clinical or research use. We agree with their suggestions and have now developed some add-in macros to be used in Microsoft Excel to automatically calculate the standard deviation (SD) scores for maximal expiratory flow at functional residual capacity ($\dot{V}$maxFRC) for any infant, together with the expected, and range of expected, values (based on $\pm$ 2 SD scores). These scores can be calculated based on either the infant's height or age plus height SD scores, and can be used for interpretation of results either from individual infants or from an entire dataset. This program and instructions on how to install and use the Vmax.xla file can now be downloaded from the online supplement associated with our publication (1) at http://ajrccm.atsjournals.org/ or from section B/Respiratory epidemiology/key papers, at http://www.ich.ucl.ac.uk/ich/html/academicunits/portex/rmp/research1_resp_function.html

The reference dataset comprised 654 measurements of $\dot{V}$maxFRC from 459 healthy infants. Data were obtained within the first 20 months of life from three centers (London, Indianapolis, and Boston), over a height range of 40–90 cm (1). To facilitate automatic calculations of height SD score when using the macro based on age and height SD score, a selected portion of the Child Growth Foundation reference data (2) (pertaining to the growth charts from 0–20 months of age) has been incorporated into this program.

Similar prediction equations were obtained whether or not data from preterm infants studied shortly after birth (n = 92) were included in this dataset. These equations therefore seem appropriate for calculating an SD score for preterm infants up to 8 weeks corrected postnatal age. However, they may not be appropriate for older preterm infants, since significant reductions in $\dot{V}$maxFRC SD score have been observed in such infants by 1 year of age, even in the absence of any neonatal or subsequent respiratory disease (3). Wherever possible, users should ascertain whether these equations and the derived score are applicable to their own laboratory, equipment, and local population by undertaking measurements in a group of healthy infants to check whether mean (SD) of the $\dot{V}$maxFRC SD score from such infants approaches 0 (1). Appropriate use of SD scores, which indicate a "normal" range ($\pm$ 2 SD score) for $\dot{V}$maxFRC during infancy, should improve interpretation of both clinical and research studies.

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