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*J.M. is Associate Editor of *AJRCCM*. His participation complies with American Thoracic Society requirements for recusal from review and decisions for authored works.

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Do More Injured Lungs Need More Protection? Let's Test It

Driving pressure, calculated as the difference between plateau pressure and positive end-expiratory pressure (PEEP) during mechanical ventilation in a relaxed subject, has an independent association with the risk of death in patients with acute respiratory distress syndrome (ARDS) (1, 2), suggesting that interventions in these patients such as PEEP titration are beneficial only if associated with a decrease in driving pressure. Lung computed tomography demonstrating heterogonous aeration in ARDS typically reveals dependent nonaerated lung, which is central to both our current understanding of ventilation strategies (3) and the typical increase in respiratory system stiffness (static elastance) estimated as the driving pressure divided by the V_T. Perhaps readers will be more familiar with compliance (the inverse of elastance); both static respiratory system elastance and compliance are largely influenced by the volume of aerated lung. As both the stress and strain resulting in ventilation-induced lung injury reflect V_T and end-expiratory lung volume, targeting driving pressure makes sense, as driving pressure, in effect, scales V_T to the magnitude of the reduced lung volume for a given patient with ARDS.

In this issue of the *Journal*, Goligher and colleagues (pp. 1378–1385) now provide supporting data, with a secondary

Originally Published in Press as DOI: 10.1164/rccm.202101-0154ED on February 9, 2021

analysis from five randomized trials, demonstrating a significant interaction of elastance and the effect of randomized V_T on mortality (4). With the use of Bayesian multivariable logistic regression and long-term (60-d mortality) as the primary outcome, patients with higher elastance (and hence higher driving pressures) are likely to accrue a greater mortality benefit with lower V_T compared with patients with lower elastance (and hence lower driving pressures), who are likely to accrue less mortality benefit. A Subpopulation Treatment Effect Pattern Plot analysis confirmed heterogeneity of the V_T treatment effect. Although their analysis provides credence that lung-protective ventilation strategies, and perhaps PEEP selection, should primarily target driving pressure, several considerations are required to reconcile this with earlier studies.

Lower V_T appears beneficial in both healthy and injured lungs. In the pivotal ARDS Network study examining lower versus higher V_T ventilation (5), the interaction between the randomized V_Ts and the quartile of static compliance at baseline was not significant. Further analysis by Hager and colleagues of the ARDS Network data confirmed the lack of interaction and concluded that the benefit of lower V_T ventilation strategy was not associated with plateau pressure (6), suggesting that lower V_T was beneficial even when plateau pressure was low (and by extension, there was benefit when the elastance was also low). Analyzing a larger cohort than Hager and colleagues, Goligher and colleagues' analysis failed to find this relationship, perhaps because of the larger sample size and more sensitive analytic approaches. The elastance-dependent effect of V_T reduction is consistent with the observation in models of ventilation-induced lung injury, in which damage is exacerbated by the degree of preexisting lung dysfunction (7). Taken together, this suggests the maximum benefit of lowering V_T is found in the most severely injured lungs.

Goligher and colleagues and Amato and colleagues used Day 1 postrandomization respiratory system elastance and driving pressure values, respectively; ideally prerandomization elastance would be used, but these values are not available for many patients in this database. This is important, as ventilation with either higher or lower V_T could alter the post-treatment elastance. For example, randomization to higher V_T overnight could result in either tidal recruitment (and reduced elastance) or early ventilator-induced lung injury (and increased elastance) and introduce bias. Moreover, respiratory system elastance in patients with ARDS is not static; it changes over time, perhaps suggesting that a prospective study examining this concept would also need to be dynamic, reflecting regular assessments of elastance.

Respiratory system elastance is composed of both lung and chest wall compliance, making it a poor surrogate for transpulmonary pressure. Multiple factors such as increased body weight, chest wall deformity, markedly positive cumulative fluid balance, and raised intraabdominal pressure, among others, can all affect the chest wall elastance and, consequently, the respiratory system elastance. The respiratory system elastance was adjusted either to the predicted or the actual body weight based on data availability in the five examined studies, but as discussed by Goligher and colleagues, the driving pressure may need to be reconsidered when chest wall elastance is abnormally elevated.

