as possible effects on DNA and changes in low-abundance proteins. In addition, the functional consequences of the observed changes require further investigations. Finally, this study focused on using PG/PV to reproduce some of the findings in cell cultures and mice, whereas many other studies also point to flavorings and nicotine as main harmful constituents of e-cigarettes (reviewed in References 6 and 7). In fact, the same research group has reported on the toxicity of flavorings in e-cigarette liquids (11). Despite these and other issues, the present study does provide important insight into the effects of (long-term) e-cigarette use on human lung tissue, and is therefore extremely useful for a science-based continuation of the discussion on the safety of e-cigarettes, balancing harm reduction, and causing harm by e-cigarette use. The present findings are clearly not in line with the statement that e-cigarettes are a harmless alternative to tobacco products. They point to the need for safety data provided by independent researchers that compare the consequences of e-cigarette use with non-use, instead of with the use of tobacco products. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Pieter S. Hiemstra, Ph.D.
Department of Pulmonology
Leiden University Medical Center
Leiden, the Netherlands

Robert Bals, M.D., Ph.D.
Department of Internal Medicine V—Pulmonology, Allergology and Critical Care Medicine
Saarland University
Homburg, Germany

ORCID ID: 0000-0002-0238-5982 (P.S.H.).

References

1. Levy DT, Yuan Z, Li Y. The prevalence and characteristics of e-cigarette users in the U.S. *Int J Environ Res Public Health* 2017;14:14.
2. Singh T, Arrazola RA, Corey CG, Husten CG, Neff LJ, Homa DM, *et al*. Tobacco use among middle and high school students—United States, 2011–2015. *MMWR Morb Mortal Wkly Rep* 2016;65:361–367.
3. Royal College of Physicians. Nicotine without smoke: tobacco harm reduction. A report by the Tobacco Advisory Group of the Royal College of Physicians. Royal College of Physicians. London; 2016 [accessed 2018 Feb 2]. Available from: <https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction-0>.
4. U.S. Department of Health and Human Services. E-cigarette use among youth and young adults: a report of the Surgeon General. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. Atlanta: GA; 2016 [accessed 2018 Feb 2]. Available from: https://www.cdc.gov/tobacco/data_statistics/sgr/e-cigarettes/index.htm.
5. Fairchild AL, Lee JS, Bayer R, Curran J. E-cigarettes and the harm-reduction continuum. *N Engl J Med* 2018;378:216–219.
6. Hiemstra PS, Bals R. Basic science of electronic cigarettes: assessment in cell culture and in vivo models. *Respir Res* 2016;17:127.
7. Chun LF, Moazed F, Calfee CS, Matthay MA, Gotts JE. Pulmonary toxicity of e-cigarettes. *Am J Physiol Lung Cell Mol Physiol* 2017;313:L193–L206.
8. Lee HW, Park SH, Weng MW, Wang HT, Huang WC, Lepor H, *et al*. E-cigarette smoke damages DNA and reduces repair activity in mouse lung, heart, and bladder as well as in human lung and bladder cells. *Proc Natl Acad Sci USA* 2018;115:E1560–E1569.
9. Ghosh A, Coakley RC, Mascenik T, Rowell TR, Davis ES, Rogers K, *et al*. Chronic e-cigarette exposure alters the human bronchial epithelial proteome. *Am J Respir Crit Care Med* 2018;198:67–76.
10. Reidel B, Radicioni G, Clapp PW, Ford AA, Abdelwahab S, Rebuli ME, *et al*. E-cigarette use causes a unique innate immune response in the lung, involving increased neutrophilic activation and altered mucin secretion. *Am J Respir Crit Care Med* 2018;197:492–501.
11. Rowell TR, Reeber SL, Lee SL, Harris RA, Nethery RC, Herring AH, *et al*. Flavored e-cigarette liquids reduce proliferation and viability in the CALU3 airway epithelial cell line. *Am J Physiol Lung Cell Mol Physiol* 2017;313:L52–L66.

Copyright © 2018 by the American Thoracic Society

Pediatric Acute Respiratory Distress Syndrome: Increase the Positive End-Expiratory Pressure?

