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Reply to Voelkel and Newman

From the Authors:

We thank Dr. Voelkel and Dr. Newman for their interest in our recent manuscript (1) and their insightful commentary.

Our report focused on the challenges associated with treating pulmonary hypertension (PH) due to heart failure with preserved ejection fraction (HFpEF), interstitial lung disease (ILD), and pulmonary venoocclusive disease (PVOD)/pulmonary capillary hemangiomatosis with pulmonary arterial hypertension (PAH)-specific therapies. We likened elevated pulmonary artery pressure and right ventricular dysfunction in these PH subtypes to "the tip of the iceberg." The intent of the analogy was to emphasize the molecular and pathological mechanisms below the surface when considering appropriate therapy and future clinical trials but does not preclude unifying mechanisms across the different PH classifications. Although discovery of distinct endophenotypes is one potential outcome of comprehensive PH phenotyping, we may also uncover similarities that are otherwise obscured by our current focus on disease-based classification (2). Thus, we concur that unifying pathobiological mechanisms do exist across World Health Organization classifications (e.g., inflammation and endothelial dysfunction) and may suggest shared therapeutic targets (3). For example, spironolactone increases survival in patients with left heart failure by improving endothelial dysfunction and reducing inflammation, providing a biological rationale for studying the treatment in PAH (4).

Dr. Voelkel and Dr. Newman underscore the extent of heterogeneity even among patients with PAH. We agree that just as there are important pathobiological differences between HFpEF-PH, ILD-PH, PVOD, and PAH that impact treatment responses, PAH clinical subtype also influences therapeutic responses (5). In addition to recognizing differential therapeutic responses in patients with PAH, based on clinically defined subtypes (e.g., idiopathic PAH, systemic sclerosis-associated PAH, and congenital heart disease–associated PAH), studies have also suggested that genetic polymorphisms (6) and gene expression patterns (7) are associated with therapeutic responses and represent encouraging progress toward personalized medicine. NHLBI-funded projects such as the PAH Biobank and Pulmonary Vascular Disease Phenomics program (PVDOMICS) as well as ongoing efforts internationally (8) are further evidence that the field is moving ahead and diving deeper below the surface. Furthermore, advances in clinical trial design including the use of master protocols and innovative methodologies (e.g., umbrella, basket, and platform trials) are particularly appealing for studying mechanistic-based therapies and/or rare diseases (9).

The field of oncology has made a tremendous amount of progress in the development of precision therapies owing in large part to the accessibility of the target tissue and the ability to stage tumor progression. In contrast, determining whether candidate or even current therapies have a direct impact on the pulmonary vasculature and/or the right ventricle is both a major challenge and an opportunity for advancing precision therapy in pulmonary vascular disease (10). Pilot studies using [^{18}F]deoxyglucose positron emission tomography of the heart (11) and lung (12), gadolinium-enhanced magnetic resonance imaging of lung perfusion (12), and cardiac magnetic resonance imaging (13) are notable examples of the type of innovative measures of treatment responses that will be necessary to realize the potential of precision therapy in pulmonary vascular disease. Thus, we are in agreement with Voelkel, Newman, and Will Rogers that "even if you're on the right track, you'll get run over if you just sit there." ■

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Consider Using Attributable Fraction of Mortality from Acute Respiratory Distress Syndrome to Guide Sample Size Estimates

To the Editor:

We note with interest the recent article by Khemani and colleagues on positive end-expiratory pressure (PEEP) and mortality in the pediatric acute respiratory distress syndrome (ARDS) population (1), and commend the authors for providing much-needed data about the use of PEEP and outcomes, using robust statistical analysis. The data suggest an association between PEEP lower than ARDS Network recommendations in the first 24 hours of admission, and increased mortality, which raises questions around current management approaches to these patients. The authors themselves and the accompanying editorial commentary (2) quite rightly point out some of the key limitations and challenges in interpretation of the findings from this retrospective analysis, most notably the issue of confounders and the duration of and differences between the datasets analyzed. We wish to highlight a few further key considerations regarding interpretation of mortality risk and ARDS.

The authors extracted time-matched PEEP and $F_{I_{O_2}}$ values every 6 hours during the first 24 hours after diagnosis of ARDS. There is no robust evidence to suggest that early PEEP levels matter more than PEEP throughout the duration of ARDS management, unlike other scenarios in critical care such as oxygen during reperfusion and so on. It is biologically plausible that time-matched PEEP and $F_{I_{O_2}}$ values may need to be studied for at least several days into the disease process, if not its entirety. In addition, cumulative exposure to PEEP may be of more prognostic significance than individual values abstracted at separate times. However, given the limitations of a retrospective analysis and variability in duration of disease process among patients, analyzing only the early PEEP values seems an acceptable compromise, but a compromise nevertheless.

Although mortality provides a clear outcome measure, numerous different factors contribute to an individual's mortality risk. In sepsis, Shankar-Hari and colleagues have described the estimation of attributable fraction of mortality to sepsis (3). They note that many sepsis trials have no statistically significant difference in mortality and argue that this may be a result of excess attribution of mortality to sepsis. By using control groups of critically unwell adults without sepsis, as well as the overall population of adults, they calculate a range for the attributable fraction of mortality resulting from sepsis. Using this figure results in significantly larger sample size estimates. This principle could be applied to ARDS, using critically unwell individuals without ARDS as control patients and thereby giving an attributable fraction of mortality resulting from ARDS. This is perhaps a more important confounder, as ARDS may be secondary to other underlying disease processes (such as bone marrow failure or cardiac failure) with a more direct link to the patients' outcome. In other words, a significant proportion of patients may have died with ARDS, rather than because of it.

In summary, we support the authors' call for further randomized controlled trials regarding PEEP management in ARDS. We suggest that further trials should consider the use of attributable fraction of mortality resulting from pediatric ARDS to guide sample size estimation. ■

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