The association presented in the present article, and multiple sensitivity analyses to address some of these concerns, provide some compelling data, but design and implementation of high-quality prospective randomized clinical trials testing these findings to better inform management will be difficult. Theoretical analysis of mechanical power applied during ventilation (8), another newer approach to understanding ventilator-induced lung injury, groups driving pressure and V_T together, suggesting that it will be hard to separate the two during a clinical study. Furthermore, higher inspiratory flow rates increase mechanical power transmission, adding additional complexity to clinical trials of optimal lung protective ventilation. A contemporary usual care arm will include lower V_T ventilation and PEEP titration, noting that today's patients are more likely to also receive prone ventilation and restrictive fluid therapy. Early appropriate antibiotics, resuscitation and mobilization, reduced transfusion-related lung injury, and early corticosteroids (9) in appropriate patients with ARDS are among many other practice changes that reduce lung damage and improve outcomes, requiring even larger clinical trial enrollment to achieve adequate power.

The current analysis suggests that elastance (and thus driving pressure) predicts the effect of treatment with lower V_T and provides additional support for targeting an upper limit for driving pressure of 15 cm H_2O. Prospective testing of such a strategy could also stratify patients based on their respiratory system elastance; those with a high elastance could then be randomized to an ultra-low V_T strategy to decrease driving pressure further, possibly coupled with the use of extra corporeal carbon dioxide removal. Similarly, patients with low elastance could be randomized to higher V_Ts that may be better tolerated. Until such studies are complete, the simplicity of repeated titration based on driving pressure is an attractive personalized approach as we strive to further improve outcomes from ARDS. ■

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

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The Conundrum of Cleaner Cookstove Interventions: Necessary but Insufficient?

Forty percent of the world's population, nearly 3 billion people, rely on biomass fuels for daily cooking and energy needs. Incomplete combustion of biomass fuels results in high exposures to household air pollution (HAP), a complex and toxic mixture. The most commonly measured pollutants include fine particulate matter ($PM_{2.5}$) and carbon monoxide (CO). In 2019, HAP was responsible for 2.3 million deaths and 91.5 million disability-adjusted life years (1). Together, cardiovascular disease and chronic respiratory diseases account for approximately 63% of all HAP-attributable deaths and 40% of disability-adjusted life years. Much of the burden is concentrated in low- and middle-income countries where, on average, an estimated 65% of households cook with solid fuels (2).

Despite this extraordinary burden of disease, randomized controlled trial (RCT) evidence supporting cleaner cookstove interventions to improve adult cardiopulmonary outcomes is lacking. Romieu and colleagues in 2009, and Hanna and colleagues in 2016, reported household-level chimney stove interventions versus traditional open-fire stoves, and intention-to-treat analyses found no effect on lung function decline, likely driven by low intervention uptake (3, 4). A report by Guarnieri and colleagues in 2015 similarly found no evidence that a household-level chimney stove intervention improved adult lung function, but separately published exposure-response analyses were suggestive of an effect (5, 6). Zhou and colleagues did conversely find that improved ventilation or biogas stoves for 9 years improved FEV_1 decline as compared with open fire, suggesting that a long duration of follow up may be required to see health effects (7). Although broader prospective cohorts, including work from our group, generally show a positive association between HAP exposure and blood pressure (BP) and, over the life course, cardiovascular mortality, data from RCTs is limited (8–10). For example, a secondary analysis of an ethanol intervention and a pre-/postimproved cookstove study suggests that interventions to reduce HAP exposure may improve diastolic or systolic BP, respectively (11, 12). Given these mixed results, the global health community continues to seek evidence in support of a cookstove intervention strategy to improve health.

In this issue of the *Journal*, Checkley and colleagues (pp. 1386–1397) examine the effect of a year-long, multifaceted liquefied petroleum gas (LPG) cookstove intervention as compared with biomass (commonly animal dung) cookstove on cardiopulmonary health in adults, specifically resting BP, peak expiratory flow (PEF), and respiratory symptoms as measured by the St. George's Respiratory Questionnaire (13). The intervention included provision of a three-burner LPG stove, education and behavioral messaging, and biweekly LPG fuel refills and stove inspections and repairs for the duration of the study. Repeated personal exposures to $PM_{2.5}$, black carbon, and CO exposures as well as kitchen area $PM_{2.5}$, CO, and, in a subset, nitrogen dioxide (NO_2) were measured. To understand patterns of stove use, temperature loggers were placed on LPG and biomass stoves in intervention homes and biomass stoves in control homes; 24 control homes also had temperature loggers placed on LPG stoves (71% of control households already owned an LPG stove). The authors are to be commended on the strength of their intervention, exposure measurement strategy, and objective health outcome assessments.

The primary finding of this impressive study was that a year-long LPG intervention with robust measures to enable LPG stove use was

Supported by NHLBI K23HL135349 and NIMHD R01MD013310 (to A.G.L.), and by NIEHS R01ES026991.

Originally Published in Press as DOI: 10.1164/rccm.202012-4353ED on December 24, 2020