The goals of mechanical ventilation in acute respiratory distress syndrome (ARDS) are to maintain adequate oxygenation and ventilation while simultaneously avoiding injurious stress and strain. Standard maneuvers to improve arterial oxygen saturation are delivery of higher FiO_2 and increasing positive end-expiratory pressure (PEEP) to improve ventilation and perfusion matching and recruit collapsed alveoli. PEEP has the added benefit of

potentially reducing ventilator-induced lung injury by diminishing atelectrauma and minimizing exposure to potentially toxic high FiO_2 , if balanced appropriately with the risk for alveolar overdistension (1, 2). Substantial research has been performed on PEEP optimization, but the current standard of care for adults with ARDS derives from the ARDS Network (ARDSNet) trials employing a fixed titration table of FiO_2 and PEEP that was generated by expert consensus (3, 4). Three large trials examined higher versus lower PEEP (4–6), and although no individual trial showed a difference in outcomes, a meta-analysis suggested that in moderate-severe ARDS, higher PEEP was associated with improved survival (7). A recent trial of alveolar recruitment and higher PEEP for ARDS, however, showed an increased mortality in the intervention arm that runs counter to the trend of improved survival with higher PEEP (8).

L.B.W. was supported by NHLBI grant HL103836. The funding institution had no role in analysis, interpretation, preparation, review, or approval of the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.201802-0266ED on February 16, 2018

Although pediatric ARDS (PARDS) shares common pathology and pathophysiology with adult ARDS, data from adult trials may not always translate to younger populations: infants have markedly reduced chest wall elastance compared with adults, and elastin and collagen composition of lungs change with age (9, 10). Prospective studies of optimal PEEP levels in PARDS are sparse, leading to variability in the relative reliance on FiO_2 , PEEP, and other treatments for hypoxemia in the absence of clear evidence (11, 12).

In this issue of the *Journal*, Khemani and colleagues (pp. 77–89) examined previously collected data from 1,134 mechanically ventilated children with PARDS to learn more about the association between PEEP levels and mortality (13). The authors performed a thoughtful and detailed analysis in the largest study to date to explore PEEP in a pediatric population, strengthened by its size and inclusion of multiple centers. They used four datasets: two from Children's Hospital Los Angeles (CHLA), one from Children's Hospital of Philadelphia (CHOP), and one from the Collaborative Pediatric Critical Care Research Network. Because the Network dataset contained fewer descriptive variables, the most informative part of the study derived from the two hospitals (CHLA and CHOP).

Higher PEEP and higher FiO_2 reflect PARDS severity and are individually associated with mortality, so the authors compared the administered PEEP to the PEEP recommended by the original ARDSNet PEEP– FiO_2 table (3) for the administered FiO_2 , using the median values in the first day of PARDS. In these cohorts, there was a striking tendency to use 8–10 cm H_2O of PEEP without much escalation across the spectrum of FiO_2 , meaning that children with less severe PARDS were likely to receive PEEP at or above that recommended by the ARDSNet table, whereas those with more severe PARDS were likely to receive PEEP lower than recommended. This results in an association between lower-than-recommended PEEP with higher severity of lung injury, and consequently an association with higher mortality. The question is whether the finding persists when accounting for confounders.

Using multivariable modeling controlling for hospital and markers of disease severity ($\text{PaO}_2\text{:FiO}_2$ ratio, Pediatric Risk of Mortality III score, immunodeficiency, stem cell transplant, driving pressure, and inhaled nitric oxide [iNO]), the authors found a doubling of odds of death among children managed with PEEP less than recommended by the ARDSNet table compared with children managed with recommended or higher PEEP. If borne out in prospective research, the findings would suggest that clinicians should increase the PEEP to at least that recommended by the ARDSNet table. However, caution is advised, as there are important limitations to the current study.

The first limitation is the nonrandom application of PEEP and other therapies, a problem that is inherent to the observational study design. Correctly accounting for multiple confounders that are closely related and interdependent, (e.g., PEEP application modifies the $\text{PaO}_2\text{:FiO}_2$ ratio and pulmonary compliance [14, 15], and the $\text{PaO}_2\text{:FiO}_2$ ratio and airway pressures are likely to influence the decision to initiate iNO and other ancillary therapies) is challenging in a retrospective, observational study. The authors' efforts to control for severity of lung injury with $\text{PaO}_2\text{:FiO}_2$ ratio, driving pressure, and iNO help reduce confounding, but residual confounding likely persists.

