

Correspondence

Peer Review and Manuscript Triage

To the Editor:

Dr. Hoppin has performed a great service to the scientific community by writing his article (1). He makes the point that a good review cannot be completed in 3 hours – especially when there are significant issues to address. I wonder if this problem could be helped in part by more prescreening by journal editors. For example, the “ $n = 10$ ” studies that merit publication only in abstract form, the obvious “fishing expeditions,” and those written in poor English could be sent back for revision prior to submission to reviewers for detailed technical review. Also, if more reviewers were selected per submission, guidance could be provided as to which specific areas each reviewer should pay closer attention. Speaking personally, time constraints are the major reason for which I decline a reviewing opportunity.

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1. Hoppin F. How I review an original scientific article. *Am J Respir Crit Care Med* 2002;166:1019–1023.

From the Authors:

Peer review sets standards for publication, and can substantially improve the science and clarity of submitted articles (1). These goals are compromised when scientists refuse invitations or conduct hasty reviews because of the attendant time. Dr. Druce's letter, above, offers two suggestions that might ease that burden. Each has merits, but must be balanced against other considerations.

- 1) *Triage*. The prevalence of poorly prepared submissions reporting weak studies is frustrating and discouraging to reviewers. Triage of such articles would presumably reduce that problem, and prestigious journals could presumably afford to miss a few worthy articles without substantially compromising their quality. The practice, however, of rejecting a paper that represents a man-year's work without giving it a serious, broadly informed examination, and without giving careful feedback seems both unfair and unwise. Judging a study as a “fishing expedition,” for example, can be glib, a judgment of scientific style rather than of merit. Accountability demands participation by more than one scientist and responsible communication with the authors.
- 2) *Guidance to specific areas* for each reviewer's attention already occurs to some extent through the Associate Editor's selection of reviewers. Further narrowing of each reviewer's focus, however, would walk away from a comprehensive assessment of a submission's science and its appeal to a reasonably broad audience.

Other possible approaches fall logically into two categories—although I do not find them particularly promising:

- 1) *Increase the tangible benefits of reviewing*. These are indeed limited (2, 3). Editors might consider sending letters of thanks to their best reviewers with copies to their Chairs. They might also push the idea that good reviewing leads

to invitations to submit editorials. But that's about it! Meaningful reimbursement is probably impractical.

- 2) *Better submissions*. For any journal, there is opportunity in enhancing its image; e.g., through the powerful positive feedback of good reviews. More generally, promoting good science runs into a variety of problems – structural (strong pressures within a system that does not reward quality very well), cultural (local practices of limited consulting and debate, particularly across disciplines), even topical (e.g., less rigorous research training for clinicians than for basic scientists). There may be more practical approaches to improving the preparation of manuscripts by persuading authors that it is distinctly in their best interests either to apply the necessary discipline (2–5) or to corral help with the writing. Tobin's recent editorial (6) may be a useful model.

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From the Editor:

Dr. Druce agrees with Dr. Hoppin (1) that a worthwhile review of a manuscript requires a considerable expenditure of time. Dr. Druce asks whether journals might not improve the efficiency of peer-review by declining a greater fraction of manuscripts without sending them out to experts for assessment.

At *AJRCCM*, we believe that a scientific journal represents a great deal more than the articles published within its covers (2, 3). We try to provide a service to authors even when we do not accept their manuscript for publication; we hope that feedback on rejected manuscripts influences the quality of research in pulmonary and critical care medicine. Since September 1999, when the current editorial team began its term, we have received over 6,500 manuscripts and more than 98% were entered into peer review.

It is true that many journals reject a considerable fraction of manuscript without peer review. For example, *The Lancet* rejects about 70% of manuscripts without external review (4). *The Journal of Clinical Investigation* rejects 25% or more of manuscripts without formal assessment (5). Editors who reject a high fraction of manuscripts without peer review give two justifications for their action. One, a rapid rejection enables authors to rapidly submit their manuscript to another journal. Two, the editors wish to expedite the processing of manuscripts that appear more meritorious (4). Rapid rejection certainly shortens the time for

submission to another journal. Nevertheless, all manuscripts submitted to *AJRCCM* undergo complete peer review within 30.3 days (median), and accepted manuscripts are published on our website within one week of acceptance.

AJRCCM interprets the term "peer-reviewed journal" to mean that decisions on submitted manuscripts are almost invariably based on assessments by fellow experts in a research field. I recall several instances where I judged a manuscript to have minimal merit on an initial superficial reading. After receiving favorable critiques from the reviewers, however, I changed my mind and a revised version of the manuscript was published in the *Journal*.