The second limitation derives from the fact that the data sets used for the multivariable modeling come from just two hospitals. Although neither hospital used a formal protocol for PARDS, there was more frequent use of iNO and alternative ventilation modes and higher PEEP at CHOP compared with CHLA. The CHLA cohort also had a higher incidence of immunodeficiency (26.3% vs. 19.2%) and a higher mortality rate (22.4% vs. 14.4%). A formal test of interaction between hospitals and the association of PEEP (relative to recommended) with mortality was negative ($P = 0.4$), but analyses of interaction terms tend to have low power. When the model was separately derived on the CHLA and CHOP cohorts, the doubling of risk for mortality for lower-than-recommended PEEP persisted in the CHLA cohort, but the point estimate for the CHOP cohort went in the opposite direction, albeit with a wide confidence interval (0.87; 95% confidence interval, 0.32–2.34 points). This suggests that the association of lower-than-recommended PEEP to increased mortality is driven by the CHLA cohort. The authors also performed an adjusted risk model with a propensity score for use of lower-than-recommended PEEP, and belonging to the CHLA cohort is the variable with the highest odds ratio in the propensity score. One must wonder whether unaccounted-for hospital-level differences such as the timing of initiation of nonconventional ventilator modes, threshold for use of iNO, and potentially use of other nonprotocolized therapies uncontrolled for in the multivariable model could explain the difference in the direction of association between mortality and lower-than-recommended PEEP between hospitals.

In the absence of prospective trials to guide PEEP selection in PARDS, the investigation by Khemani and colleagues is a welcome addition to the evidence base, but because of its limitations, it should not yet inform clinical care. Nonetheless, having demonstrating a variability in use of PEEP for PARDS that appears to be independently associated with mortality, the authors establish a clear need for prospective studies of PEEP in PARDS. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Andrew C. McKown, M.D.
Division of Allergy, Pulmonary, and Critical Care Medicine
Vanderbilt University School of Medicine
Nashville, Tennessee

Lorraine B. Ware, M.D.
Division of Allergy, Pulmonary, and Critical Care Medicine
Vanderbilt University School of Medicine
Nashville, Tennessee

and
Department of Pathology, Microbiology and Immunology
Vanderbilt University School of Medicine
Nashville, Tennessee

ORCID ID: 0000-0002-7017-3615 (A.C.M.).

References

1. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med* 2013;369:2126–2136.
2. Asfar P, Schortgen F, Boisramé-Helms J, Charpentier J, Guérot E, Megarbane B, et al.; HYPER2S Investigators; REVA research network.