It is possible for *AJRCCM* to provide detailed critiques on virtually all submissions only because more than 6,000 individuals in our Web-based database express willingness to selflessly donate time and expertise to this task.

MARTIN J. TOBIN
Editor

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Insulin Effect on Lung Diffusion: NO Pathway

To the Editor:

The article by Dr. Guazzi and colleagues (1) regarding impaired pulmonary diffusion in patients with diabetes mellitus and heart failure reported very interesting observations about the synergistic effect of these conditions in pulmonary gas exchange. It was shown that acute infusion of insulin facilitated immediately diffusion in diabetes, through an influence on alveolar-capillary conductance. The authors suggested three possible mechanisms for this result: reduction of hydrostatic forces, increased alveolar epithelial fluid clearance and activation of NO or vasodilating prostaglandins.

Type 2 diabetes is characterized by hyperglycemia and insulin resistance. Hyperglycemia causes many diabetic complications leading to increased oxidative stress in tissues through stress-sensitive intracellular signaling pathways that also seem to play a key role in causing insulin resistance, enhanced oxygen free radical-mediated NO inactivation, and increased generation of vasoconstrictive prostanoids (2, 3). In diabetic patients, pulmonary dysfunction is thought to involve the presence of thickened alveolar capillary basal lamina due to microangiopathy and non-enzymatic glycosylation of tissue proteins (4). The observation of reduced baseline DL_{CO} and DL_{CO}/VA in diabetic patients compared with control subjects presented by the authors (1) is in accordance with our study (5).

The fact that *in vivo* a single small dose of intravenous insulin improved alveolar-capillary conductance in diabetic patients raises questions concerning the pathophysiological consequences of insulin action on the alveolar-capillary unit leading to this result as: 1) the effect was immediately observed and 2) hemodynamic parameters were not involved, since insulin infusion did not affect pulmonary capillary blood volume. On the other hand, this insulin effect was produced in an environment in which

lung tissue alterations affecting gas exchange due to diabetic metabolic parameters had already been established.

We believe that the most tenable explanation for the acute effect of insulin in the alveolar-capillary unit involves, as the authors propose, the activation of the NO pathway. Hyperglycemia resulted in a significant downregulation of NO production, whereas insulin caused a dose-dependent upregulation of NO production in cultured human coronary endothelial cells (3). Our research group previously reported that insulin attenuated rabbit tracheal smooth muscle contraction by acting on epithelium and releasing NO and that this result was abolished by the presence of a nitric oxide synthase inhibitor (L-NAME) (6).

The finding that insulin causes an acute effect in the improvement of pulmonary diffusion in diabetic patients intensifies the need to clarify the pathophysiological basis of insulin biological effects on lung tissue, since clinical application could be of great importance in diabetic patients.

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From the Authors:

We would like to thank Dr. Boulbou and associates for their appreciation and the emphasis placed on the pathophysiological and clinical relevance of our recent finding that insulin improves the alveolar-capillary membrane gas diffusive properties in patients with both type 2 diabetes and chronic heart failure (1).

We hypothesize that chronic heart failure and diabetes can synergistically impair the alveolar-capillary membrane gas conductance through a number of mechanisms (1). We think it is important that insulin had little or no effect on alveolar gas diffusion in patients with chronic heart failure alone, but was beneficial in patients with diabetes without chronic heart failure (2), suggesting that diabetes provides the main substrate for the insulin activity.

The mechanisms involved in this newly discovered pharmacological property of insulin cannot be determined with our data. We agree that nitric oxide (NO) release could mediate the effects on the alveolar membrane properties, but we do not believe that the evidence is sufficient to rule out many other possibilities. Experimental models that can help to elucidate the relative contribution of NO pathway in this setting need to be developed. The evidence provided by Papayianni and coworkers (3) that insulin attenuates tracheal smooth muscle contraction by releasing NO in a rabbit model, may or may not be relevant to our

findings because of differences in the pathophysiological background that cause and sustain alveolar dysfunction in the presence of chronic heart failure and diabetes. Fluid clearance from the alveolar epithelial surface to capillary basement is dependent on specific Na^+ channels as well as on a Na^+ -glucose co-transport system. In the presence of diabetes, insulin might activate this defective pathway, promote fluid reabsorption, and thereby improve gas exchange by shortening of the diffusion path (4). An active participation of others EDRFs, such as vasodilator prostaglandins, cannot be definitively ruled out.

As to the clinical impact of our report, we take this opportunity to mention that recent findings from our laboratory (5) show that in patients with chronic heart failure and diabetes, improvement in lung diffusion translates into improved ventilatory efficiency (VE/VCO_2) during exercise and a greater oxygen uptake at peak exercise. Considering the high prognostic power of both ventilatory efficiency and peak oxygen consumption, these results, at a minimum, support the need for an in-depth evaluation of the mechanisms whereby insulin affects lung microcirculation in diabetes, and the clinical correlates.

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Lung Growth and Development after Preterm Birth

Further Evidence

To the Editor:

While we agree with the interpretation and general message of the recent editorial by Jobe (1), which proposed that the relative reduction in airway function during the first year of life in preterm infants recovering from chronic lung disease of prematurity might represent the additive adverse effects of very preterm birth plus bronchopulmonary dysplasia, we should like to point out that his suggestion that Hofhuis and colleagues (2) were the first to note such deterioration is not strictly true. The publication by Hofhuis and colleagues was in fact preceded by that from Hoo and colleagues (3), who showed that airway function may deteriorate during the first year of life in infants born prematurely in the absence of any neonatal disease or therapy. This provides further evidence regarding the importance of prematurity *per se* on subsequent lung growth and development and for Jobe's proposal that such infants may be "functionally growing out of their airways." Preliminary findings from Hannover (4) have reported similar findings.

Given the potential clinical significance of these findings, we

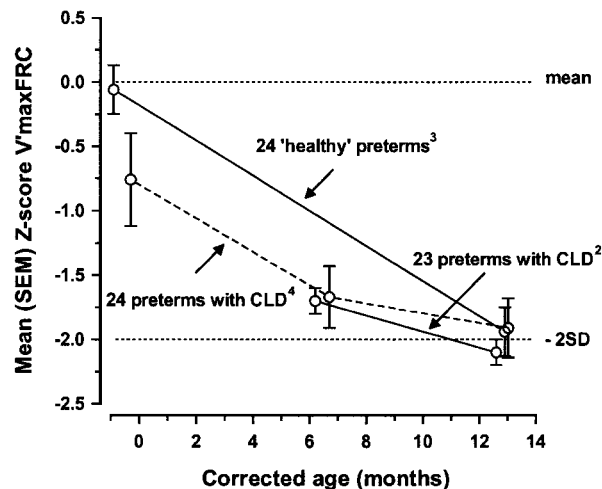


Figure 1. Development of maximal expiratory flow at functional residual capacity (\dot{V}_{maxFRC}) as a measure of airway function in two groups of infants born prematurely, who were ventilated and developed CLD (2, 4), (mean [SD] gestational age of 27 ± 2 and 28 ± 2 weeks, respectively) or who had no respiratory disease (GA = 33 ± 2 weeks) (3). \dot{V}_{maxFRC} was measured on at least two occasions during follow-up and is expressed in standard deviation scores (Z-scores) based on equations published by Hoo and colleagues (6).

have collated recent data from preterm infants with and without chronic lung disease of prematurity, from three centers in Germany, Britain, and the Netherlands. As can be seen from Figure 1, these suggest a similar decrement in airway function at one year of age, irrespective of prior disease severity or mode of treatment. While these findings need confirmation in a larger prospective study, they emphasize the importance of sequential measurements and of using an appropriate control group when interpreting long-term effects of respiratory disease or management in the neonatal period. Mechanisms underlying these observations remain speculative, but may include the fact that maturation, dimensional growth, and alveolar septation occur out of phase following preterm delivery, thereby resulting in airways that are more compliant, smaller, and/or have fewer alveolar attachments. Hence, pulmonary changes in preterm infants may be characterized by an arrest in both lung and airway development. This adds concern to the possibility that chronic lung disease of prematurity may be associated with subsequent chronic obstructive pulmonary disease in later life (5). In conclusion, there is growing evidence that reduced lung and airway function following preterm delivery may be related to developmental changes as much as to initial disease severity or to treatment effects. Improved antenatal care and avoidance of prematurity may be as important for future lung health as further improvements in neonatal ventilation strategies.

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From the Authors:

Gappa and Merkus point out that others have reported a deterioration in $\dot{V}_{max} FRC$ prior to the report of Hofkuis and coworkers (1). I was in error to say that was the first report of deterioration

of $\dot{V}_{max} FRC$ in preterms in the first year of life (2). However, I was not far wrong based on the publication dates of other similar observations. The number of recent publications reflects an appropriate interest in exploring clinically how the preterm lung develops. Hofkuis and colleagues did evaluate very small preterms with a history of bronchopulmonary dysplasia. The composite figure provided by Gappa and Merkus is helpful and clearly points out that prematurity *per se* may be a more important contribution to the decrease in $\dot{V}_{max} FRC$ at 1 year of age than the superposition of bronchopulmonary dysplasia.

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