- Hyperoxia and hypertonic saline in patients with septic shock (HYPER2S): a two-by-two factorial, multicentre, randomised, clinical trial. *Lancet Respir Med* 2017;5:180–190.
3. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A; Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–1308.
 4. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, et al.; National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med* 2004;351:327–336.
 5. Mercat A, Richard JC, Vielle B, Jaber S, Osman D, Diehl J-L, et al.; Expiratory Pressure (Express) Study Group. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299:646–655.
 6. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, et al.; Lung Open Ventilation Study Investigators. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008;299:637–645.
 7. Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA* 2010;303:865–873.
 8. Cavalcanti AB, Suzumura EA, Laranjeira LN, Paisani DM, Damiani LP, Guimarães HP, et al.; Writing Group for the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial (ART) Investigators. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA* 2017;318:1335–1345.
 9. Kneyber MCJ, Zhang H, Slutsky AS. Ventilator-induced lung injury: similarity and differences between children and adults. *Am J Respir Crit Care Med* 2014;190:258–265.
 10. Jeffries HE, Martin LD. Respiratory physiology. In: Wheeler DS, Wong HR, Shanley TP, editors. The respiratory tract in pediatric critical illness and injury. London: Springer-Verlag; 2009. pp. 1–12.
 11. Santschi M, Jouvet P, Leclerc F, Gauvin F, Newth CJL, Carroll CL, et al.; PALIVE Investigators; Pediatric Acute Lung Injury and Sepsis Investigators Network (PALISI); European Society of Pediatric and Neonatal Intensive Care (ESPNIC). Acute lung injury in children: therapeutic practice and feasibility of international clinical trials. *Pediatr Crit Care Med* 2010;11:681–689.
 12. Khemani RG, Sward K, Morris A, Dean JM, Newth CJL; NICHD Collaborative Pediatric Critical Care Research Network (CPCCRN). Variability in usual care mechanical ventilation for pediatric acute lung injury: the potential benefit of a lung protective computer protocol. *Intensive Care Med* 2011;37:1840–1848.
 13. Khemani RG, Parvathaneni K, Yehya N, Bhalla AK, Thomas NJ, Newth CJL. Positive end-expiratory pressure lower than the ARDS Network protocol is associated with higher pediatric acute respiratory distress syndrome mortality. *Am J Respir Crit Care Med* 2018;198:77–89.
 14. Borges JB, Hedenstierna G, Larsson A, Suarez-Sipmann F. Altering the mechanical scenario to decrease the driving pressure. *Crit Care* 2015;19:342.
 15. Villar J, Pérez-Méndez L, Blanco J, Añón JM, Blanch L, Belda J, et al.; Spanish Initiative for Epidemiology, Stratification, and Therapies for ARDS (SIESTA) Network. A universal definition of ARDS: the PaO₂/FiO₂ ratio under a standard ventilatory setting—a prospective, multicenter validation study. *Intensive Care Med* 2013;39:583–592.

Copyright © 2018 by the American Thoracic Society

Lessons from Cancer: Subcellular Drug Targeting of Mitochondrial HSP90 in Pulmonary Arterial Hypertension

In 1998, Voelkel and colleagues published a visionary review highlighting apparent similarities between pulmonary arterial hypertension (PAH) and cancer (1). The cancer concept of PAH was initially fueled by the identification of a monoclonal expansion of endothelial cells in lesions of patients with idiopathic PAH (2), but has since been complemented by other characteristic features shared by cancer and PAH cells alike, such as the frequent occurrence of DNA damage, upregulation of the antiapoptotic protein survivin, and the metabolic switch from mitochondrial oxidative phosphorylation to aerobic glycolysis (the Warburg effect), all of which are considered to contribute to the cancer-like phenotype with exaggerated proliferation and resistance to apoptosis of pulmonary artery smooth muscle cells in PAH (3, 4). The cancer hypothesis has fueled the translation of concepts and therapies originally established in cancer research toward a better understanding and treatment of PAH disease. Yet, although some anticancer drugs (e.g., tyrosine kinase inhibitors) have proved effective in preclinical or clinical trials, their clinical utility has been limited by severe adverse events due to off-target effects on non-PAH cells (3, 5).

In a study published in this issue of the *Journal*, Boucherat and colleagues (pp. 90–103) translate another paradigm of increased cellular resistance to stress from cancer to PAH, with the unique perspective that therapies based on this concept may exclusively target PAH but not healthy, nonaffected cells (6). In their study, the authors focused on HSP90 (heat shock protein 90), a molecular chaperone that is ubiquitously expressed in the cytosol, where it assists in the folding and stabilization of other proteins. Cancer cells hijack this evolutionarily conserved system to protect oncoproteins, which has recently fueled interest in HSP90 inhibitors as potential anticancer drugs. In tumor cells, but not in normal tissue, HSP90 is also present in considerable amounts in mitochondria, where it antagonizes the function of the proapoptotic molecule cyclophilin D (7) and maintains energy production under low-nutrient conditions (8). Selective accumulation of HSP90 in tumor mitochondria requires HIF-1 α (hypoxia-inducible factor 1 α) (8), a transcription factor with key relevance in PAH, yet the exact molecular mechanisms underlying the translocation of HSP90 into mitochondria and the specificity of these mechanisms for cancer cells remain unknown.

In an elegant series of translational experiments, Boucherat and colleagues found that similarly to cancer cells, pulmonary artery smooth muscle cells (PASMCs) from patients with PAH contained